Journal of Food and Drug Analysis, Vol. 8, No. 3, 2000, Pages 208-212 藥物食品分析 第八卷 第三期

Enhanced Inhibitory Effect from Interaction of Curcumin with Amphotericin B or Fluconazole against *Candida* Species

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(Received: March 16, 2000; Accepted: June 27, 2000)

ABSTRACT

The antifungal activity of curcumin against seven *Candida* species was studied by investigating the growth of 200 clinical isolates from patients with fungal infections. The MICs of curcumin against *Candida* species were in the range of 32 to 128 μg/mL. The interaction of curcumin with amphotericin B or fluconazole against these fungi was determined by FIC index and % reduction in turbidity. Synergistic effect was shown in all combinations of curcumin and amphotericin B; whereas both synergistic and additive effects were observed in the combinations of curcumin and fluconazole. This evidence suggests that when curcumin is combined with amphotericin B or fluconazole, it could provide greater fungicidal effects for the treatment of systemic fungal infections such as candidiasis and candidemia.

Key words: curcumin, amphotericin B, fluconazole, *Candida* species

INTRODUCTION

Candidiasis and candidemia are very common nosocomial fungal infections occurring in many hospitals. Immunocompromised patients such as those with organ transplants, cancer, human immunodeficiency virus (HIV) infection or prolonged antibiotic treatments are susceptible to fungal infections[1-3]. These fungal infections might be fatal if antifungal treatment is not prescribed. The common isolates of candidiasis or candidemia are *Candida albican, C. krusei, C. glabrata, C. tropicalis*, and *C. guilliermondii*, in which *C. albican* is the most common; however, *C. krusei* and *C. glabrata* have become increasingly important for hospitalized patients[2-4].

Amphotericin B belongs to the class of polyenes and is a clinically popular antifungal agent. However, the clinical use of amphotericin B is limited because of severe adverse reactions such as diarrhea, malnutrition and progressive renal toxicity[5-8]. Azole compounds such as fluconazole (FCZ), itraconazole (ICZ) are another class of antifungal agents used for systemic fungal infections. These azoles are less toxic than amphotericin B[7,8]; however, some side effects of azoles have been reported[9]. In order to cure fungal infections successfully and to lower the dose of amphotericin B or azoles, there is a need for the development of less toxic antifungal agent, or to find one that is able to work with amphotericin B or azoles additively or synergistically.

Curcumin, a yellow phenolic compound isolated from turmeric (*Curcuma longa*), is responsible for the yellow color of turmeric and curry. Based on its safe property, it has long been used as a spice, food preservative and food coloring agent in India and Southeast Asia[10,11]. The content of curcumin in turmeric is 1-5% (or 4-8% of dry weight); and 40% in turmeric oleoresin[11]. Many studies have proven that curcumin has several important pharmacological properties such as antioxidant, antimutagenic and antitumor activities[12-14]. Therefore, it is being evaluated as a chemopreventive agent by the National Cancer Institute. Li *et al*.[15] indicated that curcumin could block HIV-1 replication by inhibiting the activity of its long terminal repeat; moreover, curcumin could work with a reverse transcriptase inhibitor (e.g. dideoxyinosine) on HIV-1 synergistically. Although curcumin is a potent anti-viral agent[15,19], it remains unknown whether curcumin is an antifungal agent for *Candida* species.

This study was aimed to assay the *in vitro* inhibitory effect of curcumin against seven *Candida* species. The interactions of curcumin with amphotericin B or fluconazole against these fungi were also studied.

MATERIALS AND METHODS

I. *Fungi Strains and Medium*

Seven *Candida* species (*Candida albican, C. krusei, C. tropicalis, C. kefyr, C. guilliermondii, C. parapsilosis, C. glabrata*) were isolated from patients with fungal infections such as candidiasis or candidemia in the Chungshan Hospital (Taichung, Taiwan). A total of 200 isolates were tested in this study. All isolates were identified by conventional methods[16]. All cultures were routinely maintained on Sabouraud dextrose agar (Difco, Detroit, MI) at 25˚C before use.

