

Pyrvinium Pamoate Synergizes with Azoles in vitro and in vivo to Exert Antifungal Efficacy Against *Candida auris* and Other *Candida* Species

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Introduction: Treating infections caused by azole-resistant *Candida spp.* poses a significant challenge. Previous research has indicated that pyrvinium pamoate (PP) has the potential to augment the antifungal efficacy of azole antifungals against filamentous fungi. The objective of this study was to investigate the antifungal properties of PP, both independently and in conjunction with azoles, against *Candida auris* and other *Candida spp.*

Materials and Methods: A total of 21 clinical *Candida spp.* strains and five azoles were assessed. The antifungal efficacy of PP, either alone or in combination with azoles, was tested according to the reference method. *Galleria mellonella* larvae were employed to evaluate the antifungal efficacy of PP and/or azoles in the treatment of *C. auris* infections in vivo.

Results: When used to treat these different fungal isolates in vitro, the single-agent efficacy of PP was relatively poor, with minimum inhibitory concentration values ranging from 2 µg/mL - >32 µg/mL. However, PP and azoles exhibited synergistic activity against the majority of analyzed *C. albicans* and *C. auris* isolates. To extend these results in vivo, *G. mellonella* was infected with *C. auris* strain AR385 and both survival and fungal burden were assessed for treated larvae. The inclusion of PP in combination with itraconazole, voriconazole, or posaconazole resulted in varying degrees of improvement in the survival rates of these larvae.

Conclusion: Combining PP with azoles represents a promising approach to effectively disrupting the growth of azole-resistant *C. auris* and other *Candida spp.* such that it may be a promising anti-*Candida* therapeutic option.

Keywords: *Candida auris*, pyrvinium pamoate, synergy azoles, *Galleria mellonella*

Introduction

Invasive fungal infections pose an increasingly serious threat to the health of humans throughout the globe. *Candida auris* is an emerging pathogen that has been linked to severe invasive infections¹ and high rates of patient mortality, having been detected in multiple nations since its initial identification in a female patient in Japan in 2009.^{2,3} Strikingly, most of these clinical *C. auris* isolates exhibit resistance to one or more of the antifungal drugs typically employed for the treatment of infections caused by *Candida spp.*⁴ Given these multidrug resistance characteristics, rapid spread throughout the globe, and potential to kill infected patients, there is a clear need for the design of novel therapeutic regimens that can more reliably combat *C. auris* and related fungal pathogens.

A variety of compounds have been explored in this therapeutic context, including both novel antifungal agents and drugs purported to synergistically enhance the efficacy of other antifungal drugs.⁵ The anthelmintic drug pyrvinium pamoate (PP) initially received US Food and Drug Administration (FDA) approval in 1955 for the treatment of pediatric pinworm infections. With the emergence of novel antiparasitic agents, the use of PP as an anthelmintic in the United

States progressively diminished during the 1970s and 1980s. Despite the declining use of PP as an anthelmintic over the years, interest in PP has experienced a resurgence since the early 2000s due to its potential for targeting disease-causing organisms across various levels, including viruses, bacteria, fungi, and multicellular organisms.^{6–8} Notably, PP reportedly suppresses the growth of fluconazole (FLU)-resistant *C. albicans* and can synergize with FLU treatment to more effectively kill these pathogenic fungi.⁹ Whether PP similarly exerts single-agent or combination efficacy against *C. auris*, however, has yet to be tested. Accordingly, this study was designed to explore the antifungal activity of PP as a treatment for *C. auris* and other common *Candida* spp. both in vitro and in vivo.

Materials and Methods

Fungal Isolates

For this study, 21 clinical *Candida* spp. isolates were used, including *C. albicans* (n=5), *C. parapsilosis* (n=2), *C. tropicalis* (n=2), *C. glabrata* (n=2), and *C. auris* (n=10). *C. auris* strains used in this study were obtained through the CDC and FDA Antibiotic Resistance Isolate Bank. These strains were subjected to morphological assessment and also underwent ITS and D1/D2 region sequencing to validate their strain designations. *C. parapsilosis* ATCC22019 was also incorporated into this study for quality control.

