Chemical composition and biological activity of essential oil of *Teucrium scordium* L. subsp. *scordioides* (Schreb.) Arcang. (Lamiaceae) from Sardinia Island (Italy)

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**ABSTRACT**

The aim of this study is to demonstrate the antifungal, anti-inflammatory and anti-migratory potential of the essential oil of *Teucrium scordium* subsp. *scordioides* (Schreb.) Arcang, a plant widely used in traditional medicine in Sardinia. The oil was rich in germacrene D (25.1%), δ-cadinene (12.9%) and alloaromadendrene (11.3%). The yeast *Cryptococcus neoformans* and the dermatophytes *Trichophyton rubrum*, *T. mentagrophytes* var. *interdigitale* and *Epidermophyton floccosum* were the most susceptible fungi to the action of the oil. In lipopolysaccharide (LPS)-stimulated macrophages, the oil was able to decrease nitric oxide production by ca. 30% at 1.25 \(\mu\)L/mL, without affecting cell viability. In the scratch wound assay, it allowed for ca. 36% of wound closure after 18 h, thus showing anti-migratory properties. Overall, this study highlights the potential of this species to mitigate fungal infections associated with an inflammatory response. Furthermore, we also reported for the first time its anti-migratory capacity, thus suggesting anticancer properties.

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1. Introduction

*Teucrium* L. (Lamiaceae) is a large and highly polymorphic genus that includes more than 300 species distributed in Europe, North Africa and temperate parts of Asia, although more prevalent in the Mediterranean region (Bini Maleci et al. 1995). Plants of this genus have been described as important sources of essential oils, iridoid glycosides, phenolic and polyphenolic compounds, evidencing the medicinal interest of the plants of this genus (Semiz et al. 2016; Belarbi et al. 2018; Frezza et al. 2018; Farahbakhsh et al. 2020; Maccioni et al. 2020). Several traditional uses of *Teucrium* spp. have been recently reviewed (Candela et al. 2021). In Sardinia 11 *Teucrium* taxa are described and several of them are widely used in Sardinian traditional medicine as cicatrizing agents, antiseptic, antibacterial, antifungal, tonics, among several other purposes (Maccioni et al. 2021). Particularly, *Teucrium scordium* subsp. *scordioides* (Schreb.) Arcang is used as antiseptic and anthelmintic (Atzei 2003); however, the scientific validation of these claims is still lacking. Interestingly, the anticancer effect of *T. scordium* subsp. *scordioides* has been reported for phenolic extracts (Stankovic et al. 2011), but there is still no studies in the literature reporting this activity for the essential oil. Therefore, the aim of this study is to characterize the essential oil of *T. scordium* subsp. *scordioides* as well as to demonstrate its antifungal, anti-inflammatory and anti-migratory potential.

2. Results and discussion

2.1. Chemical composition

The results concerning the qualitative and quantitative analysis of the essential oil are presented in Table S1, where the components are listed in order of elution from a HP-5 column. The oil was characterized by a very high percentage of hydrocarbon sesquiterpenes (67.6%) and oxygenated sesquiterpenes (21.6%). The main compounds include germacrene D (25.1%), δ-cadinene (12.9%), alloaromadendrene (11.3%), α-cadinol (6.2%), germacrene D-4-ol (6.0%), α-pinene (4.9%), γ-cadinene (4.7%) and α-epi-cadinol (4.7%).

