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Synergistic Growth Inhibition of Herbal Plant Extract Combinations against *Candida albicans*

Jeemin YOON[1] · Tae-Jong KIM[1,†]

ABSTRACT

Many skin diseases are caused by microbial infections. Representative pathogenic fungus and bacterium that cause skin diseases are *Candida albicans* and *Staphylococcus aureus*, respectively. *Malassezia pachydermatis* is a fungus that causes animal skin diseases. In this study, we propose a method for removing pathogenic microorganisms from the skin using relatively safe edible herbal extracts. Herbal extracts were screened for skin health through the removal of pathogenic microorganisms, and combinations for effective utilization of the screened extracts were identified. In this study, among methanol extracts of 240 edible plants, *C. albicans*, *S. aureus*, and *M. pachydermatis* were killed by extracts of 10 plants: Acori Gramineri Rhizoma, Angelicae Tenuissimae Radix, Cinnamomi Cortex, Cinnamomi Ramulus, Impatientis Semen, Magnoliae Cortex, Moutan Cortex Radicis, Phellodendri Cortex, Scutellariae Radix, and Syzygii Flos. By evaluating the synergistic antifungal activities against *C. albicans* using all 45 possible combinations of these 10 extracts, five new synergistic antifungal combinations, Acori Gramineri Rhizoma with Magnoliae Cortex extracts, Acori Gramineri Rhizoma with Phellodendri Cortex extracts, Angelicae Tenuissimae Radix with Magnoliae Cortex extracts, Magnoliae Cortex with Phellodendri Cortex extracts, and Phellodendri Cortex with Syzygii Flos extracts, were identified. By utilizing the selected extracts and five combinations with synergistic antifungal effects, this work provides materials and methods to develop new and safe methods for treating candidiasis using natural products.

Keywords: *Candia albicans*, *Malassezia pachydermatis*, plant extract, *Staphylococcus aureus*, synergistic antifungal activity

1. INTRODUCTION

Candida spp. are resident fungi isolated from skin, digestive tract, vagina, and oral cavity (Hedderwick and Kauffman, 1997). They are generally harmless to humans, but their overgrowth can cause infectious diseases. Among *Candida* spp. causing pathogenic infections, *Candida albicans* is the species most frequently isolated from clinical specimens (Kumamoto and Vinces, 2005). *Candida* spp., including *C. albicans*, exist in up to 75% of microbiota in the oral cavity (Calderone and Clancy, 2011), and oral candidiasis can occur due to overgrowth or infection (Epstein, 1990). Vulvovaginal candidiasis is a common disease suffered by approximately 75% of women at least once in their lifetime (Sobel, 1992, 1997). It has been reported that more than 90% of cases of vulvovaginal candidiasis are caused by *C. albicans* (Sobel, 2007). *Candida* spp. have also been reported to cause bloodstream infections in patients in intensive care units (Stover *et al.*, 2001; Wisplinghoff *et al.*, 2004),

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[1] Department of Forest Products and Biotechnology, Kookmin University, Seoul 02707, Korea
[†] Corresponding author: Tae-Jong KIM (e-mail: bigbell@kookmin.ac.kr, https://orcid.org/0000-0002-7483-0432)

and such infections lead to prolonged hospitalization and high mortality (Falagas *et al.*, 2006). According to surveys, candidiasis is the second leading cause of death due to nosocomial infections (Beck-Sagué *et al.*, 1993).

Fluconazole, intraconazole, and voriconazole, which are azoles, and amphotricin B, a polyene, are used for treating *C. albicans* infection (Garcia-Cuesta *et al.*, 2014; Pfaller *et al.*, 2009). However, recent studies have reported the identification of fluconazole-resistant *C. albicans* strains (Raschig *et al.*, 2023; Xiang *et al.*, 2013; Zhao *et al.*, 2013). As the need for safe antifungal agents increases, plant-derived materials are being actively investigated as a source of such agents. Between 1966 and 1994, 115 papers were published in PubMed on the antimicrobial activity of medicinal plants, but during the decade between 1995 and 2004, this number increased sharply to 307 (Ríos and Recio, 2005). Many plants used in traditional medicine contain natural bioactive agents that exert health-promoting activities with little or no side effects. These traditional medicinal plants are known to have various secondary metabolites such as tannins, terpenoids, alkaloids, and flavonoids with antimicrobial activities (Cowan, 1999). Many extracts and chemicals from plants showed antifungal activity (Adfa *et al.*, 2020; Hidayat *et al.*, 2019), antibacterial activity (Ham *et al.*, 2020; Mun *et al.*, 2021), and antibiofilm activity (Ham and Kim, 2018, 2019, 2022).

