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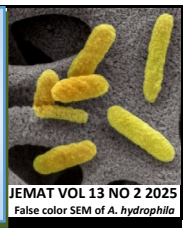

Evaluation of the Antimicrobial Activity of Selected Psychotropic Drugs Against Yeast Species

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Abstract

The antimicrobial activity of psychotropic drugs forms the basis for their repurposing for antibiotic applications and concurrently requires care in their disposal due to their potential role in the evolution and spread of antimicrobial resistance. Four psychotropic drugs of the sedative class, namely barbiturate, benzodiazepine, non-benzodiazepine, and chloral hydrate, were tested for their antimicrobial activity against three different types of yeasts, viz, an ascomycetous non-pathogenic yeast *Saccharomyces cerevisiae*, an ascomycetous pathogenic yeast *Candida tropicalis*, and a basidiomycetous emerging pathogenic yeast *Rhodotorula mucilaginosa*; biofilm-forming ability was used as the parameter of pathogenicity. All drugs showed antibiofilm activity; chloral hydrate was more effective (causing 66.3%, 42.355 and 25.44% in *S. cerevisiae, R.mucilaginosa* and *C. tropicalis* respectively) at lower concentrations (MIC_{50}), *S. cerevisiae* was the most resistant yeast except in the case of chloral hydrate, while *R. mucilaginosa* was the most sensitive yeast (up to 76.85% and 74.67% inhibition by benzodiazepine and non-benzodiazepine respectively) towards the selected sedative drugs. Some of these drugs may be repurposed for use as antibiotics, while care must be taken in their disposal, as they may contribute to the evolution and spread of antimicrobial resistance.

INTRODUCTION

Psychotropic drugs (PDs) are medicines prescribed for handling certain mental health issues e.g., anxiety, depression, schizophrenia, and so on. Currently, these drugs have fetched attention because of their antimicrobial activity against certain microbes [1]. The drugs are also considered as potential candidates for certain repurposing applications, viz. as antibacterial [2-3], antifungal [4-6], antimicrobial [7], and anticancer [8] drugs. During the COVID-19 period, the unprecedented stress led to a sharp rise in the PD user population. In the USA, 25 % of the population, for example, was using PDs during 2011-2014 [9]. Owing to these widespread uses, more PD residues have also been released into the environment. PDs like antibiotics released into the environment are suspected to be responsible for supplementing the evolution and spread of antimicrobial resistance (AMR) as well [10]. The long-term use of PDs by the people has been experimentally demonstrated to enhance the frequency of AMR genes in the gut microbiota [8,11-12].

Evidence does indicate that PDs may aggravate the spread of AMR genes across bacterial species [13]. AMR is currently a serious health challenge as it is implicated in claiming about 4.95 million lives annually in the world [13]. Therefore, there is a debate going on over the safety of the use of these PDs [1,8,10]. Pathogenic yeasts such as *Candida albicans*, *Candida parapsilosis*, *Candida fermentati*, *Candida lusitaniae*, *Cryptococcus* spp., *Meyerozyma guilliermondii*, *Pichia kudriavzevii*, *Rhodotorula* spp., *Trichosporon* spp., are an emerging threat [14-19], especially to immunocompromised persons. *C. tropicalis* [20] and *R. mucilaginosa* [21] find special mention as emerging threats to human beings, especially immunocompromised individuals. The situation worsens in view of the limited classes of available medicines and consequent growing AMR in them.

Certain virulence factors, such as adhesion to the surface of host or medical devices, biofilm formation, secretion of hydrolytic enzymes, and phenotypic switching, enable these yeasts to cause infections in humans [22-31].

Of these, biofilm formation is a highly studied virulence factor characterized by a compact layer of microbial population embedded within an extracellular matrix so firmly that it discourages the penetration of a therapeutic or access to the host defense system [28-29]. PDs like aripiprazole [32] and fluoxetine [33] have been demonstrated to have inhibitory activity on biofilm-forming activity in *C. albicans* and fluconazole- resistant *Candida* spp. respectively. In order to further consolidate the concept, we undertook experiments to study the effect of antidepressant class of PD, viz., barbiturate, benzodiazepine, non-benzodiazepine, and Chloral hydrate on the biofilm-forming ability of two pathogenic, viz. *C. tropicalis*, *R. mucilaginosa,* and a control *S. cerevisiae* yeast.

METHODS

Yeast strains

Three yeast strains *C. tropicalis*, *R. mucilaginosa* and *S. cerevisiae* were used in this study. *C. tropicalis* and *S. cerevisiae* were collected from the National Collection of Industrial Microorganisms (NCIM), Pune. *R. mucilaginosa* was collected from laboratory stock.

Culture condition

Yeast cultures were maintained in potato dextrose agar (PDA) and routinely cultured in yeast extract peptone dextrose (YEPD) broth for various assays. For inoculum preparation, a loopful of colonies was inoculated into liquid YEPD medium and incubated at 30 °C (*S. cerevisiae* and *C. tropicalis*) and 25 °C (*R. mucilaginosa*) at 180 rpm overnight [34].

