Indigenous community-guided chemical genomic insight into synergy of rapamycin with nerolidol derived from a leaf extract of kānuka (Kunzea robusta) in Tairāwhiti, Aotearoa New Zealand

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Added by: Manu Caddie | | Researcher
Project Contact: Manu Caddie | manucaddie@gmail.com

Contributors:

Project Description:

Maximizing efficacy and minimizing toxicity are essential in drug discovery. Utilizing a natural product combinatorial approach can offer a promising strategy to preserve bioactivity while reducing the dosage of potentially toxic drugs in patient treatment. Kānuka (Kunzea robusta) is a well-known endemic plant of Aotearoa New Zealand that has therapeutic value with traditional knowledge and preliminary laboratory studies indicating antimicrobial bioactivities, yet combinatorial bioactivity studies of this plant are non-existent. Via a research collaboration led by an indigenous Māori social enterprise that ensured indigenous landowners contributed biological material and knowledge with free, prior and informed consent at each stage of the study, we show that a steam extract of kānuka leaves has synergistic activity with the well-known immunosuppressive agent, rapamycin, resulting in amplified bioactivity in the model organism Saccharomyces cerevisiae. Network analysis of a genome-wide gene deletion screen suggested the extract increased the bioavailability of rapamycin. Subsequent fluorescent microscopy analyses revealed the importance of endocytic and oxidative stress pathways. Bioassay-guided metabolomic analyses elucidated the main component of the steam extract, α-pinene, to not be responsible for the synergistic bioactivity, rather, highlighting nerolidol as a strong synergistic candidate. Given rapamycin is an advanced compound in many clinical studies involving anti-cancer, anti-ageing, and anti-microbial activities, albeit associated with several toxic side-effects, this study provides mechanistic insight into this previously unknown bioactivity of kānuka leaves and illustrates how a lower, and safer, concentration of rapamycin could be potentially used in these diverse clinical settings.

Project Links

- https://doi.org/10.1016/j.phyplu.2025.100771

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