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Synthesis of dihydropyrimidinone derivatives using kelubi fruit (*Eleiodoxa conferta*) as a catalyst and its antibacterial activity

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ABSTRACT
Kelubi fruit is one of the many fruits that grow in Bangka Belitung which has a sour taste. Kelubi fruit contains ascorbic acid, malic acid and oxalic acid. The potency and sour taste of Kelubi fruit can be used as a catalyst in the synthesis of dihydropyrimidinone compounds and activity as antibacterial. Dihydropyrimidinone compounds were synthesized using synthesis with the basic ingredients of benzaldehyde, urea and ethyl acetoacetate using natural catalysts that are more environmentally friendly. The purpose of this study was to determine the optimum volume, time and temperature catalyst used by kelubi fruit to synthesize pyrimidine-derived compounds as antibacterial. The optimization results on the synthesis of dihydropyrimidinone compounds using kelubi fruit water as a catalyst (*Eleiodoxa conferta*) with a lot of 0.3 mL catalyst, temperature of 50ºC and reaction time of 4 hours with yield of 46.75%. Antibacterial activity of dihydropyrimidinone compounds against *Stapylococcus aureus* bacteria at a concentration of 10 ppm, 30 ppm including the category and a concentration of 75 ppm including the medium category. Antibacterial activity against *Eschericia coli* bacteria at concentrations of 30 ppm and 75 ppm was categorized as weak.

KEYWORDS
Dihydropyrimidine; Eleidoxa conferta; Fruit catalyst; Antibacterial

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Introduction

Indonesia is a country with a tropical climate which has two seasons, namely the dry season and the rainy season. During the prolonged dry season it can cause dusty air conditions, warm temperatures, while during the rainy season it makes the air moist so that microbes can grow quickly. This situation makes it easier for infectious diseases to occur. According to Gobel (2016) *Stapylococcus aureus* and *Escherichia coli* bacteria can cause infection. *Staphylococcus aureus* bacteria can cause pneumonia, pneumonia and endocarditis (Angelica, 2013). Escherichia coli bacteria are found in the human intestine which have a role in the process of removing waste products from the digestive tract, however, in abnormal conditions they are pathogenic which can infect the intestines, causing diarrhea (Putri, 2017).

Antibacterial is the activity of compounds that can inhibit the growth of bacteria. Bacterial growth needs to be controlled so that the spread of the disease (Rahmawati, 2020). Bacterial resistance to antibiotics is a condition where the growth of bacteria is not inhibited by the administration of antibiotics. (Paramita *et al.*, 2018).

According to Kappe (2000), dihydropyrimidine derivatives have anti-inflammatory, antihypertensive, antiviral and antimicrobial activities. The need for antimicrobials is still a priority to inhibit pests and diseases caused by bacteria.

Literature review

Synthesis of pyrimidine derivatives using 1,3-dicarbonyl, urea and aldehyde derivatives with catalysts of $FeCl_3$/salikalit-1 and $CuSO_4$/salikalit-1 (Zuliato, 2016), $SnCl_4$ (Bose, 2015), H_2SO_4 (Ma *et al*, 2007) , $CaCl_4$ (Gangadasu, *et al.*, 2006). If used for metallic catalysts, the separation is also a problem, which requires many applications and catalysts for hazardous environments. Therefore, it is necessary to replace catalysts with natural ingredients or acidic fruits such as kelubi.

Kelubi fruit with ethanol solvent at a drying temperature of 55ºC with a yield of 48.91% and has a water content value of 13.53%, vitamin C 99.73 mg/100g, total phenol 567.33 mg GAE/100g, pH 2.34 and total acid 199.62 mg/100g (Atisanto, 2017). The acidic nature of the kelubi fruit can be used as an acid catalyst, especially the Biginelli reaction which produces pyrimidine derivative compounds and their activity as antibacterial (Narahari, 2012).

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According to Padmashali (2019) Synthesis of dihydropyrimidine compounds using benzohydrazide as a substrate with sulfuric acid catalyst and antibacterial activity obtained in S. aureus with concentrations of 50 µg/L and 100 µg/L respectively 11 mm and 16 mm, while in E. coli it was 11 mm and 16 mm, respectively 10mm and 14mm.

Methods

Preparation of natural acid catalyst of Kelubi fruit (Eleiodoxa conferta)

The sample of this research was kelubi fruit that comes from Nyelanding Village, Air Gegas District, South Bangka Regency. Furthermore, the flesh of the kelubi was taken and then it was blended and then squeezed using a clean cloth, centrifuged and filtered to got the kelubi fruit water which was clean from fruit solids (Roanisca *et al.*, 2019). Kelubi fruit water aws ready to be used as a catalyst (Patil, 2011).

