8 Antifungal Activities of Curcuminoids and Difluorinated Curcumin Against Clinical Dermatophyte Isolates

Hossein Zarrinfar, Mahsa Behnam, Mahdi Hatamipour, and Amirhossein Sahebkar

Abstract

Dermatophytes are a group of fungal agents that can invade humans' keratinized tissues such as skin, nail, and hair, thereby causing dermatophyte infection (dermatophytosis) or ringworm. Some natural products have been reported to possess fungicidal effects. Hence, the present study investigated the effect of curcuminoids (CUR) and difluorinated curcumin (CDF) against clinical isolates of dermatophytes. CUR and CDF powders were evaluated against dermatophyte species including *Trichophyton tonsurans* (n = 21), *T. mentagrophytes* (n = 19), *T. interdigitale* (n = 18), *Microsporum canis* (n = 4), *T. benhamiae* (n = 1), and *T. verrucosum* (n = 1), based on the CLSI M38-A2 guideline. The minimum inhibitory concentration (MIC) ranges of CUR were 4–16, 8–16, 4–16, 8, 8, and 16 μg/ml for *T. tonsurans*, *T. mentagrophytes*, *T. interdigitale*, *M. canis*, *T. benhamiae*, and *T. verrucosum*, respectively. In addition, MIC ranges of CDF were obtained as 2–32, 4–16, 0.125–16, 8–16, 8, and 16 μg/ml, for *T. tonsurans*, *T. mentagrophytes*, *T. interdigitale*, *M. canis*, *T. benhamiae*, and *T. verrucosum*, respectively. CUR and CDF showed an inhibitory effect against dermatophyte isolates. CDF showed a stronger effect than CUR, especially against *T. interdigitale*. CUR and CDF have the capacity to be developed for use in dermatophytosis to augment existing preventative/therapeutic strategies.

Keywords

Curcumin · Difluorinated curcumin · Dermatophyte · Antifungal

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8.1 Introduction

Dermatophytes as keratinophilic fungi can invade to keratinized tissues of vertebrates. They can cause dermatophytosis (tinea or ringworm), as various disorders in the skin, nails, and hair, and also deep tissue in some cases [1]. More than 50 species of dermatophytes have been introduced as causative agents of dermatophytosis in different parts of the world [2]. The dermatophytosis prevalence and causative agents varies depending on the geographical area and its climate, as well as the lifestyle of the people [3]. However, the dermatophyte species express various susceptibility to antifungal drugs [4]. Some of species may cause chronic and do not respond well to the usual therapeutic procedure [5]. There are reports regarding drug resistance among various dermatophyte species in vitro and in vivo results [6]. Thus, it can lead to fail or requires long-term treatment, and cause anxiety with serious complications for this group of patients [7]. As resistance to antifungal drugs has been increased, natural products and nanoparticles can being widely screened as the potential sources of novel antifungal agents [8, 9]. In many cases and in recent years, herbal extracts and their derivatives have been used to cure infectious diseases, especially fungal infections [10, 11]. These plants can usually produce aromatic chemicals and secondary metabolites against microbial pathogens [12]. Many studies have been conducted to determine antifungal susceptibility by testing the clinical isolates [9]. However, these studies have been limited to some specific types of fungal agents and the antifungal patterns [13]. Nonetheless, there is restricted information regarding the in vitro activity of herbal plants against various species of dermatophytes. Therefore, the determination of antifungal susceptibility of herbal plants on dominant dermatophytes seems necessary. Curcuminoids (CUR) are natural polyphenols extracted from turmeric, which are known to have numerous pharmacological effects [14–20]. A fluorinated analog of CUR, named difluorinated curcumin (CDF), has been introduced with improved metabolic stability and pharmacological activity [21, 22]. The fungicidal activity of CUR against some fungi has been shown [10]. However, no information has been provided on the antifungal effect of this plant and its synthetic derivatives against different species of dermatophytes. Concerning this, the aim of present study was to investigate the effect of CUR and CDF against clinical isolates of dermatophytes obtained from patients with dermatophytosis.

8.2 Materials and Methods

The clinical isolates of dermatophytes were previously identified based on molecular method (ITS sequencing) [23, 24]. They included six species of *Trichophyton tonsurans* (n = 21), *T. mentagrophytes* (n = 19), *T. interdigitale* (n = 18), *Microsporum canis* (n = 4), *T. benhamiae* (n = 1), and *T. verrucosum* (n = 1).

Difluorinated curcumin was prepared using the synthesis method previously described [25]. Briefly, a solution comprising curcumin (1 mmol) and piperidine (0.05 mmol) was added to difluorobenzaldehyde (1 mmol) in methanol. At room temperature under a nitrogen stream, the reaction mixture was stirred for 48 h. The chemical structure of difluorinated curcumin was confirmed with the use of nuclear magnetic resonance (NMR).

