

Aprepitant, an antiemetic agent, interferes with metal ion homeostasis of *Candida auris* and displays potent synergistic interactions with azole drugs

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Supplementary Table S1. List of strains used in this study

Fungal Strains	Source	Description
<i>C. auris</i> 381	CDC	Drug sensitive isolate
<i>C. auris</i> 382	CDC	Drug sensitive isolate
<i>C. auris</i> 383	CDC	Clinical isolate exhibiting resistance to fluconazole
<i>C. auris</i> 384	CDC	Clinical isolate exhibiting resistance to fluconazole and Voriconazole
<i>C. auris</i> 385	CDC	Resistant to fluconazole, itraconazole, voriconazole, and amphotericin B
<i>C. auris</i> 386	CDC	Resistant to fluconazole, voriconazole, and amphotericin B
<i>C. auris</i> 387	CDC	Drug sensitive isolate
<i>C. auris</i> 388	CDC	Resistant to fluconazole, itraconazole, voriconazole, and amphotericin B- overexpression of <i>CDR1</i>
<i>C. auris</i> 389	CDC	Resistant to fluconazole, itraconazole, voriconazole, and amphotericin B- overexpression of <i>CDR1</i>
<i>C. auris</i> 390	CDC	Resistant to fluconazole, itraconazole, and amphotericin B- overexpression of <i>MDR1</i> and <i>CDR1</i>
<i>C. albicans</i> SC5314	ATCC	Wild-type strain
<i>C. albicans</i> ATCC MYA-573	ATCC	Fluconazole-resistant bloodstream isolate (from an AIDS patient in Germany)
<i>C. albicans</i> TWO7241	Professor Theodore White (University of Missouri-Kansas City)	Fluconazole-resistant clinical isolate that has increased efflux activity (<i>MDR1</i> overexpression) and overexpression of the azole target (<i>ERG11</i>)
<i>C. albicans</i> TWO7243		Fluconazole- and itraconazole-resistant clinical isolate that has increased mRNA levels of <i>CDR1</i> , <i>MDR1</i> , and <i>ERG11</i>
<i>C. glabrata</i> ATCC-66032	ATCC	Not available
<i>C. glabrata</i> ATCC-64677	ATCC	Not available
<i>C. glabrata</i> ATCC-15126	ATCC	Not available
<i>C. krusei</i> CAB39-6420	Bei Resources	Human blood isolate
<i>C. krusei</i> ATCC-14243	ATCC	Not available
<i>C. krusei</i> ATCC-34135	ATCC	Clinical specimen isolated in Minnesota, USA
<i>C. tropicalis</i> ATCC-13803	ATCC	Not available
<i>C. tropicalis</i> ATCC-1369	ATCC	Not available
<i>C. parapsilosis</i> ATCC-22019	ATCC	Clinical specimen isolated in Puerto Rico
<i>C. parapsilosis</i> CAB50-2638	Bei Resources	Human blood isolate

Supplementary Table S2. List of primers

Gene name	Primer	
<i>ACT1</i>	Forward	GAAGGAGATCACTGCTTTAGCC
	Reverse	GAGCCACCAATCCACACAG
<i>FTR1</i>	Forward	GTCAACTGCTGCAATCCTGA
	Reverse	TTCTTGCAGAATGGCAAGTG
<i>CTR1</i>	Forward	TACTATGGATCACGCCACA
	Reverse	CACATGTTTCATGCCATCAT
<i>ZTR2</i>	Forward	TGTTGGTCAGGTTGTGCAAT
	Reverse	AGAAACACCAACCAGGCAAC
<i>ERG2</i>	Forward	CTTTGACGACTGGGTGTTCA
	Reverse	CCACAGAAGTGCCGAAAAA
<i>ERG10</i>	Forward	CTCGGAAACCAACACCAAAG
	Reverse	TCAAGGGCACCAGAGGTAAG
<i>ERG1</i>	Forward	CCGTGCTCATTTACCAGACA
	Reverse	AGGGCAACACCTCATCTCTC

Supplementary Table S3. Effect of aprepitant on the antifungal activity of itraconazole (ITC) against clinically relevant *Candida* species.

Isolates	MIC ($\mu\text{g/mL}$)				ΣFICI^*	Interaction
	Aprepitant		ITC			
	Alone	Combined	Alone	Combined		
<i>C. albicans</i> SC-5314	> 128	8	0.25	0.0156	0.13	SYN
<i>C. albicans</i> ATCC-MYA 573	> 128	8	1	0.25	0.31	SYN
<i>C. albicans</i> TWO743	> 128	8	1	0.25	0.31	SYN
<i>C. albicans</i> TWO741	> 128	8	0.5	0.0625	0.19	SYN
<i>C. glabrata</i> ATCC-64677	> 128	2	0.5	0.5	1.02	IND
<i>C. glabrata</i> ATCC-15126	> 128	2	0.25	0.25	1.02	IND
<i>C. glabrata</i> ATCC-66032	> 128	2	0.5	0.5	1.02	IND
<i>C. krusei</i> CAB 396420	> 128	8	0.5	0.0625	0.187	SYN
<i>C. krusei</i> ATCC-14243	> 128	8	0.25	0.015	0.13	SYN
<i>C. krusei</i> ATCC-34135	> 128	8	0.5	0.062	0.19	SYN
<i>C. tropicalis</i> ATCC-13803	> 128	8	0.25	0.062	0.31	SYN
<i>C. tropicalis</i> ATCC-1369	> 128	2	0.5	0.031	0.08	SYN
<i>C. parapsilosis</i> ATCC-22019	> 128	8	0.25	0.062	0.31	SYN
<i>C. parapsilosis</i> CAB-502638	> 128	8	0.25	0.062	0.31	SYN

