

The in vitro Activity of Echinocandins Against Clinical *Trichophyton rubrum* Isolates and Review of the Susceptibility of *T. rubrum* to Echinocandins Worldwide

Huilin Su^{1-3,*}, Weiwei Jiang^{4,*}, Paul E Verweij^{3,5}, Li Li², Junhao Zhu², Jiande Han¹, Min Zhu², Shuwen Deng⁶

¹Department of Dermatology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, People's Republic of China; ²Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, People's Republic of China; ³Department of Medical Microbiology and Center of Expertise in Mycology, Radboud University Medical Center, Nijmegen, the Netherlands; ⁴Department of Dermatology, Hospital affiliated to the 72nd Army of Chinese PLA, Huzhou, People's Republic of China; ⁵Department of Medical Microbiology and Center of Expertise in Mycology, CWZ Hospital, Nijmegen, the Netherlands; ⁶Department of Medical Microbiology, The People's Hospital of SND, Suzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shuwen Deng, Department of Medical Microbiology, The People's Hospital of SND, Suzhou, People's Republic of China, Email shuwen.deng@gmail.com; Min Zhu, Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, People's Republic of China, Email juneminmyco@126.com

Introduction: The emergence of resistance in *Trichophyton rubrum* to azoles and terbinafine has become increasingly evident in recent years, necessitating the development of novel antifungal drugs and the exploration of new indications for existing agents.

Methods: In this study, we retrospectively evaluated the in vitro antifungal activity of 3 echinocandins (anidulafungin, caspofungin, and micafungin) against 73 clinical isolates of *T. rubrum* collected from a teaching hospital in Shanghai, China, using EUCAST E.DEF 9.3.1 with minor modification. We also reviewed the susceptibility of *T. rubrum* to echinocandins globally by literature searching.

Results: Our findings revealed that micafungin exhibited the lowest modal minimum effective concentration (MEC) value (0.08 mg/L, $n = 28$) and the lowest geometric mean (GM) MEC value (0.014 mg/L) among the 73 isolates of *T. rubrum* tested, followed by anidulafungin with a modal MEC value of 0.016 mg/L ($n = 67$) and a GM of 0.018 mg/L. Caspofungin displayed a higher modal MEC value of 0.5 mg/L ($n = 35$) and a GM of 0.308 mg/L. Despite variations in methodologies, similar results were obtained from the review of five relevant studies included in our analysis.

Discussion: Echinocandins exhibited excellent in vitro activity against *T. rubrum* isolates, with micafungin and anidulafungin demonstrating greater potency than caspofungin. These findings suggest that echinocandins could be considered as potential treatment options for managing recalcitrant dermatophytoses resulting from the emergence of resistance. However, it is important to note that the clinical efficacy of these in vitro findings has yet to be established and warrants further investigation.

Keywords: echinocandins, *Trichophyton rubrum*, antifungal activity, review

Introduction

Dermatophytosis is a prevalent superficial fungal infection primarily affecting keratinized tissues, including the skin, hair, and nails, with a remarkably high incidence rate of 20–25%.¹ Dermatophyte species are the most common causative agents of dermatophytosis. Of the more than 40 dermatophyte species infecting humans, *Trichophyton rubrum* is the most common species,² although there has been a rise in infections caused by the *Trichophyton indotineae* in *Trichophyton mentagrophytes*/*Trichophyton interdigitale* complex in India.^{3,4} Generally, dermatophytosis is easily cured with a wide range of topical and oral antifungal drugs. Azoles and allylamines are the primary recommended topical and systemic agents for treating *T. rubrum* infections. Terbinafine, renowned for its clinical efficacy, is the most commonly prescribed

