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POTENTIAL INHIBITORY POWER OF "*CURCUMA LONGA LINN.*" EXTRACT AGAINST *CANDIDA ALBICANS* FUNGUS

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ABSTRACT

Oral candidiasis is a fungal infection that often appears on the oral mucosa. These lesions are caused by the fungus *Candida albicans*. *Candida albicans* is the most common pathogenic *Candida* species causing fungal infections of the oral cavity. The use of antifungal drugs is the most common way of giving, but there are many side effects that can be caused. Herbal ingredients that have antifungal effects can be alternative therapies with fewer side effects, one of which is turmeric (*Curcuma longa Linn*.). Turmeric has various compounds that have the potential as antifungals including *curcumin*, *flavonoids*, and essential oils that work by inhibiting the growth of fungi including *Candida albicans*. The purpose of this literature study is to provide scientific evidence related to the potential inhibition of turmeric extract (*Curcuma longa Linn*.) against *Candida albicans*. This writing is a literature study made based on reference sources or references obtained from journals accessed through the databases of Google Scholar, Hindawi, PubMed, Scopus, DOAJ, Research Gate and textbooks. The results of the study stated that turmeric extract had an inhibitory effect on the growth of *Candida albicans*, the greater the concentration of turmeric extract used, the greater the inhibition caused. Turmeric also has fewer side effects than antifungal drugs.

INTRODUCTION

Dental and oral health is still a problem in society that needs attention. It is shown by the prevalence of people who have dental and oral problems in Indonesia according to Riskesdas 2018 which has increased sharply from 23.2% in 2007 to 57.6% in 2018 (Riset Kesehatan Dasar, 2018). One of the causes of dental and oral problems is a fungal infection. Fungi are a group of microorganisms that can be freely present in the environment, become part of the normal flora of humans and have the ability to cause mild superficial infections to

life-threatening invasive infections. *Candida albicans* is by far the most common pathogenic *Candida* species and can cause a wide spectrum of diseases including skin, mucosal and systemic infections. *Candida albicans* infection is very common on mucosal surfaces (Gow & Hube, 2012).

WHO (World Health Organization) estimates that out of about 6.3 billion global population, around 4 billion (80%) mainly in developing countries, depend on traditional medicine, especially herbal medicines for their health care needs (Busia, 216 C.E.). The use of traditional medicine is generally considered safer and has relatively fewer side effects than modern medicine (Suharsanti & Wibowo, 2016). Turmeric is one of the spices that is in great demand both from the medical world and from the culinary world (Hewlings & Kalman, 2017).

Turmeric is an ancient Asian coloring spice and has been conventionally used as an antimicrobial agent and insect repellent (Paul et al., 2018). Turmeric has been used in traditional medicine and therapy for centuries in various parts of the world (Prasad & Aggarwal, 2011). Ayurvedic medicine uses turmeric to treat anorexia, diabetic wounds, bile disorders, liver disorders, and coughs whereas traditional Chinese medicine claims its use for stomach pain and jaundice management (Alafiatayo et al., 2019).

South Asian countries use it as an antiseptic for burns, bruises, and as an antibacterial agent. Pakistan and Afghanistan use turmeric to clean wounds and stimulate healing by applying it to a burnt piece of cloth and placing it over the wound (Prasad & Aggarwal, 2011).

Turmeric rhizome contains essential oils, *curcumin*, *flavonoids*, *resins*, *oleoresin*, *dimethoxy curcumin*, and *bisdementhoxy curcumin*. The active ingredients that act as antimicrobials and can inhibit the growth of *Candida albicans* are *curcumin*, *flavonoids* and essential oils (Nadifah et al., 2018). *Curcumin*, *dimethoxy curcumin*, and *bisdementhoxy curcumin* belong to the class of phenolic compounds as antifungals that can inhibit the growth of *Candida albicans* by damaging cell membranes and protein denaturation. (Mubarak et al., 2019).