Synthesis of Dihydropyrimidine Compound Derivatives with Kelubi Fruit Catalyst

Benzaldehyde (0.2 mL), ethyl acetoacetate (0.3 mL), urea (144 mg) and an acid catalyst of Kelubi fruit water (0.1 mL; 0.2 mL; 0.3 mL and 0.4 mL) were added. in an erlenmeyer then stirred at temperatures (50 ^{0}C, 60 ^{0}C and 70 ^{0}C) with time (1 hour, 2 hours, 3 hours and 4 hours). Then stop the stirrer from heating. The reaction mixture that has solidified is then added with distilled water and then filtered the result. The filtrate was then put in the refrigerator for 1 day until crystals form and then filtered to obtain filtrate and solids, then recrystallization and monitoring of the TLC plate was carried out.

The solid produced from the synthesis was added with 96% ethanol as a beaker in a hot glass beaker at 75^{0}C until the solid was completely dissolved after which it was filtered and then cooled at room temperature for 2 hours. The resulting crystals were filtered through filter paper whose weight was known and then baked in the oven. Perform calculations to find out product yield

Product characterization

The characterization of the synthesized compounds was carried out to identify the functional groups using an FTIR spectrophotometer. The test is carried out by sending samples to the Greenlabs (Glabs) Office & Beyond Building laboratory, Bandung-Indonesia with a wavelength of 500-4000/cm. As well as a melting point test on the resulting crystal products.

Another characterization of the synthesized compound was carried out to identify it by proton H-NMR signal. The test was carried out at the Greenlabs (Glabs) office & Beyond Building, Bandung-Indonesia using a Brucker H-NMR spectrometer with 60 MHz with $CDCl_3$ solvent

Product characterization

Heat 150 mL of media to solidify and wait for it to melt, then cool it then put it in a sterile petri dish and let stand until the media solidifies again. Next, spread the agar medium evenly with Stapylococcus aureus and Escherichia coli bacteria. The concentration of crystals from the synthesis of dihydropyrimidine compounds was 10 ppm, 30 ppm and 75 ppm. The crystals were dissolved using DMSO and then impregnated in paper discs (5 mm in diameter). Positive control used 50 ppm amoxilin and negative control used 1 mL DMSO. The paper discs were then placed on agar media that had been smeared with bacteria and then incubated for 18-24 hours at 37 ^{0}C in an incubator. Measurement of the diameter of the inhibition zone using a caliper (Fasya *et al.*, 2013).

Results and Discussion

Kelubi fruit (*Eleiodoxa conferta*) contains oxalic acid, ascorbic acid and malic (Mokhtar & Aziz, 2015) so that it can be used as a catalyst and the red color of the rabbit is due to the presence of anthocyanin compounds (Jaafar, *et al.*, 2018). The Kelubi fruit used is peeled first and then separated from the Kelubi fruit flesh and seeds. The resulting Kelubi fruit flesh is blended and then centrifuged and filtered to produce an acid catalyst of Kelubi fruit water. Kelubi fruit water is red with a pH of 2-3 which contains alkaloids, hydroquinone phenols, saponins, and flavonoids.

Synthesis of pyrimidine derivative compounds through biginelli reaction by reacting benzaldehyde, urea, ethyl acetoacetate put in a beaker heated with temperature variations (50ºC, 60ºC and 70ºC), catalyst volume variations (0.1 mL; 0.2 mL; 0.3 mL) and time variations (1 hour, 2 hours, 3 hours and 4 hours). The reaction mixture is stirred using a magnetic stirrer so that the frequency of collisions between molecules increases so that the kinetic energy of the molecules increases and the reaction speed also increases. The reaction product was added with distilled water and stirred after that it was filtered. The addition of distilled water serves to remove impurities contained from the synthesis of dihydropyrimidine compounds. Stirring serves to accelerate the impurity carried away by the aquadest. The resulting filtrate is fed into the cooler until crystals form. The synthesized crystals were then recrystallized by adding hot ethanol drop by drop until they were completely dissolved, then filtered and the resulting

phytrate was put in a cooler so that crystals of pure dihydropyrimidine compounds were obtained. Pure white crystals. Recrystallization is a method that is often used to purify compounds in solid form.

The synthesis of dihydropyrimidine compounds through the biginelli reaction can be identified by their physical properties, namely in the form of solids, white in color and slightly pungent odor. Synthesis of dihydropyrimidine compounds was carried out by varying the volume of the kelubi fruit water catalyst, namely 0.1 mL; 0.2 mL and 0.3 mL (table 1).

