Formosa Journal of Sustainable Research (FJSR)
Vol.2, No.8, 2023: 1717-1728

The Activity of Active Compounds of Papaya Leaf (Carica Papaya L.) in Inhibiting the Growth of Fungus Candida Albicans in the Oral Cavity

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A R T I C L E I N F O

keywords: Candida Albicans, Papaya Leaves (Carica Papaya L.), Flavonoids, Alkaloids, Saponins and Tannins

Received : 5 June
Revised : 20 June
Accepted: 22 July

A B S T R A C T

Candida albicans is the most frequently isolated candida species from the oral cavity. The overgrowth of C. albicans can cause opportunistic infections in the oral cavity, called oral candidiasis. On the other hand, papaya leaves (Carica papaya L.) have benefits and are efficacious as antifungal drugs. The results of various studies reveal that papaya leaves (Carica papaya L.) contain various active compounds, such as flavonoids, alkaloids, saponins, and tannins, which can inhibit the growth of C. albicans fungus. This literature review, therefore, aims to ascertain the activity of active compounds in papaya leaves in inhibiting the growth of C. albicans in the oral cavity

DOI: https://doi.org/10.55927/fjsr.v2i7.5306
ISSN-E: 2830-6228
https://journal.formosapublisher.org/index.php/fjsr

INTRODUCTION

Candida albicans is the most frequently isolated candida species from the oral cavity, the most common cause of oral candidiasis. The fungus *C. albicans* is an opportunistic pathogenic fungus that causes human diseases, such as thrush and gastrointestinal candidiasis. Overgrowth of *C. albicans* can cause opportunistic infections in the oral cavity, called oral candidiasis. *C. albicans* can also multiply rapidly and cause oral candidiasis infections when there is an imbalance, such as due to local environment (change in pH or nutrition), use of antibiotics, changes in the immune system (caused by infection or immunosuppressant therapy), malnutrition, poor oral hygiene, dental malocclusion, decreased immune system, impaired salivary gland function, drugs, dentures, high carbohydrate diet, smoking, diabetes mellitus, and immunosuppressive conditions.

Moreover, *Candida* overgrowth can cause local discomfort, altered taste sensation, dysphagia of the esophagus resulting in poor nutrition, slow recovery, prolonged hospital stay, burning sensation in the mouth, which increases when eating spicy food7, the presence of slight bleeding in the area around the base of the lesion, and dry mouth.

The incidence of candidemia in European countries and Brazil from an analysis demonstrated that 63% and 40.9% were due to *C. albicans*. Candidemia is the presence of *Candida* species in the blood. In Indonesia, a retrospective study conducted in 2010-2014 at Dr. Hasan Sadikin (RSHS) Bandung revealed that during this period, 49 patients suffered from oral candidiasis, with the highest prevalence being men, as many as 34 people (69.3%).

On the other hand, Indonesia is a country that has natural wealth with a wide variety of flora and fauna. Plants that grow around the environment have benefits and are efficacious as medicine. Specifically, the papaya plant can be used as medicine because almost all parts have health value. One part of this plant is the leaves. Papaya leaves are often used in traditional medicine due to the role of the active compound content. The active compounds in papaya leaves, such as alkaloids, saponins, flavonoids, and phenols, have an antifungal role. For this reason, this literature review aims to ascertain the activity of active compounds in papaya leaves (*Carica papaya* L.) in inhibiting the growth of the fungus *C. albicans* in the oral cavity.

LITERATURE REVIEW

Candida overgrowth can cause local discomfort, altered taste sensation, dysphagia of the esophagus resulting in poor nutrition, slow recovery, prolonged hospital stay, burning sensation in the mouth, which increases when eating spicy food, the presence of slight bleeding in the area around the base of the lesion, and dry mouth.

METHODOLOGY

A literature search was conducted on 2000-2020. The boundaries of the literature review were used to guide the literature search process, and titles were then chosen from each database using the PICO framework, combined terms, and medical subject. Using a mix of keywords, journals from databases like Google Scholar and PubMed were added. "*Candida albicans*", "papaya leaves (Carica Papaya L.)", "flavonoids", "alkaloids", "saponins", and "tannins". Search engines and other journals' references were used in some journals.

