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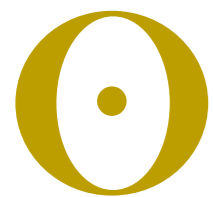


The flower of Helichrysum Italicum

Our Helichrysum Italicum plants are grown on the sunny shores of the Adriatic Sea, in beautiful Croatia and Bosnia & Hercegovina. The plants are harvested by hand and brought in for distillation.



Helichrysum Italicum plantation Herzegovina



“It may take from 1 to over 1.5 tons of flowers to extract 1 liter of Helichrysum Italicum essential oil.”

The Benefits of Helichrysum Italicum

The potent oil from the Italicum flowers, produced through a steam- distilling process, goes by several names, including “Everlasting” or “Immortelle.” But no matter what you call it, Helichrysum Italicum is an amazingly well-rounded essential oil with a laundry list of benefits.

Powerful Bruise relief: For those really severe bruising you can apply the Helichrysum Italicum essential oil directly on the hematoma either in its pure form or diluted in a vegetable oil in a proportion of 5 to 10%, I find that apricot oil is really good but other people like rose hip oil.

Organic Helichrysum essential oil is a warm, sweet and woody oil with the strongest anti-inflammatory properties of all the essential oils. Clusters of yellow flower heads during summer. Essential oil extracted from Helichrysum italicum is used for medicinal purposes. Helichrysum italicum forms a delicate color and textural combination with purple sage.

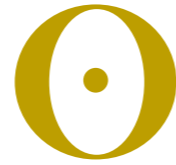
Why we love Helichrysum Italicum

The essential oil of Helichrysum is relatively unknown in many regions, though interest in this natural healing phenomenon is growing, and with very good reason.

There are numerous health benefits from Helichrysum Italicum Essential Oil. A list with detailed information and instructions are included below.

Due to recent high demand of this essential oil, its price went up 100% within two years (2011-2013) in the world market. The Helichrysum Italicum oil from Bosnia-Herzegovina that we offer is still very attractive for the market today.

Our Helichrysum Italicum has a therapeutic grade, produced to the highest quality standards possible chosen for its integrity (all chemical constituents important for aromatherapy are intact), ecological ‘soundness’ and wonderful aromas.



The following properties may apply to your particular needs:

Anti Spasmodic:

Helps in relieving headaches, migraines, asthma, bronchitis and irritable bowels. Spasm, unbalanced or excessive contractions in the body. It may be in respiratory tracts, lungs, muscles, nerves and intestines and may result in severe coughs, breathlessness, cramps, convulsions and severe abdominal pains respectively. In extreme cases, spasm can also be fatal. So, it is always advisable to treat it at the very outset. Now here enters Helichrysum Essential Oil for your help. It is anti-spasmodic and can give you quick relief in cases of spasm discussed above.

Vitiligo:

Vitiligo is a disease of skin pigments called melanin. Rather, it is a disease where there is a loss of skin pigment or color. Vitiligo affects about 2% of world population and close to 8% of Indian and Mexican populations. Vitiligo is not a serious disease, medically speaking. Its social significance is more than medical importance, as it does not cause any major harm to the body. Helichrysum Italicum has an important action against all skin issues and at such as beneficial effect on this issue.

Dermatitis, Eczema, Psoriasis:

They may be calmed with 1 to 3 % of Helichrysum in Hazelnut oil. It really makes it a valuable oil for any rash, acne, eczema, skin infection, dermatitis and other allergic conditions, spots, abscesses and boils, and it's also helpful for burns and inflammation of any kind

Analgesic effects:

Mixing Helichrysum oil with a cream for sports-injury treatment may safely increase the analgesic effects for some people. The oil is well-tolerated, and no sensitivity should occur, though one should always be aware of their own body's reactions, and discontinue use if necessary. Otherwise, while it is hoped you are never in need of this oil's benefits in the first place, it may be worth a try – you could be surprised by the effectiveness of this aromatherapeutic treatment.

Anti-Coagulant:

This is a very important and life-saving feature of Helichrysum Essential Oil. It may be somewhat difficult to digest for those who think that being a haemostatic or styptic can only help because they can check haemorrhage. But let me tell you that an anti-coagulant can be a blessing for those who run the risk of heart attack due to thickening of blood due to high cholesterol content in it. It can immediately give relief in such a crisis by liquefying or thinning blood. These days, extensive research is going on to derive anti-coagulants from natural substances (even saliva of mosquitoes and vampire bats is not spared), since heart diseases and cases of heart attacks are growing at an alarming rate.

Anti Allergenic:

This again, can save your quality of life. Now you must be thinking that I am exaggerating things too far and allergy is limited only to some rashes on skin and stomachache. You will be surprised to know that these are only

external symptoms or expressions of allergy. Allergy first shows up in internal organs such as liver, spleen, lungs, respiratory tracts, intestines and even heart and in extreme cases may result in severe attacks of asthma, cardiac arrest, unbearable pain in stomach, convulsions and even death. So why risk life. Keep this oil within reach and use it without delay before visiting a doctor.

Anti-Microbial:

Helichrysum Oil checks microbial growth and protects from microbial infections.

Anti Septic:

This oil does not let your wounds go septic. It can be safely applied on wounds, cuts, pricks etc.

Anti Hematoma:

The essential oil of Helichrysum helps clear the accumulation of bloods or blood clots which result from a hemorrhage. This can be very helpful to clear blood clots in brain after a brain hemorrhage. These clots often interfere with normal functioning of brain. This oil promotes dissolution or melting away of such clots.

Anti Phlogistic:

Helichrysum Essential Oil is effective in reducing inflammations resulting from fever, being an anti Phlogistic. This can help the patient to go less worn out and exhausted during a fever and it also aids fighting fever.

Anti Inflammatory:

Apart from giving relief in inflammations resulting from fever, this oil also gives relief from inflammations due to other causes and soothes body. Very effective in treating cuts, burns, infections and rheumatoid arthritis.

Anti-Tussive:

This property is beneficial for those who are tired and exhausted of continuous coughing.

Being an anti-Tussive, Helichrysum Oil gives relief from coughs due to deposition of phlegm in the respiratory tracts as well as due to itchiness in throat caused by infections (cold etc.).

Nervine:

