SYNTHESIS OF PMCA (p-METHOXY CINNAMIC ACID) USING PERKIN REACTION AND ITS ACTIVITY AS PHOTO PROTECTIVE AND ANTIFUNGAL AGENT

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SYNTHESIS OF PMCA (p-METHOXY CINNAMIC ACID) USING PERKIN REACTION AND ITS ACTIVITY AS PHOTO PROTECTIVE AND ANTIFUNGAL AGENT

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ABSTRACT

This study aimed to synthesize p-methoxy cinnamic acid through the Perkin reaction and to determine its activity as a photoprotective and antifungal agent against Candida albicans. The PMCA compound was synthesized by reacting p-methoxy benzaldehyde with acetic anhydride using a sodium acetate catalyst in a sonicator at 50oC for 60 minutes. The synthesized was a white precipitate with a % yield of 2.09% and a melting point of 172-175°C. ATR-FTIR identified this compound with several functional groups, C=O, OH carboxylic acid, para-substituted benzene, and C=C. Analysis by GC-MS showed a single peak at a retention time of 11.710 minutes with m/z 178. Characterization of this compound by 1H-NMR spectrometry showed several chemical shifts showing the presence of OH groups of carboxylic acids, C=C groups, aromatic benzene groups, and methoxy. The results of this characterization indicated that the synthesis product was PMCA. The antioxidant activity of PMCA using the DPPH radical gave IC50 at a concentration of 352.6138 ppm. In vitro sunscreen activity against PMCA compounds provided high protection at a concentration of 30 ppm with SPF 32,505. The antifungal activity against Candida albicans showed inhibition zones of 0.257cm± 0.044, 1.397cm± 0.093, and 1.533cm± 0.111, respectively at concentrations of 5%, 10%, and 15%. The PMCA compounds can be synthesized through the Perkin reaction assisted by ultrasonic waves and can potentially be photoprotective and antifungal agents.

Keywords: *antifungal, antioxidant, p-methoxy cinnamic acid, photoprotective, sunscreen*

INTRODUCTION

P-methoxy cinnamic acid is one of the cinnamic acid derivative compounds substituted for a methoxy group at the para position [1]. The compound p-methoxy cinnamic acid has activity as an antibacterial [2-3], an anti-inflammatory and anticancer [4], antioxidant, antidiabetic [5], hepatoprotective, neuroprotective, and chemopreventive activity [1]. P-methoxy cinnamic acid can be obtained through a hydrolysis reaction by transforming ethyl p-methoxycinnamate from the isolation of natural ingredients, namely aromatic ginger (*Kaempheria galanga* L.) [2] and the Perkin reaction. The Perkin reaction

is the most frequently used method for synthesizing cinnamic acid and its derivatives [6].

The Perkin reaction has the advantage that the process is easy, and the synthesis starting material is easy to obtain [7]. Synthesis of p-methoxy cinnamic acid was synthesized through the Perkin reaction by reacting a certain amount of p-methoxy benzaldehyde as an aldehyde with an acetic acid anhydride and using anhydrous sodium acetate as a catalyst. However, the conventional Perkin reaction is carried out through a reflux process at high temperatures, for a long time, and with low yield [7]. So, this needs an alternative that uses ultrasonic waves.

Ultrasonic waves will propagate through the medium and cause cavitation events, namely the formation, growth, and bursting of bubbles. Bubbles' bursting increases temperature and pressure by 5000 K and 1000 atm, which causes the chemical bonds to break [8]. The use of sonochemical methods has been chosen for synthesis in recent years. This technique is easier to control than traditional methods [9], using ultrasonic waves as an energy source to generate radicals that affect chemical yields and rates [10]. In addition, sonochemical are easy to operate and minimize waste. This method has been used in the synthesis of ethyl cinnamate gave 96.61% yield in 40 minutes of reaction time at 60°C [9], and cinnamic acid gave 4,98% yield in 60 minutes of reaction time at 70°C [10].

