Exploring the antifungal potential of the antidepressant vortioxetine

Silvia Rizzo[1*], Margherita Cacaci[1], Debora Talamonti[1], Stefano Di Bella[3], Luigi Principe[4], Umberto Albert[3], Brunella Posteraro[1], Maurizio Sanguinetti[1,2], Francesca Bugli[1,2], Riccardo Torelli[2]

[1] Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, 00168 Rome, Italy
[2] Dipartimento di Scienze di Laboratorio e Infettivologiche, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, 00168 Rome, Italy
[3] Clinical Department of Medical, Surgical and Health Sciences, Trieste University, Trieste, Italy
[4] Microbiology and Virology Unit; Great Metropolitan Hospital "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

***silvia.rizzo@unicatt.it**

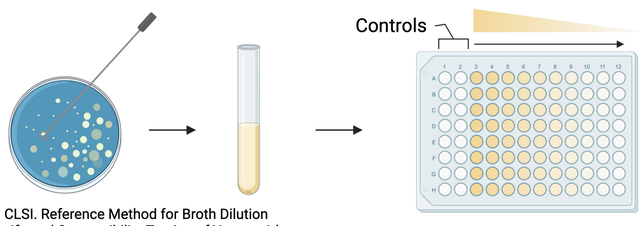
INTRODUCTION

Vortioxetine was approved in 2013 by the *Food and Drug Administration* for the treatment of adults with major depressive disorder. This molecule acts as an inhibitor of serotonin reuptake receptors and as an antagonist, agonist and partial agonist of multiple serotonin receptors. In a microbial community as complex and diverse as the intestinal ecosystem, it is logical to assume that some of the microbes would be able to metabolize the drugs consumed and that this will have a growth promoting effect or a growth inhibiting effect (antimicrobial) on microbes. This study explores the antifungal activity of the multimodal antidepressant vortioxetine against *Candida* spp. (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei,* and *C. auris*), aiming to assess its inhibitory effects on planktonic growth.

METHODS

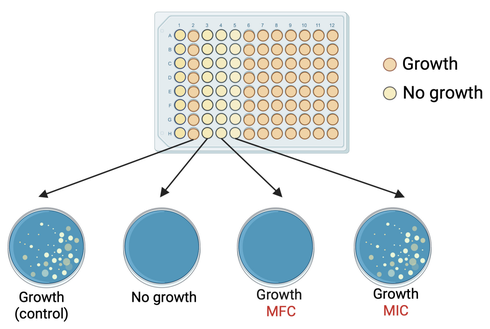
1 Preparation of inoculum at a concentration of 1:500 of 0.5 McFarland

2 Serial diluition of vortioxetine

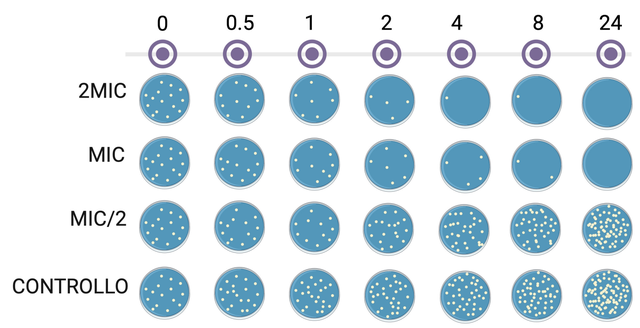


CLSI. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. 4th ed. CLSI standard M27. Wayne PA: Clinical and Laboratory Standard institute; 2017.

3 *Candida spp.* incubation for 24 h with vortioxetine and seeding of postive control and no grown samples



4 Time kill curves seeding positive control and 2MIC, MIC and MIC/2 samples after 0, 0.5 1, 2, 4, 8, 24 hours of incubation



5 ROS measurement using DCFDA assay

MIC: minimum inhibitory concentration
MFC: minimum fungicidal concentration
ROS: reactive species of oxygen

RESULTS

1- Antifungal activity of vortioxetine against *Candida spp.* and time-kill curves

Species (no. of isolates)	MIC_{90} (µg/mL)	MFC_{90} (µg/mL)
C. albicans (10)	8	16
C. auris (10)	16	16
C. glabrata (10)	8	16
C. krusei (10)	8	16
C. parapsilosis (10)	16	16
C. tropicalis (10)	8	16

Table 1

Table 1. *In vitro* susceptibilities of 60 clinical isolates of *Candida spp.* determined by the CLSI broth microdilution method. The reported MIC90 and MBC90 values are median values of 3 isolate experiments for each species.