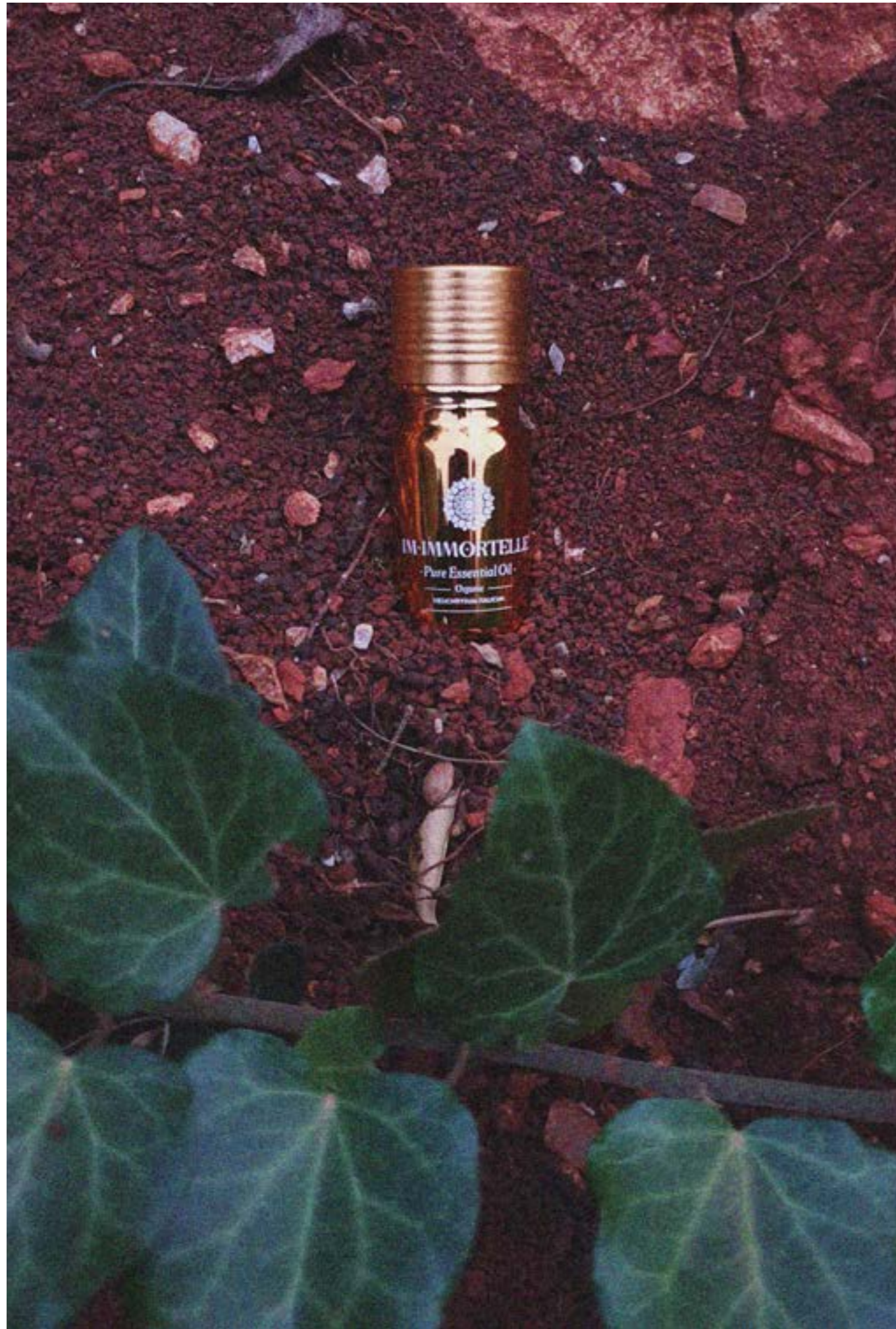
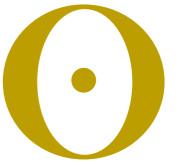
Helichrysum Oil is a nervine. It keeps your nervous system in order, strengthens it and protects it from disorders. A regular use can protect you from nervous disorders resulting from age and otherwise for a long time. You won't go nervous over small issues.

Cicatrisant:

This property of Helichrysum Essential Oil makes your wounds and cuts heal up and scar marks disappear fast. It is equally effective on spots left on your skin by pox, boils etc. It is equally effective on spots left on your skin by pox, boils, etc.

Expectorant:

Helichrysum Essential Oil is also an expectorant. It gives warmth to the respiratory system, loosens deposition of phlegm in it and does not let new phlegm deposit. It gives relief from continuous cough and Febrifuge: Fever is not a disease in itself. It is just a symptom which shows that the immune system of our body is fighting against infections or unwanted substances. Thus, you will see, fever never comes alone. It always accompanies cold, viral infections, bacterial infections and infections on wounds, liver malfunctions, pox, boils, allergy or arthritis. Helichrysum Oil, simultaneously being an anti allergenic, anti microbial, anti inflammatory, anti tussive, cicatrisant, fungicidal and anti septic at a stretch, helps cure the root of fever and eventually reduces fever, thereby acting as a febrifuge. Burning helichrysum is also beneficial for bronchial conditions as it helps break up mucus and ease lung congestion. It is useful as an expectorant when gargled



Cholagogue:

Helichrysum Oil has Cholagogue properties, which means it promotes discharge of bile into stomach and helps neutralize acids, thereby promoting digestion, curing acidity and acidosis.

Emollient:

This property of Helichrysum Oil makes the skin smooth, soft and helps it retain moisture. It prevents dehydration and cracking of the skin.

Mucolytic:

Mucus helps keep all the internal tracts (larynx, pharynx, trachea, bronchi, food pipe, intestines etc.) moist and slippery and thereby protecting them from scratches and infections etc. Mucus is essential for the body and without this these tracts may suffer from severe wounds and infections. But problem occurs when it starts depositing and thickening in the respiratory system following any infection. Then it results in coughs, congestions etc. Being a Mucolytic, Helichrysum Oil promotes thinning of excess or hardened mucus through hydrolysis and its removal from the body along with excreta. This can effectively cure congestion and cough resulting from cold.

Fungicidal:

Fungal infections are some of the most dangerous types of infections. This oil prohibits and inhibits fungal infections effectively.

Hepatic:

Being a hepatic, this oil soothes liver, relieves it of inflammations, regulates its discharges, protects it from infections and keeps it healthy, active and strong. It stimulates the

regeneration of liver cells. Di-ketones, which have a regenerative effect. Huge amounts of di-ketones are found in Helichrysum oil alone. However I am still researching into this aspect and I am waiting for medical back up on this. I will develop this section further in the months to come.

Diuretic:

It has diuretic properties, i.e. it promotes and facilitates urination, in frequency and in quantity, thereby helping removal of toxic substances from the blood through urine. Urination also helps in lowering blood pressure, losing weight by losing fat and improving digestion.

Splenic:

This property of Helichrysum Essential Oil can be very beneficial for the anemic people. Spleen is involved in the production and recycling of red blood cells. Having a healthy spleen means you never run short of blood and this oil keeps your spleen healthy and free from infections.

Cytophylactic:

Helichrysum Oil promotes cell health and also encourages recycling of dead cell and production of new cells. This helps in the growth of the body This property can be particularly beneficial for skin care, especially when used in rejuvenating facial oils. This property can be particularly beneficial for growing children or children who have obstructed growth.

Relaxant and Anti-Depressant:

Curbs negative emotions and stimulates positive thoughts and actions.



Other Benefits:

It detoxifies liver, relieves congestion, neutralizes effects of nicotine and caffeine and helps cure herpes, cystitis, arthritis, sinusitis, colitis, neuralgia and varicose veins. It has uplifting effects on mind and improves meridian flow.

Powerful Bruise relief:

For those really severe bruising you can apply the Helichrysum Italicum essential oil directly on the haematoma either in its pure form or diluted in a vegetable oil in a proportion of 5 to 10%, I find that apricot oil is really good but other people like rose hip oil. It's a question of taste or in this case, smell.

Anti-phlebitis:

Stimulates the blood circulation and can treat old bruises therefore reliving skin tissue and can also be applied to scars, even old ones, phlebitis, varicose veins, oedema and blotches can be treated in an effective way with great results. It activates the arterial circulation and the micro computing blood circulation alleviating suffering in distressed skin tissue. It is particularly active against blood clots.

Anticatarrhal, mucolytic (loosens bronchi):

Helichrysum Italicum can be used very successfully as a bronchial expectorant which will elevate congestion. A few drops of this oil in either hot water or an inhaler will help to relieve and cure this uncomfortable ailment.

Cholesterol:

Regulates the cholesterol level A and B

Healing and astringent cutaneous and desclerosant:

A high proportion of anti-inflammatory sesquiterpene hydrocarbons. This compound disperses free radicals. The unique chemical composition of essential oils from individual plants provides the oil its healing features. For instance, Helichrysum essential oil is distilled from the Helichrysum Italicum flowers. The oil includes a very effective blend of compounds that are anti-inflammatory, anti-free-radical a very powerful anti-oxidant, a tissue regenerative, and anti-haematomata.

