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In Vitro Antifungal Susceptibility of *Cladophialophora carrionii*, an Agent of Human Chromoblastomycosis

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A global collection of *Cladophialophora carrionii* strains ($n = 81$) was tested against nine antifungal drugs. MIC_{90}s of all strains were as follows in increasing order: itraconazole and posaconazole, 0.063 μg/ml; terbinafine, 0.125 μg/ml; isavuconazole and voriconazole, 0.25 μg/ml; caspofungin, 2 μg/ml; micafungin, 4 μg/ml; amphotericin B, 8 μg/ml; and fluconazole, 64 μg/ml.

Chromoblastomycosis is a chronic, progressive, polymorphic implantation mycosis. Lesions are limited to cutaneous and subcutaneous tissues, causing hyperproliferation leading to verrucous or nodular clinical features (1–3). Two genera of melanized hyphomycetes, *Cladophialophora* and *Fonsecaea*, both belonging to the family *Herpotrichiellaceae* in the order *Chaetothyriales*, are common causes. They have in common that a pathogenic invasive phase is formed in skin with the expression of muriform cells. Occasional cases have been reported due to species of *Phialophora*, *Exophiala*, and *Rhinocladiella*, which also belong to this family (4). The disease is encountered worldwide in subtropical and tropical climate zones, with a clear distinction between the vicarious species of *Cladophialophora* in arid climates and *Fonsecaea* and *Rhinocladiella* in humid, tropical climates (5).

Cladophialophora carrionii is a relatively frequent etiologic agent of chromoblastomycosis in arid and semiarid climate zones of South and Central America (6, 7), Australia (8), and Asia (9, 10). The infection is very difficult to treat. Several therapies have been applied, but there is no standard for treatment (3). Small series of *in vitro* susceptibility studies with itraconazole, voriconazole, and terbinafine have been published showing considerable variation between and within genera and species (11, 12).

The aim of the present study was to determine the susceptibility profiles of a large collection of *C. carrionii* strains to nine antifungal agents, including isavuconazole (13). Isolates were taken from the reference collections of the CBS-KNAW Fungal Biodiversity Centre (CBS, Utrecht, The Netherlands) or the Institute Pasteur (CNRMA/IP, Paris, France). The set comprised isolates from Venezuela ($n = 46$), China ($n = 20$), Madagascar ($n = 9$), and Australia ($n = 6$). Seventy-five clinical isolates originated from patients with chromoblastomycosis, and six environmental isolates were from dry plant debris in Venezuela (Table 1). All strains were identified to the species level by sequencing of the internal transcribed spacer of the ribosomal DNA (rDNA) region and partial translation of the elongation factor 1-α and β-tubulin genes (S. Deng, A. H. G. Gerrits van den Ende, L. Yang, H. Badali, M. J. Najafzadeh, R. Y. Li, C. H. Klaassen, F. Hagen, J. F. Meis, B. Papierok, J. Sun, W. D. Liu, G. S. De Hoog, submitted for publication). *In vitro* activities of nine antifungal agents were determined with the reference guideline M38-A2 (14). Three reference strains, *Paecilomyces variotii* (ATCC 22319), *Candida parapsilosis* (ATCC 22019), and *Candida krusei* (ATCC 6258) were included as quality controls. Kruskal-Wallis and Mann-Whitney U tests were used for comparison of the MICs of all antifungal agents among strains from four groups (Latin America, Asia, Africa, and Australia).

Table 2 summarizes the MIC results in terms of the MIC ranges, geometric mean (GM) MIC, and MIC_{50} and MIC_{90} values of nine antifungal agents for 81 *C. carrionii* strains. All strains had low MICs of itraconazole, voriconazole, posaconazole, isavuconazole, and terbinafine, while the highest MICs were consistently found with fluconazole, amphotericin B, micafungin, and caspofungin. The MIC_{90}s of fluconazole, amphotericin B, micafungin, and caspofungin were 64 μg/ml, 8 μg/ml, 4 μg/ml, and 2 μg/ml, respectively. These data are in agreement with previously reported findings for *Cladophialophora* (11, 15), *Rhinocladiella* (16), and *Fonsecaea* (17). No difference was found in the activities between voriconazole and isavuconazole against *C. carrionii* (MIC range, 0.016 to 1 μg/ml; GM, 0.148/0.136 μg/ml; MIC_{90}, 0.25 μg/ml). The MIC range and MIC_{90} of voriconazole were 2 $\log_2$-dilution steps more active than values found in *C. bantiana* (range, 0.125 to 4 μg/ml; MIC_{90}, 2 μg/ml) (15) and in *Phialophora* and *Cyphellophora* (MIC range, 0.125 to 4 μg/ml; MIC_{90}, 1 μg/ml) (18). Table 3 shows rare *Cladophialophora* species causing (sub)cutaneous disorders but which are related to *Fonsecaea* (19) and to *C. yegresii*, an environmental sibling of *C. carrionii*. The values were in the same range, with the exception of lower MICs of caspofungin and micafungin in the cutaneous species *C. immunda* and *C. saturnica* and of voriconazole in *C. yegresii* and *C. samoensis*.

