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# The role of stereochemistry on the biological activity of essential oil compounds

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## Abstract

Essential oils and their compounds are often investigated for their biological properties, including their antimicrobial activity, however, what is often overlooked is the influence of the specific stereochemical configuration of the chiral essential oil constituents. The aim of this study was to investigate whether a selection of optical enantiomers related to essential oil chemistry differed in terms of the antimicrobial activity observed, both independently and in combination with a selection of 14 essential oil compounds.

To observe the effects of the compounds against planktonic micro-organisms, the broth micro-dilution assay was undertaken against Gram-positive (*Staphylococcus aureus* and *Enterococcus faecium*) and Gram-negative (*Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) strains, as well as yeasts (*Candida albicans* and *Cryptococcus neoformans*). Combination studies were investigated at equal ratios of 1:1, and results interpreted using the fractional inhibitory concentration (FIC) index. The results of the 1:1 combination study revealed that the most prevalent interaction observed was additivity (56.46%), followed by non-interactive (37.93%) interactions. A total of 5.61% of the combinations were found to be synergistic, most of which was seen against the two yeast pathogens. No antagonism was observed in any of the combinations tested. Although little variation was observed between the enantiomeric pairs independently, a total of 17.18% of the combinations (enantiomer with essential oil compound) exhibited varied interactive efficacy. Overall, (+)-β-Pinene, (–)-

Borneol, (–)-α-Pinene and (–)-Limonene often displayed better interactive activity over their enantiomeric counterparts.

Anti-quorum sensing (QS) testing was undertaken with *Chromobacterium violaceum* as the monitor strain, using the broth macro-dilution method in order to obtain a minimum quorum sensing inhibitory concentration (MQSIC). The results revealed that, singularly, all enantiomers and selected essential oil compounds had strong anti-QS activity, with MQSIC values ranging between 0.13 - 0.50 mg/mL. The only exceptions were (–)-α-Pinene and (–)-β-Pinene, which had MQSIC > 0.50 mg/mL. The percentage of violacein inhibition at the MQSIC values ranged between 3.84 - 90.68%. The combination studies were carried out through evaluation of the fractional quorum sensing inhibitory concentration index (ΣFQSIC) and the fractional percentage violacein reduction index (ΣFPVR). The ΣFQSIC studies revealed that the majority of the combinations were non-interactive (44.90%), followed by additive (20.41%), synergistic (8.16%), and antagonistic (0.51%). In terms of the ΣFQSIC, (+)-Limonene and (+)-Citronellal often (dependent on the compounds in combination) displayed better interactive activity than their enantiomeric counterparts, where variations were observed. The ΣFPVR studies revealed that the majority of the combinations were non-interactive (40.82%), followed by additive (29.08%), and synergistic (4.08%) interactions. In terms of the ΣFPVR, (–)-Camphor, (+)-Borneol and (+)-Menthone often displayed better interactive activity than their enantiomeric counterparts, where variations were observed.

The toxicity of enantiomers and selected compounds, both singularly and in combination, was screened using the brine shrimp lethality assay (BSLA) after an exposure period of 24 hrs and 48 hrs. The only variation observed when investigated independently was between the enantiomers of β-Pinene after 48 hrs, where (+)-β-Pinene had a percentage mortality (PM) of 30.75% and (–)-β-Pinene had a PM of 93.82%. The results of the combination ΣFPM studies revealed that at 24 and 48 hrs, the majority of the combinations were antagonistic (34.69 - 40.82%), followed by non-interactive (17.35 - 30.61%), synergistic (18.37 - 23.47) and additive (9.69 - 15.51%). Variations in terms of the toxicity of the enantiomers were observed in 19.39% and 26.02% of the combinations at 24 and 48 hrs, respectively. Where variations in terms of ΣFPM were observed, (+)-Menthone, (+)-Limonene and (–)-β-Pinene (at 24 and 48 hrs), (–)-Camphor (at 48 hrs) often showed reduced toxicity in combination, when compared to their enantiomeric counterparts.

This study provides further in-depth knowledge of how enantiomers interact when combined with other essential oil compounds. It has been demonstrated that an often-neglected evaluation of the enantiomeric configuration of the essential oil compounds is in fact an important consideration, with the potential to identify therapeutically active combinations with safe toxicological profiles.