RESEARCH RESULT

A. Candida Albicans (C. Albicans)

Candida albicans is an endogenous microorganism in the oral cavity, gastrointestinal tract, female genital tract, and occasionally on the skin, which is part of the normal flora and can be an invasive pathogen. In the oral cavity, *C. albicans* is the most dominant fungal species, which was found isolated from dentures, canker sores, and dental plaque. *C. albicans* can cause opportunistic infections in the oral cavity, called oral candidiasis[15]. Oral candidiasis is an infection caused by *C. albicans* that can attack the oral mucosa in humans[16]. Triggers for oral candidiasis can be caused by three factors, namely local factors, systemic factors, and a combination of local and systemic factors. Local factors are such as poor oral hygiene conditions or the presence of other people's lesions. Meanwhile, systemic factors include the use of systemic drugs (Chemotherapy), bacterial infections, viral infections (HIV), and autoimmune diseases (Pemphigus, SJS, SLE).

The most common location for oral candidiasis lesions is on the dorsum of the tongue. Because the surface is not flat and is often in direct contact with food, the area is retentive to leftovers and bacteria collection. Apart from the tongue, oral candidiasis lesions are found on the buccal mucosa, labial mucosa, hard palate, ventral tongue, corners of the lips, gingiva, soft palate, lateral tongue, and base of mouth.

The main type of lesion in oral candidiasis may be erythematous macules or pseudomembranous plaques, whereas at a more advanced stage or due to involvement of a systemic disease affecting the oral mucosa in the oral cavity, lesions can be found in the form of ulcers, erosions, or crusts. Given this, the masticatory function will be disrupted and exacerbate the condition of oral candidiasis. Pseudomembranous candidiasis (Thrush) presents as a yellow-white lesion on the surface of the oral mucosa that is not painful or slightly sensitive. This type can occur anywhere in the oral cavity but is most common on the hard and soft palate, buccal or labial mucosa. Meanwhile, erythematous

candidiasis may appear as red patches on the buccal or palatal mucosa or may also be associated with depapillation of the tongue. Furthermore, hyperplastic candidiasis is the rarest form and can be seen on the buccal mucosa and tongue. Angular cheilitis may also appear on the commissures of the lips and appear erythematous with hardening of the skin surface and forming fissures.

The classification of *C. albicans* consists of Phylum (*Fungi Imperfecta*), Order *(Moniliales),* Family *(Cryptococcaceae),* Genus *(Candida),* and Species *(Candida albicans)*[18]. Morphologically, *C. albicans* can be seen in several fungal elements, i.e., yeast cells (blastospores/yeast), hyphae, or intermediate/pseudohyphae. Round, oval, or round-oval with a size of 2-5 µ x 3-6 µ to 2-5.5 µ x 528 µ is the shape of a yeast cell. The fungus will reproduce by forming buds, which will continue to elongate to form pseudohyphae. Optimum growth can occur at a pH between 2.5–7.5 and a temperature between 20°C–38°C. Fungal growth can occur rapidly between 48–72 hours in solid or liquid media. Nevertheless, the growth rate will be higher in liquid media.

***B. Papaya (Carica Papaya* L.)**

Papaya (*Carica papaya* L.) is a plant from the *caricacae* family, cultivated in most tropical and subtropical countries. Papaya is native to Southern Mexico, Central America and northern South America. This papaya plant is also known by other names as *papaw, paw paw, kapaya, lapaya, tapaya, papaya, papaya, papaia, papita, lechosa, fruta bomba, mamon, mamona, mamao,* and tree melon. All parts of the papaya plant, such as leaves, fruit, seeds, skin, roots, and flowers, are used as a source of medicinal plants. This plant has a single soft stem that grows 5-10 m tall. The leaves are arranged sparsely at the top of the stem and are very large, with squiggly edges around the edges.

The taxonomic classification of papaya (*Carica papaya* L.) consists of the kingdom (*Plantae*), order (*Brassicales*), family (*Caricaceae*), genus (*Carica*), and species (*C. papaya*). The parts widely used are the tree's fruit, leaves, and bark. Papaya (*Carica papaya* L.) provides many benefits due to its high content of vitamins A, B, and C proteolytic enzymes such as papain and chymopapain, which have antiviral, antifungal and antibacterial properties. The chemical constituents of papaya leaves include carpaine alkaloids, pseudocarpaine, dehydrocarpaine I and II, choline, vitamins C and E, and carposide.