drug against *Trichophyton* species due to its fungicidal properties.⁵ However, since the first reported case of *T. rubrum* resistance to terbinafine in 2003,⁶ reports of *T. rubrum* resistance to antifungal agents have been increasing in the Americas, Europe, and Asia.^{7–9} Several studies have demonstrated that *T. rubrum* can develop resistance to terbinafine, azoles, and amorolfine after prolonged exposure to sub-inhibitory concentrations of these drugs.^{6–12} An epidemiological study conducted in India reported a remarkably high frequency of terbinafine-resistant *T. rubrum* strains, reaching 44% (8 out of 18 isolates).¹³ A review encompassing 26 global studies on *T. rubrum* susceptibility revealed that 15 studies (57.69%) exhibited a terbinafine geometric mean above 0.03 mg/L (the epidemiological cut-off value), indicating the presence of non-wildtype *T. rubrum* strains with potential pandemic characteristics.¹⁴ In India, *T. indotineae* in *T. mentagrophytes*/*T. interdigitale* complex replaces *T. rubrum* as the most common skin infection in the last decade.¹⁵ Notably, the highest resistance rates of the *T. indotineae* have been observed in northern India, with a terbinafine resistance rate of 76% (MIC ≥ 0.5 mg/L).¹³ *T. indotineae* appears to be spreading towards Europe and other Asian countries.¹⁵ Therefore, the development of new antifungal drug classes is crucial in overcoming the existing and future challenges in managing dermatophyte infections.

Echinocandins are lipopeptides derived from the fermentation broths of various fungi, which have been synthetically modified. These compounds act by inhibiting the synthesis of cell wall β -1,3-glucan.¹⁶ Echinocandins have been approved for invasive aspergillosis and candidiasis. Echinocandins generally exhibit fungistatic and fungicidal activities against *Aspergillus* and *Candida* species, respectively.^{17,18} Echinocandins have also shown in vitro activity against dermatophytes but reports on clinical use are lacking;¹⁹ however, the data on the antifungal efficacy of echinocandins to dermatophytes in vitro are limited.^{19–23} In this study, we aimed to evaluate the potency of echinocandins (anidulafungin, caspofungin and micafungin) against a large set of clinical *T. rubrum* isolates collected from China and review the existing literature on in vitro susceptibility of echinocandins against clinical isolates of *T. rubrum* worldwide.

Materials and Methods

T. rubrum Isolates and Identification

A total of 73 clinical isolates of *Trichophyton rubrum* were collected from patients diagnosed with dermatophytosis between 2014 and 2018 at Huashan Hospital, Fudan University in Shanghai, China. The diagnosis of dermatophytosis was established through a combination of clinical presentation and mycological examination:²⁴ (a) the presence of skin lesions indicative of dermatophytosis; (b) positive direct microscopy demonstrating the presence of hyphae in the specimen; and (c) positive culture of dermatophytes.

The 73 clinical *T. rubrum* isolates were identified using morphological features and subsequently confirmed by sequencing the ITS gene as described previously.²⁵ Isolates information and GenBank accession numbers for the generated ITS sequences of the 73 *T. rubrum* isolates are listed in [Table S1](#).

Antifungal Susceptibility Testing

In vitro antifungal susceptibility testing of the 73 isolates of *T. rubrum* was performed according to the EUCAST E.DEF 9.3.1 (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Files/EUCAST_E_Def_9_3_1_Mould_testing_definitive.pdf) and adjusted part of the parameters for dermatophytes. The isolates were subcultured on potato dextrose agar and incubated at 28°C for 7 days or longer to sporulate sufficiently. Cover colonies with sterile water supplemented with 0.1% Tween-20. Then, the culture was gently swabbed with a cotton tip and the conidia are transferred with a pipette to a sterile tube. After vortexed, the suspension was counted with a haemocytometer chamber and checked the no presence of hyphae. If a significant number of hyphae is detected, transfer the suspension to the filter to remove hyphae and yield a suspension composed of conidia. The suspension is then diluted with sterile distilled water to obtain a final working inoculum of $2\text{--}5 \times 10^5$ CFU/mL. Anidulafungin and caspofungin were purchased from Sigma-Aldrich (MO, USA). Micafungin was bought from Toronto Research Chemicals (Toronto, Canada). The testing range for micafungin was 0.002 to 2 mg/L; for anidulafungin and caspofungin were both 0.016 to 16 mg/L. Vortex the inoculum suspension and inoculate each well of a microdilution plate with 100 μ L of the conidial suspension. Panels were incubated at 28°C for 4–5 days. MECs were first read at 4 days incubation. The final results were determined when the control well got sufficient growth. The MEC denotes the lowest echinocandin concentration at which the fungus displayed growth