This composition is very distinct from the oils obtained from plants from other regions. Indeed, the essential oil from plants collected in Sicily, Italy, are rich in caryophyllene oxide (25.8%), α-pinene (19.4%) and β-pinene (8.5%) (Gagliano Candela et al. 2021) while those from Serbia are characterized by menthofuran (11.9%), (Z)-octadec-9-enoic acid (11.5%), and hexadecanoic acid (6.4%) (Radulović et al. 2012). Other studies address the composition of *T. scordium*, however, they fail to mention the subspecies, making the comparison to the present study difficult. Indeed, the oil from the aerial parts of *T. scordium* growing in North Iran was characterized by β-caryophyllene, (E)-β-farnesene, caryophyllene oxide, 1,8-cineole and β-eudesmol (Morteza-Semnani et al. 2007). In another study, samples from Serbia and Montenegro had a distinct composition, with α- and β-pinene being the major compounds (Kovacevic et al. 2001).
2.2. Antifungal activity

The antifungal effect of the essential oil is summarized in Table S2. Our results showed that Cryptococcus neoformans was the most susceptible yeast (MIC = 0.32 μL/mL). The dermatophytes Trichophyton mentagrophytes var. interdigitale, T. rubrum and Epidermophyton floccosum were the most susceptible filamentous fungi (MIC = 0.32 μL/mL) followed by T. mentagrophytes, Microsporum canis and M. gypseum with MIC = 0.64 μL/mL.

To the best knowledge of the authors, there are no studies in the literature assessing the antimicrobial effect of T. scordium essential oil; indeed only two studies assessed this effect using non-volatile extracts that were ineffective against C. albicans (Tatjana et al. 2011; Stanković et al. 2012).

Currently available therapies are often associated with problems related with drug safety, undesirable side effects, narrow activity spectrum and a small number of targets (Fuentefria et al. 2018), as well as the emergence of resistant strains (Martinez-Rossi et al. 2018; Mourad and Perfect 2018). Indeed, dermatophytes from the genus Trichophyton have been reported to show resistance to terbinafine and fluconazole, the two most widely used antifungals to control dermatophytosis (Arendrup et al. 2021). Resistance to all the classes of antifungals has also been reported for C. neoformans (Bermas et al. 2020). In this scenario plant extracts, despite having lower antifungal activity, can emerge as effective alternatives/complements. Indeed, these extracts are able to act on multiple cell targets, an important feature when considering microorganisms that are intrinsically or became resistant to conventional therapies. Several studies have demonstrated the effectiveness of essential oils in fungal infections (Zuzarte et al. 2011; Lopes et al. 2017) such as Teucrium capitatum (MIC = 0.32 – 0.64 μL/mL for dermatophytes and C. neoformans) (Maccioni et al. 2020), T. polium subsp. geyrii (MIC = 2.45 μL/mL for C. albicans) (Roukia et al. 2013) and Santolina impressa (MIC = 0.32 μL/mL against C. neoformans, Epidermophyton floccosum and Trichophyton rubrum (Alves-Silva et al. 2019). These activities are similar to the reported activity of T. scordium subsp. scordoides. Also, its major compounds, namely germacrene D, δ-cadinene, α-cadinol, epi-α-cadinol and α-pinene have been reported to inhibit the growth of several pathogenic fungi (Schmidt et al. 2007; Chang et al. 2008; Ho et al. 2011; Takao et al. 2012; Pinto et al. 2013; Lawson et al. 2020), thus suggesting that the activity of the oil might be attributed to their presence in the mixture.

2.3. Anti-inflammatory properties

Since the successful colonization of the host tissues by pathogenic fungi is fuelled by inflammation, an antifungal drug concomitantly presenting anti-inflammatory activity can be a valuable therapeutic strategy to fight fungal infections. Therefore, we also assessed the anti-inflammatory potential of the essential oil using an in vitro model of inflammation, specifically macrophages stimulated with the Toll-like receptor 4 agonist lipopolysaccharide (LPS), and the effect on NO production was analysed by measuring the accumulation of nitrites in the culture medium. NO is a well-established marker of inflammation and inhibition of its production upon activation with an inflammatory
stimulus, such as LPS, might be a useful strategy to disclose new anti-inflammatory drugs. Our results show that pre-treatment with 1.25 μL/mL of the essential oil decreased the nitrite production evoked by LPS by ca. 30% (Figure S1A), without affecting macrophages viability (Figure S1B), thus suggesting and validating the safety profile of the essential oil at concentrations presenting pharmacological activity. Although we cannot state that the anti-inflammatory effect of the oil is superior to standard anti-inflammatory drugs, such as diclofenac, it is interesting to notice that for the concentration of the oil used in our experimental conditions (1.25 μL/mL), the percentage of nitric oxide inhibition is similar to that achieved by 1.591 μg/mL diclofenac without presenting as much toxicity (79.5% vs 94.5% macrophages viability for diclofenac and the essential oil, respectively). The reported activity is similar to other essential oils, even from different species, e.g., the essential oil from *Distichoselinum tenuifolium* decreases NO production by 40% at 1.25 μL/mL (Tavares et al. 2010). Although the anti-inflammatory potential of several *Teucrium* spp. has been widely reported (Barrachina et al. 1995; Puntero et al. 1997; Mukarram Shah 2015), the present study is pioneer in assessing the anti-inflammatory activity of *T. scordium* subsp. *scordioides* essential oil.

