PHYSICAL RESPONSE OF ACRYLIC RESIN IN EFFECT OF Ziziphus mauritiana LAM RELATED TO GROWTH AND BIOFILM FORMATION OF Candida albicans

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ABSTRACT
This study evaluated the potential of Ziziphus mauritiana Lam (Z. mauritiana Lam) ethanol extract improves thermal stability and strength to prevent the growth and biofilm formation of C. albicans. The assessment of heat release (thermal equilibrium) of acrylic resin using Differential scanning calorimetry, the strength of acrylic resin with the universal testing machine, growth assessment of C. albicans by spectrophotometry, and biofilm assay with crystal violet and visual images used to a microscope. Z. mauritiana Lam 12.5% provides better thermal stability with a cooling peak enthalpy of -223.27 cal/g. In addition, concentrations of 6.25% and 3.125% at 48 hours had a better ability to increase the strength of acrylic resin (p>0.05). Z. mauritiana Lam at all concentrations and incubation of 24 and 48 hours were similar in decreasing the growth of C. albicans (0.06-0.08 or equivalent to <300 CFU/mL). Concentrations of 3.125% and 6.25% had a better ability to inhibit the biofilm formation of C. albicans on the acrylic resin surface. There was no significant difference between the inhibition of growth and biofilm formation on acrylic resin based on incubation time and concentration (p>0.05). The Z. mauritiana Lam increased heat release (thermal stability) in acrylic resin, which caused an increase in transverse strength. At the same time, it reduces the growth and biofilm formation of C. albicans on the acrylic resin surface.

Keywords: Biofilm, Candida albicans, Growth, Denture stomatitis, Ziziphus mauritiana Lam.

INTRODUCTION
The denture is a prosthesis that replaces missing natural teeth and their supporting tissues. Different dentures can be used as fixed, removable, partial, and complete.1 Several factors, including tooth decay, periodontitis, and trauma, can cause tooth loss.2 Treatments that can be done to overcome tooth loss using dentures. Acrylic-based dentures are generally used in partial and complete dentures. These acrylic resin dentures are easy to perform Occlusal Adjustment, have high resilience, and have good chemical bonding to the denture base.3 Using acrylic resin as a denture base material is cheap, aesthetically pleasing, easy to modify, and has good properties for surface roughness, surface tension, electrostatic interactions, and good dimensional stability.4 However, acrylic resin material as a denture can act as a reservoir of microorganisms because the pores on the surface of acrylic resin-based dentures can trigger the growth and development of oral pathogens such as C. albicans is involved in denture stomatitis.5 Growth of C. albicans on denture acrylic resin begins with adhesion to the denture surface or through accumulated plaque, thereby increasing the occurrence of denture stomatitis.6 The growth of microorganisms and adhering to the acrylic resin can disrupt the balance of the acrylic resin.7 The impact of the biological activity of C. albicans on the acrylic resin surface can reduce the strength and elongation of the material, in addition to increasing heat absorption, which can facilitate the occurrence of porosity and changes in the chemical properties of the material, such as loss of material-forming compounds.8 Material properties include physical and chemical properties, generally influenced by external (humidity, temperature, pressure) and internal (internal energy and enthalpy) conditions.9 The more microorganisms that grow and adhere to the acrylic resin, the more

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disturbed the balance of the acrylic resin will be. Denture disinfectants tend only to clean and reduce the development of *C. albicans* or other pathogenic bacteria in the oral cavity. Still, long-term use affects acrylic resin's physical and chemical properties as a denture base. *Ziziphus mauritiana* Lam contains some antioxidant, anti-inflammatory, and adhesive compounds. Several compounds provide biological value for *Z. mauritiana* Lam to be involved as phyto-pharmacy agents applied for various medical purposes. The use of *Z. mauritiana* Lam as a disinfecting agent means the coating material on the surface of acrylic resin is expected not only to help reduce or prevent the destructive agent of acrylic resin material it can also to maintain its physical and chemical properties, to maintain a balance of biological, physical, and chemical use in a relatively long time and not toxic to host tissues. This phenomenon is expected in research on acrylic resin materials, so the solution of using acrylic resin as a biocompatible denture base and immunotolerant has become a focus for research on advanced dental materials. This research has examined the impact of *Z. mauritiana* Lam disinfectant coating to increase thermal stability, increase transverse strength, and decrease its effect on *C. albicans* by inhibiting growth and biofilm formation.