retardation and/or microscopic morphological changes in contrast to the control well. There are no clinical breakpoints available for all these drugs yet. *Candida parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were used as the quality control strains. The original antifungal susceptibility testing data are listed in [Table S1](#).

Literature Review

Literature searching was carried out in databases including PubMed, Scopus, and Web of Science. We retrieved the papers using the terms “(Trichophyton rubrum) AND (echinocandins OR anidulafungin OR caspofungin OR micafungin)” in the title and abstract.

Results

[Table 1](#) lists the MEC ranges, geometric mean (GM), modal MEC, and MEC distribution of three echinocandins against 73 clinical *T. rubrum* isolates tested in this study. [Figure 1](#) shows the modal MEC and MEC distribution of three echinocandins against 73 clinical *T. rubrum* isolates tested in this study. The MEC ranges of micafungin, anidulafungin and caspofungin were 0.002–0.063 mg/L, 0.016–0.063 mg/L and 0.031–1 mg/L, respectively. Micafungin had the lowest modal MEC (0.008mg/L, n = 28) and MECs geometric mean (GM) (0.014 mg/L), followed by anidulafungin (modal MEC 0.016mg/L, n = 67, GM 0.018 mg/L) and caspofungin (modal MEC 0.5mg/L, n = 35, GM 0.308 mg/L) against all *T. rubrum* isolates tested.

The literature review resulted in 5 publications reporting the susceptibility of *T. rubrum* to echinocandins worldwide from 2013 to 2022^{19–23} ([Table 2](#), [Figure 2](#)). [Table 2](#) summarizes the susceptibility data of *T. rubrum* isolates to echinocandins based on the 5 publications and the results of our study. Of all 6 studies, our study included the largest set of *T. rubrum* isolates (73 isolates) and 3 echinocandins (micafungin, anidulafungin, caspofungin), the rest of the studies tested sample sets varying from 7 to 43 isolates of *T. rubrum*, and 4 literatures involved only two echinocandins. The methods used in all 6 studies included Clinical and Laboratory Standards Institute (CLSI) M38-A2, European Committee on Antimicrobial Susceptibility Testing (EUCAST), modified EUCAST, and E-Test. The culture mediums for *T. rubrum* were mainly potato dextrose agar (PDA) and oatmeal agar (OA). Only the modified method in Rissleger’s study used Sabouraud –2% glucose agar (SAB) to get fragmented mycelium for inoculum preparation. The incubation temperature was 28°C in Aktas’s study using the E-test method.²⁰ Similarly, in our study, we utilized the modified EUCAST method and maintained the incubation temperature at 28°C. Rissleger’s study adopted a slightly higher temperature of 30°C while using the modified EUCAST method.²² In the remaining studies, the incubation temperature was set at 35°C. The incubation period varied from 2 to 9 days.

Caspofungin is the most common echinocandin tested for the activity against *T. rubrum* in all 6 studies. MEC ranges and GM, MEC₉₀ values are variable in different studies, with the highest MEC range (1–8mg/L) in Badali et al’s study and the lowest MEC range (0.008–0.032mg/L) in Baghi et al’s study ([Table 2](#), [Figure 2](#)).^{21,23}

Micafungin exhibited the lowest MEC value with MIC value relatively consistent (GM varying from 0.010 to 0.034 mg/L, MIC₉₀ from 0.016 to 0.06mg/L) among 4 studies in which Micafungin was included ([Table 2](#), [Figure 2](#)).