II. *Antifungal Agents*

Curcumin was purchased from Sigma Chem. Co. (St. Louis, MO). Amphotericin B (AMB) and fluconazole (FCZ)

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Journal of Food and Drug Analysis, Vol. 8, No. 3, 2000

were prepared from pharmaceutical solutions in sterile water. All solutions were filtered through 0.22 μM filter for sterilization.

III. *Antimicrobial Assays*

All agents were further diluted with RPMI 1640 medium (1:5, v/v). The broth macrodilution method was performed as described in National Committee for Clinical Laboratory Standards (NCCLs) document M27-A[17]. The final inoculum was 2×10^3 CFU/mL and was confirmed by plating 10 and 100 μL from the agent-free control tube onto Sabouraud dextrose agar. The final volume was 1 mL. The agent concentrations ranged from 256 to 0.0625 μg/mL. Agent-free and fungi-free controls were included. The turbidity was measured at 530 nm by a spectrophotometer after 48 hr incubation at 35˚C in RPMI 1640 medium containing 0.165 M morpholinepropanesulfonic acid (MOPS) (pH 7.0). The MIC was defined as the concentration which produced an 80% reduction in turbidity, compared with that of controls. According to the standard of NCCLs, the isolates were classified as susceptible if the MIC was ≦ 8 μg/mL; resistant if the MIC was ≧ 64 μg/mL; susceptible but dose dependent if the MIC was 8~64 μg/mL.

IV. *Interaction of Curcumin with AMB or FCZ*

The effects of combinations of amphotericin B or fluconazole with curcumin were evaluated by the checkerboard method recommended by the NCCLs. One hundred μL aliquots of each drug at 10X the targeted final concentration was used. Drug interaction was classified as synergistic, additive or less-than-additive based on the fractional inhibitory concentration (FIC) index, which is the sum of FICs for each drug. The FIC of each drug was calculated as the MIC of this drug in combined treatment divided by that of the drug used alone. Drug-drug interactions are considered synergistic if the FIC index was less than 1.0; additive if the FIC was equal to 1.0; less-than-additive if the FIC index was greater than 1.0. The interaction of curcumin with amphotericin B or fluconazole were examined by combining 0.25, 0.5, 0.75 MIC AMB (or FCZ) with curcumin at various MIC values. The total MIC values in each combination were ≦ 1. The final inoculum was 2×10^3 CFU/mL and the final volume was 1 mL. The turbidity of each combination was then measured at 530 nm by a spectrophotometer after 48 hr incubation at 35˚C in RPMI 1640 medium containing 0.165 M (MOPS) (pH 7.0).

RESULTS AND DISCUSSION

The MICs of curcumin, amphotericin B and fluconazole against *Candida* species are presented in Table 1. The inhibitory effect of amphotericin B and fluconazole against these *Candida* species has been studied[9,18]. It was reported that the MICs of amphotericin B and fluconazole were in the range of 0.125-2 and 0.25-128 μg/mL, respectively. The observed MICs (Table 1) of amphotericin B and fluconazole in our present study were close to those of previous studies. It was reported that fluconazole is inactive to *C. krusei* and the MIC90 was 128 μg/mL[9]. In our present study, the MIC80 of fluconazole against *C. krusei* was 128 μg/mL. This result supported that *C. krusei* was resistant to fluconazole.

