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Review

Helichrysum italicum: From traditional use to scientific dataDaniel Antunes Viegas^a, Ana Palmeira-de-Oliveira^a, Lúgia Salgueiro^b,
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ABSTRACT

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.

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Abbreviations: 5-LO, 5-Lipoxygenase; COX, cyclooxygenase; IC, inhibitory concentration; IL, interleukin; TNF α , tumor necrosis factor α ; PGE₂, prostaglandin E₂; LPS, lipopolysaccharides; MIC, minimum inhibitory concentration; HIV, human immunodeficiency virus; LTR, long terminal repeat; HSV, Herpes Simplex Virus; LC, lethal concentration; UVB, ultraviolet radiation B; TPA, 12-O-tetradecanoylphorbol-13-acetate; PLA₂, phospholipase A₂; ID, inhibitory dose; LTb₄, leukotriene B₄; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; CYP, cytochrome P450

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1. Introduction

Medicinal plants play an important role in the discovery and isolation of new drugs, as has been the case for morphine, digitoxin, quinine, reserpine and pilocarpine (Balunas and Kinghorn, 2005; Gurib-Fakim, 2006). Consequently, there is a clear indication that this is a viable path of clinical innovation, as evidenced by some plant species from the *Helichrysum* Miller genus (family Asteraceae). This genus includes more than a thousand taxa that have a higher occurrence in the Mediterranean areas of Europe (Facino et al., 1988; Perrini et al., 2009; Morone-Fortunato et al., 2010). The name of the genus is derived from the Greek words “helios” and “chryos”, which mean, respectively, “sun” and “gold”, in direct relation to the fact that the plant species of this genus typically have inflorescences of a bright yellow color (Perrini et al., 2009).

One of the earlier mentions of the medicinal uses of plants from the *Helichrysum* genus appears in the work of the Greek Theophrastus of Eresos “Historia Plantarum” (3rd–2nd century B.C.). There, he reports that “*Heleiochrysos*” may be used in the treatment of burns (mixed with honey) and stings/bites of venomous animals (Scarborough, 1978). Another example of an ancient report of *Helichrysum* medicinal properties comes in book four of “De Materia Medica” (1st century A.D.), written by the Greek Pedanius Dioscorides, where the decoction of the filaments of *Helichrysum* flowers macerated in wine is described as possessing diuretic properties and being useful in the treatment of urinary disorders, snake bites, sciatica and hernias (Quer, 1993). Concerning the Renaissance period, the first written record of the medicinal uses of *Helichrysum* species in South Africa is attributed to the Dutch botanist Herman Boerhaave, who reported their use in the treatment of nervousness and hysteria in 1727 (Lourens et al., 2008). Other authors from the same period have cited *Helichrysum* sp., as is the case of Robert Morison who named the species *Helichrysum chrysocome angustifolia vulgaris* (now *Helichrysum stoechas* (L.) Moench) (Morison, 1699).

In the early descriptions of the medicinal uses of plants from this genus, *Helichrysum* is frequently addressed as a whole, without a clear indication of the specific species to which the information pertains. The fact that *Helichrysum* is considered a very complex genus, with great similarities between some species (Sala, 2001) may justify historical and popular difficulties in the correct identification of the plants.

In recent decades, some of the most studied species of this genus are *Helichrysum arenarium* (L.) Moench (Czinner et al., 2000), *Helichrysum stoechas* (L.) Moench (Carini et al., 2001), *Helichrysum*

graveolens (M.Bieb.) Sweet (Aslan et al., 2007) and *Helichrysum italicum* (Roth) G. Don (Facino et al., 1988). The interest in these species has been motivated by their traditional therapeutic applications: *Helichrysum arenarium* inflorescences use in Central Europe has been reported for its antiseptic, coleretic and spasmolytic properties (Sala, 2001), while *Helichrysum graveolens* traditional applications in controlling the symptoms of diabetes mellitus, wound healing and as a diuretic have been reported in Turkey (Aslan et al., 2007). *Helichrysum stoechas* is particularly referred in Spanish folk medicine for its anti-inflammatory and wound healing properties as well as uses for toothache, urologic conditions (Mulet, 1991; Rivera et al., 2008) and digestive disorders (González-Tejero, 1989; Peris et al., 2001). *Helichrysum italicum* use has also been reported in inflammatory and allergy conditions such as those related with the respiratory tract, as well as skin conditions (Peris et al., 1995; Peris et al., 2001), among others. For *Helichrysum italicum* essential oil in particular, wound healing and other skin conditions (such as hematoma and scars) have been pointed out as interesting aromatherapy applications being stated that “its effects are so convincing that it has never met with any kind of criticism despite the absence of data on its effectiveness” (Schnaubelt, 1999).

Since *Helichrysum italicum* pharmacological data are rather dispersed in the literature, this review aims to describe the traditional use and the available scientific data on *Helichrysum italicum* pharmacological activity and establish the relationship between them. Available safety and toxicity data are also addressed. This knowledge allows a discussion of the existing gaps, highlighting the need and interest for scientific validation of specific traditional uses and may be important in the identification of potential therapeutic applications not yet fully clinically explored for *Helichrysum italicum* plant or extracts.

The first scientific studies on the medicinal properties of *Helichrysum italicum* are attributed to Leonardo Santini, whose clinical research in patients with psoriasis was conducted in the 40s and 50s of the 20th century. However, his findings were published in journals of very little importance and were largely ignored after his death (Campanini, 2004; Appendino et al., 2007; Bauer et al., 2011). Consequently, the search of the keywords “*Helichrysum italicum*” or “*H. italicum*” in a scientific database such as PubMed reveals that the majority of research work related to this plant has been published after the 90s and up to now. However, considering the important role that *Helichrysum italicum* plays in the traditional medicinal practice of Mediterranean countries, it is surprising that review articles on its traditional

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