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Properties and limits of some essential oils: chemical characterisation, antimicrobial activity, interaction with antibiotics and cytotoxicity

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ABSTRACT

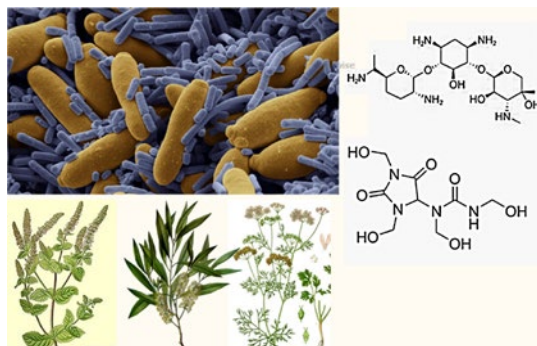
Because of the emergence of multi-drug resistance bacteria and fungi, alternatives to conventional antimicrobial therapy are needed. This study aims to evaluate *in vitro* the antimicrobial activity of: *Mirtus communis*, *Coriandrum sativum*, *Pelargonium capitatum*, *Cuminum cyminum*, *Ocimum basilicum*, *Citrus aurantium amara*, *Cymbopogon winterianus*, *Cymbopogon martini*, *Salvia sclarea*, *Melaleuca alternifolia* and *Mentha suaveolens* essential oils on bacteria and fungi, in relation to their chemical composition. The potential interaction of *M. alternifolia* (TTO), *C. sativum* (CDO) and *M. suaveolens* (EOMS) essential oils when used in combination with gentamicin and fluconazole has been evaluated. The results obtained showed a synergic effect on some bacteria and fungi, with FICI values ≤ 5 . The cytotoxicity of TTO, CDO and EOMS was investigated towards HeLa cells. Only EOMS did not result cytotoxic at the active concentrations on micro-organisms. Further studies are necessary to obtain optimal ratios and dosing regimens for higher therapeutic efficacy and to decrease toxicological profiles.

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Bacteria; fungi; essential oils–antibiotic interaction; fluconazole; gentamicin



1. Introduction

Plant-derived compounds are always a source of novel therapeutics. Plants are known to produce an enormous variety of small molecules (MW <500 kDa) known as phytoalexins such as terpenoids, glycosteroids, flavonoids and polyphenols. Most of these small molecules have weak antimicrobial activity, several orders of magnitude less than that of common antibiotics produced by bacteria and fungi. In spite of the fact that plant-derived antibacterials are less potent (Seow et al. 2014), plants fight infections successfully. Aromatic and medicinal plants also produce a wide variety of volatile aliphatic and cyclic hydrocarbons, corresponding oxygenated isoprenoid derivatives and analogues that form complex mixtures called essential oils (Hammer et al. 1999; Rios & Recio 2005). Essential oils are a rich source of biologically active compounds; they were shown to possess antibacterial, antifungal, antiviral, insecticidal and antioxidant properties (Solorzano-Santos & Mirandas-Novales 2012). Some oils have also been used in cancer treatment (Gautam et al. 2014) in food preservation, aromatherapy and fragrance industry. Because of all these properties, medicinal and aromatic plants which constitute a major source of important organic compounds (Gurib-Fakim 2006) and World Health Organization noted that the majority of world's population depends on traditional medicine for primary healthcare. Commercially available essential oils from aromatic plants such as *Melaleuca alternifolia* (tea tree oil), *Thymus vulgaris* (Thyme), *Mentha piperita* (Peppermint), *Rosmarinus officinalis* (Rosemary), *Citrus aurantium* (Lime oil) and *Cymbopogon martini* (Palmarosa oil) have been extensively used for the treatment of topical bacterial (Prabuseenivasan et al. 2006) and fungal infections. Indeed, *Coriandrum sativum* has been recommended for dyspeptic complaints, loss of appetite, convulsion, insomnia and anxiety (Emamghoreishi et al. 2005) in addition to its antimicrobial activity (Silva et al. 2011). Also, essential oils from *Cuminum cyminum* (cumin) (Iacobellis et al. 2005), *Ocimum basilicum* (basil) (Hussain et al. 2008), *Mirtus communis* (myrtle) (Ragno et al. 2008) are known for antimicrobial and antioxidant properties. Gram positive and negative bacteria, in addition to fungi, are responsible for several human infections. Effective antimicrobials have been developed over the years; however, it has been observed a dramatic increase in resistance to antimicrobial drugs. Although antibiotics have been effective to fight infectious diseases for a long time, resistance to these drugs has also led to the reemergence of old infectious diseases. For this reason, the development of new antimicrobial compounds appears necessary. Actually, one strategy employed to overcome resistance mechanisms has been the use of combinations of drugs, such as beta-lactams together with beta-lactamase inhibitors or combinations of different classes of drugs (Rey-Jurado et al. 2013). Medicinal plants and herbs represent preferred sources of active molecules which could become lead compounds for new pharmaceutical products. Moreover, several plant extracts exhibited 'in vitro' synergic activity when utilised in combination with different drugs against several micro-organisms and could represent a new alternative approach to infectious diseases treatment. Further studies are necessary to better define cytotoxicity of EOs, since in literature, a data reported mainly the effect on tumoral cell lines. (Elsayed et al. 2015). This article reports the antimicrobial screening of eleven essential oils against some bacterial and fungal species, the interaction of *C. sativum*, *M. alternifolia* and *Mentha suaveolens* EOs with conventional antimicrobial drugs such as gentamicin or fluconazole and toxicity studies towards a cell line of human origin (HeLa).

