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Title of the Abstract: Apoptosis and Pathogenicity Modulation in *Candida albicans* by Essential Oil of Tulsi (*Ocimum sanctum*) and its Lead Molecules

Abstract:

Candida albicans is the predominant cause of virtually all types of Candidiasis, but other emerging *Candida* species - *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis* are now posing serious nosocomial threats to patient populations. Conventional drugs are insufficient due to undesirable side effects and inefficacy against new or re-emerging resistant. Azoles have been a predominant therapy drug for *Candida* infections for a long time now. However, treatment failures are increasing especially in AIDS patients as prolonged use of fluconazole has led to resistance in *Candida* spp. probably due to fungistatic rather than fungicidal action. New therapeutic strategies are required to reduce the toxicity and improve the efficacy of these drugs by combinational therapy. Plant essential oils possess broad spectrum antimicrobial action due to presence of wide variety of bioactive molecules. We have studied the relative antifungal efficacy of five Indian medicinal plants traditionally known for their antimicrobial potential –Neem (*Azadirachta indica*), *Aloe vera*, Mint (*Mentha Piperita*), Tulsi (*Ocimum sanctum*) and Turmeric (*Curcuma longa*) against *Candida species. Ocimum sanctum* essential oil (OSEO) with an MIC of 0.024%v/v was found to be the most effective. OSEO's antifungal potential was further investigated after a detailed GC-MS analysis which revealed presence of methyl chavicol (MET CHAV) and linalool (LIN) as lead bioactive constituents. OSEO, MET CHAV and LIN were found effective against all isolates tested including FLC resistant isolates. The mode of action of OSEO and its major components seemed to vary depending upon the dose and period of exposure. Short exposures of 5-15 minutes resulted in reduced H^+ efflux by PM-ATPase. 1h ≤MIC exposure resulted in externalization of phosphatidylserine, DNA fragmentation, cytoplasmic shrinkage,

chromatin condensation and membrane vesiculation characteristic of PCD. During exposure, cytochrome c release was not observed suggesting dubious involvement of mitochondrion in mediating apoptosis. Exposure of >MIC resulted in necrosis. Prolonged exposures of 16h resulted in highly reduced ergosterol content. Prolonged exposures of 8h, at very low concentrations resulted in membrane oxidation, production of free radicals (ROS) and oxidative stress induction. Elevation of ROS stimulated enzyme SOD & catalase and decreased activity of GPx, GR, G6PDH, GST and GSH levels. OSEO, MET CHAV & LIN significantly inhibited pathogenicity markers including germ tube induction, proteinases and phospholipases secretion. OSEO exhibited strong synergy with azoles -FLC and ketoconazole. This study encouraged use of OSEO and its major components especially LIN for topical application in the management of superficial infections and a combination use with FLC or ketoconazole.