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TABLE 1 *Cladophialophora* strains used in this study

Species	Accession no.	Source	Origin
Cladophialophora carrionii	CBS 108.97	Chromoblastomycosis, male	Venezuela
	CBS 109.97	Chromoblastomycosis, male	Venezuela
	CBS 164.54	Chromoblastomycosis, male	Venezuela
	CBS 165.54	Chromoblastomycosis, male	Venezuela
	CBS 166.54	Chromoblastomycosis, male	Venezuela
	CBS 986.96	Clinical material	Venezuela
	CBS 857.96	Chromoblastomycosis, male	Venezuela
	CBS 858.96	Chromoblastomycosis, male	Venezuela
	CBS 114392	Chromoblastomycosis, female	Venezuela
	CBS 114393	Chromoblastomycosis, male	Venezuela
	CBS 114394	Chromoblastomycosis, male	Venezuela
	CBS 114395	Chromoblastomycosis, female	Venezuela
	CBS 114397	Chromoblastomycosis, male	Venezuela
	CBS 114398	Chromoblastomycosis, female	Venezuela
	CBS 114399	Chromoblastomycosis, female	Venezuela
	CBS 114400	Chromoblastomycosis, male	Venezuela
	CBS 114401	Chromoblastomycosis, female	Venezuela
	CBS 114402	Chromoblastomycosis, female	Venezuela
	CBS 114403	Chromoblastomycosis, male	Venezuela
	CBS 114404	Chromoblastomycosis, male	Venezuela
	CBS 117889	Chromoblastomycosis, female	Venezuela
	CBS 117890	Chromoblastomycosis, male	Venezuela
	CBS 117891	Chromoblastomycosis, male	Venezuela
	CBS 117892	Chromoblastomycosis, male	Venezuela
	CBS 117893	Chromoblastomycosis, male	Venezuela
	CBS 117895	Chromoblastomycosis, male	Venezuela
	CBS 117896	Chromoblastomycosis, male	Venezuela
	CBS 117897	Chromoblastomycosis, male	Venezuela
	CBS 117898	Chromoblastomycosis, female	Venezuela
	CBS 117899	Chromoblastomycosis, male	Venezuela
	CBS 117900	Chromoblastomycosis, male	Venezuela
	CBS 117901	Chromoblastomycosis, female	Venezuela
	CBS 117902	Chromoblastomycosis, male	Venezuela
	CBS 117903	Chromoblastomycosis, male	Venezuela
	CBS 117904	Chromoblastomycosis, male	Venezuela
	CBS 117905	Chromoblastomycosis, male	Venezuela
	CBS 117906	Chromoblastomycosis, male	Venezuela
	CBS 117908	Chromoblastomycosis, male	Venezuela
	CBS 117909	Chromoblastomycosis, male	Venezuela
	CBS 121844	Chromoblastomycosis, male	Venezuela
	CBS 859.96	Dry plant debris	Venezuela
	CBS 860.96	Dry plant debris	Venezuela
	CBS 861.96	Dry plant debris	Venezuela
	CBS 862.96	Dry plant debris	Venezuela
	CBS 863.96	Dry plant debris	Venezuela
	CBS131736	Soil	Venezuela
	CBS131833	Chromoblastomycosis, male	China
	CBS131834	Chromoblastomycosis, male	China
	CBS131835	Chromoblastomycosis, male	China
	CBS131836	Chromoblastomycosis, male	China
	CBS131838	Chromoblastomycosis, male	China
	CBS131839	Chromoblastomycosis, male	China
	CBS131840	Chromoblastomycosis, male	China
	CBS131841	Chromoblastomycosis, male	China
	CBS131842	Chromoblastomycosis, male	China
	CBS131843	Chromoblastomycosis, male	China
	CBS131844	Chromoblastomycosis, male	China
	CBS131845	Chromoblastomycosis, male	China
	CBS131846	Chromoblastomycosis, male	China
	CBS131847	Chromoblastomycosis, male	China
	CBS131848	Chromoblastomycosis, male	China
	CBS131850	Chromoblastomycosis, male	China
	CBS131851	Chromoblastomycosis, male	China
	CBS132096	Chromoblastomycosis, male	China
	CBS132097	Chromoblastomycosis, male	China
	CBS132100	Chromoblastomycosis, male	China
	CBS131854	Chromoblastomycosis	Madagascar
	CBS131855	Chromoblastomycosis	Madagascar
	CBS131856	Chromoblastomycosis	Madagascar
	CBS131734	Chromoblastomycosis	Madagascar
	CBS131735	Chromoblastomycosis	Madagascar
	CBS131857	Chromoblastomycosis	Madagascar
	CBS 100434	Chromoblastomycosis, male	Madagascar
	CBS 260.83	Chromoblastomycosis, male	Madagascar
	CBS 362.70	Human skin, male	Madagascar
	CBS 160.54	Chromoblastomycosis, male	Australia
	CBS 162.54	Chromoblastomycosis, male	Australia
	CBS 163.54	Chromoblastomycosis, male	Australia
	CBS131852	Unknown	Australia
	CBS131853	Unknown	Australia
	CBS 406.96	Chromoblastomycosis, male	Australia
Cladophialophora yegresii	CBS 114405	Plant, Cactaceae	Venezuela
	CBS 114406	Plant, Cactaceae	Venezuela
	CBS 114407	Plant, Cactaceae	Venezuela