**EXPERIMENTAL**

This study used acrylic resin material coated with *Ziziphus mauritiana* Lam ethanol extract with concentrations of 3.125%, 6.25%, and 12.5%. Then interact with *C. albicans* ATCC 10231 under the influence of 24 h and 48 h incubation. Furthermore, an examination of the growth and biofilm formation of *C. albicans* on the surface of the acrylic resin was carried out, as well as the thermal stability (heat release) and the transverse strength of the acrylic resin.

**Plant Material**

*Ziziphus mauritiana* Lam specimens were obtained from Aceh Farm School, located in Aceh Besar District, Aceh Province, Indonesia (coordinates: 5.570704102637194, 95.35980633540842). *Z. mauritiana* Lam was extracted at the Chemical Laboratory of Syiah Kuala University in Darussalam Banda Aceh, Indonesia. The alphanumeric code "D1101" serves as the designated voucher number. The assay materials were obtained by Basri A. Gani from the Oral Biology Laboratory, Dentistry Faculty, Syiah Kuala University, Darussalam, Banda Aceh, Indonesia.

**Extraction of *Ziziphus mauritiana* Lam**

Yusuf *et al.* (2020) extracted assay materials. One kg of *Ziziphus mauritiana* Lam leaves was chopped and macerated for 24 hours in 5 L of 96 percent ethanol, stirring every four hours. Additionally, it is decanted and filtered. The residue was macerated again for 48 hours in new 96 percent ethanol. The filtrate is then evaporated using a rotary vacuum evaporator to obtain a concentrated extract. Additionally, it was heated to 45 °C to remove any remaining ethanol from the section.

**Preparation of Acrylic Resin Mold**

Twenty-four acrylic resin molds were acquired, each created from a red wax pattern with dimensions of 10 mm x 10 mm x 2 mm. During the initial phase, the powder and water were combined following the manufacturer's guidelines for type III gypsum (specifically dental stone). The mixture was stirred for 30 seconds and subsequently transferred into a cuvette. After that, allowing the gypsum mixture to undergo a partial hardening process is advisable. Following this, four samples of acrylic resin, which have been appropriately sectioned, should be placed within a cuvette containing gypsum. It is essential to ensure that the specimens are positioned so that their flat surfaces are in contact with the gypsum, facilitating the solidification process of the gypsum material. Subsequently, the gypsum is allowed to undergo the process of hardening. Next, immerse the cuvette in water that is at its boiling point for a duration of 40 to 60 minutes. Subsequently, drain the cuvette and carefully remove the acrylic resin residue adhered to the gypsum surface. In the initial stage, the upper and lower cuvette molds are treated with a cold mold seal (CMS) liquid layer. Subsequently, transfer the monomer liquid into a receptacle made of porcelain and proceed to incorporate the polymer powder following the guidelines provided by the manufacturer. Continue this process until the mixture attains a dough-like consistency that is manageable and devoid of stickiness. Next, place the dough into the designated mold, ensuring the top and bottom cuvettes are securely closed. Apply pressure to the dough by utilizing a hydraulic press. In addition, the cuvette was subjected to boiling at a temperature of 100°C. Subsequently, the cuvette was unsealed, allowing for the retrieval of the polymerized...
acrylic resin. During the final phase, the surplus portion of the acrylic resin was eliminated utilizing a Fraser bur and subsequently subjected to a polishing process. In addition, the acrylic resin is submerged in distilled water for 24 hours to minimize the presence of any residual monomer.\textsuperscript{13}

**Candida albicans Culture on Surface Acrylic Resin**

*Candida albicans* were cultured on Sabouraud Dextrose Agar (SDA) media and incubated at 37 °C for 24 hours. Suspension of *C. albicans* was prepared by taking 4-5 colonies of fungi that had been set into a test tube containing 10 mL of Peptonr media and homogenized using Vortex for 15 seconds and equalizing the turbidity with 0.5 McFarland Solution (1.5x10^8 CFU/mL). Acrylic resin coated with *Z. mauritiana* Lam is placed on a well plate and then incubated for 1.5 – 2 h to attach to acrylic resin in a shaker platform for the adhesion phase. Furthermore, *C. albicans* was cultured on acrylic resin at 37 °C for 24 h and 48 h.\textsuperscript{14}