Previous studies on cinnamic acid have shown that this compound can be used as a photoprotective agent[10], and PMCA has the potential as an antibacterial against *E. coli* [3]. In addition, cinnamic acid derivatives also showed activity as a sunscreen[11-13]. So, it can be expected that PMCA also has better activity than these compounds.

Synthesis of PMCA using Perkin reaction assisted by ultrasonic waves has never been done so the aim of this research to synthesize p-methoxy cinnamic acid through the ultrasonic wave-assisted perkin condensation reaction and determine its activity as an antioxidant, sunscreen, and antifungal against *Candida albicans*. From this research, it is expected to develop medicinal raw materials from the synthesis as a photoprotective and antifungal agents.

METHODS

1. Material and Instrument

The materials used in this research were p-methoxy benzaldehyde (p.a., Sigma-Aldrich), acetic acid anhydride (p.a., Merck), sodium acetate (p.a., Merck), diethyl ether (p.a., Merck), HCl (p.a., Merck), $NaHCO_3$ (p.a., Merck), ethanol (p.a., Merck), methanol (p.a., Merck), chloroform (p.a., Merck), *Candida albicans*, Diphenyl Picryl Hidrazil (DPPH; p.a Sigma Aldrich), Potato Dextrose Agar CM0139B, Ketokonozole (Kimia Farma), and DMSO (Merck). The instruments used in this study were glassware commonly used in laboratories, the reactor for the synthesis used the Bransonic Ultrasonic Bath series CPX1800H 40 KHz, melting point apparatus, ATR-FTIR (Agilent Cary 630), GC-MS (Shimadzu QP 2010 SE), column GC-MS Rtx 5 MS, UV-1700 Shimadzu

spectrophotometer, ^{1}H-NMR spectrometer with Jeols brand with a frequency of 500 MHz using CD_3OD eluent at LPPT UGM.

2. Procedures

a. The p-methoxycinnamic acid synthesis via Perkin reaction

The synthesis of p-methoxy cinnamic acid was carried out based on the research method by Indriyanti and Prahasiwi [10] with modifications to temperature and the starting material. A total of 0.073 mol (7.4460 g) of acetic acid anhydride was added to an Erlenmeyer, 0.05 mol (6.800 g) of p-methoxy benzaldehyde, and 0.03 mol (2.46 g) of anhydrous sodium acetate were added with the ratio of p-methoxy benzaldehyde: acetic acid anhydride: sodium acetate (2.43:1.6:1). The mixture was sonicated within 60 minutes at a temperature of 50°C which was then stored in the refrigerator for one night to optimize the reaction to form stable crystals.

The mixture was added with 25 ml of distilled water and saturated $NaHCO_3$ until it reached pH 8. The mixture was put into a separating funnel, and 2x20 ml of diethyl ether was added. The separation will occur between the aqueous phase (lower phase) and diethyl ether phase (upper phase) in a separating funnel. The lower phase was acidified with HCl to pH 2 and cooled in an ice bath to form crystals. The crystals formed were filtered using a vacuum pump and washed with cold distilled water. The crystals were oven-dried at 50°C and tested for solubility and melting point tests. Structure elucidation of the crystal using FTIR-ATR spectrophotometry, GC-MS, and ^{1}H-NMR spectrometer.

b. Antioxidant activity using DPPH

The synthesized PMCA was made at a concentration of 200-500 ppm. Each series of solutions was added with 7.6080 x 10^{-8} mM DPPH solution in a ratio of 1:1. The mixture was incubated for 30 minutes in a dark room, and the absorbance was measured using UV-Vis spectrophotometry at a wavelength of 517 nm. The blank used was a DPPH solution without a sample [10]. The absorbance read from the instrument was used to calculate the % inhibition based on equation 1 [10]. The positive control was ascorbic acid at a concentration of 2-10 ppm.

$$\%inhibition = \frac{A_{blank} - A_{sample}}{A_{blank}} \quad (1)$$

Antioxidant activity is expressed by the IC_{50} value, which can be seen from the linear regression equation.