TABLE 2 MIC values of nine antifungal agents against 81 *C. carrionii* strains

Strain (*n*) and drug	MIC (μg/ml)[a]			
	GM	Range	50%	90%
All *C. carrionii* strains (81)				
Amphotericin B	2.643	0.5–8	2	8
Fluconazole	25.04	4–64	32	64
Itraconazole	0.03	0.008–0.125	0.031	0.063
Voriconazole	0.148	0.016–1	0.125	0.25
Posaconazole	0.025	0.016–0.063	0.016	0.063
Isavuconazole	0.136	0.016–1	0.125	0.25
Caspofungin	1.367	0.25–4	2	2
Micafungin	0.296	0.016–8	0.25	4
Terbinafine	0.049	0.008–1	0.031	0.125
C. carrionii, Venezuela (46)				
Amphotericin B	2.767	0.5–8	2	8
Fluconazole	31.07	8–64	32	64
Itraconazole	0.038	0.016–0.125	0.031	0.063
Voriconazole	0.181	0.031–1	0.125	0.25
Posaconazole	0.029	0.016–0.063	0.031	0.063
Isavuconazole	0.168	0.016–1	0.125	0.5
Caspofungin	1.363	0.25–4	1	2
Micafungin	0.206	0.016–8	0.25	0.5
Terbinafine	0.053	0.016–1	0.031	0.125
C. carrionii, China (20)				
Amphotericin B	2.639	0.5–8	4	8
Fluconazole	19.027	8–32	16	32
Itraconazole	0.022	0.016–0.063	0.016	0.031
Voriconazole	0.109	0.016–0.5	0.125	0.25
Posaconazole	0.021	0.016–0.063	0.016	0.031
Isavuconazole	0.092	0.016–0.25	0.125	0.125
Caspofungin	1.625	0.25–4	2	2
Micafungin	0.342	0.063–4	0.25	1
Terbinafine	0.037	0.008–0.125	0.031	0.063
C. carrionii, Madagascar (9)				
Amphotericin B	3.175	1–8	4	4
Fluconazole	18.664	4–64	16	32
Itraconazole	0.023	0.016–0.125	0.016	0.031
Voriconazole	0.116	0.016–0.5	0.125	0.25
Posaconazole	0.02	0.016–0.063	0.016	0.031
Isavuconazole	0.107	0.031–0.5	0.063	0.25
Caspofungin	1.361	0.25–4	1	4
Micafungin	1.47	0.125–8	2	4
Terbinafine	0.053	0.008–0.125	0.063	0.125
C. carrionii, Australia (6)				
Amphotericin B	1.414	0.5–4	NC	NC
Fluconazole	17.96	8–64	NC	NC
Itraconazole	0.02	0.016–0.063	NC	NC
Voriconazole	0.125	0.031–0.5	NC	NC
Posaconazole	0.022	0.016–0.063	NC	NC
Isavuconazole	0.14	0.063–0.5	NC	NC
Caspofungin	0.793	0.5–1	NC	NC
Micafungin	0.281	0.063–4	NC	NC
Terbinafine	0.07	0.016–0.25	NC	NC

[a] GM, geometric mean; 50% and 90%, MIC_{50} and MIC_{90}, respectively; NC, no comparison because there were <9 strains per species available.