***C.* Uses of Papaya Leaves (*Carica Papaya* L.)**

Papaya (*Carica papaya* L.) has been known for a long time due to its nutritional content and medicinal value. The benefits of papaya leaves include curing severe jaundice, expelling guinea worms, healing broken bones, constipation, and digestive disorders, and treating oral candidiasis, malaria, and dengue. Papaya leaves also have various therapeutic activities, such as antibacterial, antioxidant, antipyretic, insecticidal, antimicrobial, and anti-mollusk. Papaya leaves have antibacterial properties because they have the effect of killing and inhibiting the growth of bacteria. It is due to the ability of one of the chemical ingredients of the leaves, namely flavonoids. Papaya leaves in India are used to treat stomachache, beriberi, and asthma. In Australia, the leaves are used as traditional medicine for jaundice, malaria, dengue fever, and antiviral activity. These leaves also act as antioxidants and antiseptics.

D. The Activity of Active Compounds in Papaya Leaves (*Carica Papaya* L.) in Inhibiting the Growth of the Fungus *C. Albicans* in the Oral Cavity

Papaya leaves (*Carica papaya* L.) contain various active compounds. As in the study of the phytochemical test of papaya leaf methanol extract, it was shown that the test results of the papaya leaf methanol extract contained alkaloids, saponins, flavonoids, and Steroidterpenoid. The papaya leaf phytochemical screening results also contained alkaloids, flavonoids extracted with methanol, and other active compounds, such as steroids, extracted with n-hexane.

Various studies have uncovered that papaya leaves can inhibit the growth of *C. albicans.* According to a study using a sample of 96% ethanol extract of papaya leaves on the growth of *C. albicans,* there were significant differences between treatment groups. Papaya leaf extract affects the growth process of the fungus *C. albicans*. The antifungal effect is because papaya leaf extract contains chemical compounds, such as alkaloids, flavonoids, and saponins. It is consistent with the phytochemical screening results of 96% ethanol extract of papaya leaves, revealing that they contain alkaloids, flavonoids, saponins, tannins, quinones, steroids, and triterpenoids.

Other studies have also proven that papaya leaves can inhibit the growth of the *C. albicans* test microbe, which was verified through experimental laboratory studies using papaya leaf extract with respective concentrations of 5%, 10%, 15%, and 20%. The method used was the agar diffusion method. The results showed that papaya leaf extract could provide the greatest antifungal activity against *C. albicans* at a concentration of 20% with an inhibition zone of 12.5 mm. The formation of an inhibition zone around the disc blank was due to active antifungal compounds, i.e., alkaloids, phenols, flavonoids, and saponins contained in papaya leaves.

Another study assessed the antimicrobial potential of various concentrations of 70% ethanol extract of papaya leaves against *C. albicans.* The results demonstrated that the largest inhibition zone formed was 13 mm at a concentration of 30%, while the positive control used was fluconazole, which showed an inhibition zone of 11 mm. In addition, the minimum inhibitory content (MIC) formed was 2.5%. It could happen because it could be associated with phytochemical constituents, such as flavonoids, saponins, alkaloids, and tannins, primarily responsible for antimicrobial properties. The phytochemical screening test results of 70% ethanol extract of papaya leaves (*Carica papaya* L.) also showed results that there are active compounds in papaya leaves in the form of tannins, terpenoids, quinones, alkaloids, and flavonoids.

Another research using papaya leaf extract and its Following a phytochemical examination, alkaloids, flavonoids, glycosides, reducing sugars, saponins, steroids, both tannins. Antimicrobial activity was assessed against two resistant endodontic pathogens: *Enterococcus faecalis* and *Candida albicans.* The test results unveiled the presence of all bioactive compounds, such as saponins, flavonoids, reducing sugars, steroids, and tannins, except for glycosides. It corroborates with the phytochemical test study of 70% ethanol extract of papaya leaves, which found that they contain tannins, flavonoids, alkaloids, saponins, and steroids[30]. The presence of these bioactive compounds is the antimicrobial

potential of papaya extract. It can occur in bacteria and fungi due to the inhibition of cell wall formation in cells, which results in leakage of cytoplasmic constituents by the bioactive components of the extract.