Psychotropic drugs

Barbiturate (Phenobarbitone), Benzodiazepine (Diazepam), Non-benzodiazepine or Z-drugs (Zolpidem), and Chloral hydrate were used in this study. All drugs were purchased from registered local medical shops (Bhopal) except chloral hydrate that was obtained from old laboratory stock at the Botany Department, Patna University (courtesy Dr. Birendra Prasad). Stock solution: The stock solution was prepared at a final concentration of 10 mg/mL and stored at 4 °C.

Antiyeast activity

Susceptibility testing was determined by the macro-dilution method. Briefly, Stock suspensions were made from 48 h cultures of yeasts on Sabouraud dextrose agar at 35 °C (30 °C for two isolates). Turbidities were spectrophotometrically adjusted, and the suspensions were diluted 1 to 100 and then 1 to 20 in YEPD medium, resulting in a concentration of 0.5×10^3 to 2.5×10^3 cells per mL. Serial dilutions from standard drug stocks were prepared within 24 h of testing and stored at 4 °C until use. Each tube containing 0.1 mL of drug solution was inoculated with 0.9 mL of inoculum suspension. The tubes were incubated without agitation at 30 °C and 35 °C until growth was sufficient (72 h) for the determination of the MIC. The MIC resulting in 50% growth inhibition (MIC_{50}) was determined [35].

Biofilm inhibitory activity

Biofilm was produced as previously described by Silva et al. [36]. Briefly, cell suspensions were obtained from a single colony of each yeast following growth for 96 h at 28 °C. Standardized cell suspensions (500 µl containing 5 × 107 cells/mL in YPD) with and without drugs were placed into polystyrene petri dishes and incubated at 37 °C at 120 rpm for 48 h. The medium was then decanted, and non-adherent cells were removed by washing the biofilms twice with sterile pure water.

Biofilm-forming ability was assessed visually using crystal violet (CV) staining. After washing, the biofilms were fixed with 20 mL of methanol (99%), which was then removed after 15 min. The plates were allowed to dry at room temperature, and 20 mL of CV (1% v/v) was added and incubated for 5 min. The plates were then gently washed with sterile, pure water, and 20 mL of acetic acid (33% v/v) was added to release and dissolve the stain.

The absorbance of destaining solution was measured at 570 nm using a spectrophotometer. 33% acetic acid was used as a blank. The experiments were performed in triplicate and repeated twice in independent assays [37]. Percentage biofilm inhibition is calculated by the following formula:

$$\% \text{ biofilm inhibition} = \frac{= \text{ OD (control)} - \text{OD (sample)}}{\text{OD (control}} x100\%$$

The antibiofilm activity of psychotropic medicines on yeast was carried out by including MIC and MIC_{50} doses of drugs in the above experiment. MIC determination and Biofilm inhibition studies were made in triplicate (n=3) thrice. One-way ANOVA was carried out manually, and statistical significance was considered at P-value <0.05.

RESULTS AND DISCUSSION

Microorganisms can form biofilms on biotic surfaces, such as host tissues, and abiotic surfaces, such as implants and medical devices. The most common biofilm-forming yeasts include *Candida* spp., *Cryptococcus neoformans,* and *S. cerevisiae*. Biofilm are the irreversible association of cells, attached or adhered to the surface and produces an extracellular polymeric matrix. This structure makes organisms tolerant to harsh environmental conditions, and the extracellular matrix protects them from antimicrobials. Biofilm formation is a sequential process in which early development involves reversible attachment or adherence of yeast cells to the surface, proliferation of yeast cells on the surface, and induction of invasive hyphae formation, while the mature phase of development involves production of extracellular polymer matrix resulting in an irreversible attachment [38].

Psychotropic drugs (PDs) are used to manage certain mental illnesses. Their antimicrobial effect is important for two reasons: a. they may be repurposed as antimicrobial medicines, and b. their residues in the environment may also be responsible for the evolution and spread of antimicrobial resistance. To assess the antimicrobial (against yeasts) activities of selected psychotropic drugs we used two important parameters i.e., anti-yeast (killing) activity and anti-biofilm-forming ability.

Antiyeast activity

The yeasts responded differently to the selected PDs; *C. tropicalis* was more resistant to barbiturate, while *R. mucilaginosa* and *S. cerevisiae* were more resistant to non-benzodiazepine (Table 1). All the yeasts were the most sensitive to chloral hydrate, while *S. cerevisiae* exhibited, in general, a higher MIC value to all the tested PDs. Although all the PDs used are central nervous system depressants with sedative and hypnotic features, their actual action and uses differ. Barbiturates are administered to control seizures, and benzodiazepines are used to manage seizures and anxiety. Non-benzodiazepine is applied to control moderate insomnia, while chloral hydrate is used to control insomnia and anxiety [39]. Use of choral hydrate has been discontinued due to its toxicity [40].

Table 1. Minimum inhibitory concentration (MIC) values of selected psychotropic drugs against different yeast species.