c. Determined SPF using spectrophotometry UV

Determination of SPF value used Mansur's equation based on research of Indriyanti and Praharsiwi [10]. This method is simple and can be applied in this research. The PMCA solution concentration series from 10-30 ppm (ethanol solvent) was measured for absorbance using UV spectrophotometry at a wavelength of 290-320 with a range of 5 nm [9]. Then, the absorbance obtained was calculated using the Mansur equation (2) to determine the SPF value.

$$SPF = CFx \sum_{290}^{320} EE_{(\lambda)} x I x A_{(\lambda)} \quad (2)$$

Where, CF = correction factor (10), EE (λ) = erythmogenic effect of radiation with wavelength λ, Abs (λ) = spectrophotometric absorbance values at wavelength λ. The

values of EE (λ) x I are constants are given in Table 1 [13].

Table 1. Values of EE (λ) x I at a different wavelength

Wavelength (nm)	Value of EE x I
290	0.0150
295	0.0817
300	0.2874
305	0.3278
310	0.1864
315	0.0837
320	0.0180

d. Antifungal activity against *Candida albicans*

The antifungal activity against *Candida albicans* was carried out at concentrations of 5%, 10%, and 15% PMCA in DMSO solvent. The method used in this measurement was the well method, the medium used was Potato Dextrose Agar with positive control of 0.01% ketoconazole tablet and negative control of DMSO. Replication was carried out five times. First, the incubation process was carried out at 24˚C for 3x24 hours, and then the diameter of the clear zone formed around the test solution was measured using a caliper [14].

RESULTS AND DISCUSSION

1. PMCA synthesis using the Perkin reaction

The synthesis of PMCA can be seen in Figure 1. The mixture of these substances was put in an Erlenmeyer lid and sonicated in a simple sonicator at 50°C for 60 minutes. [15]. The propagation of ultrasonic waves on the reactant media in the form of a liquid causes the phenomenon of cavitation. The cavity will expand to its maximum size and then burst to cause a shock wave in the reactant medium, which causes extreme conditions. This condition caused the breaking of chemical bonds in the reactants, thereby accelerating the reaction to form p-methoxy cinnamic acid[8].

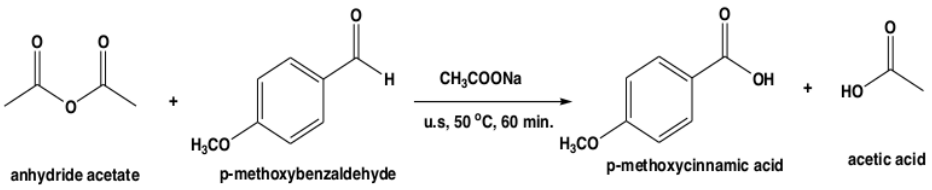

Figure 1. The synthesis of PMCA

The reaction mechanism for the synthesis of PMCA in Figure 2 begins with the breakdown of sodium acetate catalyst into acetate ions and sodium ions. Next, the acetate ion reacts with hydrogen in anhydride acetic acid to form a carbanion which then reacts with p-anisaldehyde. The reaction produces an alkoxide which reacts with acetic acid to produce p-hydroxy anhydride. P-hydroxy anhydride undergoes dehydration and hydrolysis to produce p-methoxy cinnamic acid compounds [16].

The sonication process resulted in a slightly thick yellowish liquid, which was left to

stand for one night in the refrigerator. This process aimed to optimize the Perkin reaction. The result of standing was added with 25 mL of distilled water for separation and withdrawal of the remaining acetic acid anhydride. The liquid was conditioned at pH 8 by adding saturated $NaHCO_3$. This addition aimed to form a sodium salt of p-methoxycinnamate so that it dissolved in water. The salt formed was extracted with diethyl ether in a separating funnel. Diethyl ether was used to attract compounds that do not react with an acetic acid anhydride, namely p-anisaldehyde [17]. The aqueous phase was added with concentrated HCl until it reached pH 2. This addition aimed to restore the formed salt to the acid form [18]. The mixture was left in an ice bath to accelerate the formation of p-methoxy cinnamic acid crystals.

