Antifungal Potential of Propolis Extract Against Candida Albicans: Literature Review

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Abstract

The increasing rate of Candida resistance against pharmacological drugs has become a particular focus in the medical world, especially considering the high mortality rate due to systemic infections caused by Candida. It is evident that the urgency of developing alternative medicines applies for potential natural ingredients like propolis. This literature review aims to discuss the antifungal effectiveness of propolis against C. albicans which is described by the MIC (minimum inhibitory concentration) and MFC (minimum fungicidal concentration) values from the test results. The search for relevant literature was conducted using the Google Scholar, ScienceDirect, and PubMed databases using the keywords "Propolis AND MIC AND MFC AND Candida albicans". There were nine articles that had been adjusted to the inclusion and exclusion criteria based on the PICOS Framework. The propolis in the article uses various solvents with various extraction methods, and various antifungal tests are carried out on standardized and clinical isolates of C. albicans. All the reviewed articles consistently support the finding that propolis has a strong ability to inhibit the growth and kill the pathogenic fungus C. albicans. The lowest MIC value found was 0.06 μg/mL, and the MFC value was 0.121 μg/mL. Propolis has potential as an ingredient that can be further developed as a non-pharmacological therapy for pathogenic fungal infections.

Keywords: *Antifungal, MIC, MFC, Propolis, Candida Albicans.*

A. INTRODUCTION

Candida is a genus of fungi belonging to the fungal order Saccharomycetales. Of the approximately 200 Candida species that exist, 20 of them have been identified as being able to cause disease in humans (Szabó et al., 2021) . The genus Candida is responsible for the majority of fungal pathogen infections in humans. The species Candida albicans is the most common cause, followed by Candida glabrata, Candida auris, Candida tropicalis, Candida parapsilosis, and Candida krusei (Lopes & Lionakis, 2022).

Infections caused by Candida are referred to as candidiasis. Due to its opportunistic nature, candidiasis most often occurs as a secondary infection in individuals with weakened immune systems (R and Rafiq, 2022) . Infections caused by C. albicans themselves can be classified into two: mucosal and systemic. The mucosal surfaces that are often affected are the vagina (vulvovaginal candidiasis), oral (oropharyngeal candidiasis), esophagus (esophageal candidiasis), and nails (onychomycosis) (Lopes and Lionakis, 2022) . Meanwhile, systemic Candida infection is called candidemia, which can be defined as the presence of Candida species in the blood circulation. According to CDC (2022), the most common species causing systemic candidiasis is C. albicans (37%), followed by C. glabrata (27%), C. parapsilosis (14%), C. tropicalis (8%), and C. krusei (2%). According to Mora Carpio and Climaco (2023) , the main risk factors causing candidemia are the installation of a central venous catheter, exposure to antibiotics, laparotomy (especially if there is repeated laparotomy or anastomosis leakage), malignancy, acute necrotizing pancreatitis, organ transplantation, and total parenteral nutrition. Candidemia needs to be in special focus because it tends to have a high mortality rate of 64.8%, with an average length of stay of 27 days (Kalista et al., 2017). The high mortality rate due to this condition is often caused by invasive candidiasis, namely infection by multiple Candida species simultaneously (McCarty, White & Pappas, 2021).

In the past two decades, azole antifungal drugs (fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole) have been most frequently used because of their broad spectrum of activity, good safety profile, and sufficient bioavailability. However, this group has fungistatic properties, allowing the fungal population to survive for a long time. In addition, the use of azoles as prophylaxis is often used extensively, so that these two things cause the incidence of resistance to azoles to continue to increase (Robbins, Wright & Cowen, 2016).

Currently, the first line drugs used for Candida infections are echinocandins (caspofungin, micafungin, and anidulafungin). Fluconazole is also still used orally or intravenously as an alternative treatment for patients who are not critically ill and it is considered impossible to have Candida that is resistant to fluconazole (Pappas et al., 2016) . Although the prevalence of resistance to echinocandins as first-line drugs is currently still low, the increased use of prophylaxis and long-term treatment has begun to result in an increase in the incidence of resistance (Perlin, 2011). Management of infections by this organism is very dependent on the efficacy of antifungal drugs and there is an urgency to find alternative drugs with minimal side effects and are easily available (Robbins, Caplan & Cowen, 2017).