Only 3 studies reported the activity of anidulafungin against *T. rubrum*. Generally, anidulafungin exhibited a similar MEC range (0.008–0.063mg/L) among 3 studies although small samples were tested in studies by Badali et al and Rissleger et al.^{21,22} However, there are two diluted steps difference for MIC₉₀ value (0.016mg/L) of anidulafungin against *T. rubrum* in our results compared to those in the other two studies (MIC₉₀, 0.063mg/L) ([Table 2](#), [Figure 2](#)).

Discussion

Echinocandins are a class of antifungal drugs with milder side effects compared to polyenes and azoles, since these agents only inhibit the fungal-specific metabolic pathway— β -(1,3)-glucan biosynthesis.²⁶ Caspofungin acetate was the first synthesized echinocandin and then approved for clinical use by the US Food and Drug Administration (FDA) in 2001, followed by micafungin in 2005 and anidulafungin in 2006. Because of the good drug safety, echinocandins were even approved for the treatment of children over 3 months of age and there is no need to adjust the dose in renal or hepatic insufficient patients.²⁷ The FDA has approved the indications of echinocandins in the empirical treatment of febrile neutropenia, *Candida* infections, invasive aspergillosis in refractory patients, or intolerant to other therapies.

Table 1 MEC Ranges, GM, Modal MEC, and MEC Distribution of 3 Echinocandins Against 73 Clinical *T. rubrum* Isolates from China

Antifungal Agent	MEC Range (mg/L)	GM (mg/L)	MEC ₅₀ (mg/L)	MEC ₉₀ (mg/L)	No. of Isolates with MEC (mg/L) of:													
					0.002	0.004	0.008	0.016	0.031	0.063	0.125	0.25	0.5	1	2	4	8	16
Micafungin	0.002–0.063	0.014	0.016	0.031	1	6	28	16	17	5								
Anidulafungin	0.016–0.063	0.018	0.016	0.016				67	2	4								
Caspofungin	0.031–1	0.308	0.5	0.5					3	2	8	21	35	4				

Note: Modal MEC values in bold indicate modal or most frequent MICs.
Abbreviations: MEC, minimum effective concentration; GM, geometric mean.

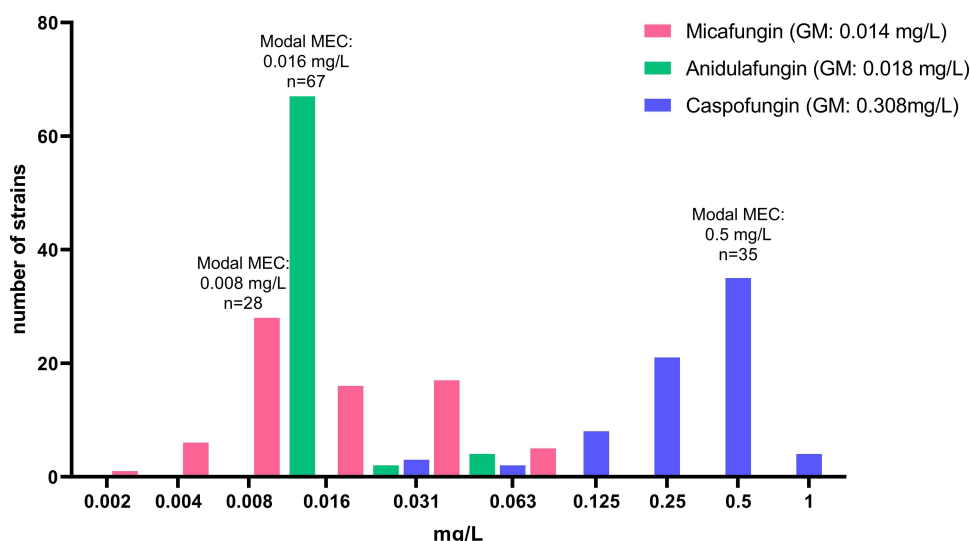


Figure 1 MEC distribution of 3 echinocandins against 73 clinical *T. rubrum* isolates from China.

