Antifungal Activity of Curcuminoids and Difluorinated Curcumin Against Clinical Isolates of *Candida* Species

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Abstract

Background: Acquired resistance to antifungals is rising particularly among *Candida* species. Herbal ingredients have biological and pharmacological activities, which make them potential fungicidal agents. The present study investigated the effects of curcumin (CUR) and difluorinated curcumin (CDF) on *Candida* species.

Material and Method: CUR and CDF were examined against *Candida* isolates obtained from patients candidemia due to *C. albicans* (n = 13), *C. dubliniensis* (n = 2), *C. parapsilosis* (n = 2), and *C. tropicalis* (n = 1); and laboratory strains of *C. albicans* (TIMML 1292 and TIMML 183), *C. krusei* (TIMML 1321), *C. parapsilosis* (TIMML 2201), and *C. tropicalis* (TIMML 731) based on the M27-A3 guideline.

Results: At the concentrations of 1–512μg/mL, none of the CDF and CUR showed a significant minimum inhibitory concentration (MIC) range against *Candida* isolates. There

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A. Sahebkar, T. Sathyapalan (eds.), *Natural Products and Human Diseases*, Advances in Experimental Medicine and Biology 1328, https://doi.org/10.1007/978-3-030-73234-9_8

was no significant difference between the effects of CUR and CDF against *Candida* species.

Conclusion: The CUR and CDF did not exert any inhibitory effect on the growth of *Candida* strains. Any possible effect on other yeast and filamentous fungi needs to be further investigated.

Keywords

Curcumin · Difluorinated-Curcumin · *Candida* · Antifungal

1 Introduction

Nowadays, *Candida* species have become more frequent and common because of different factors such as the increase in the use of systemic antibiotics, chemotherapy, corticosteroids, etc. [1–3]. As reports show, in the United States, *Candida* species are the fourth leading cause of hospital-acquired bloodstream infections [4]. More than 90% of invasive candidiasis are caused by *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei* [1]. However, recently non-*albicans Candida* species have emerged as important opportunistic pathogens in humans [5]. The quick rise of multidrug-resistant *Candida* and the slow pace of novel antifungals development has become a serious concern [6]. Thus, various studies express more interest in natural products such as medicinal plants or essential oils, and testing for their antifungal activities [7, 8]. Recently, many studies have determined the efficiency of herbal extracts and their derivatives in treating bacterial and fungal infections [9, 10]. Often these medicinal plants have chemicals or metabolites that can be effective against human pathogens; nevertheless, their antimicrobial susceptibility should be tested on clinical isolates [7, 11]. However, there is not enough evidence about the *in vitro* activity of herbal plants against clinically significant *Candida* species. As a result, it is necessary to determine the antifungal susceptibility of these plants on common invasive *Candida* species. Curcumin (CUR) or diferuloylmethane is the main polyphenolic compound that can be found in the rhizome of Curcuma longa (turmeric) [12]. Turmeric is a well-known member of the Zingiberaceae family, which is used in South Asian traditional medicine to heal fresh wounds, and as a counterirritant for insect bites [13]. CUR has shown an acceptable safety plus numerous biological activities such as antioxidant, anti-inflammatory, antimutagenic, anti-tumor, antimicrobial, immunomodulatory, and anti-proliferative effects which can be effective against a wide variety of diseases [11, 14–24]. Owing to its relatively low bioavailability, several structural analogs of CUR have been developed. 3,4-difluorobenzylidene curcumin, or difluorinated curcumin (CDF), is one of the analogs that has been shown to have improved bioavailability and metabolic stability compared with CUR [25, 26]. Some reports show that CUR has an effective fungicidal activity against a limited number of fungi [27]. Nonetheless, there is not enough evidence about the antifungal effect of these compounds against various *Candida* species. The main focus of this study is to find out the impact of CUR and CDF against clinical isolates of *Candida* species obtained from patients with candidemia, along with *Candida* laboratory strains.