Propolis is a complex natural substance produced by honey bees from tree buds, sap, resin, mucus, lattice and other plant sources (Araújo, Bosco and Sforcin, 2016) . The use of propolis dates back to 3000 BC in early Egypt by ethnobotanists and traditional practitioners for preserving corpses. In ancient Greece, propolis was used as a disinfectant and antiseptic. The use of propolis was then developed over time. The development of research on propolis in this decade is mainly related to the analysis of the chemical composition and utilization of propolis (Zabaiou et al., 2017).

The main chemical compound groups of propolis are resin, wax, polyphenols (phenolic acids, flavonoids) and terpenoids. Flavonoids themselves include chrysin, pinocembrin, apigenin, galangin, kaempferol, quercetin, tectochrysin, pinostrobin and others. The phenolic compounds contained in propolis (artepillin C) and also terpenes (terpineol, camphor, geraniol, nerol, farnesol) are responsible for its distinctive aroma. Another group of propolis chemical compounds are aromatic acids such as ferulic, cinnamic, caffeic, benzoic, salicylic and p-cumaric acids (Przybyłek and Karpiński, 2019). Propolis chemical compounds which vary depending on the type and location of origin have therapeutic and health benefits as antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant and antiproliferative agents (Zulhendri et al., 2021).

Because of the many potential benefits of propolis, this ingredient has begun to be widely researched over the last decade. Ota et al. (2001) conducted an experimental study using in vitro tests to determine the activity of Brazilian propolis against 80 Candida strains. Propolis extract shows excellent performance against pathogenic fungi. This makes propolis an ingredient that has potential as an alternative in the medical field. Thus, this literature review summarizes the latest research regarding progress in evaluating the antifungal activity of propolis extracts against Candida albicans strains. The studies reviewed were studies with antifungal activity results expressed as minimal inhibitory concentration (MIC) and/or minimal fungicide concentration (MFC).

B. METHOD

Writing this literature review begins with selecting a topic and determining a title, followed by searching for journals, websites and textbooks using keywords relevant to the topic through several databases, namely Google Scholar, PubMed and ScienceDirect. The literature search used in the writing was limited to a publication time of 10 years in Indonesian and English adapted to the topic of the antifungal potential of propolis extract against Candida albicans. Keywords used in English searches are "MIC", "MFC", "propolis", and "Candida albicans". The literature that has been obtained is adjusted to the inclusion criteria based on the PICOS Framework, namely population, intervention, comparator, outcome, and study design (Table 1).

Table 1. Research Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Population	Studies involving both standard and clinical isolates of the fungal species *Candida albicans.*	Studies involving fungal species other than *Candida albicans.*
Intervention	Study that tested the effect of propolis as an antifungal agent against *Candida albicans.*	Studies that do not involve testing the effects of propolis as an antifungal agent against *Candida albicans.*
Comparison	No specific comparisons were required in the study.	There were no specific exclusion criteria for comparison.
Outcomes	Studies that report antifungal effects include MIC and MFC values of propolis extract against *Candida albicans isolates.*	Studies that do not report antifungal effects include MIC and MFC values of propolis extract against *Candida albicans isolates.*
Study Design	Experimental, *randomized control trial* (RCT), *comparative study,* and *cross-sectional study.*	*Systematic review, literature review*, or not available *full text.*
Year of publication	2013-2023.	Under 2013.
Language	English or Indonesian.	Not in English or Indonesian.

C. RESULTS AND DISCUSSION

The results of searching for articles using keywords in Indonesian and English were from the Google Scholar database with 845 articles, ScienceDirect with 58 articles, and PubMed with 9 articles. After going through the study selection stage according to the inclusion and exclusion criteria using the PRISMA flow (Page et al., 2021). As shown in Figure 1, the total number of articles reviewed in this research was 9 articles from international journals and all of them were experimental research. The entire article discusses the antifungal potential of extracted propolis against the growth of Candida albicans fungus which is described through MIC and MFC values in mass per volume units. Table 2 shows the characteristics of all articles that have been reviewed in this writing. The propolis used in these articles uses various solvents with different extraction methods, and uses various test methods on standard and clinical isolates. From a total of nine articles that have been reviewed, it was found that propolis has a good ability to prevent the growth and kill the fungus C. albicans. Propolis showed the lowest MIC value of 0.06 μg/mL and the lowest MFC value of 0.12 μg/mL.