Furthermore, experimental laboratory studies, with samples of *Carica papaya* leaves of solo and solo mix varieties extracted using 95% ethanol and n-hexane, were investigated to prove the presence of secondary metabolites. The secondary metabolite research results of 95% ethanol extract and n-hexane of *Carica papaya* showed the presence of alkaloids. Flavonoids, glycosides, and saponins were only found in 95% ethanol extract, while tannins were present in n-hexane extract. The antimicrobial study showed that the ethanol extract, both solo and solo mix varieties, demonstrated activity against *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Bacillus subtilis,* and *Candida albicans.* Nevertheless, the inhibition zone obtained was not greater than the Ciprofloxacin positive control. The antibacterial activity is due to the presence of phytoconstituents in the ethanol extract of *Carica papaya* leaves, including alkaloids, tannins, and flavonoids, which have been shown to have antibacterial properties. Flavonoids are secondary metabolites, identified as a broad class of polyphenols found in abundance in plants. Flavonoids are a major group of phenolic compounds reported to have antiviral, antimicrobial, and spasmolytic properties. Several in vivo and clinical studies have also reported that flavonoids exhibit pharmacological functions, i.e., having antifungal activity.

The use of flavonoids to fight The first goal of bacterial, protozoan, and fungal infections is to kill microbial cells, second, to combat bacterial toxins' spread and consequences. Flavonoids act as bactericidal and bacteriostatic by damaging the cytoplasmic membrane through perforation mechanisms and decreasing membrane fluidity, inhibiting energy metabolism and the synthesis of nucleic acids against different microorganisms. In addition, the flavonoids' mode of action is through their inhibitory effect on the process of cell membrane synthesis and inhibition of cell wall synthesis. Fungal cell protein will be denatured by flavonoids, resulting in damage to the cell wall, and the lipid layer will be disrupted due to the activity of the flavonoids.

Additionally, flavonoids frequently inhibit fungal growth by multiple underlying mechanisms, including plasma membrane disruption, induction of mitochondrial dysfunction, inhibition of cell wall formation, cell division, RNA and protein synthesis, and efflux-mediated pumping systems. Besides, the chemical content of flavonoids also interferes with the process of diffusion of food into cells by damaging cell membranes, thereby stopping the growth of fungi or killing the fungi.

Flavonoids also inhibit enzyme activity by forming complexes with bacterial cell walls, extracellular and soluble proteins, and lipophilic flavonoids interfere more with the integrity of cell walls or microbial membranes at low concentrations. The lipophilic nature of flavonoids interferes with the permeability of cell membranes by binding to phospholipids in the fungal cell membrane.

Meanwhile, saponins are a class of bioorganic compounds found in certain abundances in the plant kingdom. Structurally, saponins have one or more hydrophilic glycoside sugar groups combined with lipophilic triterpene molecules. Saponins exhibit biological roles and medicinal properties, such as hemolytic factors, anti-inflammatory, antibacterial, antifungal, antiviral, insecticidal, anticancer, cytotoxic, and molluscicide actions. Saponins are more modern in biotechnology and used as adjuvants in vaccines. Saponins will break down the coating fat in the cell membrane, disrupting cell membrane permeability, disrupting the diffusion process of materials or substances needed by the fungus, and eventually, the cell swells and bursts.

As an antifungal, the mechanism of saponins is through membrane destruction and induction of apoptosis in fungi. Damage to the cell membrane through the binding of ergosterol will result in a loss of function of the cell membrane. Saponins can also disrupt the stability of cell membranes, resulting in microbial cell lysis. In addition, as antifungals, saponins will interfere with cell wall permeability by working to form complexes with sterols, which are enzymes that make up fungal cell walls, resulting in the loss of cell wall permeability. The mechanism of antifungal action on saponins is also through inhibition of cell wall formation, fungal mitochondrial dysfunction, cell division inhibition, RNA/DNA synthesis and protein synthesis, and inhibition of the efflux pump.