Yeast Species	Chloral Hydrate (MIC)	Benzodiazepine (MIC)	Barbiturates (MIC)	Non-benzodiazepine (MIC)
S. cerevisiae	250	500	1000	1000
C. tropicalis	250	500	1000	500
R. mucilaginosa	150	250	250	500

Biofilm inhibitory activity

Yeasts' ability to form biofilm exhibited variable responses to the presence of the PDs used. Chloral hydrate showed the highest percentage of biofilm inhibition in *S. cerevisiae*, moderate inhibition in *R. mucilaginosa,* and the lowest in *C. tropicalis* at both MIC and MIC_{50} doses. Another highlight of its effect was that it caused a better effect at MIC_{50} dose in all three yeasts.

Benzodiazepine showed more than 60% biofilm inhibition in *R. mucilaginosa* at both MIC and MIC_{50} doses. About 50% biofilm inhibition was obtained at 500 µg/mL in *C. tropicalis*. However, % biofilm inhibition (45%) in *S. cerevisiae* by benzodiazepine was obtained at 500 µg/mL. Earlier, benzodiazepine was reported to exhibit antibacterial activity against biofilm-forming strains of *Staphylococcus aureus*, the molecular causes involved DNA fragmentation and protein-carbonylation [41]. The PD drug diazepam showed anti-yeast activity against *Candida* spp. and *C. albicans* and affected biofilm formation in them via interaction with virulence proteins ALS3 and SAP5 implicated in biofilm formation [42].

Barbiturate shows 47% biofilm inhibition in *S. cerevisiae* at 1000 µg/mL. In *R. mucilaginosa,* maximum inhibition was obtained at MIC 250 µg/mL. More than 50% biofilm inhibition was observed at 500 µg/mL in *C. tropicalis*. The derivatives of barbiturates have been demonstrated to exhibit antifungal and antibacterial effects [43]. Non-benzodiazepine showed more than 70% biofilm inhibition in *R. mucilaginosa* at 500 µg/mL It showed low % biofilm inhibition in *S. cerevisiae*. More than 60% biofilm inhibition was observed in *C. tropicalis* at MIC and MIC_{50} i.e. 500 µg/mL and 250 µg/mL, respectively. Non-benzodiazepine and its anagrams have been found to indicate antituberculosis activity against replicating *Mycobacterium tuberculosis* (Mtb) H37Rv [44].

In general, chloral hydrate was found to be a more effective biofilm inhibitor at lower concentrations, *S. cerevisiae* was the most resistant yeast, except in the case of chloral hydrate, while *R. mucilaginosa* was the most sensitive yeast towards the selected PDs.

C. tropicalis is an ascomycetous yeast that is now an established human pathogen [20], while *R. mucilaginosa* is a basidiomycetous yeast whose clinical importance is increasingly being proved [14]. Advances in medical science are expected to result in more organ transplants and cancer survivors with compromised immunity. As a result of constant exposure to PDs and antifungal drugs, the natural mutation, on the other hand, may lead to evolution of multiple types of AMR strains in these yeasts. Thus, in the coming years, these opportunistic pathogenic yeasts infected patients are expected to rise in number and severity. Given very limited drug targets against emerging pathogenic yeasts, revisiting the PDs for their antimicrobial activities may provide opportunities to design newer antimicrobial drugs or repurpose them for antimicrobial applications. Another dimension of this work is to contemplate the potential role of leaked PDs in the environment in the evolution and spread of AMR. The findings are therefore important for all the stakeholders, including policy makers, to design SOP as to their production and disposal policy in view of their potential role in AMR evolution.

CONCLUSION

The four PDs studied exhibited antiyeast and antibiofilm activities. Since very limited drug targets against emerging pathogenic yeasts are available, the antimicrobial activities of PDs may provide opportunities to design newer antimicrobial drugs or repurpose them for antimicrobial applications. Also, the findings indicate the potential role of PDs in the evolution and spread of AMR.

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AUTHORS' CONTRIBUTION

K.C. and S.S. contributed to conceptualization and design of the study, K.C. and VJ. drafted the manuscript.

DATA AVAILABILITY STATEMENT

Data is available on request.

AI USAGE DECLARATION

The authors did not use generative artificial intelligence tools were used in the manuscript preparation.

Table 2. Minimum inhibitory concentration (MIC) and MIC_{50} values of selected psychotropic drugs against different yeast species.

Yeast Species	Chloral Hydrate MIC	Chloral Hydrate MIC_{50}	Benzodiazepine MIC	Benzodiazepine MIC_{50}	Barbiturate MIC	Barbiturate MIC_{50}	Non-benzodiazepine MIC	Non-benzodiazepine MIC_{50}
S. cerevisiae	59.70	66.30	45.06	5.02	47.11	33.24	33.42	25.13
C. tropicalis	14.52	25.44	50.70	44.54	46.30	57.30	60.38	68.66
R. mucilaginosa	23.36	42.35	76.85	66.37	68.34	55.67	74.67	50.87

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