* ΣFICI (fractional inhibitory concentration index) is used to measure the interaction between the tested combinations. ΣFICI interpretation corresponded to the following definitions: synergism (SYN), $\Sigma\text{FICI} \leq 0.5$; additivity (ADD), $\Sigma\text{FICI} > 0.5$ and ≤ 1 ; and indifference (IND), $\Sigma\text{FICI} > 1$ and ≤ 4 .

Supplementary Table S4 - Significantly upregulated GO terms in APR/ITC treatment group

Category	GOID	Description	Gene Ratio	BgRatio	P value	Padj	Gene ID	Count
CC	GO:0016020	membrane	7/7	466/926	0.00799	0.03197	40025314/40025409/ 40027146/40028243/ 40028953/40029187/ 40029690	7

Supplementary Table S5- Significantly downregulated GO terms in APR/ITC treatment group

Category	GOID	Description	Gene Ratio	BgRatio	P value	Padj	Gene ID	Count
BP	GO:0030001	Metal ion transport	3/11	22/1815	0.00024	0.00255	40027445/40027663/40028877	3
BP	GO:0055085	Transmembrane transport	7/11	267/1815	0.00027	0.00255	40026939/40027169/40027170/40027445/40027663/40028877/40029413	7
BP	GO:0044765	Single-organism transport	7/11	341/1815	0.00128	0.00693	40026939/40027169/40027170/40027445/40027663/40028877/40029413	7
BP	GO:1902578	Single-organism localization	7/11	348/1815	0.00146	0.00693	40026939/40027169/40027170/40027445/40027663/40028877/40029413	7
BP	GO:0006810	Transport	7/11	397/1815	0.0033	0.00912	40026939/40027169/40027170/40027445/40027663/40028877/40029413	7
BP	GO:0051234	Establishment of localization	7/11	400/1815	0.00346	0.00912	40026939/40027169/40027170/40027445/40027663/40028877/40029413	7
BP	GO:0006812	Cation transport	3/11	55/1815	0.00366	0.00912	40027445/40027663/40028877	3
BP	GO:0051179	Localization	7/11	407/1815	0.00384	0.00912	40026939/40027169/40027170/40027445/40027663/40028877/40029413	7
BP	GO:0006811	Ion transport	3/11	69/1815	0.00697	0.01472	40027445/40027663/40028877	3
BP	GO:0098655	Cation transmembrane transport	2/11	30/1815	0.01325	0.02063	40027445/40027663	2
BP	GO:0098660	Inorganic ion transmembrane transport	2/11	30/1815	0.01325	0.02063	40027445/40027663	2
BP	GO:0098662	Inorganic cation transmembrane transport	2/11	30/1815	0.01325	0.02063	40027445/40027663	2

BP	GO:0034220	Ion transmembrane transport	2/11	31/1815	0.01411	0.02063	40027445/40027663	2
CC	GO:0044425	Membrane part	6/7	304/926	0.00612	0.03265	40026939/40027169/40027170/40027445/40027663/40029413	6
CC	GO:0016020	Membrane (n=7)	7/7	466/926	0.00799	0.03265	40026939/40027169/40027170/40027445/40027663/40028877/40029413	7
CC	GO:0016021	Integral component of membrane	5/7	239/926	0.01451	0.03265	40026939/40027169/40027170/40027663/40029413	5
CC	GO:0031224	Intrinsic component of membrane	5/7	239/926	0.01451	0.03265	40026939/40027169/40027170/40027663/40029413	5
MF	GO:0022857	Transmembrane transporter activity	7/12	153/2359	2.54E-06	4.68E-05	40026939/40027169/40027170/40027445/40027663/40028877/40029413	7
MF	GO:0005215	Transporter activity	7/12	161/2359	3.60E-06	4.68E-05	40026939/40027169/40027170/40027445/40027663/40028877/40029413	7
MF	GO:0046873	Metal ion transmembrane transporter activity	3/12	20/2359	0.00011	0.00095	40027445/40027663/40028877	3
MF	GO:0022890	Inorganic cation transmembrane transporter activity	3/12	44/2359	0.00119	0.0077	40027445/40027663/40028877	3
MF	GO:0008324	Cation transmembrane transporter activity	3/12	49/2359	0.00162	0.00845	40027445/40027663/40028877	3
MF	GO:0015075	Ion transmembrane transporter activity	3/12	58/2359	0.00265	0.01086	40027445/40027663/40028877	3
MF	GO:0022891	Substrate-specific transmembrane transporter activity	3/12	60/2359	0.00292	0.01086	40027445/40027663/40028877	3
MF	GO:0022892	Substrate-specific transporter activity	3/12	66/2359	0.00384	0.01249	40027445/40027663/40028877	3