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Anticholinesterase inhibitors from *Aloysiacitrodora* Palau. Leaf essential oil

Inhibition of the enzyme AChE has been shown to alleviate early cognitive symptoms in neurodegenerative diseases prompting several attempts to discover and optimize new AChE inhibitors [Lu et al. 2011; Abuhamdah et al., 2015]. In our previous work [Abuhamdah et al., 2015], we showed that *A. citrodora* essential oil displayed significant AChE inhibitory activity.

The aim of this study is to identify the components underpinning the AChE activity using structure based *in silico* screening with the Molecular docking GOLD version 3.0.1 (Cambridge Crystallographic Data Centre, Cambridge, UK) programme. Donepezil was used as the reference compound for alignment, and eighty-eight comparator AChE inhibitors (including donepezil, galantamine, huperzine A, rivastigmine and tacrine) were taken from [Lu et al., 2011]. AChE activity was assayed as described in [Lu et al., 2011]

GC-MS analysis was performed as in [Abuhamdah et al., 2015] and over sixty chemicals were detected, principally mono- and sesqui-terpenes. The crystal structure of human AChE (PDB:4EY7) was used for structure-based *in silico* screening of *A. citrodora* EO constituents for AChE inhibitor activity, the top scoring hits with highest pharmacophore fit values showed common interactions with residues at the active site to that of donepezil. The top seven hits in order of fit score, were β-curcumene, γ-/*ar*-curcumene, β-/(*Z*)-α-bisabolene, *trans*-calamenene, caryophyllene oxide, β-sesquiphellandrene and geranyl acetate, respectively. The scores of top binding hits had values comparable to those possessed by optimal conformations of huperzine A, rivastigmine, donepezil and galantamine in the hAChE active site, with TYR 341, 337, PHE 338 and HIS 447 being primary contact points; the majority of these interactions comprise hydrogen bonding, hydrophobic and π-π interactions. *In vitro* screening of thecommercially available hits revealed two micromolar electric eel AChE inhibitors, caryophyllene oxide and geranyl acetate with IC_{50} values of 52 μM and 119 μM, respectively.

This indicates that *A. citrodora* may yield a novel effective and potentially safe AChE Inhibitor. A combination of molecular docking, and virtual screening of medicinal plants constituents is a promising strategy for discovering new effective AChE inhibitors.

Lu SH et al. (2011) *J Biomed Sci* ***18****:* 8–18.

Abuhamdah S et al. (2015) *J Pharm Pharmacol*. **67**: 1306-15

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