Antifungal Drug Selection

FLU, itraconazole (ITC), voriconazole (VOR), posaconazole (POS), and PP were purchased from Selleck Chemicals (TX, USA) and prepared as in M27-A4.¹⁰ All drugs were prepared at a stock concentration of 1600 µg/mL with DMSO.

Inoculum Preparation

Following growth on potato dextrose agar (PDA) for 2 days, yeast cells were harvested and suspended in sterile dH₂O, followed by adjustment with a hemocytometer to a final concentration of $1\text{--}5 \times 10^6$ CFU/mL.

In vitro Antifungal Efficacy Testing

A microdilution checkerboard approach was performed as per the CLSI M27-A4 reference method to test the antifungal efficacy of PP either alone or in combination with azoles. Briefly, each of these drugs was subject to serial two-fold dilution using RPMI-1640 to a final concentration at twice the target concentration level, with respective working concentration ranges for PP and azoles of 0.25–32 µg/mL and 0.031–16 µg/mL. An inoculum concentration of $1\text{--}5 \times 10^3$ CFU/mL was established by diluting yeast cells with RPMI-1640 and then adding these fungi to 96-well plates followed by a 48h incubation at 35°C. Minimum inhibitory concentration (MIC) values were determined by identifying the lowest drug concentration capable of suppressing 50% of fungal growth relative to control treatment. Interactions among drugs were determined with the fractional inhibitory concentration index (FICI): $FICI = (Ac/Aa) + (Bc/Ba)$, where Ac and Bc, respectively, denote the MIC values for the two antifungal drugs in combination, and Aa and Ba, respectively, denote the MIC values for those two antifungal agents when applied as single-agent treatments.¹¹ Synergy, indifference, and antagonism were, respectively, defined by FICI values ≤ 0.5 , $0.5 < FICI \leq 4.0$, and > 4.0 . All testing was repeated three times with triplicate analyses.

In vivo Antifungal Efficacy Testing

To assess the antifungal efficacy of PP and/or azoles when used to treat *C. auris* infections in vivo, *G. mellonella* larvae were prepared as in a prior report.⁸ Briefly, sixth instar larvae (300–350 mg, 2–3 cm, Chengdu Pets and Insects Company, Sichuan, China) were raised in the dark. *C. auris* AR385 was cultured for 2 days on PDA at 37°C, after which yeast cells were harvested, resuspended in dH₂O at 1×10^8 CFU/mL, and each larva was injected with 10 µL of this *C. auris* suspension, with saline instead being injected into control larvae. In total, seven treatment groups were established (PP, ITC, VOR, POS, PP+ITC, PP+VOR, and PP+POS). There are twenty larvae in each group. Therapeutic (1 µg per agent) or control solutions were performed via the last left leg with a Hamilton syringe (25 gauge, 50 µL) after cleaning the area

using alcohol. Rates of larval survival were assessed every 24 h for 120 h post-infection. Analyses were repeated three times with triplicate analyses.

Statistical Analysis

GraphPad Prism 9.0 was used for all statistical testing and figure preparation. *G. mellonella* survival was assessed using Kaplan–Meier curves and log-rank (Mantel-Cox) tests. A P-values below 0.05 were considered statistically significant.

Results

Analysis of the in vitro Single-Agent and Combination Antifungal Activity of PP

When employed as a single-agent treatment, the antifungal activity of PP was relatively poor, with MICs from 2 µg/mL to >32 µg/mL (Table 1) for the tested *Candida* spp. However, synergistic activity was detected when combining PP and azoles for the treatment of several of these *Candida* isolates (Table 1 and 2). The combination of PP + ITC exhibited synergistic activity against one *C. albicans* strain (20%) and four *C. auris* strains (40%), while PP + VOR synergistically suppressed the growth of three *C. albicans* strains (60%), one *C. tropicalis* strain (50%), and five *C. auris* strains (50%). More obviously, the combination of PP + POS synergistically inhibited four *C. albicans* strains (80%), one *C. tropicalis* strain (50%), one *C. glabrata* strain (50%), and nine *C. auris* strains (90%). PP also exhibited synergistic activity when combined with FLU and used to treat four *C. albicans* isolates (80%) and one *C. tropicalis* isolate (50%). PP and the tested azoles failed to exhibit any synergistic activity against *C. parapsilosis* in all experiments.