The activities of itraconazole and posaconazole against *C. carrionii* were comparable (Table 2) and similar to those of *C. bantiana* and of *Fonsecaea* species (15, 17). *Phialophora* and *Cyphellophora* (18) had responses to posaconazole (MIC_{90}, 0.063 μg/ml) similar to those found in *C. carrionii*, but the itraconazole value was different (MIC_{90}, 0.5 μg/ml). Terbinafine varied considerably in its activity against strains of *C. carrionii* (MIC range of 0.008 to 1 μg/ml). MIC ranges and MIC_{90}s of posaconazole, isavuconazole, voriconazole, and terbinafine showed potent activity against *C. carrionii* (Table 2). Posaconazole was the drug with the best overall *in vitro* activity. The latter also holds true in an animal model of *C. carrionii* infection (20).

For micafungin, most *C. carrionii* isolates from Venezuela had low MICs. The range was 0.016 to 8 μg/ml, the GM was 0.26 μg/ml, and the MIC_{90} was 0.5 μg/ml. Some strains deviated sig-

TABLE 3 MIC values of nine antifungal agents against *C. carrionii* and rare environmental *Cladophialophora* species eventually causing chromoblastomycosis or other types of skin disease

Drug	MIC (μg/ml)[a]							
	C. carrionii ($n = 28$)				*C. samoensis* ($n = 1$)	Range		
	GM	Range	50%	90%		*C. yegresii* ($n = 3$)	*C. immunda* ($n = 6$)	*C. saturnica* ($n = 4$)
Amphotericin B	2.499	0.5–8	2	4	2	0.25–0.5	0.5–4	1–2
Fluconazole	35.33	16–64	32	64	32	16–32	16–32	8–16
Itraconazole	0.039	0.016–0.125	0.031	0.063	0.25	0.25–0.5	0.031–0.25	0.031–0.25
Voriconazole	0.205	0.063–1	0.25	0.5	4	2–2	0.25–1	0.5–1
Posaconazole	0.033	0.016–0.063	0.031	0.063	0.125	0.125–0.125	0.031–0.063	0.031–0.125
Isavuconazole	0.2	0.063–1	0.25	0.5	1	0.125–0.5	0.25–0.5	0.25–0.5
Caspofungin	0.313	0.25–4	1	2	2	1–1	1–2	2–8
Micafungin	0.906	0.125–4	1	2	0.25	0.25–0.25	4–8	4–8
Terbinafine	0.05	0.016–0.25	0.063	0.125	ND	0.063–0.063	ND	ND

[a] GM, geometric mean; 50% and 90%, MIC_{50} and MIC_{90}, respectively; ND, not determined. Note that for *C. immunda* ($n = 6$) and *C. saturnica* ($n = 4$), only eight antifungal agents were tested.

nificantly (Table 2), and all nine strains from Madagascar had 3 log_2-dilution-step-higher MICs than the majority of Venezuelan strains (range, 0.125 to 8 μg/ml; GM, 1.47 μg/ml; MIC_{90}, 4 μg/ml) ($P < 0.01$). The activities against Chinese and Australian strains were intermediate. For amphotericin B, the MIC range (0.5 to 8 μg/ml) and MIC_{90} (8 μg/ml) were much higher than those of *C. bantiana* (MIC range, 0.125 to 2 μg/ml; MIC_{90}, 1 μg/ml) (15) and *Fonsecaea* (MIC range, 0.5 to 2 μg/ml; MIC_{90}, 2 μg/ml) (17) and confirmed the results from a recent study (11).

The 81 investigated isolates of *C. carrionii* represented a worldwide collection from four continents: South America ($n = 46$), Asia ($n = 20$), Africa ($n = 9$), and Australia ($n = 6$). In a molecular phylogenetic analysis (Deng et al., submitted), three main populations were recognizable: an Asian group, a South American group, and a variable African/Australian group. The susceptibility against itraconazole, voriconazole, posaconazole, isavuconazole for the Latin American group was less than that of remaining groups ($P < 0.05$), and micafungin was active against most strains from Venezuela (GM, 0.206 μg/ml; MIC_{90}, 0.5 μg/ml), but inactive for strains from Madagascar (GM, 1.47 μg/ml; MIC_{90}, 4 μg/ml) and some scattered isolates from other continents. There was a significant difference ($P < 0.01$) in the MICs of micafungin between Madagascar and Venezuelan strains, but the activity of terbinafine among these three groups showed no difference ($P > 0.05$).

These results suggest that *C. carrionii*, the etiologic agent of chromoblastomycosis in arid climates, is particularly susceptible *in vitro* to the newer azoles and terbinafine, but resistant to amphotericin B, fluconazole, and caspofungin. This profile is similar to that of melanized fungi studied previously (12, 16, 17). The results for micafungin are variable because all strains from Madagascar and some from other continents deviate significantly from the remaining strains. In general, these *in vitro* data still need to be verified by clinical studies.

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