2. Results and discussion

2.1. Antimicrobial activity of essential oils by diffusion test

The antimicrobial activity of eleven EOs measured by diffusion test against selected species of bacteria and fungi is summarised in Table S1. The results reveal that EOs show antimicrobial activity with varying magnitudes and specie specificity. The zone of growth inhibition above 8 mm in diameter was taken as a positive result. Generally, most of the tested micro-organisms were sensitive to many of the EOs. At a concentration of 20 mg/ml, the best activity has been expressed by *M. alternifolia*, *M. communis*, *C. sativum*, *C. cyminum*, *Cymbopogon winteranius* and *M. suaveolens* EOs, with inhibition halos between 33.7 and 10.4 mm diameter for gram-positive or gram-negative bacteria and between 70 and 12 mm for fungi. In particular, *M. alternifolia*, *Coriandrum sativum* and *M. communis* EOs produced inhibition halos between 17 and 33.7 mm, or between 18.4 and 25 mm against *Staphylococcus epidermidis* strains and *Staphylococcus aureus* ATCC 25923, respectively. In the case of gram-negative bacteria, inhibition halos ranged between 17 and 29.4 mm, 29–30 mm, 23.5 and 29.5 mm for the multi-resistant clinical isolate of *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Escherichia coli* ATCC 25922, respectively. Moreover, the same oils showed a strong activity towards *Candida albicans* strains with inhibition halos between 30 and 60 mm. *M. suaveolens*, *C. cyminum* and *C. winteranius* showed a lower antibacterial activity with inhibition halos ranging from 13.5 to 19.6 mm for all tested bacteria, while they resulted active towards fungi with inhibition halos between 20 and 40 mm. The observed variability in sensitivity might be due to the different chemical composition of each essential oil and to the kind of micro-organism tested. These differences could also be referred to a different rate of essential oils constituent's penetration through the cell wall and cell membrane structures. For example, the antibacterial properties of tea tree oil (TTO) have been attributed to the monoterpenoid, terpinen-4-ol. Because of its lipophilic nature, it is thought to diffuse into and damage cell membrane structures, or to inhibit membrane-bound enzymes (Zengin & Baysal 2014). Linalool, which is the main constituent in *C. sativum* EO, is known to bind to membrane ergosterol, increasing ionic permeability and causing membrane damage leading to cell death. Linalool is inactive (Freires et al. 2014) on cell wall biosynthesis-related pathways. The ability of essential oils to disrupt the permeability barrier of the cell membrane structures and the accompanying loss of chemiosmotic control are the most likely reasons for their lethal action. The active concentrations of oils were generally about 100 times higher than those of gentamicin or fluconazole. This difference could be explained taking into account that essential oils are complex mixtures of different compounds, where only some molecules could have antimicrobial properties. Identification and purification of the different components could highlight the most active antimicrobial molecules.