2 Materials and Methods

In this study, the antifungal effect of CUR and CDF was evaluated on 18 *Candida* clinical isolates collected from blood specimens of patients with candidemia (specialized pediatric Hospital, Mashhad, Iran), and 4 *Candida* laboratory strains. All of the clinical isolates were identified using the Vitek MS instrument (bioMérieux, Marcy-L'Etoile, France). The laboratory strains included *C. albicans* (TIMML 1292, and TIMML 183), *C. krusei* (TIMML 1321), *C. parapsilosis* (TIMML 2201), and *C. tropicalis* (TIMML 731). Moreover, the identified clinical isolates included *C. albicans* (n = 13), *C. dubliniensis* (n = 2), *C. parapsilosis* (n = 2), and *C. tropicalis* (n = 1). The

antifungal susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) M27-A3 guidelines [28].

Curcuminoids were obtained from Sami Labs Ltd. (C3 Complex®, Bangalore, India). Synthesis of CDF was performed on the basis of a previously published method [29]. In brief, the mixture of curcumin (1 mmol) and piperidine (0.05 mmol) was added to difluorobenzaldehyde (1 mmol) in methanol. The reaction mixture was stirred for 48 h under N2 stream at room temperature. Synthesis of CDF was confirmed by the validation of its chemical structure using nuclear magnetic resonance spectroscopy.

Briefly, all isolates were sub-cultured on sabouraud dextrose agar (SDA, Sigma, Germany) and incubated at 35 °C for two days. To prepare inoculum suspensions, yeasts were dissolved in a sterile saline solution. The transmittance rate of these yeast suspensions was set to 75–77% at a wavelength of 530 nm using a spectrophotometer. Subsequently, suspensions were diluted 1:1000 in RPMI 1640 medium to reach the final concentration of 1–3 × 10^3 CFU/ml. Moreover, 3-N-morpholinepropanesulfonic acid (MOPS) (Bio basic, Canada) was used as a buffer for RPMI 1640 medium. First, all of the 96-well plates were filled with 0.1 ml of RPMI 1640 medium; then, the indicated concentrations of CUR and CDF (previously dissolved in dimethyl sulfoxide (DMSO) 1%) along with the fungal suspensions were added to them, and then incubated at 35 °C for two days. The final concentrations of CUR and CDF were 1–512 (1, 2, 4, 8, 16, 32, 64, 128, 256, and 512) μg/ml. Eventually, the minimum inhibitory concentration (MIC) ranges were evaluated visually as the lowest concentration of CUR or CDF, which inhibited at least 80% of the fungal growth, in comparison to positive control well.

3 Results

Based on the results, neither CUR nor CDF could inhibit the fungal growth compared to the control. Therefore, CUR and CDF could not exert a significant MIC range on clinical isolates and laboratory strains of *Candida*. Moreover, there was no significant difference between CUR and CDF against *Candida* species. On the other hand, *Candida* clinical isolates did not show a different susceptibility compared with laboratory strains.

Table 1 summarizes information about the efficacy of CUR and CDF as antifungal agents used in this study.

4 Discussion

The development of new resistance mechanisms against antifungal agents, especially azoles, in *Candida* species is a critical issue for public health worldwide [30]. Azole resistance among *Candida* species can happen owing to cellular changes induced by stress responses or upregulation of drug transporters [31]. Moreover, some *Candida* species such as *C. glabrata* and *C. auris* are described to be multidrug-resistant [32]. This study aimed to evaluate the antifungal activity of CUR and CDF against the clinical isolates and laboratory strains of *Candida*. In general, none of these compounds showed admissible antifungal activity against the tested isolates. Though some studies found the formulation of curcumin and its analogs can be developed against fungal pathogens like *Candida* species [27, 33]. Various studies show that some natural products can have antifungal activities. Thus, they are valuable as the potential source to develop novel antifungal agents [10, 34]. In traditional medicine, some plants or herbal extracts are described to be effective in preventing or curing infectious diseases [35]. This, mainly the aromatic compounds and secondary metabolites, as a line of defense, can act against microbial invasions [11]. Polyphenols are a great example of such products, can be found in a wide variety of edible plants [9]. Turmeric is a well-known medicinal plant that comes from the Zingiberaceae family [36]. The most active component of turmeric is a lipophilic polyphenol called curcumin [37]. Many factors, such as geographical conditions, can impact the growth and nutrition composition of turmeric. Therefore, 100 grams of turmeric powder may

Table 1 The antifungal susceptibility profiles for curcuminoids and *difluorinated curcumin* among clinical isolates and laboratory strains of *Candida*

