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A multifunctional amino-lipid carrier: Combating antifungal drug resistance and improvising nano drug delivery

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Management of invasive candidiasis in immune compromised patients exhibits a major challenge for the clinicians since, antifungal monotherapy becomes ineffective. Moreover, switching between new antifungal agents and drug combinations intensify the situation by creating parallel adverse effects and drug toxicities. Furthermore, combining two drugs in a unit dosage form bring pharmaceutical challenges. This in turn, decreases the pharmaco-economic efficiency in treatment associated with drug resistant candidiasis. Hence, we suggest replacing drug-drug therapy with drug-active lipid therapy, wherein the active lipid is a synthesized amino-lipid based multifunctional carrier (PFA 18) which exhibit combinatorial synergy with existing first line antifungal agents like fluconazole and polyenes such as Amphotericin B against clinically isolated drug resistant *Candida species*. As suggested by our computerized simulation studies, this lipid forms a strong hydrophobic and Van der Waals interaction with antifungal agents supporting its stabilization into a nano emulsion system. Sensitivity testing against gene deleted S. *cerevisiae* library also represented a possibility of effect on mitochondrial outer membrane and cell membrane of yeast. These activities were confirmed by flow cytometric mitochondrial assay and topographical cryo-imaging studies. *In vitro* cytotoxicity confirmed that PFA 18 alone and in combinations with Fluconazole/Amphotericin B did not show any cytotoxic effect on Hep2G or HEK cell lines. Moreover, *in vivo* acute toxicity testing of PFA 18 showed that its toxicity range lies between 200-300 mg/kg. *In vivo* efficacy studies in Swiss albino mice model infected with multidrug resistance *Candida* revealed that, PFA 18 played a major role in reducing drug dose and toxicity thereby increasing the probability of survival.

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