2.2. Chemical composition of essential oils

Taking into account the chemical composition of the EOs reported in Table 1, their activity towards gram-positive or gram-negative bacteria and fungi could be related to the functional group that characterises the main component. Nevertheless, it has to be considered that the presence of minor components might also play a role to determine such an effect. The antibacterial and antifungal activity of *C. aurantium amara* essential oil could be attributed to the presence of limonene, a monoterpene that represents 90.7% of the total extract. The

Table 1. Chemical composition of essential oils (weight %).

Functional group	Compound	<i>Citrus aurantium amara</i>	<i>Coriandrum sativum</i>	<i>Cuminum cyminum</i>	<i>Cymbopogon martini</i>	<i>Cymbopogon winterianus</i>	<i>Peltandra capitatum</i>	<i>Mentha suaveolens</i>	<i>Myrtus communis</i>	<i>Ocimum basilicum</i>	<i>Salvia sclarea</i>	<i>Melaleuca alternifolia</i>
Ketone oxide Monoterpene	Piperitone oxide							38.1				
	Alpha-cubebene							2.0				
	Beta-cubebene							1.9				
	Camphene										2.4	
	Limonene		2.3		1.5			9.1	10.1		1.4	2.1
	Alpha-pinene	90.7						2.5	11.0		2.6	6.9
	4-carene										6.7	
	Beta-pinene										1.6	9.3
	Beta-myrcene							4.8				14.3
	Gamma-terpinene							1.4				
	Beta-terpinene				5.3			1.4				
	Alpha-terpene			9.6				3.5				
Aldehyde	Beta-terpene			2.4								
	o-cymene			19.9								
	Beta-trans-ocimene											
	Beta-cymene		3.0									
	Cuminal			49.6								
	Beta-citronellal											
	Viridifloral											
	Borneol										1.8	
	Linalool										3.1	
	Terpinen-4-ol		48.4		3.3		6.4	7.8	2.6	2.1	1.5	53.7
	Beta-citronellol							1.5				
	Alcohol	Alpha-terpineol					18.6	58.8				
Isopulegol												9.6
Bergamol						2.5						
Geraniol												
Isomenthone			1.3		83.9		18.9	1.6				
Camphor			4.3				7.3					
Ketone	Isomenthone											
	Camphor											
Ether	Camphor											
	Estragole									91.1		

Terpene ester	Citronellyl ester				4.3														
	Geranyl acetate	7.9		12.0		29.9								2.0					
	Myrtenyl acetate													31.8					
	Linalyl acetate													36.4		2.2		16.5	2.5
Monoterpene oxide	Eucalyptol								4.2										
Sesquiterpene hydrocarbon	Caryophyllene																	25.8	
	Alpha-caryophyllene																	22.4	
	Beta-caryophyllene								3.8										
	Alloaromadendrene																	5.9	
Not identified																			
Activity	Gram negative													6.1		4.6		8.3	1.6
	Gram positive													PA		NA		NA	A
	Fungi													PA		PA		NA	A
		5.5	14.1	13.2	0.8	5.7	4.3	8.0	3.8					PA	PA	PA	A	PA	PA
		PA	A	PA	PA	PA	ND	PA	PA					PA	PA	PA	A	NA	NA
		ND	A	NA	PA	PA	PA	PA						PA	PA	PA	A	NA	NA
		PA	A	A	A	A	A	A						PA	PA	PA	A	NA	NA

Notes: A: active; PA: probably active; NA: not active; ND: not determined.