The synthesized was a white solid with a % yield of 2.09%. This low percentage (%) yield is different from that produced by the Knoevenagel condensation method with a % yield of 92.17%, which has been previously reported [19]. In contrast, the hydrolysis method of ethyl cinnamate from the *Kaempferia galanga* was carried out by Fareza [2] and produced a % yield of 84.5%. This percent yield is also very different from the Perkin reaction by Mumtazuddin and Sinhai using a microwave [20]. The low % yield with the Perkin reaction in this study was because the Perkin reaction for p-methoxy cinnamic acid using a sonicator with a reaction time of 1 hour was still not optimal, so it required a longer reaction time.

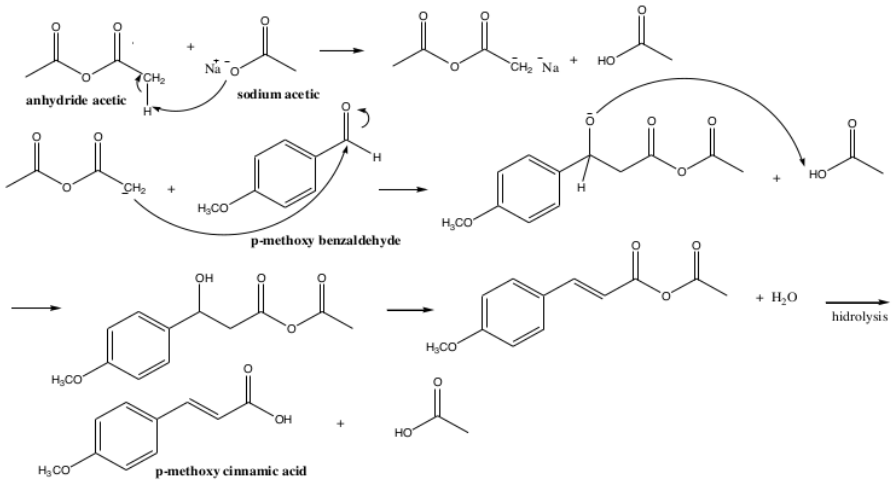

Figure 2. Mechanism synthesis of PMCA using Perkin Reaction[16]

The melting point of the synthesized compound was 172-175°C, the same as the melting point of p-methoxy cinnamic acid in the literature [20]. The synthesized crystals are insoluble in distilled water and diethyl ether but soluble in ethanol, methanol, and chloroform. According to the principle like dissolves like, this compound can be said to be semipolar.

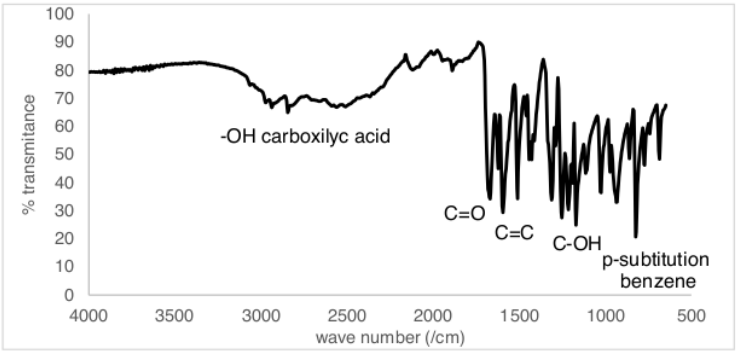

Figure 3. FTIR spectrum of synthesized compounds

The analysis of the synthesis results using ATR-FTIR spectrophotometry in Figure 3 gives the absorption of functional groups according to the target compound. The carbonyl group of carboxylic acids was shown at wavenumber 1725–1700 cm^{-1} with a reasonably strong intensity due to conjugation with an aromatic ring so that it shifts the carbonyl absorption of carboxylic acids to a lower frequency, namely 1700-1680 cm^{-1} [20]. The para-substituted aromatic ring was represented by bending vibrations at a wave number of 842 cm^{-1}. The 1599 cm^{-1} band indicated the presence of a C=C group. The band at 1573 cm^{-1} showed the bending vibration of the aromatic C=C group supported by the spectrum at 1513 cm^{-1} and 1424 cm^{-1}. The presence of strong hydrogen bonds from carboxylic acids causes the O–H absorption to be extensive and intensive at a wave number of 3300-2536 cm^{-1} [2].