The CLSI M38A2 guideline was used to antifungal susceptibility testing procedure [4]. Briefly, the dermatophytes were cultured on potato dextrose agar (Sigma, Germany) and incubated at 30 °C for 2 weeks. Fungal suspensions containing harvested conidia and hyphal fragments were prepared using sterile saline solution along with Tween 20. They were evaluated using a spectrophotometer at a wavelength of 530 nm to reach a 65–70% transmittance. The suspension was diluted 1:50 in RPMI 1640 medium to achieve the final concentrations (1–3 × 10^3 CFU/ml). The inocula along with the indicated concentrations of CUR and CDF were added to 96-well plates, and incubated at 35 °C for 3–5 days. The final concentrations of CUR and CDF were 0.0625–16 (0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16) μg/ml, Finally, the minimum inhibitory concentration (MIC) ranges were

determined visually as the lowest concentration of CUR/ CDF that resulted in at least 80% growth inhibition, compared to the growth of the control well. The definition of MIC_{50} and MIC_{90} was as inhibition the minimum concentration at which 50% and 90% of the isolates, respectively. The average geometric mean (GM) of the MICs of the antifungal compounds, and differences between the mean values were determined using the SPSS software (version 16).

8.3 Results

The detailed information on the results of antifungal effects of CUR and CDF against the dermatophyte clinical isolates is shown in Table 8.1.

According to the results, generally, CDF had a more effect than CUR, and *T. interdigitale* showed the lowest MIC with 0.125 μg/ml than other species. Followed by *T. tonsurans* at concentration of 2 μg/ml. However, CUR had a more effect on *T. interdigitale* and *T. tonsurans* than other species with 4–16 μg/ml. Accordingly, CDF had also the lowest MIC_{50} for *T. interdigitale* at concentration of 4 μg/ml. However, *T. mentagrophytes* showed the highest MIC_{50} and MIC_{90} at concentration of 16 μg/ml.

The GM of CUR for *T. tonsurans*, *T. mentagrophytes*, *T. interdigitale*, and *M. canis* were estimated at 9.75, 11.52, 9.33, and 8, respectively. Moreover, CDF of GM for *T. tonsurans*, *T. mentagrophytes*, *T. interdigitale*, and *M. canis* were estimated at 6.56, 8.92, 2.61, and 9.51, respectively. Due to small number, GM MIC values of *T. benhamiae* and *T. verrucosum* species could not be achieved. Generally, the dermatophyte isolates showed GM MIC values of 5.78 and 10.04 for CUR and CDF, respectively. Furthermore, according to the GM MIC, CDF was the most effective agent against species of *T. interdigitale*, *T. tonsurans*, and *T. mentagrophytes*, respectively.

8.4 Discussion

Although few reports of resistance to antifungal agents have been presented on dermatophytes as causative agents of dermatophytosis; the development of resistance to the current clinically used antifungal drugs, has emerged as a growing problem [26, 27]. Several dermatophyte species,

Table 8.1 The antifungal susceptibility profiles for curcuminoids and difluorinated-curcumin among dermatophyte clinical isolates

Dermatophyte species	No. (%)	Antifungal compounds (CUR/ CDF)	MIC range (μg/ mL)	MIC_{50} (μg/ mL)	MIC_{90} (μg/ mL)
Trichophyton tonsurans	21 (32.8%)	CUR	4–16	8	16
		CDF	2–32	8	16
T. mentagrophytes	19 (29.7%)	CUR	8-16	16	16
		CDF	4-16	8	16
T. interdigitale	18 (28%)	CUR	4-16	8	16
		CDF	0.125-16	4	16
Microsporum canis	4 (6.3%)	CUR	8	8	8
		CDF	8-16	8	8
T. benhamiae	1 (1.6%)	CUR	8	–	–
		CDF	8	–	–
T. verrucosum	1 (1.6%)	CUR	16	–	–
		CDF	16	–	–
Dermatophyte isolates	64 (100%)	CUR	4–16	8	16
		CDF	0.125–32	8	16

MIC minimum inhibitory concentration, Due to small number, MIC_{50} and MIC_{90} of *T. benhamiae* and *T. verrucosum* species could not be achieved

in particular, *T. interdigitale* and *T. rubrum* described are resistant or less susceptible to several classes of antifungals [28]. It appears the developed acquisition of resistance mechanisms to antifungal agents be following a prior exposure [28]. The present study was aimed at evaluating the activity of CUR and CDF against the clinical isolates of dermatophytes obtained from patients affected by dermatophytosis. In general, both tested compounds exhibited good activity against all tested isolates. Collectively, these data demonstrated that CUR/CDF have the therapeutic potential to be used in dermatophytosis. Natural products can be used as the potential sources of novel antifungal agents, particularly in the case of acquired or high antifungal resistance [8, 11]. Traditionally, medicinal plants have been investigated to prevent and cure infectious diseases [29]. They can produce aromatic chemicals and secondary metabolites as defense mechanisms and antimicrobial effects [12]. Polyphenols, found in various edible plants, may serve as an alternative source of antimicrobials [10]. CUR is a bioactive polyphenol that is extracted from the rhizomes of the *Curcuma longa* plant [30]. Curcumin constitutes typically about less than 5% of turmeric composition [31, 32]. Interestingly, it displays broad-spectrum antimicrobial activity, particularly antibacterial and antifungal properties [33–35]. Also, it is able to influence the adhesion ability of bacteria, whereby less fimbriae leads to reduced adhesion ability against planktonic and biofilm cells [36, 37]. Possibly, CUR can directly impact cell wall permeability through signaling of the MAP kinase and calcineurin-mediated signaling, pathways which play significant role in cell wall integrity [38]. Interestingly, some studies showed that CUR can reduce the production of aflatoxin B1 by *Aspergillus flavus* too [39].