Bold values are indicated as high percentage of main constituent.

antimicrobial activity described is in agreement with literature data (Viuda-Martos et al. 2008; Ulukanli et al. 2014). *C. winterianus* and *C. cyminum* essential oils are both active against fungi. The antifungal activity of these extracts can be ascribed to the two aldehydes representing the main components: cuminal (49.6%) for *C. cyminum* and β -citronellal (41.8%) for *C. winterianus*. Cuminal, an uncommon aldehyde, is present in *Eucalyptus camaldulensis* essential oils from Sardinia, which is known for antifungal activity towards common phytopathogenic fungi (Barra et al. 2010). A main component with alcoholic function characterises *C. sativum*, *C. martini*, *P. capitatum* and *M. alternifolia* essential oils; in particular, β -citronellol, the main component of *P. capitatum* (58.8%), may be responsible for the antifungal activity of this essential oil, whereas terpinen-4-ol, geraniol and linalool which are the main components of *M. alternifolia* (53.7%), *C. martini*, (83.9%) and *C. sativum* (48.4%), respectively, could account for the antibacterial activity showed by these extracts. *O. basilicum* essential oil is the only extract characterised by an ether as a main component: estragole, representing 91.1% of this oil. It is partially active against gram-positive bacteria and fungi. Regard to this component, literature data show different biological activities, in particular, it is known to increase phagocytic activity of macrophages (Silva-Comar et al. 2014). The observed antifungal and antibacterial activity of *M. suaveolens* essential oil utilised in this study could be attributed, at least partially to piperitenone, a ketone oxide that represents 38.1% of extract. It must be observed that in other extracts of *M. suaveolens*, EOs piperitenone oxide was about 90% (Angiolella et al. 2010). This fact can be attributed to the different plant cultivation zone in agreement with Khaoukha et al. (2014) and to the seasonal variations of the active constituents (Settanni et al. 2014). In the tested extract, other components are limonene 9.1%, linalool 7.8%, and other minor chemical constituents. *M. communis* essential oil is active versus fungi and gram-negative bacteria. This oil contains as main component eucalyptol, a monoterpene oxide representing 36.4% of the total extract, in agreement with Akin et al. (2010), and also other constituents such as myrtenyl acetate, a terpene ester 31.8%, limonene and α -pinene about 10%. As to, *S. sclarea* essential oil tested in this work, it is not characterised by a main component but contains more than ten different molecules with a percentage that never exceeds 20%, except for caryophyllene 25.8% and α -caryophyllene 22.4%. In our study, this oil demonstrated only poor antibacterial and antifungal activity (Table S1). On the contrary, low percentages of borneol and α -pinene in *Ampelopsis megalophylla* as reported by Xie et al. (2014) and caryophyllene (Joycharat et al. 2014) show high microbiological activity.

2.3. Minimal inhibitory concentration, FICI index and toxicity

Table S2 shows the minimal inhibitory concentration (MIC) values of tree essential oils *M. alternifolia* (TTO), *C. sativum* (CDO) and *M. suaveolens* (EOMS) towards bacteria and fungi in comparison with those obtained for gentamicin and fluconazole, respectively, used as reference antimicrobials. High resistance gentamicin values with MIC ≥ 64 μ g/ml were highlighted for clinical isolated strains of *S. epidermidis* and *A. baumannii*, while for *K. pneumoniae* strains MIC values were in a range of 2–8 μ g/ml; *C. albicans* CO23RFLU strain showed a fluconazole MIC value ≥ 64 μ g/ml (Table S2). For gram-positive bacteria, TTO and CDO MIC values resulted between 6.25 and 25 mg/ml while for EOMS MIC value was 0.19 mg/ml for *S. aureus* (Table S2). For gram-negative bacteria, MIC values ranged between 1.56 and 25 mg/ml for TTO and CDO, respectively, while those for EOMS were about 3.12–6.25 mg/ml; for *C. albicans* strains, EOMS MIC values of 0.78 mg/ml indicated a better activity than CDO and

Table 2. Effect of TTO, CDO and EOMS in combination with gentamicin (G) or fluconazole (FLU).