Aroma therapeutic:

Studies have revealed that the mere smelling of natural aromatic oils, such as Helichrysum essential oil, can help you to sleep better, focus better, improve your mood. All of these effects can have a positive effect on the athlete suffering from sports-related injuries. In fact it's a great anti depressant. The unique chemical composition of essential oils from individual plants provides the oil its healing features. For instance, Helichrysum essential oil is distilled from the Helichrysum Italicum flowers. The oil includes a very effective blend of compounds that are anti-inflammatory, anti-free-radical anti-oxidant, tissue regenerative, and anti-haematomata a renowned active against blood clots. Use in a room diffuser and it will sooth the most fraught nerves and anyone with hyper tension can certainly benefit from this manner of treatment.

This plant can do so much and I'm sure that there will be further discoveries concerning its healing properties.

The Helichrysum Italicum can contains a fairly high level of Neryl Acetate, and has a high level of Sesquiterpene Hydrocarbons

and Regenerative Diketones found in large quantities too. These main components contribute to reliving and curing the following different problems: It can relax and reduce tissues in the area of an injury. (Sports injuries treated immediately with Helichrysum works wonders).

A vital piece of info is that it treats injuries better than Arnica! It can also dissipate the free radicals responsible for wrinkles. This plants effect on the stratum corneum re pulps the extra matrices cells and is a natural anti ageing substance. Another major healing factor is its pain reducing capacities and it also has analgesic effects which are UNIQUE to Helichrysum. Which is why is used in sport injuries as it acts on pain relief.

Also Helichrysum Italicum resonates beautifully with the fourth, or heart chakra and because helichrysum is a flower that enjoys the sun, it is connected with the solar plexus energies.

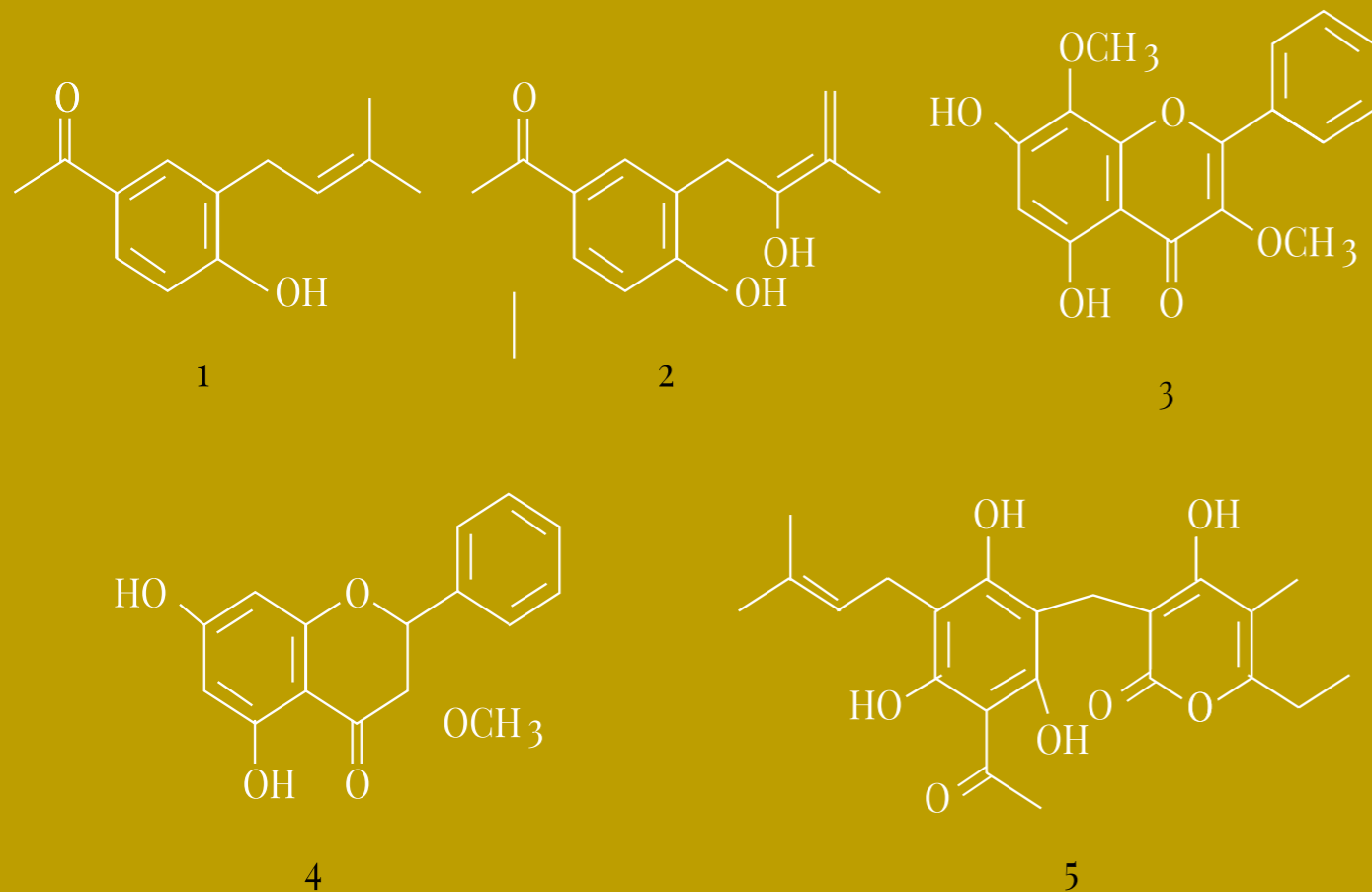


Ethnopharmacological Relevance

Helichrysum italicum (Roth) G. Don fil. (family Asteraceae) has been used for its medicinal properties for a long time and, even nowadays, continues to play an important role in the traditional medicine of Mediterranean countries. Based on this traditional knowledge, its different pharmacological activities have been the focus of active research. This review aims to provide an overview of the current state of knowledge of the pharmacological activities of *Helichrysum italicum*, as well as its traditional uses, toxicity, drug interactions and safety. Materials and methods: The selection of relevant data was made through a search using the keywords “*Helichrysum italicum*” and “*H. italicum*” in “Directory of Open Access Journals”, “Google Scholar”, “ISI Web of Knowledge”, “PubMed”, “ScienceDirect” and “Wiley Online Library”. Information obtained in local and foreign books and other sources was also included. Results: There are reports on the traditional use of *Helichrysum italicum* in European countries, particularly Italy, Spain, Portugal and Bosnia and Herzegovina. In these countries, its flowers and leaves are the most used parts in the treatment of health disorders such as allergies, colds, cough, skin, liver and gallbladder disorders, inflammation, infections and sleeplessness. In order to validate some of the traditional uses of *Helichrysum italicum* and highlight other potential applications for its extracts and isolated compounds, several scientific studies have been conducted in the last

decades. In vitro studies characterized *Helichrysum italicum* as an antimicrobial and anti-inflammatory agent. Its flavonoids and terpenes were effective against bacteria (e.g. *Staphylococcus aureus*), its acetophenones, phloroglucinols and terpenoids displayed antifungal action against *Candida albicans* and its flavonoids and phloroglucinols inhibited HSV and HIV, respectively. *Helichrysum italicum* acetophenones, flavonoids and phloroglucinols demonstrated inhibitory action in different pathways of arachidonic acid metabolism and other pro-inflammatory mediators. Regarding *Helichrysum italicum* in vivo activity, the highlight goes to the anti-erythematous and photoprotective activities of its flavonoids, demonstrated both in animals and humans, and to the anti-inflammatory properties exhibited by its flavonoids, acetophenones and phloroglucinols, as seen in animal models. Concerning its safety and adverse effects, while *Helichrysum italicum* does not display significant levels of cytotoxicity or genotoxicity, it should be noticed that one of its flavonoids inhibited some CYP isoforms and a case has been reported of an allergic reaction to its extracts. Conclusions: *Helichrysum italicum* is a medicinal plant with promising pharmacological activities. However, most of its traditionally claimed applications are not yet scientifically proven. Clinical trials are needed to further confirm these data and promote *Helichrysum italicum* as an important tool in the treatment of several diseases.