Analysis of the in vivo Single-Agent and Combination Antifungal Activity of PP

G. mellonella larval survival was next analyzed for groups treated with PP (10%), ITC (30%), VOR (20%), POS (26.67%), PP+ITC (46.67%), PP+VOR (40%), and PP+POS (48.33%) (Figure 1). Single-agent PP treatment failed to prolong the survival of *C. auris* AR385-infected larvae. However, larval survival was significantly enhanced when combining PP with POS or VOR, exceeding the survival benefits afforded by POS or VOR alone ($P < 0.05$). The combination of PP and ITC also exhibited a trend towards increased survival rates relative to ITC treatment alone, although the difference was not significant.

Discussion

Many cases of *C. auris* infection have been documented since 2009 when it was first identified in the external ear canal of a Japanese patient who subsequently experienced the infiltration of *C. auris* into her bloodstream.³ *C. auris* infections have since been reported in over 20 countries,¹² typically presenting in the form of nosocomial infections of a wide range of sites including the blood, skin, urine, bile, nares, and wounded tissues.^{13,14} Antifungal drug treatment is often insufficient to effectively treat *C. auris*, underscoring the need for novel interventional approaches such as combination therapies that can expand the overall spectrum of available antifungal drugs by simultaneously enhancing therapeutic efficacy and reducing the severity of treatment-related adverse effects.

This study revealed clear evidence of synergistic interactions between PP and the four tested azole drugs (ITC, VOR, POS, FLU) against many of the tested clinical *Candida* isolates. Consistently, the in vivo treatment of *C. auris*-infected larvae with both PP and azoles resulted in improved survival outcomes for all tested combinations other than PP + ITC relative to azole treatment alone. Given these results, combining PP with azoles represents a promising means of facilitating better *C. auris*-related survival outcomes. Additional studies will be essential to clarify the mechanistic basis for this result.

The azole resistance mechanisms associated with *C. auris* drug resistance mechanisms have yet to be established. One possibility is that these fungi may overexpress the ABC and MFS efflux pumps. Consistently, elevated levels of activity for ABC-type transporters have been documented in *C. auris* as compared to *C. glabrata* or *C. haemulonii*.⁴ Second, these fungi may harbor advantageous *ERG11* point mutations, as supported by a study of 44 *C. auris* isolates that frequently identified FLU resistance-related point mutations within the *ERG11* gene sequences in these isolates.¹⁵ Third, *ERG11* overexpression may contribute to azole resistance, in line with data supporting higher levels of *ERG11* expression in FLU-treated *C. auris* as

Table 1 Minimum Inhibitory Concentration (MIC) Values Corresponding to the Combined Use of Pyrvinium Pamoate and Azoles Against *Candida* Spp.