**Candida albicans Growth Assay**
The *C. albicans* were incubated for 24 h and 48 h at 37 °C, and the acrylic resin plate was transferred to another container. The acrylic resin slab was adapted with *C. albicans* and *Z. mauritiana* Lam for other tests. After that, the remaining solution was incubated again at room temperature (25 °C) for 60 min. Then 150 µL of the solution was put into a 96-well triple serial plate. Furthermore, the growth of *C. albicans* was assessed based on its turbidity with an Elisa reader at a wavelength of 520 nm.\textsuperscript{15}

**Biofilm Assay**
The acrylic material is subjected to surface polishing to achieve a smooth surface area. It is then immersed in a physiological NaCl solution to ensure uniform absorption pressure. The acrylic material is positioned in a vertical orientation. Subsequently, the specimen was incubated in a 10 mL solution of saliva containing phenylmethylsulfonyl fluoride (PMSF) at a pH of 6.5 in a ratio of 10:1 for 30 min. A volume of 300 µL of a *C. albicans* solution with a concentration of 1.5x10^8 CFU/mL was administered to each acrylic sample. After 15 mins, the test material was introduced following its concentration. The biofilm formation of *C. albicans* on acrylic surfaces was assessed using incubation periods of 24 hours and 48 hours. The incubation process was conducted at a temperature of 37 degrees Celsius. An experimental setup was employed to examine the biofilm formation of Candida albicans using a microscope (400x). It is involved utilizing acrylic material coated with a biofilm and incorporating *Z. mauritiana* Lam as the active component. Additionally, to provide further clarification regarding the biofilm mass and cell morphology of *C. albicans* that was adhered to the acrylic resin surface, visual observations were conducted using the JEOL JSM-6390A instrument. Scanning electron microscopes (SEM) can achieve a magnification of 1000x.\textsuperscript{16}

**Differential Scanning Calorimetry Assay**
Differential scanning calorimetry (DSC) was employed to measure acrylic resin's heat release, analyze its thermal properties, and characterize the resulting phase change. Initially, the specimens containing varying concentrations and the control group were subjected to crushing. Subsequently, they were transferred into a pan and securely sealed using a sample sealer/crimper. Thereon, the specimen was carefully positioned onto a glass plate, and a controlled flow of nitrogen gas was introduced at 30 mL/min. The temperature was then systematically incremented at a rate of 10°C per minute until it reached a final value of 600°C. In addition, the heat released will be determined through the utilization of the Differential Scanning Calorimetry (DSC) system.\textsuperscript{17} During the initial phase, the acrylic substance was extracted from its container and submerged in a 0.9% sodium chloride (NaCl) solution for 15 min. The mixture was agitated at 500 revolutions per minute (rpm) throughout this process. Subsequently, the acrylic component responsible for forming the biofilm was immersed in a solution containing 10 ml of crystal violet with a concentration of 1% for 30 min. The acrylic part was soaked in a sodium chloride solution with a concentration of 0.9% for 5 min while agitated at 500 revolutions per min. Subsequently, a volume of 10 mL of safranin solution with a concentration of 1% is introduced, followed by an incubation period of 15 minutes. The samples are then washed and stored at 4°C for 48 hours. The biofilm's determination was confirmed by utilizing an electron microscope set explicitly at magnifications ranging from 400 to 1000 times. The extent of Candida albicans biofilm formation on the acrylic surface was quantified using spectrophotometry at a wavelength of 550 nm.\textsuperscript{14}
Acrylic Resin Transverse Strength Test
The measurement of transverse strength was carried out by a 3-point bending test using a Universal Testing Machine with a compression speed of 5mm/minute and an initial load of 50 Kgf. The distance between the two supports is 50 mm. The sample is placed vertically with the tip resting on a solid grip on the test instrument, then read and recorded. Each instance is numbered, and a center line is drawn. The piece is placed perpendicular to the tool, so the device presses the model on the center line until it breaks. The transverse strength indicated on the instrument is recorded in the unit of MPa.  

Statistical Analyses
Analysis of growth inhibition, biofilm formation, and intervariable strength was tested using the Kruskal-Wallis analysis. In contrast, the two influencing factors were tested using the independent sample Test with a significance of p<0.05.