The MIC80 of curcumin against the tested *Candida* species were in the range of 32-128 μg/mL (Table 1). Curcumin was found to be weaker when compared with amphotericin B or fluconazole. Although curcumin is a food component and amounts of up to 100 mg/day have been taken by certain people for long time[11], it remains unknown whether curcumin could achieve the blood concentrations of 32-128 μg/mL via oral or i.v. administration. Moreover, further *in vivo* studies are needed to prove the safety of curcumin at these concentrations. The interaction of curcumin with amphotericin B or fluconazole, determined as FIC index, is presented in Table 2. All interactions of curcumin and amphotericin B were synergistic because the FIC indexes were less than 1. Several interactions of curcumin with fluconazole were additive because the FIC indexes were equal to 1. These observed synergistic effects showed that the interaction of curcumin with either amphotericin B or fluconazole exhibited greater effect against *Candida* species. Both synergistic and additive effects observed in these combinations also suggest that the dosage of amphotericin B or fluconazole could be decreased. The interactions of curcumin with amphotericin B or fluconazole, determined as % reduction in turbidity, are presented in Tables 3 and 4. Many combinations of amphotericin B (or fluconazole) plus curcumin demonstrated ≧ 80% reduction in turbidity. In this study, the MIC of each agent against each tested fungi was defined as 80% reduction in turbidity. Therefore, the greater turbidity reduction observed in these combinations suggests that these combinations exhibited greater anti-*Candidal* effects than each

Table 1. MIC (μg/mL) of curcumin, amphotericin B (AMB) and fluconazole (FCZ) against *Candida* species

Fungal species (number of isolates)	Curcumin	AMB	FCZ
C. albican (52)	32 ± 2	0.125 ± 0.06	0.5 ± 0.5
C. krusei (30)	128 ± 8	1.0 ± 0.5	128.0 ± 16.0
C. tropicalis (27)	48 ± 2	0.125 ± 0.06	1.0 ± 0.25
C. kefyr (25)	96 ± 4	0.25 ± 0.125	4.0 ± 0.5
C. guilliermondii (21)	108 ± 8	0.5 ± 0.25	32.0 ± 2.0
C. parapsilosis (20)	64 ± 4	0.25 ± 0.125	2.0 ± 0.5
C. glabrata (25)	80 ± 4	0.5 ± 0.25	16.0 ± 2.0

MIC was determined according to the macrodilution method recommended by NCCLs and was defined as 80% reduction in turbidity. The concentration is expressed as mean ± standard deviation (n=5).

Table 2. Interaction of curcumin with amphotericin B (AMB) or fluconazole (FCZ), determined as FIC index

Fungal species (number of isolates)	FIC AMB	FIC Curcumin	FIC Index	FIC FCZ	FIC Curcumin	FIC Index
C. albican (52)	0.5	0.25	0.75	0.25	0.5	0.75
C. krusei (30)	0.75	0.125	0.875	0.5	0.5	1
C. tropicalis (27)	0.5	0.25	0.75	0.25	0.5	0.75
C. kefyr (25)	0.25	0.5	0.75	0.75	0.25	1
C. guilliermondii (21)	0.25	0.5	0.75	0.5	0.5	1
C. parapsilosis (20)	0.5	0.25	0.75	0.25	0.5	0.75
C. glabrata (25)	0.5	0.25	0.75	0.25	0.625	0.875

The interaction of curcumin with AMB or FCZ was evaluated by the checkerboard method recommended by the NCCLs and expressed as the sum of fractional inhibitory concentration (FIC) index for each agent. The FIC of each agent is calculated as the MIC of this agent in combination divided by the MIC of this agent alone.

Table 3. Interaction of curcumin with amphotericin B (AMB), determined as % reduction in turbidity.