Moreover, alkaloids are important secondary metabolites with therapeutic properties, such as analgesic, antispasmodic, and bactericidal properties. Alkaloids isolated from plants are generally found to have antimicrobial properties. Some alkaloids are used as antiseptics because of their antibiotic activity. The pharmacological activities of the alkaloids contained include cytotoxicity, mutagenic or carcinogenic activity, antibacterial, antifungal, and antiviral properties.

The mechanism of alkaloids as antifungals is through changes in membrane permeability, impaired mitochondrial function, production of oxidative stress, target cell wall integrity pathways, HSF1 transcription shock factor, and heme modulation.[42] Besides, alkaloids inhibit esterase, DNA, and RNA polymerase, providing antifungal effects.

Next, tannins are secondary metabolites of polyphenols in higher plants, are widespread in several plant species, and are found in wood, bark, leaves, and fruits.[43] Tannin-rich plants have the ability to react with proteins to create stable, water-soluble chemicals, killing bacteria by directly destroying their cell, giving them the potential to be antibacterial membranes. As an antifungal, the mechanism of tannin is its ability to inhibit chitin synthesis for the formation of cell walls in fungi and damage cell membranes, resulting in inhibited growth of fungi. Also, tannins will inhibit the biosynthesis of ergosterol, the main sterol that makes up the fungal cell membrane. Sterols are structural and regulatory components of eukaryotic cell membranes, are the final product of fungal cell sterol biosynthesis, and play a role in the permeability of fungal cell membranes.

The mechanism of action of antifungals can be through various ways, such as inhibition of cell wall formation, disruption of cell membranes, fungal mitochondrial dysfunction, inhibition of cell division, inhibition of RNA/DNA

synthesis, protein synthesis, and inhibition of efflux pumps. fungus cell wall inhibition, cell wall development, mainly composed of β-glucan; if these chemicals' production is prevented, the integrity of the cell wall will be disrupted. Disturbance of cell wall structure and synthesis is through inhibition of ergosterol synthesis. Ergosterol is an essential component of lipid membranes, modulating fluidity and membrane permeability and thickness. These sterols have an important role in membrane function. Ergosterol can also be combined with phospholipids to stabilize membrane structure, regulate the mobility of fungal cell membranes, and ensure the integrity of the membrane structure and the activity of membrane-binding enzymes, cell viability, and cell transport. If ergosterol is not present, abnormal function of the fungal cell membrane occurs, or the cell will rupture. In inhibition of RNA/DNA synthesis or protein synthesis, if antifungal compounds enter cells, such as through active transport in ATPase and interfere with RNA, it can lead to erroneous RNA synthesis and DNA transcription inhibition. Regarding the inhibition of the efflux pump, the efflux pump is present in all living cells, and its function is to remove hazardous materials from the cell. This transport typically consists of the drug collected from the fungus cells. Overuse drug resistance can result from the use of efflux pumps. By preventing efflux pump, drug resistance can be reduced.

CONCLUSION

Based on this literature review, it can be concluded that:

1. Papaya leaves (*Carica papaya* L.) have active compounds, such as flavonoids, alkaloids, saponins, and tannins, which can inhibit the growth of Candida albicans fungus in the oral cavity.
2. The mechanism of papaya leaves (*Carica papaya* L.) in inhibiting the growth of Candida albicans is through various means, such as inhibition of cell wall formation, disruption of cell membranes, fungal mitochondrial dysfunction, inhibition of protein synthesis, inhibition of RNA/DNA synthesis, and inhibition of cell division of the efflux pump.

ACKNOWLEDGMENT

The authors would like to thank everyone who helped us in this review

REFERENCES

Lewis MAO, Williams DW. Diagnosis and management of oral candidosis. Br Dent J. November 2017;223(9):675–81.

Sardi JCO, Scorzoni L, Bernardi T, Fusco-Almeida AM, Mendes Giannini MJS. Candida species: current epidemiology, pathogenicity, biofilm formation, natural antifungal products and new therapeutic options. Journal of Medical Microbiology. 1 January 2013;62(1):10–24.

Komariah, Ridhawati Sjam. Kolonisasi Candida dalam Rongga Mulut. 2012;XXVIII:39–47.

Akpan A, Morgan R. Oral candidiasis. Postgrad Med J. 2002;455–9.