Several plant components have been shown to act synergistically with antifungal agents and to exert therapeutic effects against fungal infections with the benefits of broad efficacy, safety, reduced toxicity, and reduced antifungal resistance (Augostine and Avery, 2022; Lee *et al.*, 2021; Ogidi *et al.*, 2021). The use of two antifungal agents that act synergistically is particularly useful and effective because they can increase both the rate and the degree of sterilization (Mukherjee *et al.*, 2005), while each agent may also have a different mechanism of antifungal activity (Johnson *et al.*, 2004; Wagner and Ulrich-Merzenich, 2009). Recently, with the publication of an increasing number of reports on the azole resistance of *C. albicans*, it has become more important to increase antifungal activity by establishing appropriate mixtures of new antifungal substances and existing antifungal agents (Rosato *et al.*, 2008). In a previous study (Nweze and Eze, 2009), *Ocimum gratissimum* leaf ethanol extract showed synergistic antifungal activity with ketoconazole against clinically isolated *C. albicans*. *Ca*Thi, a plant-derived peptide component, is known to have a synergistic effect by binding with fluconazole and affecting the invasion of *C. albicans* plasma membrane (Taveira *et al.*, 2016). Basil essential oil and its main single compound, geraniol, have also been reported to exert synergistic effects on *C. albicans* and *Cryptococcus neoformans* upon mixing with antifungal agents (Cardoso *et al.*, 2016). In addition, our previous studies showed that combinations of Magnoliae Cortex extract with Syzyii Flos extract (Yoon and Kim, 2021) or Phellodendri Cortex extract (Na and Kim, 2022) showed synergistic antifungal activity.

Many studies have been conducted on the synergistic activities that can be obtained by mixing plant-derived compounds or plant essential oils with antifungal agents. However, studies demonstrating synergistic activity upon mixing plant extracts are limited. In this study, antimicrobial activities against *Staphylococcus aureus*, and *Malassezia pachydermatis* were also considered, and synergistic antifungal combinations of selected herbal extracts were screened comprehensively and systematically.

2. MATERIALS and METHODS

2.1. Strains, plant extract library, and medium

C. albicans KCTC 7965, *M. pachydermatis* KCTC 17008, and *S. aureus* KCTC 1916 were purchased from Korean Collection for Type Cultures at the Korea

Research Institute of Bioscience and Biotechnology (Jeongeup, Korea). Both fungi were mixed with 15% glycerol and *S. aureus* was mixed with 25% glycerol and stored at −80℃.

A library with extracts from 280 edible plants from a previous study (Yoon and Kim, 2021) was used here. The extract preparation method constituting the library was described in a previous study (Ham and Kim, 2018). Yeast extract peptone dextrose medium (YPD), Sabouraud dextrose medium, and RPMI-1640 medium were made in accordance with a previous study (Yoon and Kim, 2021). Modified Dixon (mDixon) medium was prepared with 3.6% malt extract, 2% desiccated ox bile, 1% Tween 40, 0.6% peptone, 0.2% glycerol, and 0.2% oleic acid. Tryptic Soy Broth (TSB) medium was prepared with 3% TSB (REF: 211825; Becton Dickinson, Franklin Lakes, NJ, USA). mDixon agar plates, Sabouraud dextrose agar plates, TSB agar plates, and YPD agar plates were prepared by adding 1.5% agar to the corresponding medium.

2.2. Measuring the growth inhibition zone of *Malassezia pachydermatis* and *Staphylococcus aureus* produced by plant extracts

A disk with the plant extract for the paper disc diffusion method was made in accordance with a previous study (Yoon and Kim, 2021). *M. pachydermatis* was pre-cultured in mDixon medium at 30℃ for 4 days. The pre-cultured cells were diluted to Abs_{600} = 1.5 using mDixon medium, and spread evenly on mDixon agar plates with 0.1 mL of diluted cells. A paper disk with 5 mg of plant extract was placed on the plate smeared with cells (Yoon and Kim, 2021). After culturing for 48 h at 30℃ with 5 mg of extract, it was judged that there was an antifungal effect when a growth inhibitory ring of 1 mm or more had formed on the paper. The width and length of the growth inhibitory ring were measured in millimeters. Six values measured in two independent experiments were averaged.

