Proanthocyanidin polymeric tannins from *Stryphnodendron adstringens* are effective against *Candida* spp. isolates and treat vaginal candidiasis

FREITAS, A. L. D.^{1*}; KAPLUM, V.²; ROSSI, D. C. P.¹; SILVA, L. B. R.³; TABORDA, C. P.^{1,3}; MELLO, J. C. P.⁴; NAKAMURA, C. V.²; ISHIDA K.¹

*Email : alineludfreitas@gmail.com

¹Instituto de Ciências Biomédicas, Universidade de São Paulo (USP), SP/Brazil; ²Departamento de Ciências Básicas da Saúde, Universidade Estadual de Maringá (UEM), PR/Brazil; ³Laboratory of Medical Mycology, Tropical Medicine Institute, USP, Brazil; ⁴Departamento de Farmácia, UEM, PR/Brazil.

INTRODUCTION

Stryphnodendron adstringens, the Brazilian plant popularly used as cicatrizing and anti-inflammatory agent, has been studied in order to determine its antifungal potential. In this study, the antifungal activity of proanthocyanidin polymeric tannins from the *S. adstringens* stem bark (presents into the fraction F2 and semi-purified subfraction F2.4) was evaluated against planktonic cells, biofilm sessile cells and biofilm dispersion cells from *Candida albicans* and *Candida non-albicans* (CNA), including fluconazole-resistant isolates. In order to determine *in vivo* activity, we tested the efficacy of a gel formulation containing hexameric tannins of proanthocyanidins (F2 fraction) in the control of vaginal candidiasis in murine model.

METHODS

FIGURE 1. Scheme of *in vitro* experiments.

FIGURE 2. Scheme of antifungal activity evaluation on murine model.

RESULTS

TABLE 1. Antifungal effect of fraction F2 and subfraction F2.4 on planktonic cells and dispersion cells of *Candida* spp. isolates (S: susceptible; R: Resistant; SDD: susceptible dose-dependent), compared with standard antifungals (amphotericin B - AMB, miconazole - MCZ and fluconazole - FCZ). PMIC₉₀ and DMIC₉₀ values are the lowest concentrations that inhibited 90% of fungal growth of planktonic and dispersion cells, respectively. Values are displayed in mg/L.

Species	Isolates	F2		F2.4		AMB		MCZ		FCZ	
		PMIC ₉₀	DMIC ₉₀	PMIC ₉₀	DMIC ₉₀	PMIC ₉₀	DMIC ₉₀	PMIC ₉₀	DMIC ₉₀	PMIC ₉₀	DMIC ₉₀
<i>C. glabrata</i>	ATCC 2011 ^{SDD}	7.81	0.48	3.91	0.48	0.25	0.13	>16	0.02	16	2
	IAL-23 ^R	3.91	0.48	1.95	0.48	0.25	0.25	0.03	0.02	32	2
<i>C. albicans</i>	SC-5314 ^S	62.5	1.95	31.25	0.98	0.25	0.5	0.02	0.13	0.5	1
	IAL-40 ^R	7.81	0.49	7.81	0.48	0.25	0.25	8	1	>128	64
<i>C. parapsilosis</i>	ATCC 22019 ^S	15.63	15.63	7.81	7.81	0.25	0.06	2	2	4	8
	IAL-15 ^R	3.91	15.63	3.91	3.91	0.5	0.25	8	4	32	32
<i>C. tropicalis</i>	ATCC 200956 ^R	7.81	3.91	1.95	0.98	>16	8	>16	2	>128	>128
	IAL-01 ^S	250	31.25	250	31.25	0.5	1	0,5	1	2	1

FIGURE 3. Vaginal fungal burden (CFU/g) in female BALB/c mice infected with *Candida albicans* ATCC 10231 (A) or *Candida glabrata* ATCC 2001 (B), and then treated with one of the following therapeutic regimens (1) intravaginal gel formulation containing 2.5% or 5% of fraction F2 from *Stryphnodendron adstringens* stem bark for 7 consecutive days; (2) vaginal cream of 2% miconazole (MCZ); (3) oral fluconazole (20 mg/kg) in the first and fourth days after infection (FCZ); or a combination of (1) and (3) [F2 (5%) + FCZ] (n = 6-10 animals/group). *p<0.05 and ***p<0.001

❖ Histopathological analysis showed that the treatment with the vaginal gel containing 5% F2 reduced the fungal burden in the vaginal tissue and vaginal canal of infected animals and caused no histological alterations on the uninfected vaginal mucosa.

CONCLUSION

Our data suggest that the inhibitory effects of both F2 and F2.4 could be important to control the dissemination and re-infection by dispersion cells from *Candida* spp. biofilms. Furthermore, it was seen that these hexameric tannins of proanthocyanidins have potential use in the treatment of vaginal candidiasis once that they were efficient to control the fungal infection by *C. albicans* and *C. glabrata* using murine model of vaginal candidiasis with no noticeable toxicity to vaginal tissue.

REFERENCES

DE FREITAS, A. L. D. et al. Proanthocyanidin polymeric tannins from *Stryphnodendron adstringens* are effective against *Candida* spp. isolates and for vaginal candidiasis treatment. *Journal of Ethnopharmacology*, 216:184-190, 2018.