However, the antifungal susceptibility profile of dermatophytes to echinocandins remains poorly examined. Among 5 literatures reviewed and our results (Table 2, Figure 2) in this study,^{19–23} the activity of caspofungin against *T. rubrum* was tested in all 6 studies, whereas micafungin was tested in 4 studies, and anidulafungin only in 3 studies. Most studies are with a limited sample set of *T. rubrum* isolates (7–43 isolates) except our study with 73 isolates of *T. rubrum*.

Though there are no reference breakpoints of echinocandins to *T. rubrum* available at the moment, in our study, three echinocandins tested showed good activity against the 73 clinical *T. rubrum* isolates in this collection, while micafungin and anidulafungin showed a lowest modal MEC of 0.008 mg/L (n = 28) and 0.016 mg/L (n = 67), respectively, followed by caspofungin with modal MEC of 0.5 mg/L (n = 35) (Table 1, Figure 1). Micafungin and anidulafungin appeared more potent than caspofungin against *T. rubrum*, and similar results have been achieved in other studies.^{19–23}

Baghi et al²³ tested in vitro activity of caspofungin and anidulafungin against clinical dermatophyte isolates using CLSI M38A2, both echinocandins demonstrated potent activities against dermatophyte isolates, the MEC₅₀, MEC₉₀, and GM values of caspofungin and anidulafungin against 29 isolates of *T. rubrum* tested in the study by Baghi et al were similar to those reported in our study (Table 2, Figure 2). Badali et al²¹ presented in vitro susceptibility patterns of clinically important *Trichophyton* and *Epidermophyton* species against nine antifungal drugs including caspofungin and anidulafungin using CLSI M38A2, caspofungin exhibited higher MEC value (GM 1.67mg/L, MEC₉₀ 4mg/L) against *Trichophyton* and *Epidermophyton* species, the GM, MEC₉₀ of caspofungin against 13 *T. rubrum* isolates tested in the study were 1.53mg/L and 4 mg/L, respectively. Nevertheless, anidulafungin exhibited potent in vitro antifungal activity against all dermatophyte isolates (GM, 0.06mg/L) and excellent activity for *T. rubrum* as well (GM, 0.02mg/L). Bao et al¹⁹ tested the potency of micafungin and caspofungin against dermatophyte isolates from China using CLSI M38-A2. Both caspofungin and micafungin exhibit good in vitro antifungal activity in most dermatophytes compared with the traditional antifungal agents (terbinafine). The GM, MEC₉₀ values of micafungin and caspofungin to 30 isolates of *T. rubrum* tested are similar to those in our study. In addition, the E-test method was used to investigate the in vitro activity of caspofungin against 43 isolates of *T. rubrum* in Aktas's study²⁰ and caspofungin exhibited as an active agent with a MEC range of 0.02–3mg/L for *T. rubrum*. Rissleger et al²² evaluated the modified EUCAST fragmented-mycelium inoculum method for in vitro susceptibility testing of dermatophytes and the activity of novel antifungal agents including 3 echinocandins. Consistency between the mycelial inoculum method and the CLSI broth microdilution method was high (93% to 100%). Echinocandins showed good activity against all tested dermatophytes and worked as the most effective agents against dermatophytes compared with other drugs like voriconazole, posaconazole, fluconazole, and amphotericin B. All the MEC values of caspofungin, micafungin and anidulafungin for *T. rubrum* isolates tested in the study are comparable to those in other studies (Table 2, Figure 2).