S. aureus was pre-cultured in TSB medium at 37℃ for 24 h. The pre-cultured strain was diluted to Abs_{600} = 1.0 using TSB medium, and 0.1 mL of diluted cells were evenly spread on TSB agar plates. A paper disk with 5 mg of plant extract was placed on the plate smeared with cells. After culturing for 24 h at 37℃, it was judged that there was an antibiotic activity when a growth inhibitory ring of 1 mm or more had formed on the paper. The width and length of the growth inhibitory ring were measured in millimeters. The four values measured in two independent experiments were averaged.

2.3. Measuring the cell growth inhibition of *Candida albicans* by selected plant extracts and their combinations

The activity of inhibiting the growth of *C. albicans* according to the concentration of plant extracts and the synergistic inhibition of *C. albicans* growth by the combination of two plant extracts were evaluated in accordance with the procedure in a previous study (Yoon and Kim, 2021). Powdered extracts and chemicals were dissolved at 100 times the concentration to be tested. The combinational antifungal activity of each 50 μL extract or chemical was evaluated in 5 mL of YPD medium.

3. RESULTS and DISCUSSION

3.1. Plant extracts having antifungal activity against *Malassezia pachydermatis* and antibiotic activity against *Staphylococcus aureus*

In a previous study (Yoon and Kim, 2021), 17 plant extracts were selected by evaluating the antifungal effect on *C. albicans* using the paper disk diffusion method. In this study, it was evaluated whether these 17 selected plant extracts exhibited antifungal and antibacterial activity against *M. pachydermatis*, another animal skin fungus, and *S. aureus*, a skin bacterium, respectively (Table 1). Additional antifungal activity against *M. pachydermatis* and antibiotic activity against *S. aureus* provide broad applications against skin fungi and bacteria.

Among the 17 tested plant extracts, 16 of them (with the exception of Polygalae Radix) exhibited antifungal activity against *M. pachydermatis*. Similar to the results for *C. albicans* (Yoon and Kim, 2021), the inhibited ring size of Cinnamomi Cortex was 42.3 mm, showing the greatest inhibitory activity. With the exceptions of Cinnamomi Ramulus, Cocculi Radix, and Polygalae Radix, larger inhibitory ring sizes were observed in *M. pachydermatis* than in *C. albicans*.

In the evaluation of the antibiotic activity of 17 plant extracts against *S. aureus*, Cocculi Radix, Polygalae Radix, and Rhizome of *Kaempferia galangal* extracts showed no antibiotic activity. Among the 14 extracts with antibiotic activity against *S. aureus*, Cinnamomi Cortex showed the greatest activity with an inhibitory ring of 22.3 mm, and Syzygii Flos showed the second largest inhibitory activity with 21.8 mm, similar to the

Table 1. Antimicrobial activity of 17 plant extracts on the growth of *Malassezia pachydermatis* and *Staphylococcus aureus*

Plant used for extracts	Diameter of growth inhibition zone (mm)	
	M. pachydermatis	*S. aureus*
Control	No zone	No zone
Acori Gramineri Rhizoma	17.0 ± 0.8	11.6 ± 0.5
Amomi Tsao-ko Fructus	11.8 ± 1.0	7.5 ± 0.0
Angelicae Tenuissimae Radix	23.5 ± 0.6	7.0 ± 0.0
Cinnamomi Cortex	42.3 ± 2.1	22.3 ± 0.5
Cinnamomi Ramulus	16.3 ± 0.5	7.3 ± 0.3
Cnidii Rhizoma	20.5 ± 0.6	7.0 ± 0.0
Cocculi Radix	7.0 ± 0.0	No zone
Flower of *Rosa multiflora*	14.4 ± 0.5	10.3 ± 0.5
Impatientis Semen	23.5 ± 0.6	12.0 ± 0.8
Magnoliae Cortex	24.8 ± 0.5	12.5 ± 0.0
Moutan Cortex Radicis	12.5 ± 1.0	10.0 ± 0.0
Phellodendri Cortex	13.3 ± 1.5	9.3 ± 0.3
Polygalae Radix	No zone	No zone
Rhizome of *Kaempferia galangal*	17.3 ± 0.5	No zone
Sanguisorbae Radix	9.8 ± 1.0	9.8 ± 0.3
Scutellariae Radix	8.5 ± 0.6	8.9 ± 0.3
Syzygii Flos	21.5 ± 0.6	21.8 ± 1.0

The diameter of growth inhibition zones is shown as the average of three samples with the SD.

results of *C. albicans* and *M. pachydermatis*.