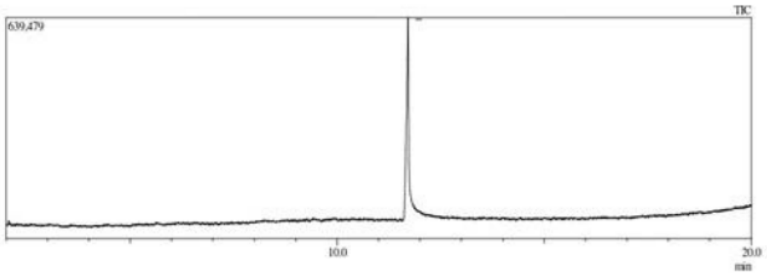

Figure 4. Chromatogram of Synthesized Compounds using GC

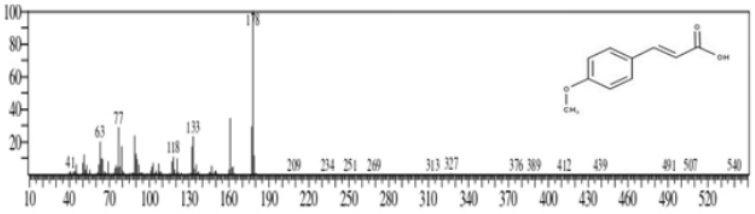

Figure 5. Mass Spectra of PMCA

Figure 4 shows the spectrum of the synthesis product using gas chromatography. This spectrum showed one peak at a retention time of 11,710 minutes with a compound abundance of 100%. The results of these peak mass spectra (Figures 5 and 6) showed m/z 178, corresponding to the molecular weight of the target compound [20]. The mass spectra pattern of the synthesis product compared to the library showed similarities to the compound p-methoxy cinnamic acid. Cation radical with m/z 178 releases OH radical to produce p-methoxy cinnamoyl ion with value m/z 161. Cation radical releases methoxy radical ion to produce cinnamyl ion with m/z 147. A p-methoxy vinyl ion with m/z value 133 is formed when a cation radical releases a COOH radical. When a molecular ion releases a propenoic acid radical, a p-methoxy vinyl cation is produced with an m/z value of 107, which then releases a methoxide radical to form a benzene cation with an m/z value of 77. Based on this, the compound synthesized is the target compound, namely p-methoxy-cinnamate acid.