Studies from various empirical experiences have been proven to gain confidence in the efficacy of using herbal medicines as antifungals in recent decades. The research of Harit et al. in 2013 stated that the ethanolic extract of turmeric has shown significant antimicrobial activity against *Streptococcus aureus, Aspergillus flavus* and *Candida albicans* with inhibition zones of 12.0, 11.0 and 10.0, respectively, at a concentration of 20 mg ml^{-1} (Harit et al., 2013). Murugesh et al. conducted a study in 2019 on four dilutions of *Candida albicans* agar, namely 1:10, 1:20, 1:40 and 1:80, then the agar plate was mixed with 7 different concentrations of turmeric alcohol extract ranging from 50, 100, 200, 400, 800, 1600 and 3200µl on 7 separate plates. The results showed that the growth of *Candida albicans* was inhibited at a concentration of 800 l which was considered as the MIC (Minimum Inhibitory Concentration) of turmeric alcohol extract on *Candida albicans* (Murugesh et al., 2019). Based on these studies, the authors would like to discuss further about the potential inhibition of turmeric extract (*Curcuma longa Linn*) against the fungus *Candida albicans*. The purpose of this paper is to study and analyze the potential of turmeric extract (*Curcuma longa Linn*.) which is effective in inhibiting the fungus *Candida albicans*.

METHOD

The type of research used in this study is a literature study. After the researcher determines the topic and sets the problem formulation, then collects data based on reference sources obtained from journals that are accessed through the databases of Google Scholar, Hindawi, PubMed, Research Gate and textbooks (Darmadi, 2011). Reference collection was carried out using the keywords "Turmeric, Candida albicans, Antifungal and Curcumin". These references are selected based on an analysis that is relevant to the topic being studied. The types

of journals taken are research journals and descriptive journals published in 2011-2021.

RESULT AND DISCUSSION

Oral candidiasis is a fungal infection that often appears on the oral mucosa. These lesions are caused by the fungus *Candida albicans*. *Candida albicans* is a component of the normal oral microflora and about 30% to 50% of people have this organism in their oral cavity (Singh et al., 2014). *Candida albicans* is a dimorphic fungus that has the ability to transition from commensal to pathogenic, which is the result of a morphological transition from yeast to hyphae, which plays an important role in the pathogenesis process and biofilm formation (Garcia-Cuesta et al., 2014).

Treatment of *oral candidiasis* is based on four things, namely: (1) making an accurate early diagnosis of infection; (2) improve predisposing factors or factors that underlie the onset of the disease; (3) evaluate the type of *Candida* infection; (4) proper use of antifungal drugs and evaluate the efficacy/toxicity ratio. Treatment will be selected taking into account the type of *Candida*, its clinical pathology and consideration of whether topical treatment is sufficient or requires more complex systemic treatment (Garcia-Cuesta et al., 2014).

Treatment for *oral candidiasis* varies based on the severity of the disease. The Infectious Diseases Society of America (IDSA) recommends that mild *oral candidiasis* be treated topically with nystatin suspension or clotrimazole. Moderate to severe *oral candidiasis* should be treated with systemic antifungals. The triazole antifungal options for *oral candidiasis* are fluconazole, itraconazole, voriconazole, and posaconazole. Amphotericin B or voriconazole oral suspension is the last-line option for patients who have failed itraconazole or posaconazole treatment. If neither oral option is successful, intravenous amphotericin B or an antifungal from the echinocandin class can be used (Glick, 2015).

The mechanism of action of turmeric as an antifungal is similar to the mechanism of action of nystatin which damages cell membranes through binding itself or combining with sterols contained in cell membranes, causing damage to cell membranes and causing leakage of cytoplasmic contents so that it can kill the fungus *Candida albicans* (Astutiningsih et al., 2014). Turmeric does not cause toxic effects, the side effects of *curcumin* are also not higher than ibuprofen, but there are still possible side effects, including constipation, stomach pain, diarrhea, allergic reactions, vomiting, and nausea (Wu et al., 2019). One of the compounds in turmeric that can cause side effects is *tannin*. *Tannin* compounds when consumed in excessive amounts will inhibit the absorption of minerals such as iron. Large intakes of *tannin*s in sensitive individuals can cause intestinal irritation, kidney irritation, liver damage, stomach irritation and indigestion. The use of ingredients containing high concentrations of *tannin*s is not recommended in the long term or excessive (Ismarani, 2012).