According to the results of Table 1 and the antifungal activity on *C. albicans* in a previous study (Yoon and Kim, 2021), Cinnamomi Cortex showed the greatest growth inhibitory activity against all tested three strains, while Syzygii Flos and Magnoliae Cortex also showed excellent antimicrobial activity.

Cocculi Radix, Polygalae Radix, and Rhizome of *Kaempferia galangal*, which had no antibiotic activity against *S. aureus*, were excluded from additional experiments because, in terms of skin hygiene, it would be highly beneficial to inhibit the growth of all three tested strains simultaneously.

3.2. Evaluation of antifungal activity according to the concentration of the extract against *Candida albicans*

Among 14 selected plant extracts, the antifungal activity of Cinnamomi Cortex, Cinnamomi Ramulus, Magnoliae Cortex, and Syzygii Flos was evaluated against *C. albicans* in a previous study (Yoon and Kim, 2021). The antifungal activity of the remaining 10 plant extracts against *C. albicans* was measured in this study. Among them, the extracts of Amomi Tsao-ko Fructus, Cnidii Rhizoma, Flower of *Rosa multiflora*, and Sanguisorbae Radix were excluded from further studies because they did not exhibit any growth inhibitory activity against *C. albicans* in liquid culture, although they showed antifungal activity in the paper disc method. Extracts of the remaining six plants, Acori Gramineri Rhizoma, Angelicae Tenuissimae Radix, Impatientis Semen, Moutan Cortex Radicis, Phellodendri Cortex, and Scutellariae Radix, showed antifungal activity against *C. albicans* in liquid culture (Fig. 1).

Acori Gramineri Rhizoma extract showed growth inhibitory activity from concentrations of 1 g/L and above. The mycelial growth inhibition of *Cladosporium cucumerinum*, *Colletotrichum orbiculare*, *Magnaporthe grisea*, and *Pythium ultimum* by β-asrone, one of the main components of Acori Gramineri Rhizoma, have been studied (Lee *et al.*, 2004; Rajput *et al.*, 2013).

Angelicae Tenuissimae Radix and Impatientis Semen extracts showed similar growth inhibitory effects of 45% and 46%, respectively, at 2 g/L.

Moutan Cortex Radicis extract showed growth inhibitory activity of 21% at 0.25 g/L. At higher concentrations, it did not show any further growth inhibitory activity.

Although the size of the inhibitory zone was not large in the paper disc method, Phellodendri Cortex extract showed relatively good antifungal activity in liquid culture. As the concentration increased from 0.13 g/L, the growth inhibitory activity increased. Antifungal activity of water and ethanol extracts of Phellodendri Cortex against *C. albicans* has been reported in a previous study (Park *et al.*, 1992), and the antifungal activity of berberine and palmatine isolated from Phellodendri Cortex was also reported (Xiao *et al.*, 2015).

The growth inhibition of Scutellariae Radix extracts also increased as the concentration increased at 0.5 g/L or more. It showed an inhibitory effect of 80.4% at 2 g/L. Considering that Scutellariae Radix extracted with ethanol did not show antifungal activity against *C. albicans* (Cho and Kim, 2001), it is suggested that compounds extracted only with methanol have significant antifungal activity.

3.3. Synergistic antifungal activity on *Candida albicans* by extract combination

Using the 10 selected plant extracts [4 plant extracts from a previous study (Yoon and Kim, 2021) and six plant extracts from Fig. 1], the antifungal activity of 45 combinations of two extracts against *C. albicans* was evaluated (Fig. 2). To evaluate the synergistic growth inhibitory activity, the concentration of the extract that