Year	Region	Plant name	Medicinal uses	Plant part	Preparation	References
1989	Granada, Spain	<i>Helichrysum italicum</i> (Roth) G. Don	Toothache	Flower	Infusion (mouth rinsing)	González-Tejem (1989)
1991	Castellón, Spain	<i>Helichrysum italicum</i> subsp. <i>serotinum</i> (Boiss.) P. Fourn.	Digestive disorders	Flower	Infusion	Mulet (1991)
1993	Murcia, Spain	<i>Helichrysum italicum</i> subsp. <i>serotinum</i> (Boiss.) P. Fourn.	Analgesic, anti-odontalgic, astringent, antiemetic and dermatologic tonic	-	-	Rivera and Obón (1993)
1997	Campidano and Urzulei, Sardinia, Italy	<i>Helichrysum italicum</i> subsp. <i>microphyllum</i> (Willd.) Nyman	Allergy	Whole plant	Infusion	Bruni et al. (1997)
1998	Córdoba, Spain	<i>Helichrysum italicum</i> subsp. <i>serotinum</i> (Boiss.) P.Fourn.	Stomach cleanser	-	Decoction	Luque et al. (1998)
1999	Giglio, Tuscany Archipelago, Italy	<i>Helichrysum italicum</i> (Roth) G. Don	Cough, colds, tracheitis and laryngitis	Leaf and flower tip	Infusion and vapors	Uncini Manganeli and Tomei (1999)
2000	Garfagnana, Lucca Province, Italy	<i>Helichrysum italicum</i> (Roth) G. Don	Colds	Aerial parts	Infusion and fumes	Pieroni (2000)
2001	Fluminimaggiore, Sardinia, Italy	<i>Helichrysum italicum</i> subsp. <i>microphyllum</i> (Willd.) Nyman	Skin diseases (alopecia)	Whole plant	Decoction	Balleru et al. (2001)
2005	Jaén, Spain	<i>Helichrysum italicum</i> (Roth) G. Don	Digestive disorders and catarrh	-	-	Pardo de Santayana et al. (2005)
2005	Ibí, Alicante, Spain	<i>Helichrysum italicum</i> (Roth) G. Don	Toothache and mouth antiseptic	Flower	Infusion (mouth rinsing)	Barber et al. (2005)
2007	Alt Empordà, Catalunya, Spain	<i>Helichrysum italicum</i> (Roth) G. Don	Digestive disorders	Flower	Infusion	Parada (2007)
2007	Bosnia and Herzegovina	<i>Helichrysum italicum</i> (Roth) G. Don	Liver and gall disorders, cough	Flower	Infusion	Redzic (2007)
2007	Calabria, Italy	<i>Helichrysum italicum</i> (Roth) G. Don	Brochitis and pharyngitis	Flowery tops	Infusion or powder mixed with honey	Passalacqua et al. (2007)
2007	Baixo Alentejo; Barlavento Algarvio, Portugal	<i>Helichrysum italicum</i> (Roth) G. Don	Dermatologic disorders	Aerial parts	Essential oil	Proença da Cunha et al. (2007)
2008	Sannio, Benevento, Campania, Italy	<i>Helichrysum italicum</i> (Roth) G. Don	Cough	Flower	Infusion or decoction	Guarino et al. (2008)
2008	La Coruña, Spain	<i>Helichrysum italicum</i> (Roth) G. Don	Skin inflammation	Flower	Infusion (external use)	Latorre (2008)
2008	Valencia, Spain	<i>Helichrysum italicum</i> (Roth) G. Don	Intestinal parasitic infections	-	-	Segarra i Durà (2008), cited by Latorre (2008)
2008	Jumilla-Yecla, Murcia, Spain	<i>Helichrysum italicum</i> subsp. <i>serotinum</i> (Boiss.) P.Fourn.	Wound healing	Flower, leaf and stem	Powder	Rivera et al. (2008)
2009	Riviera spezzina, Liguria, Italy	<i>Helichrysum italicum</i> (Roth) G. Don subsp. <i>italicum</i>	Sleeplessness, headache, sniffles and cough Inflammation and cough Stomach ache	Flower and leaf Flower Flower and leaf Young leaves and apical parts	Fumes Infusion Decoction Juice	Cornara et al. (2009)
2010	Western Granada, Spain	<i>Helichrysum italicum</i> subsp. <i>serotinum</i> (Boiss.) P. Fourn.	Helminthic infections Digestive disorders, gastralgia Cough, mouth ailments, liver disease, herpes	Flower Inflorescence Flowery plant	Decoction Infusion Infusion	Benitez et al. (2010)
2012	Portugal	<i>Helichrysum italicum</i> subsp. <i>piconii</i> Franco	Dermatomycosis	Aerial parts	Essential oil	Proença da Cunha et al. (2012)
2013	National Park of Cilento and Vallo di Diano, Campania, Italy	<i>Helichrysum italicum</i> (Roth) G. Don	Asthma	Flowering tops	Decoction	Di Novella et al. (2013)

Helichrysum Italicum

The Sleeping Giant of Mediterranean Herbal Medicine



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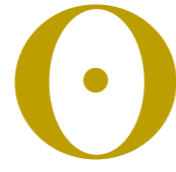
Introduction

Helichrysum italicum (Roth.) Don. (Asteraceae) is an iconic plant of the Mediterranean area (Figure 1), but the use of its essential oil in glamorous perfumes and personal care products has turned it into a veritable icon of luxury. However, just like the geographical distribution of *Helichrysum* species extends beyond the Mediterranean region, the properties of *H. italicum* are not limited to fragrance as they can benefit human health as well. In this context, *H. italicum* can be viewed as the sleeping giant of Mediterranean herbal medicine, and its extracts have the potential to be developed as dietary supplement ingredients just like its essential oil has been used successfully in perfumery and aromatherapy. Waking this giant will not be simple, but recent studies have provided the basis for a *Helichrysum* renaissance. This article outlines the fascinating ethnopharmacology of *H. italicum* in the light of modern molecular investigations of its constituents and their pharmacological targets, and highlights the extensive clinical studies carried out in 1930s Italy by Leonardo Santini, a physician and clinical investigator.



How Many Helichrysum Species Exist and Why is Their Color so Fade-Resistant?

The genus *Helichrysum* belongs to the family Asteraceae and encompasses more than 500 different species, with hotbeds of biodiversity centered in the Mediterranean basin, South Africa, and Australia — three geographically and geologically unrelated areas.¹ This split distribution is presumably the result of parallel evolution from one or more ancestral and now-extinguished species. The name *Helichrysum* (from the Greek *helios* = sun and *krysos* = gold) makes reference to the bright yellow color of the flowerheads, which is particularly striking in full sun and also remarkably persistent in the dried plant. The name of the plant in many European languages — *perpetuino* and *semprevivo* in Italian, *immortelle* in French, *everlasting* in English, *siempreviva* in Spanish — recalls this property. The yellow color of *Helichrysum*'s flowerheads has been tied to the presence of the chalcone (a particular type of flavonoid) *isosalipurposide*,² and its steadfastness may be due to stabilizing co-pigments, to the anatomy of the flower that preserves the bracts' vacuolar contents from air oxidation, or to a combination of these factors. On the other hand, recent investigations of *H. italicum* failed to detect the presence of chalcones³ — which are probably typical of the Northern species *H. arenarium* Moench.⁴ — but found *kaempferol*-type flavonols instead.³ Therefore, the exact nature of the yellow pigment from *H. italicum* and, in general, of the resistance of *Helichrysum* flowerheads to fading, seem unclear. Interestingly, when mixed with mulberry (*Morus* spp., Moraceae) leaves and fed to silkworms, the flowerheads of *H. italicum* induce the production of naturally yellow silk, a material used in central Sardinia for the production of folk garments (Figure 2). Ancient Romans and Greeks decorated the statues of gods with wreaths of *Helichrysum* flowerheads, a practice mentioned by classic writers since the 7th century BCE. This use may seem curious, since existing classic statues are now the color of the original materials from which they were made (e.g., marble or bronze). However, they were originally vividly colored, and the yellow hue of *Helichrysum* in full sun would have given the effect of a gold crown on a polychromous figure.