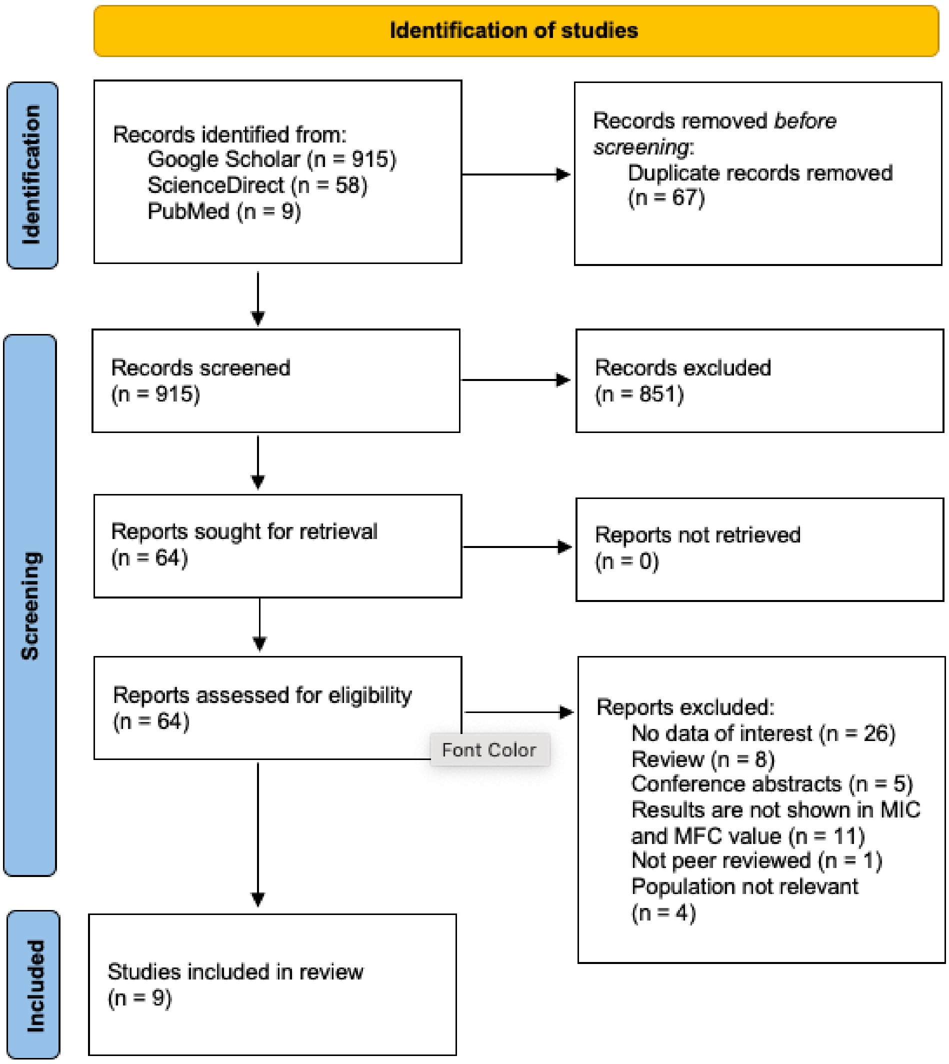

Figure 1. Flow Diagram of the Selection Process

Table 2. Journal Characteristics Based on Author, Year, Title, Sample, Location and Research Results

No.	Author, year	Title	Population/Sample	Origin of Propolis	Research result
1.	Moghim *et al.*, 2021	*Antifungal Effects of Iranian Propolis Extract and Royal Jelly Against Candida albicans In-Vitro*	Propolis ethanol extract made using the percolation method was tested against standard *Candida albicans isolates* (code no. PTCC5027)	Iran	MIC, MIC $_{50}$, MFC resulted at 30 ± 15, 61.8 ± 27, and 83.3 ± 59.9 µg/mL respectively from the *broth microdilution assay*
2.	Sokolonski *et al.*, 2021	*Activity of Antifungal Drugs and Brazilian Red and Green Propolis Extracted with Different Methodologies Against Oral Isolates of Candida spp.*	Red and green propolis, each made into ethanol extract using the conventional method and the ultrasound-assisted extraction method, were tested against clinical isolates of *Candida albicans* from lesions of oral candidiasis patients.	Brazil	Green propolis (GP) test results showed that the MIC was 2-4 mg/mL and the MFC was 4-8 mg/mL for the conventional method extract type, while the MIC was 2-4 mg/mL and the MFC was 2-> 8 mg/mL. mL for *ultrasound-assisted extract type*. Red propolis (RP) extract test results showed that the MIC was 0.5-1 mg/mL and the MFC was 1-4 mg/mL for the conventional method extract type, while the MIC was 0.25-2 mg/mL and the MFC was 2-4 mg/mL. mL for *ultrasound-assisted extract type*. MIC determination using the *broth microdilution test*.
3.	Barros *et al.*, 2022	*Promising Effect of Propolis and a By-Product on Planktonic Cells andiofilm Formation by the Main Agents of*	Green propolis ethanol extract made using the *turboextraction method* and *waste propolis extract* against *Candida*	Brazil	*waste extract* (WPE) test results obtained MIC and MFC at 214.06 and 1712.5 µg/mL. Both use the *broth microdilution test*.