	MIC in combination			MIC in combination			MIC in combination		
	G (µg/ml) + TTO (mg/ml)	FIC G + FIC TTO	FICI TTO	G (µg/ml) + CDO (mg/ml)	FIC G + FIC CDO	FICI CDO	G (µg/ml) + EOMS (mg/ml)	FIC G + FIC EOMS	FICI EOMS
<i>Gram positive</i>									
<i>S. aureus</i>	0.25 + 6.25	0.25 + 0.25	0.5	0.5 + 0.19	0.5 + 0.003	0.503	1 + 0.1	1 + 0.52	1.52
ATCC 25923									
<i>S. epidermidis</i>	0.125 + 6.25	0.001 + 0.5	0.501	0.25 + 3.12	0.003 + 0.5	0.503	ND	ND	ND
10078637									
<i>S. epidermidis</i>	16 + 3.12	0.25 + 0.5	0.75	0.25 + 3.12	0.003 + 0.5	0.503	ND	ND	ND
1058847									
<i>Gram negative</i>									
<i>E. coli</i>	0.06 + 0.78	0.24 + 0.5	0.74	0.06 + 6.25	0.24 + 0.5	0.74	0.031 + 1.56	0.12 + 0.5	0.62
ATCC 25922									
<i>K. pneumoniae</i>	2 + 6.25	0.25 + 0.5	0.75	2 + 6.25	0.25 + 0.5	0.75	2 + 3.12	0.25 + 0.5	0.75
93872									
<i>K. pneumoniae</i>	0.5 + 1.56	0.125 + 0.5	0.625	1 + 1.56	0.25 + 0.5	0.75	1 + 1.56	0.25 + 0.24	0.49
12028678									
<i>K. pneumoniae</i>	0.125 + 1.56	0.06 + 0.5	0.56	0.125 + 1.56	0.06 + 0.5	0.56	0.125 + 1.56	0.06 + 0.5	0.56
161641									
<i>K. pneumoniae</i>	0.25 + 1.56	0.12 + 0.5	0.625	0.5 + 3.12	0.25 + 0.5	0.75	2 + 1.56	1 + 0.5	1.5
161884									
<i>A. baumannii</i>	0.25 + 12.5	0.003 + 0.5	0.503	0.25 + 6.25	0.003 + 0.25	0.253	ND	ND	ND
93641									
	FLU (µg/ml) + TTO (mg/ml)	FIC FLU + FIC TTO	FICI TTO	FLU (µg/ml) + CDO (mg/ml)	FIC FLU + FIC CDO	FICI CDO	FLU (µg/ml) + EOMS (mg/ml)	FIC FLU + FIC EOMS	FICI EOMS
<i>Fungi</i>									
<i>C. albicans</i>	0.5 + 0.78	1 + 0.25	1.25	0.5 + 1.56	1 + 0.25	1.25	0.5 + 0.095	1 + 0.12	1.12
ATCC 24433									
<i>C. albicans</i>	0.5 + 0.78	0.25 + 0.25	0.5	0.5 + 0.78	0.25 + 0.25	0.5	0.5 + 0.095	0.25 + 0.12	0.37
CO23									
<i>C. albicans</i>	0.5 + 1.56	0.0078 + 0.5	0.507	0.5 + 0.78	0.0078 + 0.25	0.257	0.5 + 0.095	0.0078 + 0.12	0.127
CO23RFLU									

Notes: MIC of the most effective combinations, FIC of oil = MIC of oil in combination with antifungal drugs/MIC of oil alone, FIC of antifungal drug = MIC of antifungal drugs in combination with oil/MIC of antifungal drugs, FICI = FIC oil + FIC of antimicrobial drug, ND: not determined.

