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ANTICANDIDAL PROPERTIES OF LAVANDIN ESSENTIAL OILS

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The hydrodistillated essential oils of lavandin cultivars (*Lavandula hybrid* Medic.) Inii and Rabat, which characterized by relatively high amount of monoterpenes were tested for anticandida effects against five pathogenic fungi using *in vitro* microbial growth inhibition assays; and were compared with that of a commercial antifungal reagent, decasanum and essential oil of *Lavandula angustifolia* Mill. (lavender oil). The oils of lavandins Inii and Rabat exhibited considerable antifungal activity against all tested *Candida* spp. Both the tested oils of lavandins Inii and Rabat demonstrated inhibitory action against all the *Candida* species at low concentrations (100 or 200 μL). The most sensitive were *C. pseudotropicalis*, *C. parapsilosis*, and *C. kefir*, some less sensitive were *C. curvata* and *C. tenuis*. However, they were moderately active against Decasanum. The anticandidal effect of essential oil of both lavandins can be due to the interaction of many of their compounds especially linalool, linalyl acetate, camphor, and 1.8-cineole which amount is prevalence. It can be concluded that the oils of lavandins Inii and Rabat have potential against pathogenic *Candida pseudotropicalis*, *C. parapsilosis*, *C. curvata*, *C. kefir*, and *C. tenuis*. Essential oils of lavandin cultivars Inii and Rabat are offered for further research as possible alternatives or additional therapeutic agents for candidiasis in diabetics, patients with periodontitis, immune and urogenital system disorders. Particularly promising may be Inii and Rabat essential oils in the treatment of patients with triazole and echinocandin resistant forms of candidiasis.

Keywords: lavandin, essential oil, anti-*Candida*

Introduction

Antimicrobial agents are some of the most widely used therapeutic drugs worldwide. 'A post-antibiotic era – in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century' – Dr. Keiji Fukuda, World Health Organisation (WHO) Assistant Director – General (WHO, 2014.). This provision remains relevant today. Although a considerable amount of research has gone into the study of

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the role of microbiocidal versus microbiostatic agents in the treatment of different infectious diseases, there is no accepted standard of practice (Finberg et al., 2004). This is especially true when searching for antifungal agents, since in the last few decades opportunistic fungal infections have been increasingly recognized as major causes of various human diseases, especially among immunocompromised patients (Li et al., 2015). Recognition of the side effects of chemically synthesized antimicrobial drugs on the host is generally accepted (Kumarasamy et al., 2010). In recent years, there has been a growing interest in researching and developing new anticandidal agents from various sources to combat their resistance. It remains possible to find anticandidal agents among substances of natural origin, in particular among substances synthesized by plant varieties created by breeding methods. The ability of plant oils to inhibit the growth of fungi is known (Kalemba and Kunicka, 2003; Elshafie et al., 2016; Vorobets and Rivis, 2017). For example, lavender essential oil inhibited both the growth and the activity of *Candida albicans* more efficiently than the main used drug clotrimazole (Bona et al., 2016). Lavandins are interspecies hybrids obtained as the results of natural and artificial selection of *Lavandula angustifolia* Mill. and *Lavandula latifolia* Medic. Some of them were created by Ukrainian breeders, and among them are lavandins 'Inii' and 'Rabat' (Svydenko, 2001). Phytochemical screening of both Inii and Rabat cultivars for active components revealed a high content of essential oils (Svydenko and Glushchenko, 2018). The aim of this study is to show the anticandidal activity of Inii and Rabat lavandins essential oil against the clinically important strains of yeasts.

Material and methodology

The plant material of lavandins Inii and Rabat was obtained from the experimental lots of the Institute of Rice of National Academy of Agrarian Sciences of Ukraine, Kherson region, Ukraine in July 2017–2018. Flowering tops of the plants were harvested manually, at the maximum flowering stage.

Extraction of essential oils and identification of their compounds

Aerial parts of lavandins Inii and Rabat were subjected to hydrodistillation in a Clevenger apparatus to obtain essential oil, and final yield of extraction is 1.8 and 1.7%, respectively. Volatile compounds were identified by gas chromatography (gas chromatograph Agilent Technology 6890N and GC/mass spectrometry (Svydenko, 2001). The essential oils thus obtained served as material for subsequent microbiological studies. These oils were stored at 4 °C in the dark until analyzed. Essential oils of lavandins Inii and Rabat were evaluated for antifungal activity against *Candida* spp.

Fungal Strains

In this study *Candida pseudotropicalis* (D-14-C), *C. parapsilosis* (D-35-C), *C. curvata* (D-15-C), *C. kefir* (D-30-C), and *C. tenuis* (D-45-C) were used as tested microorganisms. The strains used from the Microbial Culture Collection of the Department of Microbiology of Ivan Franko National University of Lviv.