There is little information about the use of CUR as a natural antifungal compound for fungal pathogens so far. Unfortunately, up until now, there is no significant report about CDF antifungal effect, as a CUR analogue, against fungal pathogens too. However, most of studies investigated CUR effect again *Candida* and *Aspergillus* species [10, 35]. To our knowledge, there have been no studies that report on pathogenic dermatophytes. In a study, Martins et al. (2009) investigated the antifungal effects of CUR and fluconazole against *Candida* spp., *Cryptococcus neoformans*, *Sporothrix schenckii*, *Paracoccidioides brasiliensis* and *Aspergillus* species [35]. They reported *P. brasiliensis* isolates were the most susceptible to CUR while the growth of *Aspergillus* isolates was not affected. Moreover, CUR was much more efficient than fluconazole in inhibiting the adhesion of *Candida* species to human buccal epithelial cells. They obtained that a MIC range of 0.5–32 μg/ml against *P. brasiliensis* isolates, but in our study the MIC range were 4–16, 0.125–32 μg/ml for CUR and CDF, respectively. Our results indicate that CDF may be a promising compound for the design of new antifungal agents capable of inhibiting of *P. brasiliensis* with more impact. To the best of our knowledge, this study reports for the first time the effect of CUR and CDF on the growth of dermatophytes of clinical interest. Our *in vitro* results highlight the potential of CUR and CDF as the effective antifungals against various dermatophytes strains including *T. tonsurans*, *T. mentagrophytes*, *T. interdigitale*, *M. canis*, *T. benhamiae*, and *T. verrucosum*. Among the dermatophyte isolates examined in the present study, the widest MIC range of CDF was observed for *T. interdigitale* (0.125–16 μg/ml) that is higher than those obtained for CUR. This concentration show that CDF could act against dermatophyte species more effectively, particularly on *T. interdigitale*. This is important since the *T. interdigitale* species is one of the most common species among patients with dermatophytosis in the world. Therefore, it can play an effective role in the prevention and treatment of dermatophytosis. The widest MIC range of CUR was observed for *T. tonsurans T. tonsurans* with 4–16 μg/ml. However, CUR showed more effect against them than other species. The MIC_{50} of CDF against *T. interdigitale* (with 4 μg/ml concentration) was lower than CUR, thus showing a stronger effect against this species. However, the MIC_{50} (8 μg/ml) of CDF was equal to CUR for the 64 dermatophyte isolates in general. Nevertheless, several studies have shown that the different types of

fungal agents have different sensitivities to CUR [35, 40]. In a study performed by Alalwan et al. (2017) investigating the antifungal effects of CUR, was reported to be efficient in 50 μg/ml concentration to inhibit and kill *C. albicans* [10]. This concentration is different from the results obtained against dermatophyte isolates in the present study. It appears that different fungal pathogens could show various susceptibility to CUR. In the case of clinical pathogenic fungi, this difference can be even due to different geographical locations. In this regard, general and specific relevance of environmental conditions can affect specific secretion of enzymes and the expression of certain genes in pathogenic fungi [41]. Furthermore, the number of fungi examined and their diversity can fundamentally influence the results. Thus, one of the limitations of the present study was the low number of clinical isolates of dermatophytes.

In another study by Garcia-Gomes et al., the synergistic effect of curcumin and fluconazole was evaluated on the *C. albicans* isolate resistant to fluconazole [42]. They showed that CUR has a great capability to inhibit fluconazole resistance of the isolate of *C. albicans*, and it could restore its sensitivity to this azole. Therefore, interestingly, azole-resistant isolates can be further investigated by azole-CUR whether such combinations can be beneficial. Oglah et al. in their review article stated that analogues of CUR had antifungal activities against the genera of *Aspergillus*, *Penicillium* and *Alternaria* [43]. Therefore, the use of these analogues can be evaluated among the clinical isolates too. However, there are no reports of possible effects of CUR and its analogues on dermatophytes.

The present study was the first attempt investigating the antifungal effect of CUR and its analogue (CDF) against clinical dermatophyte isolates obtained from dermatophytosis. Based on the results of the present study, and according to GM definition, CUR and CDF, particularly CDF had an effective impact against the dermatophyte isolates. Furthermore, among dermatophyte species, *T. interdigitale* showed a greater sensitivity to CDF and CUR, respectively.

8.5 Conclusion

As the results of the present study indicated, CUR and CDF had respectively the antifungal effect against clinical isolates of dermatophyte. Furthermore, none of the dermatophyte isolates showed too high MIC to these compounds. Additionally, *T. interdigitale*, as a common agent of dermatophytosis in the world, showed the lowest GM (the highest sensitivity) to CDF and CUR, respectively.

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

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