RESULTS AND DISCUSSION
Figure-1 shows that *Z. mauritiana* Lam can reduce the growth of *C. albicans*, which is almost the same at all concentrations except for positive control (Nystatin). In positive concentrations, the growth of *C. albicans* at the incubation time of 24 hours increased by about > 1500 CFU/mL, which means that at 24 hours, Nystatin has not worked perfectly. Meanwhile, at 48 hours of incubation, there was no growth of *C. albicans*. Conceptually, Nystatin has a half-life in response to the development of *C. albicans*.

At all concentrations of each treatment group *Z. mauritiana* Lam showed the same quantity maintaining the development of *C. albicans* (<300 CFU/mL). It means that all concentrations of *Z. mauritiana* Lam have the same working principle in controlling the growth of *C. albicans*. Growth assessment using the operating code of Sutton (2011), Soraya (2020), dan Syafriza (2020). Estimation formula 0.08-0.1 (<300 CFU/mL); 0.1-0.15 (300-600 CFU/mL); 0.15-0.2 (600-1200 CFU/mL); 0.2-0.3 (1200-1500 CFU/mL); and 0.3-0.5 (1500> CFU/mL). Based the statistical analysis of the Kruskal-Wallis test showed that the growth inhibition of *C. albicans* on acrylic resin under the influence of *Z. mauritiana* Lam there was no significant difference (p>0.05; 0.512), as well as the concentration of *Z. mauritiana* Lam there was no significant difference between concentrations (p> 0.05;0.512). However, both had a positive relationship with the growing value of *C. albicans*, meaning that the concentration and incubation time were the determinants of the inhibitory strength of *C. albicans*.
Table-1 shows that *Z. mauritiana* Lam provides better thermal stability than without assay material (acrylic/negative control). However, Nystatin had a better effect at 24 hours of incubation and decreased at 48 hours. In the treatment group with an incubation time of 24 hours, the peak cooling enthalpy occurred at 12.5% *Z. mauritiana* Lam, with a value of -223.27 cal/g. Meanwhile, at 48 hours of incubation, the cooling peak enthalpy occurred at a concentration of 3.125%, similar to the positive control (Nystatin), which was -243.88 cal/g.

Figures-2A and 2B show that *Z. mauritiana* Lam can inhibit the biofilm formation of *C. albicans* between 24 and 48 hours. A concentration of 6.25% had better inhibition than other concentrations at an incubation time of 24 hours, including positive control. However, at 48 hours, the concentration of 3.125% had better inhibition. In general, the positive control had a relatively increased inhibition according to the increase in
incubation time, similar to the concentration of 3.125%. Based on the statistical analysis of the Independent Samples Test, it was shown that the incubation time did not show a significant difference in the inhibition of biofilm (p>0.05; 0.897) with a positive correlation, meaning that the longer the incubation time, the higher the inhibition of biofilm formation of *C. albicans* as shown at a concentration of 3.125%. In addition, based on the Kruskal-Wallis analysis, it was revealed that there was no significant difference between the concentration on the inhibitory power of *C. albicans* biofilm by *Z. mauritiana* Lam (p>0.0.222) with a positive correlation, meaning that the concentration of *Z. mauritiana* Lam influenced the quantity and quality of inhibition biofilm formation by *C. albicans*. This test evaluates the transverse strength of acrylic resin after being adapted to *C. albicans* and given *Z. mauritiana* Lam extract with various concentrations and incubation times. In Fig.-3, it is shown that at 24 hours of incubation, there was an increase in strength at the lowest concentration, while at the highest concentration, there was a decrease. At 48 hours of incubation, the concentration of 3.125% increased, but it was higher than the concentrations of 6.25% and 12.5%. In addition, Nystatin can maintain the quality of acrylic strength after being influenced by *C. albicans*. However, it is higher than the concentration group of 12.5% and 3.25% at 48 hours of incubation. Based on the statistical analysis of the independent sample Test, it was shown that the transverse strength of acryl resin in the influence of *Z. mauritiana* Lam after *C. albicans* was grown with the intensity of biofilm formation, there was no significant difference (p>0.05; 0.167) with a positive correlation, meaning that time can determine the strength of acrylic in the influence of *Z. mauritiana* Lam. In addition, based on the Kruskal-Wallis analysis, it was shown that there was no significant difference between the concentration of *Z. mauritiana* Lam on the transverse strength of acrylic resin (p>0.05; 0.928) with a positive correlation, meaning that concentration determines its effect on the strength of acrylic resin. The findings of this study are shown in Fig.-3, namely, the lower the concentration of *Z. mauritiana* Lam, the higher the strength of the acrylic resin. It means that the low concentration determines the quality of acrylic resin strength in the influence of *Z. mauritiana* Lam after growing *C. albicans* on both sides of the acrylic surface. This study reports the biological work of the ethanolic extract of *Z. mauritiana* Lam in maintaining the strength and thermal stability of acrylic resins, as well as evaluating the growth response and biofilm formation of *C. albicans* cultivated on acrylic resin surfaces.