Media, chemicals, and culture conditions

The standard agar diffusion method was used to determine the sensitivity of microorganisms to essential oils (EOs) in modification by the wells (Collins et al., 2004; Magaldi et al., 2004). The method is not considered to be most appropriate for the study of essential oils, but acceptable as a preliminary study (Kalemba and Kunicka, 2003; Balouiri et al., 2016), simple, and easy to reproduce. Nevertheless, an approximate minimum inhibitory concentration can be calculated for some microorganisms and antibiotics by comparing the inhibition zones (Nijs et al., 2003). Into 9 cm sterile Petri dishes poured up to 20 ml of the sterile medium of Sabouraud Dextrose Agar. After hardening dense nutrient medium on the surface was spread 0.3 ml suspension of microorganisms. The suspensions were prepared in separate samples in distilled sterilized water from two-day cultures of fungi of the genus *Candida*. The concentration of microorganisms in the suspension was determined according to the state standard of turbidity №5. After 20–30 minutes, the wells were made on the surface of the seeded medium with a 5 mm stamp (1–2 pc). After that, in the wells, the sample of essential oil in the amount of 100 or 200 µL was applied. Stuffed Petri dishes were incubated in a thermostat at +30 °C for 48 hours for all tested *Candida* spp. depending on the growth in the control medium. The diameter of zones of inhibition around the of test cultures was measured in mm after two days, including the diameter of the well.

Antifungal standard, and Substances

Decasanum and Essential Oil of Lavender (*Lavandula angustifolia* Mill., Lamiaceae family) were used as controls so as they were found to inhibit *C. albicans* and other *Candida* strains (D'Auria et al., 2005; Vorobets et al., 2018). When the strain showed no activity, the value considered was equal to zero or total growth inhibition. Values ranging from 6 to 8 mm and less were considered as non-active.

Statistical analysis

A bioassay was carried out in triplicate and repeated twice. Values mentioned are the mean of triplicate observations and standard deviation from the mean.

Results and discussion

Our results indicate that all *Candida* strains used in this study were completely sensitive to Inii and Rabat lavender essential oils (Table 1). Both the tested oils demonstrated inhibitory action against all the *Candida* species at low concentration (100 or 200 µL). The most sensitive were *C. pseudotropicalis*, *C. parapsilosis*, and *C. kefir*, some less sensitive were *C. curvata* and *C. tenuis*. The presence in the well of 200 µL of essential oil of Lavandin Inii and Lavandin Rabat caused total growth inhibition of strains *C. kefir*, *C. tenuis*, and *C. parapsilosis*. Significant inhibition of growth of strains *C. pseudotropicalis* and *C. curvata* was also observed.

Table 1 Antifungal activity of lavandins' inflorescences oil, zone of inhibition (mm)

Strains	*Candida pseudotropicalis*	*Candida curvata*	*Candida kefir*	*Candida parapsilosis*	*Candida tenuis*
Method of diffusion in agar in modifying the wells, 100 µL					
Lavandin Inii Essential Oil	40.2 ±0.84	30.6 ±0.89	40.4 ±0.55	40.0 ±0.71	30.8 ±0.84
Lavandin Rabat Essential Oil	40.2 ±0.45	40.4 ±0.55	40.4 ±0.55	40.0 ±0.71	39.8 ±0.84
Control1: *Lavandula angustifolia* Essential Oil	40.4 ±0.55	40.8 ±0.45	40.2 ±0.45	40.4 ±0.55	40.0 ±0.71
Control 2: Decasanum	9.4 ±0.89	8.2 ±0.84	11.8 ±1.30	11.0 ±0.71	7.2 ±0.45
Method of diffusion in agar in modifying the wells, 200 µL					
Lavandin Inii Essential Oil	40.4 ±0.55	40.1 ±0.71	total growth inhibition	total growth inhibition	total growth inhibition
Lavandin Rabat Essential Oil	40.2 ±0.45	40.2 ±0.71	total growth inhibition	total growth inhibition	total growth inhibition
Control1: *Lavandula angustifolia* Essential Oil	41.3 ±0.58	42.3 ±0.58	42.3 ±1.53	41.3 ±0.58	41.3 ±0.58
Control 2: Decasanum	12.3 ±0.23	11.3 ±0.32	12.±0.32	12.4 ±0.42	9.4 ±0.45