	AMB 0.75 MIC			AMB 0.5 MIC			AMB 0.25 MIC		
Fungal species	Curcumin			Curcumin			Curcumin		
(numberof isolates)	0.0625 (MIC)	0.125	0.25	0.125	0.25	0.5	0.25	0.5	0.75
C. albicans (52)	80 ± 3	90 ± 2	97 ± 3	71 ± 4	80 ± 3	96 ± 2	64 ± 4	85 ± 2	96 ± 2
C. krusei (30)	68 ± 4	79 ± 3	90 ± 2	62 ± 5	77 ± 2	88 ± 2	57 ± 5	75 ± 3	89 ± 3
C. tropicalis (27)	78 ± 2	87 ± 2	96 ± 2	68 ± 4	79 ± 3	94 ± 2	67 ± 3	84 ± 2	95 ± 2
C. kefyr (25)	75 ± 3	84 ± 2	93 ± 2	67 ± 3	76 ± 3	91 ± 3	57 ± 5	81 ± 3	93 ± 3
C. guilliermondii (21)	70 ± 3	82 ± 3	92 ± 3	63 ± 2	74 ± 2	93 ± 2	55 ± 4	80 ± 5	90 ± 1
C. parapsilosis (20)	78 ± 3	84 ± 2	95 ± 3	69 ± 4	80 ± 3	95 ± 2	62 ± 3	85 ± 3	94 ± 2
C. glabrata (25)	72 ± 4	82 ± 2	94 ± 2	66 ± 4	78 ± 3	92 ± 1	59 ± 4	83 ± 2	92 ± 3

AMB at 0.25, 0.5, 0.75 MIC was combined with curcumin at various MIC values. The total MIC values in each combination were ≦ 1. The turbidity of each combination was measured and expressed as mean ± standard deviation (n=5).

Table 4. Interaction of curcumin with fluconazole (FCZ), determined as % reduction in turbidity

	FCZ 0.75 MIC			FCZ 0.5 MIC			FCZ 0.25 MIC		
Fungal species	Curcumin			Curcumin			Curcumin		
(number of isolates)	0.0625 (MIC)	0.125	0.25	0.125	0.25	0.5	0.25	0.5	0.75
C. albicans (52)	77 ± 3	85 ± 2	90 ± 3	68 ± 4	76 ± 3	91 ± 2	61 ± 4	82 ± 3	91 ± 2
C. krusei (30)	57 ± 4	73 ± 2	82 ± 2	53 ± 4	68 ± 2	80 ± 2	50 ± 5	71 ± 2	82 ± 1
C. tropicalis (27)	76 ± 4	84 ± 3	91 ± 3	64 ± 3	72 ± 2	87 ± 3	59 ± 3	78 ± 3	90 ± 3
C. kefyr (25)	73 ± 2	80 ± 2	88 ± 3	61 ± 3	69 ± 2	86 ± 3	54 ± 4	75 ± 3	87 ± 3
C. guilliermondii (21)	68 ± 3	76 ± 4	85 ± 2	59 ± 4	88 ± 3	85 ± 2	51 ± 2	74 ± 2	86 ± 2
C. parapsilosis (20)	75 ± 3	80 ± 3	87 ± 3	67 ± 3	78 ± 2	88 ± 1	58 ± 2	83 ± 2	88 ± 3
C. glabrata (25)	70 ± 3	78 ± 2	86 ± 2	65 ± 4	75 ± 2	86 ± 2	53 ± 3	80 ± 3	87 ± 2

FCZ at 0.25, 0.5, 0.75 MIC was combined with curcumin at various MIC values. The total MIC values in each combination were ≦ 1. The turbidity of each combination was measured and expressed as mean ± standard deviation (n=5).

agent at 1 MIC. The various combinations included 0.75 MIC AMB (or FCZ) plus 0.25 MIC curcumin; 0.5 MIC AMB (or FCZ) plus 0.5 MIC curcumin; 0.25 MIC AMB (or FCZ) plus 0.75 MIC curucmin. It should be pointed out that the sum of MICs in the above combinations was ≦ 1. Since these combinations offered a similar or greater inhibitory effect than 1 MIC AMB or 1 MIC FCZ, the use of these combinations not only enhanced the overall fungicidal effect but also lowered the dosage of AMB or FCZ, which could reduce the risk of drug-induced cytotoxicity. These advantages should be beneficial in the treatment of candidiasis or candidemia.