Helichrysum italicum and its Baffling Scent

Helichrysum italicum is a xerophytic shrub 30 to 70 centimeters high, branched at the base with small, linear, hairy leaves that give the plant an overall grey hue until the appearance of the yellow flowerheads in June or July (Figure 3).¹ It grows in dry, stony areas at an impressive range of altitudes from sea level to more than 2,000 meters. From a botanical standpoint, *H. italicum* is an umbrella name that covers at least six distinct varieties widespread mainly in the Western European Mediterranean region. The best-known variety grows around the northern Tyrrhenian Sea, on the islands of Corsica and Sardinia and on the Tuscany islands (Figure 4). The Tyrrhenian *Helichrysum* generally is referred to as *H. italicum* Don. subsp. *microphyllum* (Willd.) Nyman — a plant that also grows on the Balearic Islands off the eastern coast of Spain (e.g., Majorca and Minorca) — but recent taxonomical work classifies it as *H. microphyllum* subsp. *tyrrhenicum* Bacch., Brullo & Giusso.⁵ Tyrrhenian *Helichrysum* is the variety most valued for the production of an essential oil that is used in perfumery and personal-care products.⁶ Markedly, the *Helichrysum* note is used in commercial fragrances for both males and females (e.g., *Magie Noire* by Lancôme, *Femme* by Rochas, and *Homme* by Van Cleef & Arpels).

Helichrysum italicum is also the most-investigated species in terms of ethnobotany and phytochemistry. Six other species of *Helichrysum* are endemic in the Western Mediterranean area, including: *H. frigidum* (Labill.) Willd., *H. montelinasanum* E. Schmid, *H. nebrodensis* Heldr., *H. saxatile* Moris, *H. siculum* (Sprengel)

Boiss., and *H. rupestre* (Rafin.) DC.¹ Each of these species has a distinct geographical distribution; *H. montelinasanum*, which grows only in a single location in Sardinia, has a particularly limited distribution.

Helichrysum italicum is famous and valued for its scent, which has been referred to as rosy, exotic, and spicy. The peculiar odor note was mentioned in the 1st century CE by Pliny the Elder, who, in his work *Naturalis Historia*, described it as not-at-all unpleasant and as being able to protect clothes from moths (*Vestes tuetur odore non ineleganti*).⁷ Indeed, the Tyrrhenian *Helichrysum* has a pleasant and persistent odor, different from that of the essential oil, and difficult to describe in terms other than “odor of *Helichrysum*.” It is reminiscent of the perfume of licorice (*Glycyrrhiza glabra*, Fabaceae), Indian curry, tobacco (*Nicotiana tabacum*, Solanaceae), and roses (*Rosa* spp., Rosaceae). Conversely, other European species of *Helichrysum* and other populations of *H. italicum* have an unpleasant phenolic note (which some people find annoying for its persistency)^{8*} that is different from the manure-like note typical of some African *Helichrysum* species.⁹ Despite its significance, the odor issue has been poorly investigated in terms of both pleasant and unpleasant notes. During steam distillation, the licorice note is lost and a bitter, woody note is generated, presumably by the degradation of non-volatile constituents. Overall, the essential oil and the plant are quite different in terms of olfactory properties.





Ethnopharmacology of *Helichrysum italicum*



The largest body of ethnopharmacological information on *H. italicum* comes from the northern Tyrrhenian area, where the use of the plant is well documented in both human and veterinary medicine for the management of respiratory and digestive problems, and for topical wound healing.¹⁰⁻¹³ Thus, the plant is considered beneficial for inflammatory and infective airway conditions, including cough, bronchitis, laryngitis, and tracheitis. *Helichrysum italicum* also is used in herbal teas as a cholagogue (i.e., a bile stimulator) and choleric agent. The so-called *tisana del Quirinale* (“Quirinale” is the Italian equivalent of the White House) is a combination of *Helichrysum*, lavender (*Lavandula* spp., Lamiaceae), and fennel (*Foeniculum vulgare*, Apiaceae), and the herbal tea was popular with two Presidents of Italy, Oscar Luigi Scalfaro and Carlo Azeglio Ciampi.¹⁴ Mixed with olive oil, *H. italicum* is used for the dermatological treatment of sun and fire burns and for wound healing. In veterinary medicine, the plant is used to treat cough in donkeys and joint ailments for both horses and donkeys.¹³ Curiously, the first modern investigations on the plant were spurred by these animal uses.

Helichrysum italicum also has culinary uses. These uses are quite different, however, from those of the archetypal edible *Helichrysum* (*H. conchinchinensis*), whose seedlings and sprouts

are used in Asia to prepare *banh khuc*, a delicacy of Vietnamese cuisine. *Helichrysum italicum* is the source of one of the most expensive and highly sought-after European honeys, *miele di spiaggia* (seashore honey).¹⁵ Bees do not forage on *H. italicum*, but, while visiting the plant, they become covered with the resinous material that coats the flowers and pass it on to the pollen collected from other plants, eventually producing a honey that retains the flavor of *Helichrysum*. In the Tyrrhenian area, the leaves are used like rosemary (*Rosmarinus officinalis*, Lamiaceae) to flavor local dishes and salads, and to impart a “curry-like” note to pork meat and stuffings.¹⁶ The plant also is an ingredient in so-called Mediterranean curry (a mixture of *H. italicum*, onion [*Allium cepa*, Liliaceae], rosemary, wild fennel, thyme [*Thymus vulgaris*, Lamiaceae], and catnip [*Nepeta cataria*, Lamiaceae]). Owing to its anti-bacterial properties, *H. italicum* also has been used as a hop (*Humulus lupulus*, Cannabaceae) replacement in the production of beer. Finally, the use of *Helichrysum* to aromatize spirits and to prepare liqueurs is well documented, especially in Sardinia.

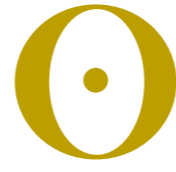


Helichrysum in the Classic Medical Treatises

Helichrysum is mentioned in all major medical treatises of the Greco-Roman tradition. In many of them, a botanical distinction is made between the species with large flowers (e.g., *H. stoechas* group, from the ancient name of the Hyères Islands off the French Côte d'Azur) and those with small flowers (e.g., *H. italicum* group) — the two main types growing in the Mediterranean area — but the same properties are assigned to both species. Theophrastus (3rd century BCE) — in his *Historia Plantarum*, the oldest extant medicinal plant treatise from the Western tradition† — mentioned the application of Helichrysum mixed with honey to treat burns and wounds,¹⁷ while Dioscorides (1st century CE) reported the use of a medicinal wine from Helichrysum to treat arthritic conditions and sciatica.^{19,20} Similar information is provided by Pliny the Elder in his *Naturalis Historia*, and the medical literature of the Renaissance often referred to these sources, with emphasis on the treatment of back and hip pain. The Italian Renaissance physician and botanist Castore Du-

rante (1529-1590) also noted the use of a medicinal wine infused with *H. italicum* flowerheads to treat liver disorders, and further recommended a decoction of the plant for catarrh.²¹