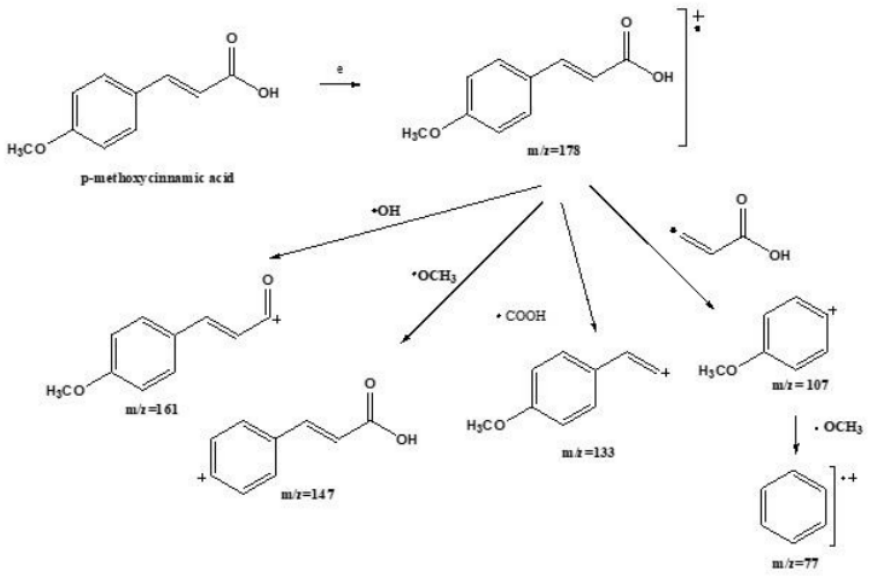

Figure 6. Fragmentation of p-methoxycinnamic acid

The synthesized compounds were tested with a ^{1}H-NMR spectrometer in CD_3OD solvent with a frequency of 500 MHz. The results of the ^{1}H-NMR spectra showed a chemical shift in the area of 9.827 ppm, indicating the presence of a carboxylic acid OH group. In addition, protons in the aromatic ring appeared in the 7.985 ppm region (2H, *d*, *J*=9) and 6,981 ppm (2H, *d*, *J*=8.5), while protons in -OCH_3 appeared at 3.04 ppm (*s*, 3H) [20]. Based on the results of structural elucidation using FT-IR, GC-MS, and ^{1}H-NMR, which is also compared with the literature[2,18], the compound was PMCA.

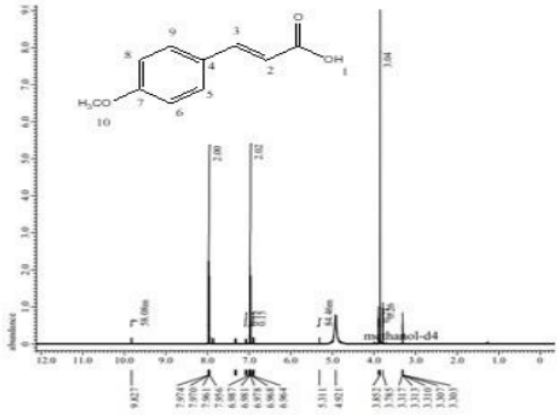

Figure 7. ^{1}H-NMR spectrum of PMCA

2. Antioxidant activity

The antioxidant activity of PMCA was tested by the visible spectrophotometric method using DPPH showed the linear regression equation is Y=0.0681x+ 25.9870, R= 0.9893 so that IC_{50} at 352.6138 ppm to DPPH. If the antioxidant activity of PMCA is compared with standard ascorbic acid with IC_{50} at a concentration of 7.875 ppm which indicates a very strong antioxidant, then PMCA is included in the category of weak antioxidant. The category of antioxidant activity can be seen from its IC_{50} value. The sample has very strong antioxidant activity, has IC_{50} <50 ppm, strong antioxidant activity has IC_{50} between 50-100 ppm, IC_{50} between 100-150 ppm has moderate antioxidant activity, and IC_{50} > 150 ppm it is said to be a weak antioxidant[21].

Several studies have shown that cinnamic acid and its derivatives are good antioxidants because they have a vinyl group, so they have potential as drugs in the treatment of various diseases, but the vinyl group is influenced by the substituent attached to the benzene ring[22]. The vinyl group has a double bond that can be used to donate its hydrogen atom to be able to bind to the DPPH radical so that it becomes a stable compound. Because of this ability, PMCA has the potential to be an antioxidant. Para methoxy cinnamic acid has a methoxy group attached to the benzene ring, which affects the antioxidant properties of this compound [23]. The methoxy group can donate electrons to the aromatic ring. The presence of resonance in the aromatic ring makes the electron impulse from methoxy increase the electron density of the aromatic ring (benzene) so that the conjugated double bond in the cinnamoyl skeleton will be stabilized. This causes the hydrogen in the vinyl to be challenging to release[23].