The synergistic activity of *curcumin* with five azole drugs and two polyenes including voriconazole, itraconazole, ketoconazole, miconazole, fluconazole, amphotericin B, and nystatin showed a 10-35-fold decrease in fungicide MIC values against 21 clinical isolates of *Candida albicans*. The combination of *curcumin* with amphotericin B also showed synergistic activity against the *Candida* species tested, while fluconazole and *curcumin* in some cases showed more additive effects than synergistic activity. These results prove that the combination of *curcumin* with existing fungicidal agents can have a more significant effect on fungal infections such as candidemia and candidiasis (Moghadamtousi et al., 2014).

The number of side effects caused when consuming chemical-based drugs has caused researchers to conduct research on antifungal drugs derived from herbal ingredients, one of which is turmeric. (Verma et al., 2018). Turmeric is a type of

herbal ingredient that contains active compounds such as *curcumin*, essential oils, phenols, *flavonoid*s, *alkaloids*, *terpenoids* and *tannin*s. The content of these secondary metabolites is thought to be able to inhibit the growth of fungi, especially *Candida albicans* (Dewayanti, 2022).

Currently, there are several studies related to the potential inhibition of turmeric extract against the fungus *Candida albicans*, a 2015 study by Septiana et al. who tested the antimicrobial activity of extracts of several parts of the turmeric plant using the paper disc diffusion method. The concentrations of the extracts used were 10,000, 15,000, and 20,000 ppm. The results of the inhibition zone diameter obtained for ethyl acetate extract of turmeric leaves against *Candida albicans* respectively from concentrations of 10,000, 15,000, and 20,000 ppm were 8 mm, 10 mm, and 12 mm. The inhibition zones formed in the ethyl acetate extract of turmeric stems against *Candida albicans* respectively from concentrations of 10,000, 15,000, and 20,000 ppm were 4 mm, 7 mm, and 10 mm. The results of this study showed that ethyl acetate in the leaves and stems of the turmeric plant could inhibit the growth of *Candida albicans* with the highest inhibitory activity found in the ethyl acetate leaf extract with a concentration of 20,000 ppm, while ethanol in all parts of the turmeric plant did not cause inhibition of *Candida albicans* (Septiana & Simanjuntak, 2015).

In contrast to the results of research conducted by Septiana, et al. (2015),), Pulungan (2017) stated that the ethanol extract of turmeric leaves can inhibit the growth of *Candida albicans*. The method used is the scratch method with Potato Dextrose Agar (PDA) media. The concentration of ethanol extract of turmeric leaves used was 10%, 20%, 30%, 40%, 50%, and 60%. The best concentration in inhibiting the growth of *Candida albicans* was at a concentration of 60% where the inhibition zone formed was 7.47 mm. The emergence of the inhibition zone indicated that around the zone there was no visible fungal growth caused by the inhibitory activity of the ethanol extract of turmeric leaves. Ethanol extract of turmeric leaves can cause the growth of *Candida albicans* fungus to be disturbed, according to the given concentration (Pulungan, 2017).

Suraini, *et al.* (2018) conducted an experimental study using turmeric decoction and turmeric + ginger decoction with the concentrations used were 100%, 80%, 50% and 20%. The parameter measured is the size of the diameter formed around the paper disc. The results showed that the average diameter of the inhibition formed in turmeric stew with treatment concentrations of 20%, 50%, 80% and 100% respectively was 7.6 mm, 8 mm, 10.2 mm, and 11.3 mm. The inhibitory power formed in turmeric + ginger decoction with treatment concentrations of 20%, 50%, 80% and 100% respectively were 7.8 mm, 8.6 mm, 12 mm, and 13.3 mm. The formation of an inhibition zone around the disc paper proves that the extract of boiled turmeric and boiled turmeric + ginger is antifungal against *Candida albicans* because it contains active compounds such as *tannin*s, essential oils, palmitic acid, alkaloids, *flavonoid*s and terpenoids. (Suraini & Putri, 2018).

