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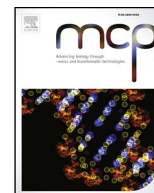

Structure-activity modelling of essential oils, their components, and key molecular parameters and descriptors

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ABSTRACT

Many essential oil components are known to possess broad spectrum antimicrobial activity, including against antibiotic resistant bacteria. These compounds may be a useful source of new and novel antimicrobials. However, there is limited research on the structure-activity relationship (SAR) of essential oil compounds, which is important for target identification and lead optimization. This study aimed to elucidate SARs of essential oil components from experimental and literature sources. Minimum Inhibitory Concentrations (MICs) of essential oil components were determined against *Escherichia coli and Staphylococcus aureus* using a microdilution method and then compared to those in published in literature. Of 12 essential oil components tested, carvacrol and cuminaldehyde were most potent with MICs of 1.98 and 2.10 mM, respectively. The activity of 21 compounds obtained from the literature, MICs ranged from 0.004 mM for limonene to 36.18 mM for α-terpineol. A 3D qualitative SAR model was generated from MICs using FORGE software by consideration of electrostatic and steric parameters. An r^2 value of 0.807 for training and cross-validation sets was achieved with the model developed. Ligand efficiency was found to correlate well to the observed activity (r^2 = 0.792), while strongly negative electrostatic regions were present in potent molecules. These descriptors may be useful for target identification of essential oils or their major components in antimicrobial/drug development.

1. Introduction

Antimicrobial resistance has greatly increased in recent years and is now considered a global public health threat [1]. Novel antimicrobials are needed to continue treating antibiotic resistant infections, yet the production of new antibiotics has stalled [2]. Natural products are a reservoir of structurally diverse compounds, so may be a source for the development of novel antimicrobial agents. Essential Oils (EOs) have been the subject of scientific interest over recent decades, with extensive screening indicating that many of these plant extracts and their isolated components possess antimicrobial activity [3].

EOs are aromatic, oily plant extracts derived by steam distillation. They are complex mixture of volatile, low molecular weight organic compounds [4]. Terpenes and their oxygenated derivatives, terpenoids, are the most common EO compounds [5], while phenylpropanoids and benzenoid compounds are less abundant [6]. Numerous EO components inhibit an array of clinically relevant pathogenic bacteria, including antibiotic resistant isolates, suggesting they may be candidates for the development of new antimicrobials. For example, carvacrol, thymol and menthol inhibited 11 important foodborne pathogens at MICs ranging 0.02–4.0 μg/mL [7]. The EO compounds 1,8-cineole, carvacrol, terpinen-4-ol, eugenol and cinnamaldehyde inhibited *Staphylococcus aureus* and Methicillin Resistant *S. aureus* (MRSA) at Minimum Inhibitory Concentrations (MICs) ranging 0.006–1.6% and *Enterococcus faecalis* at MICs ranging 0.012 to > 3.2% [8]. Wang et al. [9] reported that hinokitiol inhibited MRSA and *Escherichia coli* at 60 and 40 μg/ml, respectively. Orhan et al. [10] showed that thirty-five EO components inhibited 11 isolates of *Klebsiella pneumoniae,* including extended-spectrum beta-lactamase producing strains, at MICs ranging 8–64 μg/mL.

The mechanism by which EO components exert their antimicrobial effect is incompletely understood. Much of the published research has concluded that EO components change the structure and function of bacterial cell membranes; it has been proposed that the hydrophobic nature of these compounds allows them to partition in the membrane [11]. This non-specific mechanism of action is assumed to bypass many antibiotic resistance mechanisms and inhibit antibiotic resistant isolates. Moreover, it has been hypothesised that the risk of antibiotic resistance developing is lower than other antibiotics [12], as per other membrane-targeting antimicrobials such as cationic antimicrobial

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peptides [13]. EO components could be an attractive class of compounds for the development of new antimicrobial therapies.

Understanding the Structure-Activity Relationships (SAR) of antimicrobial agents is important in antimicrobial development to identify the most potent compounds and allow optimization of lead compounds, however there are limited published studies on the SAR of EO components as antimicrobial agents. The hydrophobicity of EO components, measured by octanal/water partitioning coefficient (log *P*) has been correlated with their antimicrobial activity [14,15]. For example, Ben Arfa et al. [15] reported that carvacrol (log $P = 3.52$) was more antimicrobial than eugenol (log$P = 2.73$). The positive correlation of hydrophobicity and antimicrobial activity relates to a greater affinity for partitioning in the bacterial cell membrane, this correlation does not hold true at log*P* greater than 4, indicating that there are other important structural characteristics [15,16].