Overall, the most common medical uses of Helichrysum documented by ancient authors were as a topical antiseptic, a cicatrizing (i.e., scar-forming) agent, for joint health and liver protection, and as a treatment for airway infections. Peculiarly, Theophrastus classified Helichrysum as a mind-altering plant,¹⁷ presumably because of its use in ritual fumigations. A similar use of Helichrysum is widespread in South Africa,⁹ and some species are traded as psychotropic agents.⁹ In fact, an African Helichrysum species is the only plant besides cannabis and hemp (*Cannabis sativa*, Cannabaceae) that contains cannabinoids, although researchers have isolated only the non-psychotropic agent cannabigerol (CBG) in the species.¹⁸



Helichrysum Essential Oil and its Use in Medicine and Aromatherapy

The essential oil of Helichrysum is obtained from biomass of various geographical origins (e.g., the Balkan Peninsula, Ukraine, Corsica, Sardinia, Provence, and Spain),⁶ and once was used mainly for the aromatization of pipe tobacco. Factors related to the Balkan wars of the 1990s as well as Helichrysum's increased popularity in aromatherapy, perfumery, and cosmetics, led to a shortage of plant material that stimulated cultivation and collection in the Western part of the Mediterranean region, especially in Corsica and Sardinia.⁶ The absolute is used only in perfumery, while the essential oil is employed in medicine and aromatherapy. The introduction of the oil of *H. italicum* in aromatherapy originated in France, and was popularized in English-speaking countries by aromatherapist and author Kurt Schnaubelt, who notably considers interchangeable the many uses of the pinene- and neryl ester-rich oils.

The essential oil of Tyrrhenian Helichrysum is significantly different from the oil of *H. italicum* subspecies and other Helichrysum species; it is characterized by a high content (25-45%) of neryl esters (acetate, isobutyrate, isovalerate), which are considered the plant's most distinctive constituents.²²⁻²⁶ Also, the sesquiterpenoid fraction of the oil (about 10-20%) is distinctive, containing the bisabolane-derivative curcumene, bisabolane cycloadducts (italicenes), and eudesmane alcohols (rosifoliol).²²⁻²⁶ The oils of Helichrysum from the Balkan peninsula and the Adriatic coast of Italy contain mainly pinenes, and, like some oils of French cultivation, they have a high curcumene content (ca. 20%).⁶ The oils of Helichrysum

also contain a series of diketones (italidiones) probably derived from the thermal degradation of non-volatile pyrones that are abundant constituents of several Helichrysum species.²²⁻²⁶ Since these diketones are likely artifacts, their concentrations may be related to the duration of the distillation process, but their value as markers is limited because of their presence in the oils of other species of Helichrysum. The licorice note of Tyrrhenian Helichrysum is lost during steam distillation, while the compound(s) responsible for the unpleasant phenolic odor of some Helichrysum plants and oils, as previously mentioned, have not been characterized yet. Despite the popularity of Helichrysum essential oil, the molecular bases of its sensory properties have not been characterized fully.

Helichrysum oil is obtained by steam distillation of the flowerheads, and its yield is rather low, rarely above 0.1% of the starting fresh biomass.²²⁻²⁶ This, along with the low biomass production of the plant, is responsible for the high price of the oil, which is currently one of the most expensive on the market (roughly 2,000 euro/kg). The composition of the oil is variable, even among samples of the same geographical origin; the texture and acidity of the soil seem to have a marked effect. Rich in neryl esters and diketones, Tyrrhenian Helichrysum oil is the variety most valued in perfumery and most used in aromatherapy, although it is not clear if the contents of neryl esters and diketones alone can explain this preference.^{6,26} Owing to differences in the composition of the essential oil from *H. italicum*,

it is possible that specific properties are associated with specific types of essential oil, but this issue has not yet been systematically investigated.

The main use of the essential oil of Helichrysum is to fade or reduce scars. Despite the lack of animal and human studies to substantiate this application, many practitioners are convinced of its utility for this purpose.²⁷ Another important use of the oil is for the treatment of bleeding wounds, an indication for which it is considered the essential oil of preference. For this indication, it has been suggested that the oil is best used undiluted to help sanitize the wound, foster its closure, and relieve pain. For all other uses, the oil is diluted in fixed oil.²⁷ The essential oil also has been used in combination with lavender (*Lavandula angustifolia*, Lamiaceae) and tea tree oil (*Melaleuca alternifolia*, Myrtaceae) to soothe skin conditions associated with chemotherapy such as palmar-plantar erythrodysesthesia, otherwise known as hand-foot syndrome (a trophic skin disorder associated with the use of anticancer drugs, including both cytotoxic [capecitabine, taxanes, camptothecins] and targeted [monoclonal antibodies such as cetuzimab as well as kinase inhibitors including erlotinib, sorafenib, and sunitinib] chemotherapy agents).²⁷ Similar combinations of essential oils with anti-VEGF (vascular endothelial growth factor) or anti-EGF (epidermal growth factor) agents can be used to manage chemotherapy-induced acne and the "face powder" desquamation associated with the use of 5-fluorouracil and irinotecan.²⁷ Despite the success of Helichrysum oil as an anti-aging agent, no published clinical

data support the "Fountain of Youth" claims of some cosmetic products, although proprietary data might exist.

The growing use of Helichrysum oil in aromatherapy and medicine should stimulate randomized, controlled trials to assess its efficacy and help define standards of composition for the medicinal use of the oil, as has been done with neryl esters for use in perfumery.



Modern Studies on Helichrysum: The Contribution of Leonardo Santini

Leonardo Santini (Figure 5) is considered the father of modern studies on Helichrysum. He was born in 1904 in Molazzana, a small village near Lucca, in Northern Tuscany.‡ His father was a physician, as were many of his relatives. Santini earned a degree in medicine from the University of Pisa and, later, started a medical practice in Castelnuovo di Garfagnana, a small town in Northern Tuscany famous for being governed during the Renaissance by the poet Lodovico Ariosto. The involvement of Santini with Helichrysum is reminiscent of that of William Withering with foxglove (*Digitalis purpurea*, Plantaginaceae). Just like Withering was “tipped” on the properties of foxglove by an “old lady” of a country village, Santini was introduced to Helichrysum’s healing properties by a mule-driver who claimed to have successfully managed his donkeys’ cough with canugioro, the local name for *H. italicum*. (Since donkeys are more stoic than horses, cough generally is indicative of an advanced

