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Title of thesis: Anticandidal activity of garlic derived compounds.

Abstract:

Candida albicans is an opportunist pathogen which causes infections ranging from oral thrush to systemic in debilitating and immune-compromised hosts. Virulence of this fungus depends on its ability to adhere to host tissues, secretion of tissue damaging proteinases, phospholipases and switching to hyphal form. Increased use of standard antifungal (azoles and polyenes) has resulted in high MIC and resistance to these drugs. Increasing incidence of infections caused by drug resistant pathogens, host toxicity, poor efficacy of drugs and high treatment costs has drawn attention to the potential of natural products as antifungal in *Candida* infection, both alone and in combination with standard antifungals.

AIM OF THE STUDY: *Allium sativum* has been employed as antimicrobial, antiviral, and anticancer agents. The aim of the present study was to evaluate antifungal effect of allyl alcohol (AA), diallyl disulphide (DADS) & diallyl sulphide (DAS) against *C. albicans.*

RESULTS:

Antifungal effect on whole cells was investigated using disc diffusion assay, broth dilution MIC determination, changes in growth pattern and time kill assay. AA is observed to be more potent than DADS and DAS. All three compounds show fungicidal activity as evident by clear halo zones in disc assays and time kill curve study. Delay in lag phase and extension in log phase was observed on growth curve in both fluconazole susceptible and fluconazole resistant isolates of *C. albicans* on exposure to test compounds. Test compounds were found to decrease H^+–ATPase and ergosterol content in Candida cell. Effect on H^+-extrusion was also correlated with the intracellular pH in *Candida*. Decrease in pHi was observed in treated *Candida*.

Activities of primary free radical scavenging enzymes, SOD, Catalase and GPx activity were determined following treatment with these test compounds at low concentrations. The results show decrease in activity of these enzymes on exposure to AA, DAS and DADS except Catalase activity which increase on exposure to DADS. The decrease in GSH and increase in lipid peroxidation was observed on exposure to sub lethal concentration of all three test compounds. Effect of these compounds was further investigated on the activity of G-6-PDH, GR and GST. Marked reduction in activity of these enzymes on exposure to sub inhibitory concentration of test compound was observed. Results revealed that test compounds generate oxidative stress in *Candida* species.

All three garlic derived compounds were found to decrease virulence in *C. albicans.* Both proteinase and phospholipase secretion decreases on exposure to test compounds. DADS and DAS decrease isocitrate lyase and malate synthase activity. Allyl alcohol decrease isocitrate lyase activity but caused increase in malate synthase activity. Morphogenetic transformation experiment demonstrated profound effect of test compounds in preventing transformation from yeast to hyphae as well as causing decrease in hyphae length. Synergistic effect of DADS with azoles and polyenes was performed by checkerboard method and by disc diffusion assay. DADS shows synergistic /additive effect with both fluconazole sensitive and resistant isolates of *C. albicans*. Test compounds display less hemolysis at their respective MIC's in comparison to the conventional drugs (amphotericin B).

Conclusion: From this work, we conclude that AA, DAS and DADS can be promising drugs after improved formulations either alone or in combination with standard antifungals. Rapidity of action, low MIC values, lethal effect, and direct effect on virulence factors, induction of oxidative stress in *Candida* and relatively less cytotoxicity on humans demand further research into molecular mechanisms of action of these compounds. Investigations based on animal models are required to resolve in vivo efficacy of these compounds.