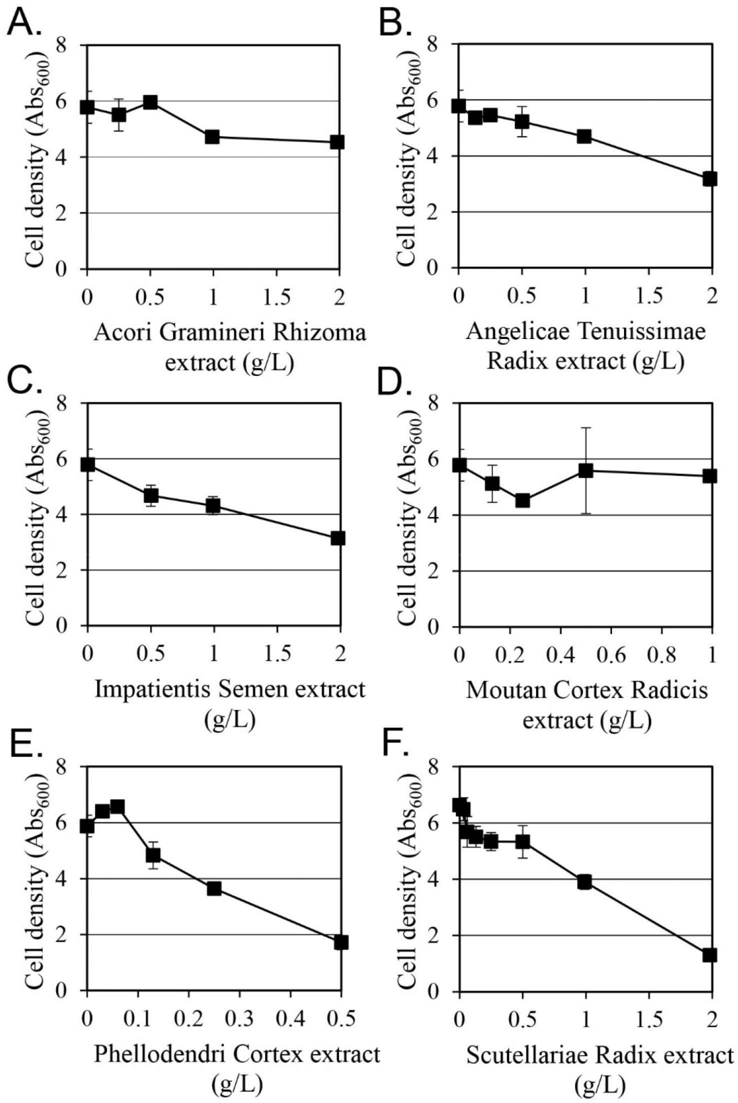

Fig. 1. Antifungal activity of plant methanol extracts against *Candida albicans*. (A) Acori Gramineri Rhizoma extract; (B) Angelicae Tenuissimae Radix extract; (C) Impatientis Semen extract; (D) Moutan Cortex Radicis extract; (E) Phellodendri Cortex extract; (F) Scutellariae Radix extract.

inhibited only about 20% of the growth was tested. The concentrations of each extract to evaluate the synergistic antifungal activity are shown in Fig. 2. The growth inhibitory activity of 40% or more should be observed to show synergistic growth inhibitory activity. Combinations of extracts showing synergistic growth inhibition of more than 40% were Acori Gramineri Rhizoma and Magnoliae Cortex, Acori Gramineri Rhizoma and Phellodendri Cortex, Angelicae Tenuissimae Radix and Magnoliae Cortex, Magnoliae Cortex and Phellodendri