3. Sunscreen activity

The PMCA sunscreen activity was determined using UV spectrophotometry at 290-320 nm wavelength with a range of 5 nm. The absorbance obtained was calculated using the Mansur equation. SPF scoring

criteria based on low to high levels are low (SPF 2-15), medium (SPF 15-30), high (SPF 30-50) and highest (SPF > 50) [24]. PMCA gave SPF values for each concentration of 10, 15, 20, 25 and 30 ppm of 18,348, 24,080, 28,056, 28,104 and 32,505, respectively (Figure 8). A concentration of 10-25 ppm gave SPF in the medium category, while a concentration of 30 ppm gave an SPF value in the high protection category (Table 2) [25]. This indicated that the compound p-methoxy cinnamic acid could act as an excellent sunscreen agent. P-methoxy cinnamic acid has a chromophore group, which is a conjugated double bond in its aromatic ring, aliphatic C=C, a C=O group, and an auxochrome group from OCH_3 [1] so that it can absorb UV B rays and can be used as an active sunscreen agent with excellent potential [22- 23].

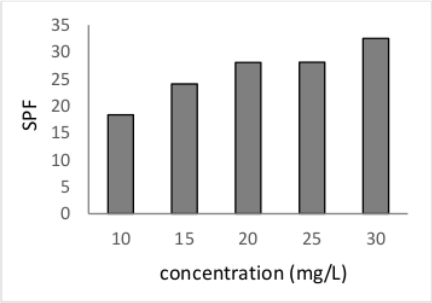

Figure 8. The SPF Value of PMCA

Table 2. Category of PMCA as sunscreen

Concentration (mg/L)	Nilai SPF	Category [24]
10	18.348	medium
15	24.080	medium
20	28.056	medium
25	28.104	medium
30	32.505	high

4. Antifungal activity

The activity test of PM**C**A compounds as antifungal agents against *Candida albicans* was carried out using the well method. Ketoconazole 0.01% was used as a positive control. The PM**C**A compounds 5%, 10%, and 15% respectively gave an inhibition zone of 0.257cm± 0.044, 1.397cm±0.093, 1.533cm±0.111 (Figure 9 and 10), while the positive control gave an inhibition zone of 3.005cm±0.118. Although the inhibition zone of the PMCA compound was not the same as the positive control, PMCA was able to act as an antifungal against *Candida albicans*.

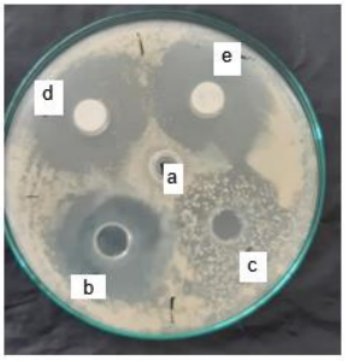

Figure 9. Inhibition of PMCA against *Candida albicans* (a= negative control; b= positive control; c = PMCA 5%; d= PMCA 10%; e= PMCA 15%)

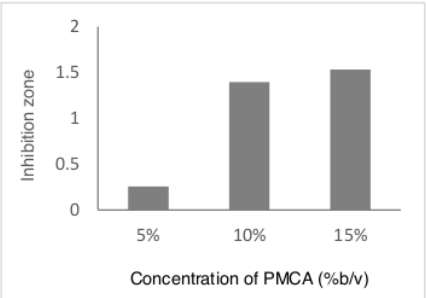

Figure 10. Antifungal activity of PMCA

The greater concentration of PMCA, the greater its activity in inhibiting *Candida albicans*. The PMCA can act as an antifungal against *Candida albicans* because PMCA has alkene (C=C) and O-CH_3 groups [1]. These results are consistent with the literature [23] that PMCA can be used as a control for the growth of microorganisms on the skin, such as *Candida albicans* (MIC 50,4 µM) [27].

CONCLUSION

The compound p-methoxy cinnamic acid (PMCA) can be synthesized by The Perkin reaction with assisted ultrasonic waves. This method requires a longer time for PMCA synthesis. The synthesized PMCA can be used as a photoprotective and antifungal agent against *Candida albicans*.

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