There are certain limitations in this study. As this work had been done before EUAST method for the susceptibility testing of dermatophytes was launched.²⁸ We followed the EUCAST E.DEF 9.3.1 edition with minor modification on incubation

Table 2 Summarized Data of the 6 Studies on Susceptibility of *T. rubrum* to Echinocandins

Publish Year	MECs (mg/liter)												No. of Strains	Methods	Incubation Temperature
	Micafungin				Anidulafungin				Caspofungin						
	Range	GM	MEC ₅₀	MEC ₉₀	Range	GM	MEC ₅₀	MEC ₉₀	Range	GM	MEC ₅₀	MEC ₉₀			
2013 Bao et al ¹⁹	0.030–0.060	0.034	0.030	0.060	/	/	/	/	0.125–1.000	0.456	0.500	1.000	30	CLSI M38-A2	35°C, 4–7 days
2014 Aktas et al ²⁰	/	/	/	/	/	/	/	/	0.02–3	/	0.064	1	43	E-Test	28°C, 72–96 hours
2015 Badali et al ²¹	/	/	/	/	0.008–0.063	0.02	0.016	0.063	1–8	1.53	1	4	13	CLSI M38-A2	35°C, 72 hours
2015 Risslegger et al ²²	0.00–0.06	/	0.01	0.06	0.00–0.06	/	0.01	0.06	0.03–0.13	/	0.06	0.13	20	Modified EUCAST ^d	30°C, 2–9days
	0.016 ^a /0.016 ^b	/	/	/	0.016 ^a /0.016 ^b	/	/	/	0.125–1.0 ^a /0.5–1.0 ^b	/	/	/	7	CLSI M38-A2 ^{a,b}	30°C, 2–9days
	0.03 ^c /0.03 ^d	/	/	/	0.016–0.03 ^c /0.016–0.03 ^d	/	/	/	0.06–0.5 ^c /0.03–0.25 ^d	/	/	/	7	EUCAST ^{c,d}	30°C, 2–9days
2016 Baghi et al ²³	0.008–0.016	0.010	0.008	0.016	/	/	/	/	0.008–0.032	0.018	0.016	0.032	29	CLSI M38-A2	35°C, 96 hours
2023 this paper	0.002–0.063	0.014	0.016	0.031	0.016–0.063	0.018	0.016	0.016	0.031–1	0.308	0.5	0.5	73	Modified EUCAST	28°C, 4–5days

Notes: ^aMicrodilution testing according to Clinical and Laboratory Standards Institute (CLSI) method using conidia for inoculum preparation. ^bMicrodilution testing according to Clinical and Laboratory Standards Institute (CLSI) method using fragmented mycelium for inoculum preparation. ^cMicrodilution testing according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) method using conidia for inoculum preparation. ^dMicrodilution testing according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) method using fragmented mycelium for inoculum preparation.

Abbreviations: MEC, minimum effective concentration; GM, geometric mean; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