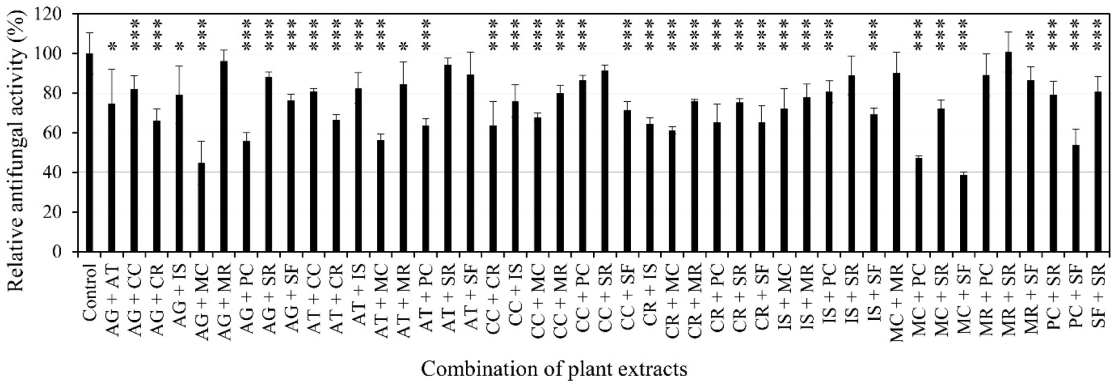

Fig. 2. Synergistic antifungal activity of combinations of antifungal plant extracts. The concentrations of plant extracts used were 0.99 g/L for Acori Gramineri Rhizoma (AG), 0.9 g/L for Angelicae Tenuissimae Radix (AT), 0.06 g/L for Cinnamomi Cortex (CC), 0.3 g/L for Cinnamomi Ramulus (CR), 0.76 g/L for Impatientis Semen (IS), 0.06 g/L for Magnoliae Cortex (MC), 0.25 g/L for Moutan Cortex Radicis (MR), 0.13 g/L for Phellodendri Cortex (PC), 0.13 g/L for Scutellariae Radix, and 0.12 g/L for Syzygii Flos (SF). *,**,*** Values that differ from the control with a 90%, 95%, or 99% confidence level in *t*-test.

Cortex, Magnoliae Cortex and Syzygii Flos, and Phellodendri Cortex and Syzygii Flos.

3.4. Combinations of two extracts with synergistic antifungal activity against *Candida albicans*

Since the synergistic antifungal activity of the Magnoliae Cortex and Syzygii Flos combination was shown in a previous study (Yoon and Kim, 2021), in this study synergistic antifungal activity was evaluated for the remaining five combinations (Fig. 3).

Combination of Acori Gramineri Rhizoma and Magnoliae Cortex extracts (Fig. 3A): The growth inhibitory activity was 47.1% and 25.6% by Acori Gramineri Rhizoma extract (0.99 g/L) and Magnoliae Cortex extract (0.06 g/L), respectively. When the two extracts were mixed, the growth inhibitory activity was 94.5%. A synergistic effect was observed because the inhibitory activity of the mixture was more than double those of the individual extracts.

Combination of Acori Gramineri Rhizoma and Phellodendri Cortex extracts (Fig. 3B): The growth inhibitory activity was 47.1% and 23.3% by Acori Gramineri Rhizoma extract (0.99 g/L) and Phellodendri Cortex extract (0.13 g/L), respectively. When the two extracts were mixed, the growth inhibitory activity was 91.5%. The growth inhibitory activity of the mixture was 3.93 times that of the Phellodendri Cortex extract and 1.94 times that of the Acori Gramineri Rhizoma extract. This showed a partial synergistic effect of the combination of Acori Gramineri Rhizoma and Phellodendri Cortex extracts.

Combination of Angelicae Tenuissimae Radix and Magnoliae Cortex extracts (Fig. 3C): The growth inhibitory activity was 11.4% and 25.6% by Angelicae Tenuissimae Radix extract (0.89 g/L) and Magnoliae Cortex extract (0.06 g/L), respectively. When the two extracts were mixed, the growth inhibitory activity was 56.1%. A synergistic effect was observed because the inhibitory activity of the mixture was more than double those of the individual extracts.

Combination of Magnoliae Cortex and Phellodendri Cortex extracts (Fig. 3D): The growth inhibitory activity was 24.3% and 25.6% by Magnoliae Cortex extract (0.06 g/L) and Phellodendri Cortex extract (0.13 g/L), respectively. When the two extracts were mixed, the growth inhibitory activity was 58.6%. A synergistic effect was observed because the inhibitory activity of the mixture was more than double those of the individual extracts.

Combination of Phellodendri Cortex and Syzygii Flos extracts (Fig. 3E): The growth inhibitory activity was 19.4% and 23.3 by Phellodendri Cortex extract (0.13