Several published papers have emphasised the role of a phenolic group in activity, for example, Andrade-Ochoa et al. [14] reported that thymol, which possesses a phenolic group had a significantly lower MIC than menthol, which has the equivalent structure but is alicyclic. The importance of a hydroxyl moiety alongside a phenolic group was demonstrated by comparing with aromatic compounds with alkyl substituents [14,16,17]. It is hypothesised that the delocalised electron system of the phenolic moiety facilitates proton exchange through the hydroxyl group, which dissipates proton motive force [16].

This study aims to construct a 3D QSAR model of EO component activity from experimental and literature sources based on electrostatic and steric descriptors to inform future antimicrobial drug target identification.

2. Materials and methods

2.1. EO components

Authentic standards of (−)-β-pinene (99%), carvacrol (98%), cuminaldehyde (98%), linalool (97%), p-cymene (99%), thymol (≥98.5%), β-caryophyllene (≥80%) and γ-terpinene (97%) were obtained from Sigma Aldrich (Gillingham, UK).

2.2. Microorganisms

Escherichia coli NCTC 8003 and *Staphylococcus aureus* NCTC 12981 were cultured using nutrient broth and agar (Oxoid, Basingstoke, UK) and grown aerobically at 37 °C for 24 h.

2.3. Minimum inhibitory concentrations

The MIC of EO components were determined using a broth microdilution method adapted from the International Organization for Standardisation (ISO) 20776-1 antibiotic susceptibility test [18]. Serial two-fold dilutions of EO components to yield final concentrations ranging 8–0.01% (v/v) in nutrient broth supplemented with 10% dimethyl sulfoxide (Fisher Scientific, Loughborough, UK) were prepared in polystyrene 96-well plates (Scientific Laboratory Supplies, Wilford, UK). An equal volume (75 µl) of bacterial suspension was added to each well to yield a final well concentration of 5×10^5 colony forming units (CFU)/ml. Controls were antimicrobial free and inoculum free wells. Bacterial growth was determined by measuring optical density (595 nm) of samples using a Spectramax Plus 384 microplate reader and Softmax Pro version 6.4 software (Molecular Devices, Sunnyvale, USA) immediately after inoculation and after 24 h incubation at 37 °C. Experiments were repeated three times and replicated twice (n = 6) [19].

2.4. Literature review

Pubmed searches for recently published papers in peer-reviewed journals containing MIC data for a range of EO components against *E. coli* and *S. aureus* that had not been tested in this study. MICs were converted to milimolar (mM) concentrations to enable comparison between studies. Where units were volumetric, densities at 25 °C according to Sigma Aldrich were used for unit conversion.

Table 1
MIC (mM) of EO components against *E. coli* and *S. aureus* (n = 6).

EO component	MIC (mM)	
	E. coli	*S. aureus*
Carvacrol	1.98	1.98
Cuminaldehyde	2.10	33.60
Linalool	57.05	114.10
p-Cymene	15.97	7.98
γ-Terpinene	250.46	62.61

Table 2
MIC (mM) of EO components against *E. coli* and *S. aureus* from the published literature sources.

EO Component	MIC (mM)		Reference
	E. coli	*S. aureus*	
1,8-cineole	18.15	18.15	[20]
Allyl isothiocyanate	1.58	1.58	[21]
α-pinene	0.06	0.04	[7]
α-Terpineol	36.18	42.20	[22]
α-thujone	0.39	0.39	[23]
β-Caryophyllene	0.29	0.29	[23]
β-pinene	0.06	0.04	[7]
β-Thujone	0.04	0.39	[23]
Camphor	0.05	0.39	[7,23]
Carvone	6.38	50.19	[24,25]
Cinnamaldehyde	0.59	0.95	[8,21]
Citral		1.75	[26]
Citronellol	8.95	4.48	[20]
Eugenol		6.50	[8]
Geraniol	9.08	4.54	[20]
Hinokitiol	0.24		[22]
Limonene	0.004	0.44	[23]
Linalyl acetate	0.05	0.31	[7,23]
Menthol	0.01	0.01	[7]
Terpinen-4-ol	0.04	12.10	[8,23]
Thymol	9.32	4.60	[20]

2.5. Computational methods

Structure activity relationships (SAR) and quantitative analogues (QSAR) have long been employed to understand the links between molecular descriptors and biological activity. Indeed, the FORGE program from the Cresset Suite of molecular modelling software used in this study is the latest in a wide toolkit of structural techniques implemented to harness the relationships between activity and molecular structure.

The FORGE 3D QSAR protocols follow traditional workflow for statistical method development. Molecules begin by forming alignments with a reference or reference set, where their structures are compared to a molecule with known favourable biological activity data. These molecules are then visually inspected to ensure that alignments performed computationally are correct, before being passed onto training and test sets. These sets can originate as a single grouping of molecules containing activity data, however a partitioning is favourable in order to use the test set molecules as questioning parameters for the model developed from the training set. The training set molecules are then superimposed onto a formulated grid and a 3D QSAR model generated from the training set. The training and test set are then scored against the model and the statistical data is reported. The model

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