An interesting finding is that 0.75 MIC AMB plus 0.25 MIC curcumin, 0.5 MIC AMB plus 0.5 MIC curcumin, and 0.25 MIC AMB plus 0.75 MIC curcumin resulted in similar fungicidal effects; indicating these combinations resulted in ≧ 85% reduction in turbidity for *C. krusei* and ≧ 90% reduction in turbidity for other tested *Candida* species (Table 3). As shown in Table 4, 0.25 MIC FCZ plus 0.75 MIC curcumin also offered similar inhibitory effect as 0.25 MIC AMB plus 0.75 MIC curcumin. Accordingly, in order to decrease the side effects of AMB (or FCZ) and to enhance the overall fungicidal effect against these *Candida* species, 0.25 MIC AMB (or FCZ) plus 0.75 MIC curcumin would be the best choice for clinical use, since the dosage of AMB (or FCZ) was very low.

The fungal cytotoxicity of amphotericin B is due to the interaction of this drug with fungal membrane ergosterol over the mammalian cell counterpart, cholesterol[6]. Like other azole compounds, the fungal cytotoxicity of fluconazole results from its binding to cytochrome p-450 molecules

involved in the synthesis of fungal ergosterol[20,21]. The failure of ergosterol synthesis then leads to the death of fungi. It has been reported that the anti-tumor effect of curcumin was due to the fact that this agent blocked arachidonic acid metabolism by inhibiting cycloxygenase and/or lipoxygenase activities[22,23]. The action mode of curcumin against fungi might be also due to its enzyme inhibitory effects, which is apparently different from that of amphotericin B. This different action mode of curcumin from amphotericin B could account in part for the enhanced inhibitory effect observed in these combinations. Nevertheless, it is not the only determinant because the effect of combined therapy was not simply additive. Further study is necessary to elucidate the fungicidal mechanism when these two agents cooperate.

Pharmacokinetic studies have indicated that following oral administration to rats and humans, curcumin was poorly absorbed and was transformed into metabolites during absorption through the intestine[24]. The major metabolites of curcumin in mice are curcumin glucuronide, dihydrocurcumin glucuronide, tetrahydrocurcumin[25]. It remains unknown whether these metabolites still possess antifungal activity like curcumin. However, the work of Shoba *et al*.[26] reported that piperine (20 mg), a major component of black pepper (*Piper nigrum* L.), remarkably enhanced the bioavailability of curcumin in humans with no adverse effects. Therefore, when curcumin is orally administrated as an antifungal agent, the concomitant use of piperine might be considered. Otherwise, i.v. administration of curcumin should be a better route for its efficacy because amphotericin B or fluconazole could be administrated via this method.

In conclusion, the combination of curcumin with amphotericin B or fluconazole exhibited a stronger fungicidal activity than monotherapy with curcumin, amphotericin B or fluconazole, respectively. The enhanced fungicidal effect observed in combined therapy suggests that the interactions between curcumin and these two agents were more than additive. These results suggest that the combined therapy of curcumin with one of these two agents may benefit the treatment of clinical fungal infections.

ACKNOWLEDGMENT

This research was supported by a grant from the National Science Council, ROC [NSC 89-2320-B-040-023].

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薑黃素與Amphotericin B或Fluconazole共同使用增強抑制念珠菌之功效

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摘　要

七種院內感染的念珠菌（共200隻取自臨床黴菌感染病患的菌株）被使用來探討薑黃素的單獨抑菌能力，及其與amphotericin B或fluconazole共同使用時的抑菌效果。此一共同使用時的抑菌效果以FIC index及turbidity降低的%來表示。結果發現，薑黃素對這七種念珠菌的最低抑制濃度爲32-128 μg/mL。薑黃素與amphotericin B共同使用時則表現出加乘效果;而薑黃素與fluconazole共同使用時，對某些菌表現出加乘效果，但是對某些菌卻表現出加成效果。由於薑黃素與amphotericin B或fluconazole共同使用時可以因這些加乘或加成效果而減少amphotericin B或fluconazole的使用劑量，如此也可降低因這兩種藥物所誘發的副作用。本研究結果支持薑黃素與amphotericin B或fluconazole共同使用將有助於院內念珠菌感染的治療。

關鍵詞：薑黃素，amphotericin B，fluconazole，念珠菌