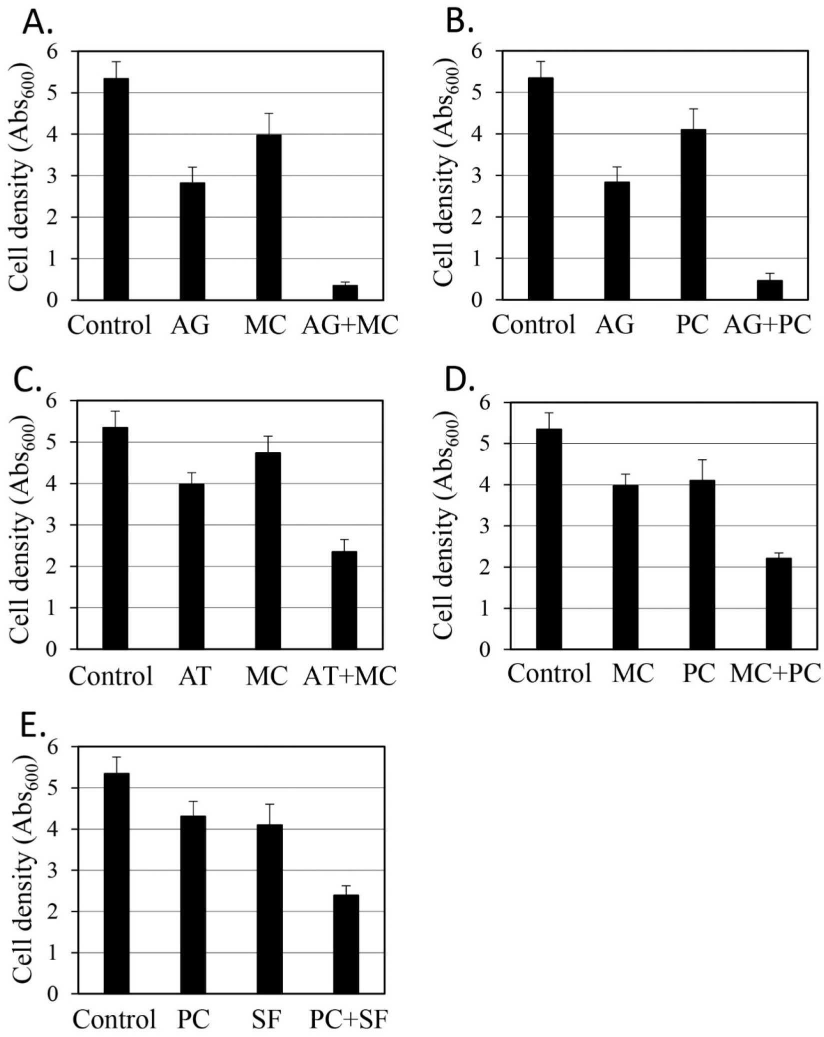

Fig. 3. Synergistic antifungal activity of combinations of two plant extracts against *Candida albicans*. The combinations of two plant extracts used were Acori Gramineri Rhizoma extract (AG) and Magnoliae Cortex extract (MC) in (A); Acori Gramineri Rhizoma extract (AG) and Phellodendri Cortex extract (PC) in (B); Angelicae Tenuissimae Radix extract (AT) and Magnoliae Cortex extract (MC) in (C); Magnoliae Cortex extract (MC) and Phellodendri Cortex extract (PC) in (D); and Phellodendri Cortex extract (PC) and Syzygii Flos extract (SF) in (E). The concentration of the plant extract used was the same as the concentration in Fig. 2.

g/L) and Syzygii Flos extract (0.12 g/L), respectively. When the two extracts were mixed, the growth inhibitory activity was 55.2%. A synergistic effect was observed because the inhibitory activity of the mixture was more than double those of the individual extracts.

In this study, combinations of plant extracts that simultaneously inhibit the growth of the skin pathogenic fungi *C. albicans* and *M. pachydermatis* and the skin bacterium *S. aureus* were used to synergistically inhibit the growth of *C. albicans*. The efficacy of these combinations of plant extracts suggests that they could be used for preventing and treating *Candida* infections, such as stomatitis, vaginitis, and candidemia. Since methanol has safety issues, it is necessary to confirm in additional experiments whether the similar antimicrobial activities are obtained in a safe extraction method using the water or ethanol solvent of the selected 10 plants.

4. CONCLUSIONS

In this study, 10 methanol extracts that simultaneously inhibited *C. albicans*, *M. pachydermatis*, and *S. aureus*, which caused infectious diseases of the skin, were selected from among 240 edible plants. By evaluating all combinations of two extracts, it was identified that five new combinations had partially or fully synergistic antifungal activity. Among the identified combinations, the growth inhibitory activity of 0.06 g/L of Magnoliae Cortex extract with 0.13 g/L of Phellodendri Cortex extract against *C. albicans* was the strongest with 59% inhibition. The extracts and their combinations in this study provide alternative methods for curing infectious diseases of the skin and developing products for safe skin hygiene.

CONFLICT of INTEREST

No potential conflict of interest relevant to this article was reported.

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