		Human Fungal Infections	*albicans isolates* ATCC 90028 standard		
4.	Ramón-Sierra *et al.*, 2019	*Partial Characterization of Ethanolic Extract of Melipona beecheii Propolis and In vitro Evaluation of Its Antifungal Activity*	Ethanol extracts of propolis from two different bee species were prepared using the *vortex-assisted method* against the standard *Candida albicans isolate* ATCC 10231 and clinical isolates	Yucatan State, Mexico	Against standard isolates: *M. beecheii* bee propolis produced an MIC of 1.62 ± 0.33 µg/mL and an MFC of 2.50 ± 0.22 µg/mL. Meanwhile, *A. mellifera* bee propolis produced an MIC of 2.30 ± 0.15 µg/mL and an MFC of 3.31 ± 0.28 µg/mL, both using the *broth microdilution test*. Against clinical isolates: *M. beecheii* bee propolis produced an MIC of 2.25 ± 0.2 µg/mL and an MFC of 2.90 ± 0.55 µg/mL. Meanwhile, *A. mellifera* bee propolis produced an MIC of 2.75 ± 0.15 µg/mL and an MFC of 3.75 ± 0.11 µg/mL, both using the *broth microdilution test*.
5.	Shehu *et al.*, 2016	*Antifungal Properties of Malaysian Tualang Honey and Stingless Bee Propolis against Candida albicans and Cryptococcus neoformans*	Non-ethanol extract of propolis made by *vortex-assisted maceration method* against standard *Candida albicans isolate ATCC 25987*	Kelantan, Malaysia	MIC was generated at 1560 µg/mL and MFC at 6250 µg/mL using a *broth dilution test*.
6.	Gavanji and Larki, 2017	*Comparative Effect of Propolis of Honey Bee and Some Herbal Extracts on Candida albicans*	Methanol extracts from propolis and several other herbal ingredients, each made using the maceration method, were tested against the standard *Candida*	Esfahan, Iran	MIC_{50} was generated at 21 µg/mL, MIC_{90} at 39 µg/mL and MFC at 65 µg/mL using a *broth microdilution assay*.

			glabrata isolate ATCC 10231		
7.	Agüero *et al.*, 2014	*Urban Propolis from San Juan Province (Argentina): Ethnopharmacological Uses and Antifungal Activity Against Candida and Dermatophytes*	Propolis ethanol extract was made using the maceration method against standard *American* and *Argentinian type Candida albicans isolates*	San Juan, Argentina	From the results of the propolis test on 7 *Candida albicans isolates*, the MIC range was 16-125 µg/mL and MFC was 31.2->250 µg/mL using the *both microdilution test*.
8.	Aboulghazi *et al.*, 2022	*Physicochemical Characterization and In vitro Evaluation of the Antioxidant and Anticandidal Activities of Moroccan propolis*	Propolis ethanol extract made using the *vortex-assisted maceration method* against clinical isolates *of Candida albicans* from vulvovaginal candidiasis patients	Fez-Meknes, Morocco	From the results of the propolis test on isolates, the MIC was 46-62.5 µg/mL and the MFC was 93-125 µg/mL using the *broth microdilution test*.
9.	Ristivojević *et al.*, 2018	*Profiling of Turkish Propolis Subtypes: Comparative Evaluation of Them 2 Phytochemical Compositions, Antioxidant and Antimicrobial Activities*	Prpolis ethanol extract made using the *vortex-assisted maceration method against Candida albicans* isolate standard ATCC 10231	Türkiye	The test results for three types of propolis subtypes produced an MIC range of 0.06->1 µg/mL and MFC of 0.12->1 µg/mL using the *well diffusion test.*

According to Sanchez et al. (2021) , to determine the antifungal activity of a natural compound, various types of in vitro tests can be carried out. In general, there are diffusion, dilution, TLC-Bioautography test methods, and other methods. Diffusion and dilution tests have increased in popularity over the last few years and are carried out to calculate minimum inhibitory concentration (MIC) values, followed by minimum fungicidal concentration (MFC) values by streaking on Saboraud Dextrose Agar media. This value indicates the antifungal activity of a natural compound. This inhibitory and killing power test aims to determine the concentration of natural compound extracts that have antifungal activity.