Species	No.	MIC ($\mu\text{g/mL}$) ^a								
		Agent alone					Combination ^b			
		PP	ITC	VOR	POS	FLU	PP/ITC	PP/VOR	PP/POS	PP/FLU
<i>C. albicans</i>	77979	4	0.25	0.5	I	2	0.25/0.25(I.063,I)	0.5/0.03I(0.187,S)	0.5/0.25(0.375,S)	0.5/0.5 (0.375, S)
	7714	4	0.5	<0.03I	0.5	2	0.5/0.125 (0.375,S)	0.25/<0.03I(1.063,I)	0.5/0.125 (0.375,S)	I/0.25 (0.375,S)
	80128	4	0.5	0.25	0.5	2	0.25/0.25(0.563,I)	0.25/0.03I(0.187,S)	I/0.125(0.500,S)	0.25/0.25(0.188,S)
	79432	4	0.5	<0.03I	0.25	2	0.25/0.25(0.563,I)	0.25/<0.03I(1.063,I)	0.25/0.25(I.063,I)	0.5/0.25(0.250,S)
	79665	4	0.25	0.125	0.5	0.25	4/0.125(I.500,I)	0.5/0.03I(0.373,S)	0.5/0.125(0.375,S)	0.25/0.25(I.063,I)
<i>C. parapsilosis</i>	22019	2	0.5	<0.03I	0.5	2	I/0.25(I.000,I)	0.25/<0.03I(1.125,I)	0.25/0.25(0.625,I)	0.25/2(I.125,I)
	78022	2	0.5	I	I	16	0.25/0.5(I.125,I)	0.25/I(1.125,I)	0.25/I(1.125,I)	0.25/16(I.125,I)
<i>C. tropicalis</i>	77437	8	0.125	0.25	0.25	0.25	4/0.03I(0.748,I)	I/0.03I(0.249,S)	2/0.03I(0.374,S)	4/I(4.500,A)
	79589	16	0.5	0.063	0.5	4	8/0.25(I.000,I)	4/0.5(8.187,A)	8/0.125(0.750,I)	0.25/I(0.266,S)
<i>C. glabrata</i>	00279	>32	2	I	I	16	0.5/2(I.016,I)	0.5/I(1.016,I)	0.5/I(1.016,I)	0.5/16(I.016,I)
	80397	4	0.125	<0.03I	0.25	0.5	0.25/0.063(0.567,I)	0.25/<0.03I(1.063,I)	I/0.063(0.502,S)	0.25/0.5(I.063,I)
<i>C. Auris</i> ^c	381	8	0.125	0.125	0.125	—	0.5/0.125(I.063,I)	0.5/0.125(I.063,I)	0.5/0.125(I.063,I)	—
	382	8	I	0.5	0.5	—	2/0.25(0.500,S)	2/0.125 (0.500,S)	I/0.125(0.375,S)	—
	383	16	I	4	2	—	2/0.125(0.250,S)	I/0.5(0.188,S)	I/0.125(0.125,S)	—
	384	16	0.5	2	I	—	I/0.25(0.563,I)	I/0.125(0.125,S)	2/0.125(0.250,S)	—
	385	8	2	8	I	—	2/0.25(0.375,S)	I/0.25(0.156,S)	I/0.125(0.250,S)	—
	386	4	0.25	16	0.5	—	2/0.25(I.500,I)	I/8(0.750,I)	I/0.125(0.500,S)	—
	387	4	I	I	I	—	I/0.25(0.500,S)	I/0.125(0.375,S)	I/0.25(0.500,S)	—
	388	8	I	4	0.5	—	4/0.5(I.000,I)	2/2(0.750,I)	2/0.125(0.500,S)	—
	389	4	I	4	0.5	—	2/0.25(0.750,I)	0.5/4(I.250,I)	I/0.125(0.500,S)	—
	390	4	I	2	0.5	—	2/0.125(0.625,I)	0.5/2(I.125,I)	I/0.125(0.500,S)	—

Notes: ^aThe MIC indicates the drug concentration suppressing growth by 50% relative to control treatment. ^bFractional inhibitory concentration index (FICI) values are provided in parentheses. S, synergy (FICI \leq 0.5); I, indifference (0.5 < FICI < 4); A, antagonism (FICI \geq 4). ^c*C. Auris* has natural resistance to FLU, so PP combined with FLU was not detected.

Table 2 Observed in Vitro Drug Interactions

Species(n)	n (%) of Isolates Showing Synergism for the Combination			
	PP/ITC	PP/VOR	PP/POS	PP/FLU
<i>C.albicans</i> (5)	1 (20%)	3 (60%)	4 (80%)	4 (80%)
<i>C.parapsilosis</i> (2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<i>C.tropicalis</i> (2)	0 (0%)	1 (50%)	1 (50%)	1 (50%)
<i>C.glabrata</i> (2)	0 (0%)	0 (0%)	1 (50%)	0 (0%)
<i>C. auris</i> (10)	4 (40%)	5 (50%)	9 (90%)	–
Total (21)	5 (24%)	9 (43%)	15 (71%)	5 (45%)