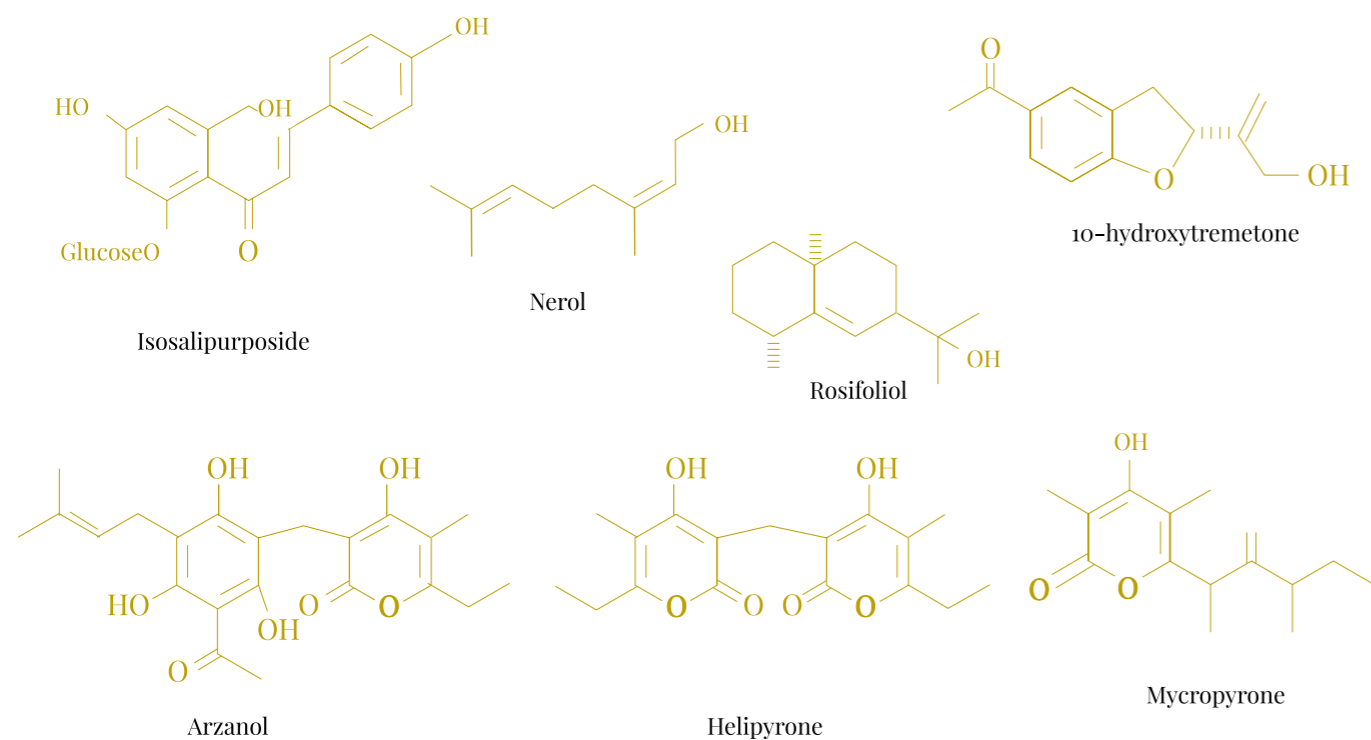
respiratory disease.) This, coupled with his awareness of the plant’s widespread use for similar conditions in horses, led Santini to administer a decoction of the plant to some of his patients who were suffering from bronchitis and asthmatic cough. Not only did their respiratory conditions improve, but also other unrelated diseases from which they were suffering — particularly psoriasis and arthritis. Intrigued by these observations, Santini started to experiment with a decoction and syrup from *H. italicum* in the late 1930s, summarizing more than two decades of observations in a series of articles that were published from 1949 to 1953 in Italian journals with unfortunately limited distribution outside the community of general practitioners.²⁸⁻³¹ Santini determined that the clinical activity of Helichrysum was similar of that of cortisone — a drug in short supply at the time — and also reported an insulin-sensitizing activity in animal experiments. The proposed cortisone-

like compound was named helichrysin, but it was never characterized chemically. Santini found the decoction’s anti-psoriatic activity to be particularly useful and treated hundreds of patients with the condition. The beneficial effects of the treatment were confirmed in two independent clinical studies carried out in the 1950s.²⁸⁻³¹ More recently, the results of a small open study from 1995 supported the use of a 5% decoction for the treatment of psoriasis.³² After three weeks of treatment, all study participants improved, with relapses observed within two months post-treatment. Though spontaneous regression of psoriasis is not uncommon, these studies provide a rationale for the initiation of controlled, double-blind, clinical trials for the use of *H. italicum* in managing psoriasis.

Santini also observed positive results from the use of an aerosolized Helichrysum decoction for allergic rhinitis and a Helichrysum ointment for the treatment of solar and fire burns, chilblains, venous stasis, varicose veins, and hemorrhoids. Interestingly, a topical product containing an extract from *H. arenarium* (L.) Moench. was developed in the former USSR for the management of radiation burns.³³

The publication of Santini’s studies in the early 1950s piqued the interest of Renzo Benigni — the chief pharmacologist of the Italian company Inverni della Beffa — who started systematic studies on the plant, including the formulation used by Santini (a simple 5% decoction of the dried flowerheads). Benigni found that filtration of the decoction led to

a considerable loss of activity, suggesting that the active constituents had limited solubility in water, where it was dispersed and not well dissolved. To obtain more reproducible animal data, he investigated an extract (“Fraction H”) produced using an organic solvent. This product exhibited some cortisone-like activity, and, at a dosage of 5 mg/day, could significantly prolong the life of rats whose adrenal glands had been surgically removed.³³ A series of clinical studies in various Italian centers substantially confirmed the findings of Santini, showing that Fraction H could replace, to varying degrees, corticosteroids in many of their uses without their adverse side effects.³³ Benigni, however, never published his findings; he only summarized them in a Helichrysum monograph that appeared in the monumental treatise on medicinal plants he coauthored with Capra and Cattorini.³³ In the wake of Santini’s studies, a Helichrysum syrup was commercialized in the Italian pharmaceutical market as a cough syrup. However, the lack of standardization and information on the active principle led to the product’s demise when more stringent rules on pharmaceutical products were introduced in Italy in the late 1960s. Notably, a small clinical study in 1981 on children affected by tracheo-bronchitis found a Helichrysum decoction highly efficacious.³⁴



Phytochemical and Pharmacological Studies on *Helichrysum italicum*

Most recent phytochemical analyses of *H. italicum* have focused on the northern Tyrrhenian variety (*H. italicum* subsp. *microphyllum*), which Santini used in his clinical studies. The most common non-volatile constituents of this plant belong to the acylphloroglucinol and pyrone classes of ketides. These compounds can occur in *H. italicum* as a monomer (micopyrone), symmetrical dimer (helipyron), or mixed dimer (arzanol) (Figure 6).³⁵

Arzanol is the best characterized of these ketides in terms of bioactivity. Its name is derived from the small town of Arzana (Figures 7) in East Sardinia, where the plant that yielded this compound was collected.³⁵ Arzanol has an anti-inflammatory profile not unlike that of curcumin, suggesting that the association of *H. italicum* with curry might extend beyond olfaction. (Both turmeric and *Helichrysum* essential oils contain the volatile curcu-

mene sesquiterpene.) Arzanol interrupts pro-inflammatory signaling and increases antioxidant protection by acting at distinct time-domain targets.³⁶ The enzymes mPGES-1 and 5-LO are key players in the generation of inflammatory eicosanoids (the prostaglandin PGE₂ and leukotrienes, respectively) and represent the short-time domain target for arzanol, while the pro-inflammatory transcription factors NF- κ B represent its primary long-term target.³⁵ The net result is the inhibition of the production of inflammatory cytokines (TNF- α , IL-1b, IL-6) and inducible inflammatory enzymes (COX2 and mPG2S). A study in 2011 found that, in contrast with non-steroidal anti-inflammatory drugs (NSAIDs), the production of beneficial prostanoids like PI₂ was not affected by arzanol, which retained activity in an in vivo model of inflammation (carrageenan-induced pleurisy in rats).³⁶



Arzanol is refractory to chemical modification, but its structure-activity relationships can be elucidated by total synthesis, highlighting the relevance of its decoration of hydroxyls and heterodimeric structure for the inhibition of mPGES-1 and 5LO.³⁷ The symmetrical pyrone dimer helipyron was much less potent against these anti-inflammatory targets, as was the monomeric phloroglucinol micopyrone. Arzanol also has shown remarkable antibacterial activity, outperforming the fluoroquinolone norfloxacin against many strains of super-bacteria of the infamous methicillin-resistant staphylococcus aureus (MRSA) type.³⁸ Polar fractions from extracts of *H. italicum* display anti-biofilm activity against the gram-negative pathogen *Pseudomonas aeruginosa*.³⁹ In this context, it is interesting to note that a mixture of heterodimeric phloroglucinols known as arenarin was developed as a skin-and-eye antibacterial agent in the former Soviet Union.⁴⁰ The polyphenolic phloroglucinyl component makes arzanol a potent antioxidant, equipotent to caffeic acid and more potent than other plant-derived polyphenolics such as nordihydroguaiaretic (NDGA) acid, magnolol, and even myrtucommulone from myrtle (*Myrtus communis*, Myrtaceae) in in vitro assays of antioxidant activity.^{37,41} Arzanol also was shown to inhibit lipid peroxidation in a series of in vivo systems.⁴² Taken together, these observations suggest that arzanol may be the major bioactive constituent of helichrysin, the crude preparation of *Helichrysum* used by Santini in his clinical investigations.