Ability of Propolis Extract to Inhibit the Growth of Candida albicans

The results of all the research used in this literature review show that propolis extract has the ability to inhibit the growth of the fungus C. albicans. This is proven by research by Moghim et al. (2021) , who tested the antifungal effect of ethanol extract of Iranian propolis on standard isolates of C. albicans using the broth microdilution test method. This research shows that at a concentration of 30 ± 15 µg/mL, propolis extract can inhibit the growth of C. albicans, so propolis has the potential as an ingredient that can be developed as an antifungal treatment in the future. This is in line with research conducted by Barros et al. (2022) who used the same type of extract (ethanol), the same test method (broth microdilution), and tested standard isolates as well. The propolis used in this research came from Parana, Brazil and the extraction method used was turboextraction. The MIC value produced was 68.75 µg/mL by propolis extract and 275.0 µg/mL by by-products from propolis extract. This shows that this natural ingredient has the ability to inhibit the growth of C. albicans. Likewise, research conducted by Agüero et al. (2014) , who obtained the MIC value of propolis extract from San Juan, Argentina of 16-125 µg/mL. In this research, the difference is the propolis extraction method used, namely the maceration method. Sokolonski et al. in 2021 we will also carry out antifungal tests on propolis ethanol extract obtained from Brazil. The propolis used was red propolis (RP_EtOH) from the Bahia area and green propolis (GP_EtOH) from the Minas Gerais area which were extracted using conventional methods. Each propolis was then given ultrasound-pretreatment before the test (RP_US and GP_US), so that in this test four different types of propolis extract were used. The MIC concentration values obtained from the RP_EtOH, GP_EtOH, RP_US, and GP_US extracts were 0.5-1 mg/mL, 2-4 mg/mL, 0.25-2 mg/mL, and 2-4 mg/mL, respectively. The results of this study showed that propolis extract treated with ultrasound did not increase its antifungal activity even though it had higher phenolic levels. However, both types of red and green propolis extract still have inhibitory power against fungi, with the red type of propolis being considered to have better ability. Ristivojević et al. (2018) also carried out an antifungal test using the same type of extract, standard isolate and test method. However, the propolis used comes from various regions in Turkey, using the well diffusion test method, and the propolis extraction method used is vortex-assisted maceration. The antifungal test carried out assessed that the propolis used in the study had good antifungal activity. From the test results of the three propolis subtypes used, the MIC value was obtained at 0.06->1 µg/mL.

Apart from testing propolis extract on standard isolates of C. albicans, several studies also carried out antifungal tests on clinical isolates, such as research conducted by Ramón-Sierra et al. in 2019 and by Aboulghazi et al. in 2022. The ethanol propolis extraction method used in both studies is the same, namely using the vortex-assisted method. Ramón-Sierra et al. conducted research using propolis from the state of Yucatan, Mexico produced by the bee species Melipona beecheii and Apis mellifera. The propolis extracts each had MIC values of 2.25 ± 0.2 µg/mL and 2.75 ± 0.15 µg/mL against C. albicans isolates tested using the broth microdilution test. Meanwhile, Aboulghazi et al. also conducted research using clinical isolates with the same test method. The clinical isolate of C. albicans used was taken from a patient with vulvovaginal candidiasis. The propolis used was taken from two different areas (Oued Amlil and Sefrou) in the Fez-Meknes area, Morocco, with the resulting MIC value at 46-62.5 µg/mL.

Ethanol is the most common solvent used in making propolis extract. Ethanol has been proven to effectively remove active compounds from propolis. However, ethanol has several disadvantages such as a strong aftertaste and side reactions. A study using propolis from Kelantan, Malaysia used sterile water as the extract solvent.