compared to controls.¹⁵ Recent data have also provided support to a model of adaptive aneuploidy in which *C. albicans* azole resistance has been tied to aneuploidy impacting the two left arms of chromosome 5.¹⁶ The stress associated with antifungal treatment has the potential to induce such aneuploidy, in turn enabling these fungi to better resist these antimicrobial agents.¹⁷ Genomic analyses have shown that many conserved orthologous antifungal resistance-related genes are present in both *C. auris* and *C. albicans*, and aneuploid *C. auris* isolates were recently documented to proliferate when exposed to azole stress. This suggests an important role for aneuploidy in shaping the antifungal resistance of *C. auris*.¹⁸

One prior study found that PP was able to effectively inhibit the ability of FLU-resistant *C. albicans* strain I(5L), which harbors two left chromosome 5 copies, to grow. PP was also able to enhance the antifungal effects of FLU when used to treat these fungi, suggesting that PP is a robust tool that can help overcome azole resistance resulting from aneuploidy.^{9,16} These results suggested that PP may also be able to more broadly enhance the antifungal potency of a range of agents, potentially via overcoming aneuploidy-associated changes in the characteristics of *C. auris*. Here, the synergistic antifungal impacts of PP and azoles were more robust when used to treat *C. auris* and *C. albicans* relative to other *Candida spp.*, likely due to the higher odds of aneuploidy occurring in *C. albicans* and *C. auris*. Another potential mechanism that may underlie this synergistic activity may be the multifaceted metabolic effects of PP when used to treat *C. auris*, limiting iron availability to these pathogens while enhancing the nutritional status and functionality of immune cells. This induction of metabolic dysfunction can compromise the ability of these fungi to utilize macronutrients, thereby impairing their growth and viability.¹⁹

In summary, these findings indicate that PP may represent an effective treatment option for *C. auris* as it can overcome azole resistance. One limitation of this analysis, however, is that the number of clinical *Candida spp.* isolates used herein was relatively limited. Subsequent studies will necessitate the more comprehensive profiling of the combined effects of PP and azoles against a wider range of isolates with various genotypic and phenotypic characteristics to better understand the mechanistic basis for their synergistic activity and their potential for clinical application.

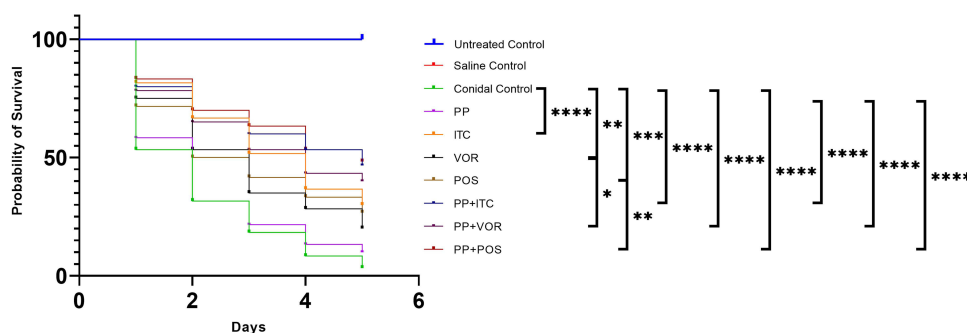


Figure 1 *C. auris* AR385-infected larval survival was monitored for different treatment groups (**** $P < 0.0001$, *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$).

Note: The curves were consisted of untouched growth control group, sterile saline group, yeast cells only group, PP treated group, ITC treated group, POS treated group, VRC treated group, PP with ITC treated group, PP with POS treated group, and PP with VRC treated group.

Conclusion

Combining PP with azoles represents a promising approach to effectively disrupting the growth of azole-resistant *C. auris* and other *Candida spp.* such that it may be a promising anti-*Candida* therapeutic option.

Ethical Approval

This study was approved by the ethics committee of Jingzhou Hospital Affiliated to Yangtze University [approval no. 2024-167-01]. We certify that the study was performed in accordance with the 1964 declaration of HELSINKI and later amendments.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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