![Fig.-3: Transverse Strength of Acrylic Resin. *Z. mauritiana* Lam had a Good Effect on Maintaining and Increasing the Transverse Strength at all Concentrations after Incubation for 24 and 48 hours. Bar (Transverse strength) and Bar Error (standard deviation)](image)

This study aims to evaluate the growth of *Candida albicans* as a benchmark for assessing the impact of *Z. mauritiana* Lam on preserving the integrity of acrylic surfaces while adapting to *C. albicans* adhesion. Figure-1 shows that *Z. mauritiana* Lam can reduce the growth of *C. albicans*, which is almost the same at all concentrations, both 24 hours and 48 hours of incubation. Statistically, the ability of each concentration of the test material did not show a significant difference (p>0.05). It means that the concentration and incubation time did not strongly influence inhibiting the growth of *C. albicans* on the acrylic resin surface. So that it can be explained that *Z. mauritiana* Lam, in addition to disrupting the growth of *C. albicans* cells, also provides an energy charge on the acrylic resin's surface, reducing the intensity of adhesion and growth.
on the surface of the acrylic resin.\textsuperscript{21} This potential can indirectly prevent the development of \textit{C. albicans}, which is involved in the pathogenesis of denture stomatitis in denture-wearing patients. \textit{Z. mauritiana} Lam has been reported to work as an antifungal agent, which can be functional or functional. Khan (2020) reported that \textit{Z. mauritiana} Lam has a Farnesol antifungal compound. This compound provides antifungal activity, which may be related to inhibiting fungal dimorphism, especially in \textit{C. albicans}.\textsuperscript{22} Taking farnesol into liposomes significantly increased antifungal activity against \textit{C. albicans}, \textit{C. tropicalis}, and \textit{C. krusei}.\textsuperscript{23} While, Nystatin works by binding to sterols in the fungal plasma membrane, causing cells to leak, which ultimately causes fungal cell death.\textsuperscript{24} Antifungal agents can be categorized into three distinct classes according to their specific site of action. The first class, known as azoles, affects the synthesis of ergosterol, the primary sterol in fungi. The second class, polyenes, interact with fungal membrane sterols through physicochemical means. Lastly, the third class encompasses 5-fluorocytosine, which inhibits the process of macromolecular synthesis.\textsuperscript{25} Figures-2A and 2B show that \textit{Z. mauritiana} Lam is relatively stable and inhibits the biofilm formation of \textit{C. albicans} at 24 hours (6.25\%) and 48 hours (3.125\%). The concentration of 3.125\% had similar biofilm inhibition with Nystatin according to the increased incubation time. The results in Fig.-2A align with Fig.-2B, where all treatment groups can suppress the biofilm formation of \textit{C. albicans}. The inhibition quality between one concentration and another of \textit{Z. mauritiana} Lam was similar to the positive control. This ability shows that \textit{Z. mauritiana} Lam can help prevent adhesion and biofilm formation on acrylic resin surfaces. The mechanism of adhesion of \textit{C. albicans} to the acrylic resin surface is strongly influenced by biofilm formation and morphological changes that facilitate colonization of the fungus, so it becomes a significant risk factor for denture stomatitis.\textsuperscript{26} \textit{Ziziphus mauritiana} Lam contains various bioactive compounds such as squalene, phytol, and vitamin E. These compounds have been documented to exhibit antifungal properties in addition to acting as antioxidants.\textsuperscript{27} This compound exhibits antifungal properties and can inhibit the formation of biofilms, which are considered a virulence factor in the pathogenicity of \textit{C. albicans}.\textsuperscript{28} Several of these compounds were verified to hinder the formation of biofilms by \textit{C. albicans} through the prevention of enhanced adhesion and reduction in the production of extracellular polymers that aid in attachment and matrix formation. Furthermore, they prevent alterations in the fungal phenotype, specifically regarding growth rate and gene transcription. Farnesol has been documented as having the ability to detect quorum-sensing molecules associated with the formation of bacteria or fungi in the context of research on polymeric materials.