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Topic of Research: "Investigating therapeutic efficacy of limonene against *Candida* and skin Cancer cells"

Key Findings

Candida species are opportunistic fungi found as commensals in human host. They become pathogenic in immunocompromised patients. Due to prolonged use of conventional drugs, a considerable increase in antifungal drug resistance has been observed. Currently prescribed antifungal drugs are highly toxic with undesirable side effects. They are responsible for increased hospital expenses in patients already struggling with chronic diseases. The search for novel, cost-effective, non-toxic and more effective antifungals, has led to plant based secondary metabolites that possess antimicrobial and antifungal properties. Limonene, a citrus based monoterpene, possesses pharmacological properties which need to be explored.

With this background, we have investigated the antifungal potential of limonene against *Candida albicans* and other non-albicans *Candida* species. Sub-inhibitory concentrations of limonene resulted in the suppression of fungal growth with delayed lag phase and restricted log phase. Cellular growth was completely arrested at MIC. In combination with conventional drug (fluconazole), limonene augments antifungal efficacy and exhibited strong synergy against clinical *Candida* isolates from cleft lip and palate patients, even in fluconazole-resistant strains. Infection process of *C. albicans* is characterized by virulence traits crucial to pathogenicity, namely, host cells adhesion, secretion of hydrolytic enzymes, germ tube induction and biofilm formation.

Limonene significantly inhibited all the pathogenicity markers even at sub-inhibitory concentrations. It significantly reduced ergosterol levels and activity of plasma membrane H^+-ATPase; both membrane components being vital to cell viability. Limonene caused concentration dependent leakage of both nuclear material and proteins. Molecular docking and MD simulation confirmed strong binding affinity and stable interaction between limonene and the target proteins. This natural compound has significant impact on *Candida* cell wall integrity, cell wall composition and ROS induction leading to generation of oxidative stress. Limonene showed negligible toxicity on human RBCs, skin cell lines and zebrafish embryos. It was also effective against skin cancer cell lines. Our results are encouraging in view of the growing treatment failures and antifungal drug resistance in managing *Candida* infections. Limonene would thus be a better alternative, also when given in combination with presently available drugs. Further studies using animal models will evaluate the *in vivo* efficacy of limonene.