Gulati M, Nobile CJ. Candida albicans biofilms: development, regulation, and molecular mechanisms. Microbes and Infection. May 2016;18(5):310–21.

Berberi A, Noujeim Z, Aoun G. Epidemiology of Oropharyngeal Candidiasis in Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome Patients and CD4+ Counts. Journal of International Oral Health. 2015;7(3):20–3.

Kohli S, Shinde CV. Candidiasis and Oral Cavity: A Review. International Journal of Research & Review. 2019;6(5):335–40.

Hakim L, Ramadhian MR. Kandidiasis Oral. Majority. 2015;4(8):53–7.

Sinatra J, Siahaan JM. PEDOMAN DALAM PENANGANAN KANDIDIASIS. MAJALAH ILMIAH METHODA. 2018;8:50–61.

Nur'aeny N, Hidayat W, Dewi TS, Herawati E, Wahyuni IS. Profil oral candidiasis di bagian ilmu penyakit mulut RSHS Bandung periode 2010-2014. Majalah Kedokteran Gigi Indonesia. 31 October 2017;3(1):23.

Suparni, Ari. Herbal Nusantara: 1001 Ramuan Tradisional Asli Indonesia. Yogyakarta: Rapha Publishing; 2012.

Muhlisah F. Tanaman Obat Keluarga. Jakarta: Swadaya; 2007.

Depkes RI. Inventaris Tanaman Obat Indonesia (I). J. akarta: (Depkes RI) Departemen Kesehatan Republik Indonesia; 2000.

Nuryanti S. Aktivitas Antifungi Sari Daun Pepaya (Carica Papaya L.) Terhadap Candida albicans. As-Syifaa. 2017;137–45.

Lestari, P. E. Peran Faktor Virulensi Pada Patogenesis Infeksi Candida albicans. Stomatognatic (JKG Unej). 2010;7(2):113–7.

Afrina, Nasution AI, Sabila CI. GAMBARAN MORFOLOGI Candida albicans SETELAH TERPAPAR EKSTRAK SERAI (Cymbopogon citratus) PADA BERBAGAI KONSENTRASI. cakradonya dental j. 4 May 2018;9(2):107–15.

Newman MG, Takei HH, Klokkevold PR. Carranza's Clinical periodontology. 13 ed. Philadelphia: Elsevier; 2019.

Chander J. Textbook of medical mycology. New Delhi: Jaypee Brothers Medical Publishers; 2018.

Basalingappa KM. Medicinal Uses of Carica Papaya. Journal of Natural & Ayurvedic Medicine. 2018;2(6):1–11.

Vij T, Prashar Y. A review on medicinal properties of Carica papaya Linn. Asian Pacific Journal of Tropical Disease. 2015;5(1):1–6.

Priyadarshi A, Ram B. A Review on Pharmacognosy, Phytochemistry and Pharmacological Activity of Carica Papaya (Linn.) Leaf. IJPSR. 2018;9(10):4071–8.

Sugito S, Suwandi E. Efektifitas Ekstrak Ethanol Daun Pepaya (Carica Papaya L) terhadap Pertumbuhan Bakteri Escherichia Coli dengan Metode Difusi. JLK. 30 November 2017;1(1):21–5.

Iskandar D, Erdiandini I, Deonesia M. Uji Aktivitas Antifungi Ekstrak Metanol Daun Pepaya (Carica Pepaya L.) Terhadap Colletotrichum Gloesporioides Penyebab Penyakit Antroknosa Pada Tanaman Kakao (Theobroma Cacao L.). Jurnal Teknologi Technoscientia. 2020;12(2):184–8.

Santi TD. Uji Toksisitas Akut dan Efek Antiinflamasi Ekstrak Metanol dan Ekstrak n-Heksana Daun Pepaya (Carica papaya L). Pharm Sci Res. August 2015;2(2):101–14.

Rosari IR, Sjahriani T. PENGARUH EKSTRAK DAUN PEPAYA (Carica Papaya L.) TERHADAP PERTUMBUHAN Candida albicans. Jurnal Ilmu Kedokteran dan Kesehatan. 2014;1(2):127–34.

Roni A, Maesaroh M, Marliani L. Aktivitas Antibakteri Biji,Kulit Dan Daun Pepaya (Carica Papaya L.) Terhadap Bakteri Escherichia Coli dan Staphylococcus Aureus. kjif. 22 April 2019;6(1):29–33.