This research was carried out using the broth dilution test method and the extraction method using vortex-assisted maceration. The result of this test was an MIC with a value of 1560 μg/mL against the standard isolate of C. albicans. Gavanji and Larki (2017) also used materials other than ethanol as a solvent for their propolis extract, namely methanol. In his research using propolis from Esfahan, Iran, a broth microdilution test was carried out on standard isolates of C. albicans. The resulting MIC50 value was at 21 μg/mL. The MIC values obtained from these two studies were higher compared to other studies which also tested standard isolates of C. albicans with ethanol extract. However, propolis extract with non-ethanol solvent also has the ability to inhibit the growth of the fungus C. albicans.

The ability of propolis extract to kill Candida albicans

Apart from its ability to inhibit fungal growth, propolis extract also has the ability to kill fungus. The killing power of this natural material is shown by its MFC value. In general, the MFC value is determined after carrying out a previous inhibitory content test by streaking the media. Research in the last decade shows that propolis extract has the ability to kill the pathogenic fungus C. albicans. Experimental research conducted by Moghim et al. (2021) showed that propolis extract had an MFC value of 83.3 ± 59.9 μg/mL against the fungus C. albicans. Meanwhile, MFC values of 214.06 μg/mL by propolis extract and 1712.5 μg/mL by extract by-products were produced by research conducted by Barros et al. (2022) . In another study, Agüero et al., (2014) obtained an MFC value from propolis extract of 31.2->250 μg/mL against C. albicans isolates. Antifungal tests carried out by Sokolonski et al. in 2021 also showed the ability of propolis extract to kill C. albicans. The resulting MFC values were 1-4 mg/mL and 4-8 mg/mL for red and green propolis. Then, MFC values were obtained of 2-4 mg/mL and 2-> 8 mg/mL for red and green propolis which were given ultrasound-pretreatment, respectively. The killing ability of propolis extract was also demonstrated by research by Ristivojević et al. (2018) used a well diffusion test which produced an MFC value of 0.12->1 μg/mL. So far, research on the antifungal effects of propolis extract has results that support each other, that propolis extract has a good antifungal effect against C. albicans. Apart from testing standard isolates, several studies also tested clinical isolates of C. albicans. MFC values resulting from the broth microdilution test by Ramón-Sierra et al. (2019) used M. beecheii and A. mellifera propolis worth 2.90 ± 0.55 μg/mL and 3.75 ± 0.11 μg/mL, respectively. Tests on clinical isolates were also carried out by Aboulghazi et al. in 2022 . From this study, an MFC value of 93-125 μg/mL was obtained for clinical isolates of C. albicans obtained from vulvovaginal candidiasis patients. Apart from propolis extract using ethanol, research using propolis with materials other than ethanol as a solvent was carried out by Shehu et al. (2016) used sterile water and Gavanji and Larki (2017) used methanol which respectively obtained MFC values of 6250 μg/mL and 65 μg/mL against standard isolates of C. albicans.

Mechanism of the Inhibitory Power of Propolis on the Growth of Candida albicans the antifungal effect of propolis can be caused by the flavonoids, phenolics, tannins, silver, mercury, copper and aromatic compounds it contains (Moghim et al.,

2021) . The content levels in propolis can be different in propolis from different locations of origin. Ristivojević et al. (2018) proved that the Turkish propolis used in their research had higher levels of flavonoids than propolis from Japan, Serbia and China. The propolis used by Aboulghazi et al. (2022) in their research obtained from the same area from different regions (Oued Amlil and Sefrou) in Morocco had slightly different total carbohydrate, protein, lipid and mineral contents. The levels of resin, wax, pH and moisture also have differences between the two propolis. Apart from the location of origin, the types of propolis-producing bees also produce propolis with different content levels. The total phenols and flavonoids from propolis produced by Apis mellifera bees are different from those produced by Melipona beecheii bees (Ramón-Sierra et al., 2019) .

D. CONCLUSION

From the results of a review of nine articles, propolis showed good effectiveness in inhibiting the growth and killing the fungus C. albicans with the lowest MIC value of 0.06 μg/mL and MFC of 0.12 μg/mL. The propolis discussed in this article uses various types of solvents and extraction methods, and various types of antifungal tests are carried out on standard and clinical isolates of C. albicans. The results of the MIC and MFC values resulting from this research are different. However, propolis shows potential as an ingredient that can be developed in the future as an alternative non-pharmacological therapy for infections by the pathogenic fungus C. albicans.

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