Another study was conducted by Nadifah, et al. (2018) which stated that turmeric rhizome essential oil was significantly able to inhibit the growth of *Candida albicans*. This type of research is experimental research with well diffusion method. The essential oil was obtained through the distillation method and the concentrations used were 20%, 40%, 60%, 80% and 100%. The treatment was repeated three times. The results of the inhibition zones formed at concentrations of essential oils of 20%, 40%, 60%, 80%, 100% respectively were 6.16 mm, 6.50 mm, 6.66 mm, 7.00 mm, and 7, respectively. 83 mm. The inhibition zone is formed due to the process of absorption of antifungal substances (essential oils) into the agar media that has been planted with fungi (Nadifah et al., 2018).

Mubarak, et al (2019) stated that turmeric extract can inhibit the growth of *Candida albicans* in various concentrations. The inhibition test in this study used the agar diffusion method (*Kirby-Bauer*) with 100 g nystatin as a positive control and blank disc paper as a negative control. The results showed that turmeric extract with 96% ethanol solvent at concentrations of 12.5%, 25%, 50%, 75% and 100% could inhibit the growth of *Candida albicans*. The diameter of the largest inhibition zone was seen at a concentration of 100% turmeric extract, which was 10.3 mm, and the smallest diameter was seen at a concentration of 12.5%, which was 6.6 mm. (Mubarak et al., 2019).

Based on these studies, it can be said that turmeric has been shown to be effective as an antifungal. 100% turmeric extract is the concentration that forms the largest inhibition zone against *Candida albicans*.

CONCLUSION

Turmeric is an herbal plant that also has an antifungal role. The active substances contained in turmeric include *curcumin*, *flavonoid*s and essential oils. The content of *curcumin* is used as an antifungal by damaging cell walls and denaturing cell proteins so that cells become lysed. This phenolic compound also inhibits several enzymes that play a role in changing the nature of *Candida albicans* from commensal to pathogenic. Essential oils are terpenoid compounds that can destroy bacterial cell membranes, while *flavonoid* compounds have activity that can inhibit adhesion, form complexes with extracellular and dissolved proteins and form complexes with cell walls so that they can damage microbial membranes.

The studies that have been conducted have shown that turmeric can significantly inhibit the growth of *Candida albicans*, the greater the concentration of turmeric extract used, the greater the inhibitory power produced. The greater concentration of turmeric extract has a more concentrated solution so that the active compounds can inhibit the growth of fungi more optimally. Turmeric can be a safe and effective option because it has minimal side effects and is well tolerated when taken in normal amounts.

Other research needs to be done to find out more about the benefits of turmeric as an antifungal, because until now there has been no antifungal herbal medicine made from turmeric to treat fungal infections in the oral cavity.

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Treatment of *oral candidiasis* is based on four things, namely: (1) making an accurate early diagnosis of infection; (2) improve predisposing factors or factors that underlie the onset of the disease; (3) evaluate the type of *Candida* infection; (4) proper use of antifungal drugs and evaluate the efficacy/toxicity ratio. Treatment will be selected taking into account the type of *Candida*, its clinical pathology and consideration of whether topical treatment is sufficient or requires more complex systemic treatment (Garcia-Cuesta et al., 2014).

Treatment for *oral candidiasis* varies based on the severity of the disease. The Infectious Diseases Society of America (IDSA) recommends that mild *oral candidiasis* be treated topically with nystatin suspension or clotrimazole. Moderate to severe *oral candidiasis* should be treated with systemic antifungals. The triazole antifungal options for *oral candidiasis* are fluconazole, itraconazole, voriconazole, and posaconazole. Amphotericin B or voriconazole oral suspension is the last-line option for patients who have failed itraconazole or posaconazole treatment. If neither oral option is successful, intravenous amphotericin B or an antifungal from the echinocandin class can be used (Glick, 2015).