\textsuperscript{29} Increased permeability of the candida membrane after being affected by \textit{Z. mauritiana} Lam may occur due to the interaction of membrane phospholipids (negative charge) with active antibacterial compounds (positive charge). This increase in membrane permeability is in line with cell leakage, thus interfering with cell penetration into tissues. A decrease followed this failure in the production of hyphal protein in the \textit{C. albicans} biofilm, which interfered with the development and intensity of interactions with the environment.\textsuperscript{30} The impact of coating with \textit{Z. mauritiana} Lam on the effect of \textit{C. albicans} was also evaluated on the transverse strength of the acrylic resin. In Fig.-3, it is shown that at 24 hours of incubation, there was an increase in strength at the lowest concentration (3.125\%), while at the highest concentration, it decreased (12.5\%). In addition, Nystatin can maintain the quality of acrylic strength after being influenced by \textit{C. albicans}. However, it is higher than the concentration group of 12.5\% and 3.25\% at 48 hours of incubation. The decrease in strength in several groups tested in this study can be ascertained as a result of the increased influence of \textit{C. albicans}, thereby interfering with the constituent elements of the acrylic resin, because the acrylic resin has a part that can act as a reservoir of microorganisms, on the inside of the denture surface, because of its smooth surface. Irregular and porous so that microorganisms can adhere and proliferate, which can reduce their strength.\textsuperscript{31} On the other hand, in the group that was able to increase acrylic strength, there was a related role of adhesive and antifungal compounds \textit{Z. mauritiana} Lam which worked synergistically to increase the stability of acrylic resins and prevent \textit{C. albicans} from sticking, thereby reducing biodegradation (changes in physical, chemical, and mechanical properties). Indirectly, the active compounds possessed by \textit{Z. mauritiana} Lam can prevent changes in acrylic resin so that it can cause a decrease in flexural forces and surface roughness, discoloration, surface damage, biodegradation, and softening of the denture base of acrylic resin, which generates resistance and stability to be disturbed of resistance and distribution of vertical and horizontal forces.\textsuperscript{32} According to the findings presented in Table- 1, it can be observed that \textit{Z. mauritiana} Lam exhibits superior thermal stability. Nevertheless, it was observed that Nystatin showed a
more pronounced efficacy after 24 hours of incubation, albeit its effectiveness diminished after 48 hours. The thermal properties of polymers are crucial physical parameters that offer insights into various aspects of the polymer, including its miscibility, phase separation, segmental mobility, degree of crystallinity, thermal stability, and the initiation of degradation in the synthesized matrix. This study exclusively evaluated the thermal stability associated with acrylic resin, specifically the heat release. According to the findings above, it was observed that Z. mauritiana Lam could inhibit the growth of C. albicans on the surface of acrylic resin. Additionally, Z. mauritiana Lam demonstrated the ability to enhance the thermal stability of acrylic resin, thereby indicating a potential increase in heat dissipation and a decrease in the adhesive properties of acrylic resin. It can be inferred that Z. mauritiana Lam possesses dynamic characteristics that enable it to preserve its structural integrity and adjust to environmental fluctuations that are impacted by the growth of C. albicans.

CONCLUSION

Based on the findings of this study, it can be explained that several active compounds, such as flavonoids, terpenoids, and saponins, can affect surface tension through mechanical heat release by controlling the acrylic channel membrane (surface) associated with heat acceptance and release. The regulation of the porosity size of acrylic resin after being influenced by Z. mauritiana Lam can be considered for further studies because the release and approval can occur in the porosity formation mechanism. In addition, the increase in additional compounds in acrylic resin after adaptation to Z. mauritiana Lam under the influence of C. albicans is why Z. mauritiana Lam maintains better thermal stability in acrylic resin.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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