All *Candida* spp. which we used for the investigation of their resistances against lavandins oils are among very virulent. *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, and *C. kefir* are among the most common *Candida* species in human infections (Diekema et al., 2012; Lockhart et al., 2012). Several articles suggest that a significant proportion of patients with hematologic malignancies, especially patients with acute myelogenous leukemia undergoing induction chemotherapy, are colonized with *C. kefir*, with a substantial risk for subsequent bloodstream infection and colonization and infection follow a seasonal distribution, with higher rates during the warm months of the year. *C. glabrata*, generally considered to be a species with low virulence but with a higher mortality rate than *C. albicans* (Colombo et al., 2003; Pappas et al., 2004). *C. glabrata* isolates and all *C. krusei* isolates are resistant to fluconazole (Shorr et al., 2011; Andes et al., 2012; Kullberg and Arendrup, 2015). Patients with diabetes are at increased risk of developing vulvovaginal candidiasis due to non-albicans *Candida* spp. such as *C. glabrata* and *C. tropicalis* (Goswami et al., 2006). *C. glabrata* rapidly develop resistance to multiple drug classes, including triazoles and echinocandins (Vale-Silva and Sanglard, 2015; Healey et al., 2016); so, as *Candida parapsilosis* (Souza et al., 2015). The detection of new anticandidal agents is relevant. The oils of both studied lavandins inhibited growth of *C. kefir*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*, so they possess biological activity. The biological activity of a compound *in vitro* and *in vivo* depends on its chemical structure. Our previous studies have shown that essential oils of both studied lavandins contain many groups of compounds. The anticandidal effect of essential oil of both lavandins can be due to the interaction of many of them.

Essential oils of lavandins could be of great interest in the biomedical field, opening new directions for the design of film-coated surfaces with anti-biofilm properties as it was proposed earlier for other EOs. The mass fraction of essential oil in inflorescences of lavandins during growing in the Kherson region varies in quite significant limits: from 0.96 to 2.2% of freshly harvested raw materials or from 2.2 to 5.5% from absolutely dry (Svydenko and Glushchenko, 2018). Thirty-three compounds were identified in the studied Lavandin Inii and forty-one in Lavandin Rabat essential oils by GC-MS analysis (Svydenko, 2001). The main components of essential oils of lavandins are given in Table 2.

Table 2 Main components of lavandins' inflorescences essential oil (% per 100 g of plant materials)

Lavandin Inii		Lavandin Rabat	
Compound	**%**	**Compound**	**%**
Linalool	57.79	**Linalool**	49.45
Linalylacetate	11.11	**Camphor**	15.40
1.8-cineole	7.38	**Linalylacetate**	8.68
Camphor	4.64	**1.8-cineole**	7.18
Lavandulyle acetate	2.67	**Borneol**	6.18
α-terpineol	2.63	**Lavandulyle acetate**	1.60
trans-Linalool oxide	2.61	**α-terpineol**	1.18
tri-enol acetate	1.94	**Lavandulole**	1.08
Borneol	1.26	**trans-Linalool oxide**	0.95
Lavandulole	0.99	**α-bisabolole**	0.64
2.6-dimetyl-3.7-oktadien-2.6-diol	0.97	**Hexyl acetate**	0.66
α-terpineol	0.74	**Hexyl butyrate**	0.66
caryophyllenoxide	0.71	**cis-Linalool oxide**	0.65
α-bisabolol	0.67	**Neryl acetate**	0.56
1-okten-3-ol	0.61	**β-farnesene**	0.50
Hexanol	0.56	**Limonene**	0.41
Geranilacetate	0.43	**Geranilacetate**	0.39
Terpinolene	0.39		
Neryl acetate	0.28		

Source: Svydenko and Glushchenko, 2018

An essential oil obtained from inflorescences of lavandins mainly contains terpenoids, which obviously can cause anti-candidiasis effect. The major volatile compounds were linalool, linalyl acetate, 1.8-cineole, and camphor. A total of four constituents, representing 80.9 and 80.7% from the total oil, were identified by GC/MS in Lavandin Inii and Lavandin Rabat, respectively. Fungicidal activity of lavender essential oil and linalool has been shown by other authors (Serra et al., 2018). Linalool is among the components of essential oils with the revealed properties to prevent the formation of at least 80% regrowth of *Candida albicans*, after the biofilm was treated with antimicrobials (Serra et al., 2018). Anticandidal activity of the essential oils of thyme, pennyroyal, and lemon on different species of *Candida* including *C. albicans*, *C. krusei* and *C. glabrata*, which are isolated from patients who suffered from vulvovaginal candidiasis have been shown (Mahdavi and Esmailzadeh, 2009). *In vitro* study found that oil of *L. angustifolia* inhibited growth of *C. albicans*, as did it is component linalool (D'Auria et al., 2005). The efficacy of clinical use of linalool has been confirmed in several *Candida* strains (*C. albicans*, *C. krusei*, and *C. tropicalis*) that contaminated the oral cavity in patients with oral candidiasis (Dias et al., 2018). Its' constituents linalool and linalyl acetate are detectable in the blood five minutes after topical application and largely disappear from the blood within 90 minutes.

With these results, it is possible to establish that the anticandidal effects attributed to lavandins Inii and Rabat are due in part to the activity of essential oil components, which has also been linked to other species of Lamiaceae family.

Conclusions

The results of the present study demonstrated the important antifungal activity of essential oils of lavandin Inii and Rabat. Essential oils of both investigated lavandins are a promising use in healthcare decontamination against *Candida* spp. Both lavandins grow well in the South of Ukraine and possible to obtain good quality and quantity of raw material for use in pharmacy and medicine. This may help us to design highly specific antifungal drugs that avoid or minimize host side effects.

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