The mechanism of action of turmeric as an antifungal is similar to the mechanism of action of nystatin which damages cell membranes through binding itself or combining with sterols contained in cell membranes, causing damage to cell membranes and causing leakage of cytoplasmic contents so that it can kill the fungus *Candida albicans* (Astutiningsih et al., 2014). Turmeric does not cause toxic effects, the side effects of *curcumin* are also not higher than ibuprofen, but there are still possible side effects, including constipation, stomach pain, diarrhea, allergic reactions, vomiting, and nausea (Wu et al., 2019). One of the compounds in turmeric that can cause side effects is *tannin*. *Tannin* compounds when consumed in excessive amounts will inhibit the absorption of minerals such as iron. Large intakes of *tannin*s in sensitive individuals can cause intestinal irritation, kidney irritation, liver damage, stomach irritation and indigestion. The use of ingredients containing high concentrations of *tannin*s is not recommended in the long term if excessive (Ismarani, 2012).

The synergistic activity of *curcumin* with five azole drugs and two polyenes including voriconazole, itraconazole, ketoconazole, miconazole, fluconazole, amphotericin B, and nystatin showed a 10-35-fold decrease in fungicide MIC values against 21 clinical isolates of *Candida albicans*. The combination of *curcumin* with amphotericin B also showed synergistic activity against the *Candida* species tested, while fluconazole and *curcumin* in some cases showed more additive effects than synergistic activity. These results prove that the combination of *curcumin* with existing fungicidal agents can have a more significant effect on fungal infections such as candidemia and candidiasis (Moghadamtousi et al., 2014).

The number of side effects caused when consuming chemical-based drugs has caused researchers to conduct research on antifungal drugs derived from herbal ingredients, one of which is turmeric. (Verma et al., 2018). Turmeric is a type of

herbal ingredient that contains active compounds such as *curcumin*, essential oils, phenols, *flavonoids*, *alkaloids*, *terpenoids* and *tannins*. The content of these secondary metabolites is thought to be able to inhibit the growth of fungi, especially *Candida albicans* (Dewayanti, 2022).

Currently, there are several studies related to the potential inhibition of turmeric extract against the fungus *Candida albicans*, a 2015 study by Septiana et al. who tested the antimicrobial activity of extracts of several parts of the turmeric plant using the paper disc diffusion method. The concentrations of the extracts used were 10,000, 15,000, and 20,000 ppm. The results of the inhibition zone diameter obtained for ethyl acetate extract of turmeric leaves against *Candida albicans* respectively from concentrations of 10,000, 15,000, and 20,000 ppm were 8 mm, 10 mm, and 12 mm. The inhibition zones formed in the ethyl acetate extract of turmeric stems against *Candida albicans* respectively from concentrations of 10,000, 15,000, and 20,000 ppm were 4 mm, 7 mm, and 10 mm. The results of this study showed that ethyl acetate in the leaves and stems of the turmeric plant could inhibit the growth of *Candida albicans* with the highest inhibitory activity found in the ethyl acetate leaf extract with a concentration of 20,000 ppm, while ethanol in all parts of the turmeric plant did not cause inhibition of *Candida albicans* (Septiana & Simanjuntak, 2015).

In contrast to the results of research conducted by Septiana, et al. (2015),), Pulungan (2017) stated that the ethanol extract of turmeric leaves can inhibit the growth of *Candida albicans*. The method used is the scratch method with Potato Dextrose Agar (PDA) media. The concentration of ethanol extract of turmeric leaves used was 10%, 20%, 30%, 40%, 50%, and 60%. The best concentration in inhibiting the growth of *Candida albicans* was at a concentration of 60% where the inhibition zone formed was 7.47 mm. The emergence of the inhibition zone indicated that around the zone there was no visible fungal growth caused by the inhibitory activity of the ethanol extract of turmeric leaves. Ethanol extract of turmeric leaves can cause the growth of *Candida albicans* fungus to be disturbed, according to the given concentration (Pulungan, 2017).