Regarding its major compounds, the anti-inflammatory potential of germacrene D, α-cadinol, epi-α-cadinol, α- and β-pinene has been already reported (Baylac 2003; Tung et al. 2011; Rufino et al. 2014; Coté et al. 2017), thus suggesting their involvement in the pharmacological activity of the oil. Since several essential oils exert their anti-inflammatory activity by inhibiting the pro-inflammatory transcription factor NF-κB (de Lavor et al. 2018) it will be of relevance to further explore the involvement of this signaling pathway on the anti-inflammatory activity of *Teucrium scordium* subsp. *scordioides* essential oil.

**2.3. Cells migration assay**

Cell migration was carried out using the scratch wound assay as reported by Martinotti and Ranzato (Martinotti and Ranzato 2019) by making a scratch on a cell monolayer and capturing images at regular intervals by microscopy.

The essential oil (1.25 μL/mL) decreased the capacity of the cells to migrate after the scratch (Figure S2A and S2B), thus suggesting its putative anti-migratory properties. Importantly, the essential oil was devoid of toxicity (Figure S2C), thus validating its safety profile.

The anticancer properties of the genus *Teucrium* have been widely reported as reviewed elsewhere (Milutinović and Cvetković 2020). Regarding *T. scordium* subsp. *scordioides* the anticancer properties have only been reported for a phenolic extract (Stankovic et al. 2011). Concerning cell migration, no studies have been conducted with this taxon; however several studies showing the anti-invasive and anti-migratory capacities of several *Teucrium* species have been reported (Kandouz et al. 2010; Haïdara et al. 2011; Tafrihi et al. 2014; Zivanovic et al. 2016; Tafrihi and Nakhaei Sistani 2017; Abdallah et al. 2018; Guesmi et al. 2018; Sheikhbahaei et al. 2018). The anti-invasive and anti-migratory properties of germacrene D, α-pinene and β-eudesmol have also been shown (Kummer et al. 2015; Ben Sghaier et al. 2016; Kang et al. 2016;
Huang et al. 2019; Schepetkin et al. 2020), reinforcing that the reported activity might be due to the presence of these compounds.

3. Experimental section

See Supplementary data

4. Conclusions

The present study shows, for the first time, the biological properties of the essential oil from *T. scordium* subsp. *scordioides*, particularly the antifungal and anti-inflammatory activities. Indeed, the oil was able to inhibit the growth of *Cryptococcus neoformans* and several dermatophytes. Furthermore, the essential oil decreased the production of nitric oxide in LPS-stimulated macrophages. Although the essential oil shows weaker activity than the standard antifungal or anti-inflammatory drugs, it exerts at the same time and at the same concentration antifungal and anti-inflammatory effects, which highlights its interest for the pharmaceutical industry due to this dual effect. Our results also showed that the essential oil possesses anti-migratory properties, which must be properly explored in an oncology context. Importantly, at pharmacological relevant concentrations, the oil was devoid of toxicity towards macrophages and fibroblasts, thus highlighting its safety.

Disclosure statement

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