TTO which exhibited MIC values of 3.12 mg/ml. Altogether these results are in agreement with the high variability of the antimicrobial activity of EOs observed with the disc diffusion method. All EOs MIC values were in the order of magnitude of milligrams and therefore significantly higher than those obtained with the reference antimicrobial drugs. The combination of antimicrobials with EOs could represent a possible alternative strategy to increase the efficacy of antibacterial and antifungal drugs. A clear synergic effect of essential oils with fluconazole has been reported against *C. albicans* (Stringaro et al. 2014) and with different antibacterial substances towards gram-negative bacteria (Toroglu 2007, 2011). FICI values reported in Table 2 indicate a positive interaction between gentamicin and fluconazole with TTO, CDO and EOMS against all bacteria and fungi tested, respectively. In particular, a synergic effect was observed for TTO plus gentamicin towards *S. aureus* ATCC 25923, *S. epidermidis*, *A. baumannii* and for TTO plus fluconazole for *C. albicans* with FICI values = 0.5. For *C. albicans* ATCC 24433 and other bacterial strains, the combination TTO-antimicrobial drugs was found to be additive with FICI value >0.5. An additive effect was also reported for CDO plus gentamicin against all bacteria obtained strains tested, except for *A. baumannii* with FICI value = 0.25, in agreement with data of Duarte et al. (2012). Interestingly, the combination of fluconazole and CDO showed a synergic effect towards fungi with FICI values = 0.5. Also, FICI values of 0.13 and 0.37 for *C. albicans* CO23RFLU and CO23 strains respectively, obtained with EOMS plus fluconazole, indicated a strong synergic effect. In the case of bacteria, EOMS plus gentamicin produced a prevalent additive effect; only for *K. pneumoniae*, the action was synergic with FICI value = 0.5. Therefore, in the case of fungi, all tested combinations of EOs plus fluconazole produced a synergic effect, except for *C. albicans* ATCC 24433. On the contrary, in the case of tested bacterial strains, the effect of EOs plus gentamicin was mainly additive, although it has been observed even towards multi-drug resistant strains. However, it must be observed that EOs concentrations necessary to decrease MIC values of gentamicin or fluconazole appear very high and therefore probably toxic for therapeutic purposes. To address this issue, TTO, CDO and EOMS were evaluated for their cytotoxicity towards an epithelial cell line of human origin (HeLa), utilised as a model. Cell monolayers were exposed to EOs diluted in cell culture medium for the same time length as for antimicrobial testing. The values of the maximum non-cytotoxic concentration (MNCC) were 1.6 mg/ml for both CDO and EOMS and 0.4 mg/ml for TTO. Comparison of data obtained between EOs cytotoxicity studies and MIC values of antimicrobial activity for bacteria and fungi, point out that TTO and CDO result cytotoxic in this cell model. Only EOMS was found not to be toxic for HeLa cell cultures at the MIC values for fungi and gram-positive bacteria. Interestingly, MICs values obtained for EOMS in combination with gentamicin or fluconazole (Table 2) were comparable to those of MNCC for eukaryotic cells. Also, the combination of reference antimicrobials with CDO produced similar results on gram-positive bacteria and fungi while in the case of gram-negative bacteria a major variability has been observed. For TTO, all MIC values were always higher than MNCC values for eukaryotic cells. As reported by Reichlinga et al. (2009), essential oils may exert cytotoxic effects to tissue cells at concentrations which do not yet show an antimicrobial effect. In addition, their use could also be limited by the concentrations that they can achieve at the site of action. Correlations studies of *in vitro* and *in vivo* toxicity data are necessary in order to develop models that allow a prediction of systemic toxicity *in vivo* from cell culture data.

3. Conclusions

Data reported in this study suggest that the antifungal and antibacterial activity of EOs could be related to their main chemical components. Some EOs can show an additive or synergic antimicrobial effect when tested in combination with sub-inhibitory concentrations of gentamicin or fluconazole, even against clinical multi-drug resistant isolates. Although results are encouraging, further studies are necessary to define the main active constituents of each oil and the optimal ratio between EOs and reference antimicrobial drugs to increase their efficacy. Finally, in a hypothetical antimicrobial therapy with EOs in combination with known antimicrobials, maximum benefit could be achieved using isolated active components from each oil. Also dosing regimens of EOs, when in combination with reference antimicrobials, should be explored for higher therapeutic efficacy and to decrease toxicological profiles.

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No potential conflict of interest was reported by the authors.

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