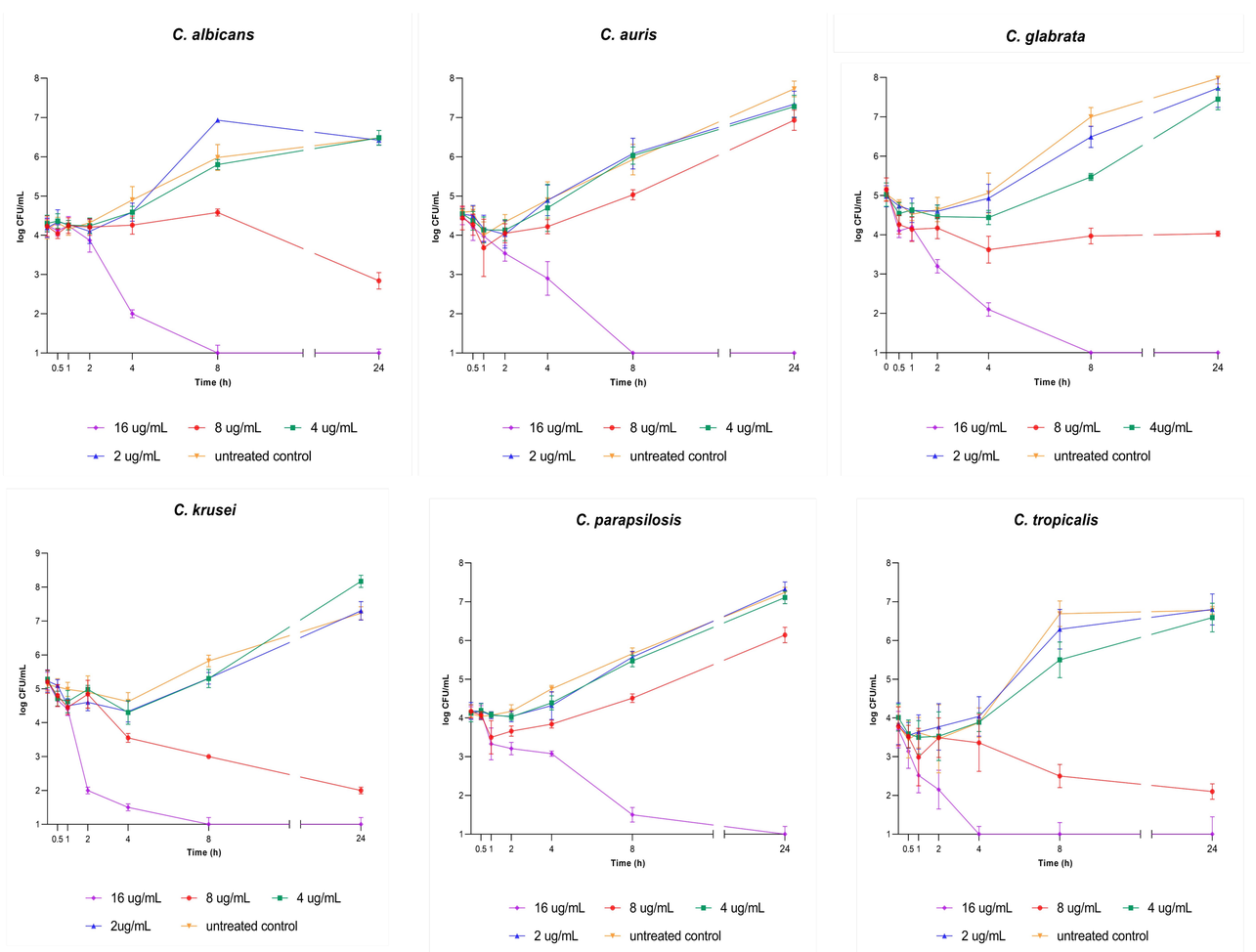


Figure 1. Time-kill studies with concentrations of vortioxetine at 16, 8, 4 and 2 µg/mL applied to six strains, each representing one of the following species: *C. albicans, C. auris, C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis*. At vortioxetine concentrations of equal to 2 x MIC for all species and MIC for *C. auris* and *C. parapsilosis* the number of CFU/mL decreased >4 log units (99.9% killing) by incubation for 24h.

2- Effect of vortioxetine on reactive oxygen species in *Candida spp.*

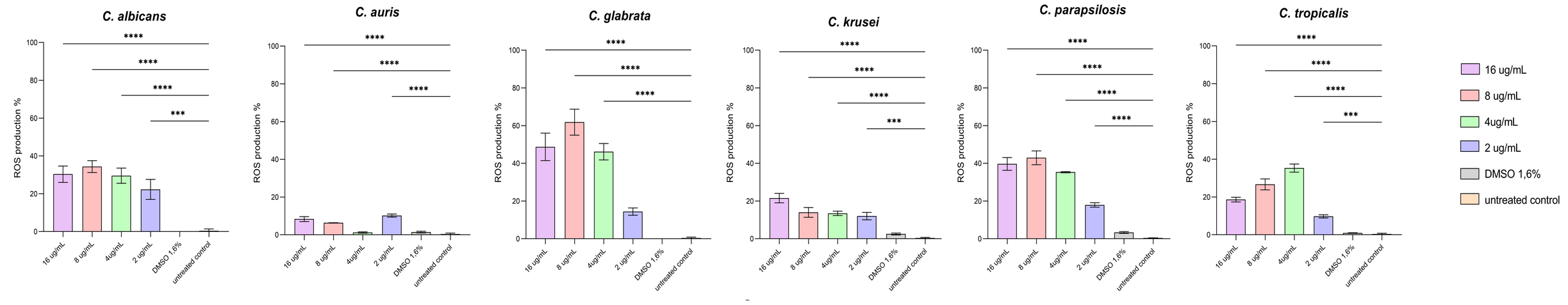


Figure 2. ROS generetion by vortioxetine examined after incubating 16, 8, 4 and 2 µg/mL of vortioxetine with the *Candida* cells. The cells exposed to vortioxetine recorded a considerable increase in the level of intracellular ROS when related to the untreated control samples. In addition, vortioxetine enhanced the production of ROS in a dose-dependent manner (**** = p<0,0005; *** = p < 0.001).

CONCLUSION

In this study was demonstrated the antifungal action of the antidepressant vortioxetine. This, along with other studies represents substantial evidence that antidepressants can affect the structure of the intestianal microbiome and that microbioma could affect the effectiveness of treatment.

REFERENCES

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