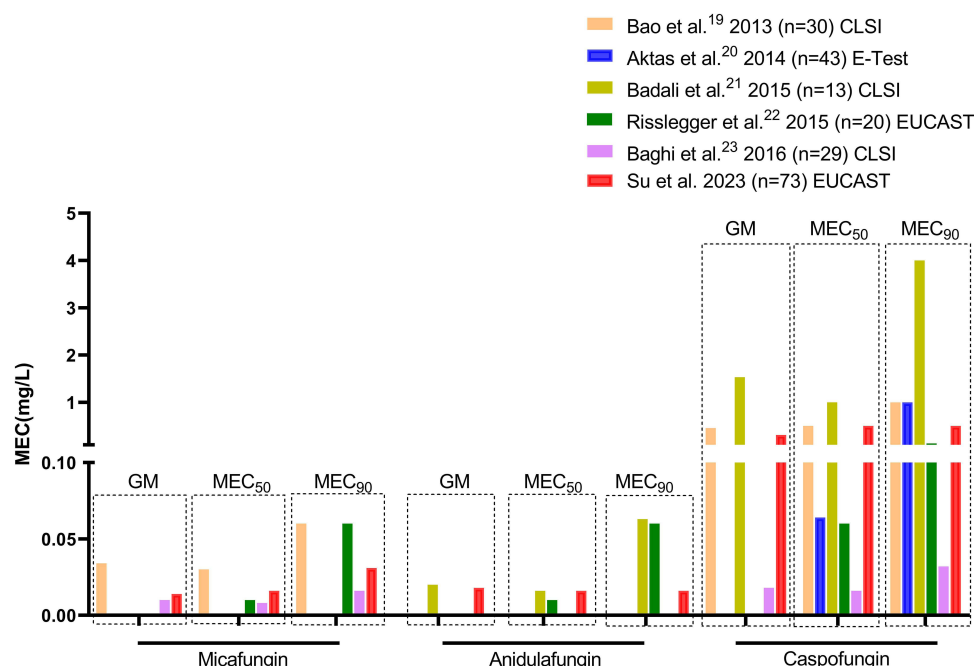


Figure 2 Summarized data of 6 studies on antifungal susceptibility of *T. rubrum* to echinocandins.

temperature and time for dermatophytes. Of note, the EUCAST method for dermatophytes²⁸ was mainly validated for terbinafine, voriconazole, itraconazole and amorolfine against *T. rubrum* and *T. interdigitale*, however, the susceptibility testing of dermatophytes to echinocandins is observed with MEC which is not included in the EUCAST method for dermatophytes yet.²⁸ The standard protocol on the susceptibility testing of dermatophytes to echinocandins is needed urgently.

Overall, micafungin and anidulafungin exhibited a low MEC range (both 0.008–0.063 mg/L) to *T. rubrum* which are similar among those studies,^{19,21–23} relatively higher MEC values for caspofungin to *T. rubrum* isolates were observed in 5 studies despite different methods and culture mediums when compared with those for anidulafungin and micafungin (Table 2, Figure 2), which indicated that micafungin and anidulafungin have better activity than caspofungin against *T. rubrum*. Micafungin has stronger in vitro antifungal activity than caspofungin in our study and also other research¹⁹ (Table 2, Figure 2). Echinocandins generally exhibit fungistatic and fungicidal activities against *Aspergillus* and *Candida* species, respectively.²⁹ Comparing the in vitro potency of echinocandins to *Aspergillus fumigatus*, anidulafungin and micafungin were also the most active drugs against *A. fumigatus* in vitro with the lowest modal MICs/MECs (0.016mg/L, n = 61 and 0.031mg/L, n = 64, respectively), followed by caspofungin (0.25mg/L, n = 119) when compared with azoles and AmB in our previous study,³⁰ and similar results reported by our previous study.³¹

Conclusion

Our study provided evidence of the good potency of micafungin, anidulafungin and caspofungin against *T. rubrum* in vitro based on our results and review of the data published on the susceptibility of *T. rubrum* to echinocandins worldwide. These findings suggest that echinocandins could be considered as potential treatment options for recalcitrant dermatophytoses infected by resistant dermatophytes. However, further clinical investigations must be conducted for the in vivo efficacy of echinocandins for the treatment of dermatophytosis caused by *T. rubrum*.

Ethics Approval

The study was approved by the Ethics Committee of Fudan University School of Medicine (20151010A330). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from individual or guardian participants.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to 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.

Funding

This study was funded by the National Natural Science Foundation of China (82102417, 82273544), and Grants from the Science and Technology Commission of Shanghai Municipality (22Y11905600), Suzhou Bureau of Science and Technology (SKY2022037) and the People's Hospital of SND (SGY2019D02).

Disclosure

Huilin Su and Weiwei Jiang are co-first authors for this study. The authors report no conflicts of interest in this work.

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