Apart from arzanol, *H. italicum* contains additional bioactive constituents that could complement its anti-inflammatory activity. For instance, the flowerheads and aerial parts are rich sources of ursolic acid (up to 0.5% by dry weight)³⁸ — an anti-inflammatory triterpenoid and popular cosmetic ingredient⁴³ — and also of benzofurans of the tremetone type,³⁸ some of which have shown

anti-spasmodic effects.⁴⁴ A mixture of methylketones and sterols known as tremetol was long considered the toxic agent responsible for the plant-induced “milk sickness” that devastated large areas of the American Midwest in the first half of the 19th century (and whose most famous victim was Abraham Lincoln’s mother).⁴⁵ However, pure synthetic tremetone was not capable of reproducing the toxicity of extracts from white snakeroot (*Ageratina altissima*, Asteraceae), which is now considered the most likely plant source of milk sickness, although the nature of the toxin(s) involved is still unclear.⁴⁶ Also noteworthy is the presence of an unusual class of lipids, named santinols in honor of Leonardo Santini, in Tyrrhenian *H. italicum*.³⁸ Santinols are glycerides of branched medium-chain acids that represent a novel type of plant lipids. Curiously, one of the acids present in santinols (2-methyl-3-oxovaleric acid) is a marker for the diagnosis of propionic acidemia, a human genetic disease, and had never been identified before in plants.³⁸

Helichrysum italicum shows remarkable plasticity in terms of growing conditions, thriving both on the coast and in the mountains with no apparent preference for a particular type of substrate (calcareous, acidic, sandy, stony). This ecological adaptability translates into a heterogeneous morphology, the presence of numerous ecotypes and varieties, and, ultimately, phytochemical polymorphisms. Thus, several chemotypes of *H. italicum* exist, characterized by distinct phytochemical profiles and therefore unlikely to be pharmacologically equivalent. In particular, the presence of high concentrations of arzanol seems characteristic of the northern Tyrrhenian population of *H. italicum* (subsp. *microphyllum*); commercial samples from the southern Tyrrhenian area as well as those of Adriatic origin did not contain significant amounts of this compound.⁴⁷



The Helichrysum italicum Supply Chain

Helichrysum species have been commercially available as ornamentals since the 17th century. The species popular in nurseries today are mainly non-European, including *H. bracteatum* Andr. from Australia, *H. bellidioides* Willd from New Zealand, and *H. petiolatum* DC from South Africa. The most popular European species available in nurseries are *H. stoechas* (L.) Moench. from the Balkans and *H. arenarium* (L.) Moench. DC. from Eastern Europe. *Helichrysum italicum* is of more limited availability in the horticultural market; the commercial material used by the perfumery and cosmetic industries is rather heterogeneous and is derived from both cultivation and wild collection in different regions.⁶ Apart from the northern Tyrrhenian area, *H. italicum* can be found along the Adriatic coast of Italy, the estuary of the river Po, and in Southern Italy. The major areas of *H. italicum* cultivation in the Western Mediterranean region are Corsica and Sardinia, and most biomass produced there is acquired by the cosmetic and perfumery industries and distilled. Essential oil production is highly fractionated, and it is difficult to estimate the total amount of oil produced. The medicinal supply chain of *H. italicum* remains underdeveloped, and, given the high price of the essential oil, many producers find it more convenient to distill the plant and sell the oil rather than to commercialize the whole plant for the production of extracts. The essential oil is produced exclusively from the flowerheads, while the rest of the plant — which contains significant amounts of secondary metabolites and could in principle be used to produce extracts — is left in situ.⁴⁸

The expense of the oil, especially of Tyrrhenian origin, provides incentive for economically motivated (i.e., intentional) adulteration. Currently, there are no established reference criteria for medicinal-grade *Helichrysum* oil, but the aromatherapy market, like the perfumery market, emphasizes oil of Cor-

sican origin, which sells at a considerably higher price. Remarkably, some vendors of “Corsican” *Helichrysum* oil provide gas chromatograph profiles on their websites that do not qualify the oil as of Corsican or Tyrrhenian origin. Low nerol contents and high hydrocarbon contents — like the Balkan and Adriatic *Helichrysum* oils — indicate either adulteration or the cultivation in Corsica of non-native chemotypes of foreign origin.⁴⁹ The limited production of Tyrrhenian *Helichrysum* oil and its relevance in the perfumery and personal care industries call into question whether or not significant amounts of the oil are in fact available on other markets.

Today, there is a huge disconnect between demand and availability of Tyrrhenian *Helichrysum*, which has been compounded by the past years’ poor harvest. Adulteration of some materials is filling this gap now, but wild harvesting is a growing problem in both Corsica and Sardinia, despite the hard-to-reach location of many populations of the plant. (Sardinia and Corsica have the longest undeveloped coastal areas in Western Mediterranean Europe.) Wild harvesting will not only significantly impact the status of the plant, but, by providing a lower-cost (but unsustainable) plant material, it also is damaging the ongoing projects intended to develop a sustainable *Helichrysum* supply chain and meet its strongly growing demand. Due to its superior properties, the Sardinian population of gentian (*Gentiana lutea*, Gentianaceae) was exterminated in the 1950s and 1960s by uncontrolled harvesting, and, despite efforts of re-introduction, it has not recovered. To avoid a similar fate for *Helichrysum*, a program to certify the plants’ sustainable cultivation through to harvest should be established for the plant, which also would foster consumer awareness of the fragility of the supply chain from wild harvesting.



Conclusions

Extracts from *H. italicum* are used in topical products for the management of hemorrhoids and lower limb venous insufficiency (i.e., heavy legs) in the Italian healthfood market. These extracts are not standardized in the phytochemicals typical of *H. italicum*, and these uses do not represent the full potential of the plant. Santini published the results of his investigations on the presence of a cortisone-like compound in *H. italicum* in the 1940s, when the first synthetic corticosteroids were developed. The availability of corticosteroids — well characterized chemically and relatively low cost — undermined interest in Santini's findings. Owing to the progress in chemistry, from the 1930s onward plant extracts had been increasingly replaced by their single primary active ingredients (lanatosides for foxglove, atropine for nightshade [Solanaceae]) or synthetic analogs (amphetamine for ephedrine). Meanwhile, the work of Santini was going in the other direction, apparently against the flow of medical history. The lack of information on the active ingredients of *Helichrysum*, the complications involved in the standardization of a phytochemically unexplored plant, and the isolation of Santini — who was not part of the medical establishment, self-financing research on *helichrysin*, and publishing his results in medical journals of limited distribution — led to a loss of interest in *H. italicum* and its cortisone-like properties. In the past decade, the discovery of arzanol, a compound with pleiotropic (multiple effects emanating from one single compound) anti-inflammatory activity, and a better phytochemical characterization of the plant have set the stage for the development of standardized preparations of *H. italicum*. A systematic investigation of their clinical potential will reposition *H. italicum* from the glittering world of perfumes and fashion to the world of medicine, where it also belongs.

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*The foul odor is mentioned in some books as a distinctive character of *H. italicum* (see, for instance: Riva E. *Piante Medicinali*. Ghedini e Tassotti Editori; 1995, p. 274.

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‡ Most information on the life of Leonardo Santini, including his picture, was provided by his son Maurizio, to whom the authors are grateful. The life of Leonardo Santini also was outlined in a commemorative speech given by Paolo Mantegazza, the Rector of the University of Milano and the former Dean of the School of Medicine of Milano, on May 9, 2004 at Castelnuovo di Garfagnana during the commemoration of the 100th anniversary of the birth of Leonardo Santini.

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