Arora M, Giriraju A, Bhat PK. Assessment of Antimicrobial Potential of Different Concentrations of Ethanolic Papaya Leaf Extract Against Candida Albicans and Enterococcus faecalis – An In Vitro Study. Scholars Journal of Dental Sciences. 2019;6(8):373–9.

Arifuddin M, Bone M. Skrining Fitokimia dan Profil Kromatografi Lapis Tipis (KLT) Tumbuhan Antimalaria Asal Indonesia. Jurnal Sains dan Kesehatan. 2020;2(3):174–81.

Shubham S, Mishra R, Gautam N, Nepal M, Kashyap N, Dutta K. Phytochemical Analysis of Papaya Leaf Extract: Screening Test. EC Dental Science. 2019;18(3):485–90.

Jati NK, Prasetya AT, Mursiti S. Isolasi, Identifikasi, dan Uji Aktivitas Antibakteri Senyawa Alkaloid pada Daun Pepaya. Jurnal MIPA. 2019;42(1):1–6.

Alorkpa EJ, Boadi NO, Badu M, Saah A. Phytochemical screening, antimicrobial and antioxidant properties of assorted Carica papaya leaves in Ghana. Journal of Medicinal Plants Studies. 2016;4(6):193–8.

Al Aboody MS, Mickymaray S. Antifungal Efficacy and Mechanisms of Flavonoids. Antibiotics. 26 January 2020;9(2):45.

Ahamd A, Kaleema M, Ahmed Z, Shaf H. Therapeutic Potential of Flavonoids and Their Mechanism of Action against Microbial and Viral Infections-A Review. Food Research International. 2015

Kurniawati A, Mashartini A. Perbedaan khasiat anti jamur antara ekstrak etanol daun Kersen (Muntingia calabura L.) dengan nistatin terhadap pertumbuhan Candida albicans. Jurnal PDGI. 2016;74–7.

Ashour AS, El Aziz MMA, Gomha Melad AS. A review on saponins from medicinal plants: chemistry, isolation, and determination. JNMR. 22 February 2019;7(4):282–8.

Julianto TS. Fitokimia Tinjauan Metabolit Sekunder dan Skrining Fitokimia. Yogyakarta: Universitas Islam Indonesia; 2019.

Wenji KY, Rukmi I, Suprihadi A. In vitro Antifungal Activity of Methanolic and Chloroform Mint Leaves (Mentha piperita L.) Extracts Against Candida albicans. J Phys: Conf Ser. May 2019;1–7.

Arifin Z, Khotimah S, Rahmayanti S. Aktivitas Antijamur Ekstrak Etil Asetat Daun Mangga Bacang. Jurnal Cerebellum. 2018;4(3):1106–19.

Jager AK, Freiesleben SH. Correlation between Plant Secondary Metabolites and Their Antifungal Mechanisms–A Review K. Med Aromat Plants. 2014;3(2):1–6.

Roy A. A Review on the Alkaloids an Important Therapeutic Compound from Plants. International Journal of Plant Biotechnology. 2017;3(2):1–9.

Bribi N. Pharmacological activity of Alkaloids: A Review. Asian Journal of Botany. 2018;1:1–6.

Khan H, Mubarak MS, Amin S. Antifungal Potential of Alkaloids as an Emerging Therapeutic Target. Current Drug Targets. 2017;18(16):1825–35.

Jaiswal H, Singh OJ, Chauhan A, Sahu MK, Prakash DV S. A Review on tannins. European Journal of Biotechnology and Bioscience, 6(3), 16-17. European Journal of Biotechnology and Bioscience. 2018;6(3):16–7.

Komala O. Y, Siwi FR. Aktivitas Antijamur Ekstrak Etanol 50% Dan Etanol 96% Daun Pacar Kuku Lawsonia Inermis L Terhadap Trichophyton mentagrophytes. EKO. 4 January 2020;19(1):12–9.

Chen C, Long L, Zhang F, Chen Q, Chen C, Yu X, et al. Antifungal activity, main active components and mechanism of Curcuma longa extract against Fusarium graminearum. PLoS ONE. 2018;13(3):1–19.