Candida species (clinical isolates and laboratory strains)	No. (%)	Antifungal compounds (CUR/CDF)	MIC (μg/ml)	Negative control	Positive control
C. albicans	15 (65.21%)	CUR	Not achieved	–	G
		CDF	Not achieved	–	G
C. parapsilosis	3 (13.04%)	CUR	Not achieved	–	G
		CDF	Not achieved	–	G
C. dubliniensis	2 (8.69%)	CUR	Not achieved	–	G
		CDF	Not achieved	–	G
C. tropicalis	2 (8.69%)	CUR	Not achieved	–	G
		CDF	Not achieved	–	G
C. krusei	1 (4.34%)	CUR	Not achieved	–	G
		CDF	Not achieved	–	G
Candida isolates	23 (100%)				

MIC Minimal inhibitory concentration, *G* Indicates the yeast growth in positive control wells, *CUR* Curcuminoids, *CDF Difluorinated curcumin*

contain around two to five grams of curcumin [27, 38]. Some researches show that this polyphenolic substance has antioxidant, antimicrobial, and anti-inflammatory activities; therefore, it is useful against bacterial and fungal pathogens [39–42]. Nonetheless, it can decrease the adhesion and biofilm growth of some fungi and bacteria, leading to less severe symptoms in patients [43, 44]. Studies suggest that curcumin can directly affect cell wall permeability by inhibiting or activating pathways such as MAP-kinase and calcineurin-mediated signaling pathways, which play an influential role in the maintenance of cell wall integrity [45]. Moreover, some studies show that curcumin can decrease the amount of aflatoxin B1 produced by *Aspergillus flavus* too [46].

However, there are limited data about the antifungal activity of curcumin as a natural compound against human fungal pathogens. Besides, there is limited evidence about the biological and pharmacological effects of difluorinated curcumin, as an analog for curcumin, and its antifungal properties. Altogether, most of the studies on curcumin centered on the effect of this compound against *Aspergillus* and *Candida* species [9, 39]. In 2015, Zhang *et al.* conducted an *in vitro* study about the inhibitory effects of curcumin against non-*C. albicans* species, and concluded that curcumin effectively prevents the biofilm formation and hyphal extension of *Candida* spp. [47]. In another study, Tsao *et al.* evaluated the effects of curcumin combined with amphotericin B or fluconazole against *Candida* isolates, and showed that curcumin, at concentrations of 32 to 128μg/ml, can increase the antifungal potential in treating Candidiasis [48]. In 2015, Carmello *et al.* investigated the effects of photodynamic therapy mediated by curcumin, which achieved the increase of reactive oxygen species (ROS) and the DNA damage of *C. albicans*. Moreover, a study by Kumar *et al.* confirmed that curcumin can damage the cell wall of *C. albicans* [43]. In 2020, Zarrinfar *et al.* studied on the

effects of curcuminoids and difluorinated curcumin against dermatophyte isolates such as *Trichophyton tonsurans, T. interdigitale, T. mentagrophtes, Microsporum canis,* etc., and concluded that this natural compound and its analog could be effective in preventing and treating dermatophytosis [49]. Interestingly, other researchers described curcumin and its analogs as effective antifungal agents against the genera of *Alternaria*, *Aspergillus*, and *Penicillium* too. Thus, it can be helpful to analyze the effect of these analogs against clinical isolates. However, there are limited data about the possible antifungal effects of difluorinated curcumin on *Candida* species [27]. In the current study, the effect of these compounds was not significant and acceptable against the clinical isolates and laboratory strains of *Candida*. These findings contradict the results obtained by other studies, which therefore requires further investigation using different designs and tested strains to explore the possible reasons underlying discrepant findings.

5 Conclusion

The results of the present study showed that neither CUR nor CDF had any significant inhibitory effect against both clinical isolates and laboratory strains of *Candida*. Thus, further investigations are required to find out whether these compounds have any other effects on *Candida* spp. or other fungal pathogens.

Acknowledgments We appreciate the staff of Medical Mycology and Parasitology Laboratory in Ghaem Hospital, Mashhad University of Medical Sciences.

Conflicts of interest The authors declare that they have no conflicts of interest.

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