Suraini, *et al.* (2018) conducted an experimental study using turmeric decoction and turmeric + ginger decoction with the concentrations used were 100%, 80%, 50% and 20%. The parameter measured is the size of the diameter formed around the paper disc. The results showed that the average diameter of the inhibition formed in turmeric stew with treatment concentrations of 20%, 50%, 80% and 100% respectively was 7.6 mm, 8 mm, 10.2 mm, and 11.3 mm. The inhibitory power formed in turmeric + ginger decoction with treatment concentrations of 20%, 50%, 80% and 100% respectively were 7.8 mm, 8.6 mm, 12 mm, and 13.3 mm. The formation of an inhibition zone around the disc paper proves that the extract of boiled turmeric and boiled turmeric + ginger is antifungal against *Candida albicans* because it contains active compounds such as *tannins*, essential oils, palmitic acid, alkaloids, *flavonoids* and terpenoids. (Suraini & Putri, 2018).

Another study was conducted by Nadifah, et al. (2018) which stated that turmeric rhizome essential oil was significantly able to inhibit the growth of *Candida albicans*. This type of research is experimental research with well diffusion method. The essential oil was obtained through the distillation method and the concentrations used were 20%, 40%, 60%, 80% and 100%. The treatment was repeated three times. The results of the inhibition zones formed at concentrations of essential oils of 20%, 40%, 60%, 80%, 100% respectively were 6.16 mm, 6.50 mm, 6.66 mm, 7.00 mm, and 7, respectively. 83 mm. The inhibition zone is formed due to the process of absorption of antifungal substances (essential oils) into the agar media that has been planted with fungi (Nadifah et al., 2018).

Mubarak, et al (2019) stated that turmeric extract can inhibit the growth of *Candida albicans* in various concentrations. The inhibition test in this study used the agar diffusion method (*Kirby-Bauer*) with 100 g nystatin as a positive control and blank disc paper as a negative control. The results showed that turmeric extract with 96% ethanol solvent at concentrations of 12.5%, 25%, 50%, 75% and 100% could inhibit the growth of *Candida albicans*. The diameter of the largest inhibition zone was seen at a concentration of 100% turmeric extract, which was 10.3 mm, and the smallest diameter was seen at a concentration of 12.5%, which was 6.6 mm. (Mubarak et al., 2019).

Based on these studies, it can be said that turmeric has been shown to be effective as an antifungal. 100% turmeric extract is the concentration that forms the largest inhibition zone against *Candida albicans*.

CONCLUSION

Turmeric is an herbal plant that also has an antifungal role. The active substances contained in turmeric include *curcumin*, *flavonoids* and essential oils. The content of *curcumin* is used as an antifungal by damaging cell walls and denaturing cell proteins so that cells become lysed. This phenolic compound also inhibits several enzymes that play a role in changing the nature of *Candida albicans* from commensal to pathogenic. Essential oils are terpenoid compounds that can destroy bacterial cell membranes, while *flavonoid* compounds have activity that can inhibit adhesion, form complexes with extracellular and dissolved proteins and form complexes with cell walls so that they can damage microbial membranes.

The studies that have been conducted have shown that turmeric can significantly inhibit the growth of *Candida albicans*, the greater the concentration of turmeric extract used, the greater the inhibitory power produced. The greater concentration of turmeric extract has a more concentrated solution so that the active compounds can inhibit the growth of fungi more optimally. Turmeric can be a safe and effective option because it has minimal side effects and is well tolerated when taken in normal amounts.

Other research needs to be done to find out more about the benefits of turmeric as an antifungal, because until now there has been no antifungal herbal medicine made from turmeric to treat fungal infections in the oral cavity.

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