Table 1. The yield of the catalyst volume variation at 1 hour and a temperature of 70ºC

Catalys Volume	Yield
0.1 mL	1.5 %
0.2 mL	5.6 %
0.3 mL	7.9 %

Based on Table 1, it can be seen that the catalyst with the highest yield was 0.3 mL with a yield of 7.9%. This is due to the addition of the number of H+ atoms. According to Mahardika, *et al.*, (2020) Kelubi fruit water has a role as an acid catalyst that can donate protons. Kelubi fruit water contains a lot of ascorbic acid and anthocyanins which allow for proton donors. Protons have a role to form iminium ion intermediates.

The results obtained from the synthesis of dihydropyrimidine compounds with variations on catalysts were resynthesized by varying the temperature. The temperatures used are 50 C, 60ºC and 70ºC (Table 2).

Table 2. The yield of temperature variations at a catalyst volume of 0.3 mL and a time of 1 hour

Temperature	Yield
50 ºC	28.8 %
60 ºC	16.15%
70 ºC	8.6%

At a temperature of 50ºC - 70ºC, the higher the temperature used, the smaller the yield. This is because ethyl acetoacetate has reactive properties because it has 2 ketones so that ΔH is easily released and at high temperatures becomes unstable.

Table 3. Yield results with time variations on a catalyst volume of 0.3 ml at a temperature of 50 ºC

Time (hour)	Yiled
1	28.8%
2	37.2%
3	43.1%
4	47.3%

Based on the results in the table, it shows that the highest yield is at 4 hours with an average yield of 46.75%. The increase in the synthesis time causes the wider opportunity for the reactant molecules to collide with each other as the reaction time increases (Rudyanti, 2012).

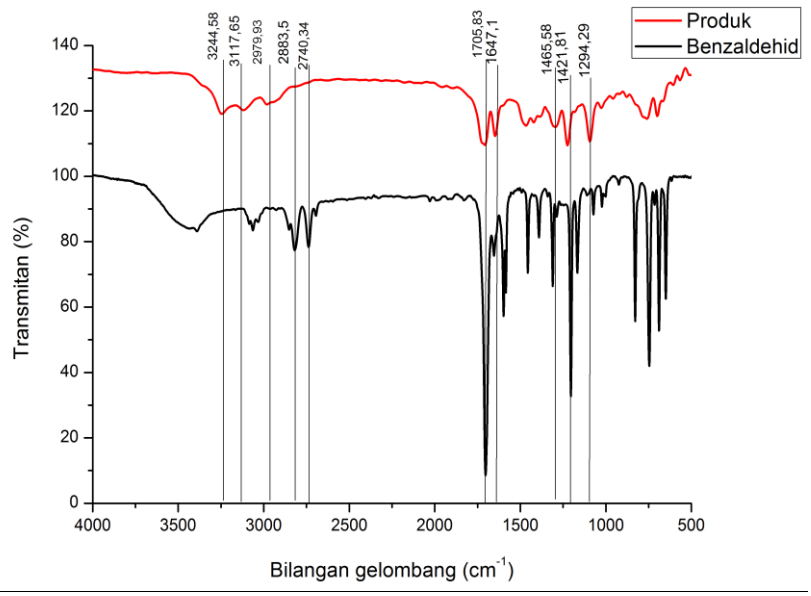

Figure 1. Product compound FTIR spectrum

In testing the synthesis of dihydropyrimidine compounds using a catalyst volume of 0.2 mL using a FeCl3 catalyst, the yield was 66% (Choudrey, 2003) and using an HCl catalyst the yield was 84% (Keppe, 1997). Septiani's research (2019) using a zeolite catalyst using a temperature of 50ºC and 60ºC, the yields were 37.33% and 30.96%, respectively, and Wang's research (2010) used a temperature of 70ºC with Fe(NO3)2.9H2O and Ce(NO3) as catalysts. 2.6H2O yield yields of 75% and 79%, respectively. Based on the results of testing the optimal value of the synthesis of dihydropyrimidine compounds at a catalyst volume of 0.3 mL, a temperature of 50ºC and a time of 4 hours with a yield of 46.6%. The yield from the use of kelubi fruit water catalyst appears to be low when compared to metal catalysts or strong acids. However, the use of Kelubi fruit water catalyst has the advantage of being non-toxic and environmentally friendly so it is safe for the environment. Based on the test results obtained the following FTIR analysis (Figure 1).

Table 4. FTIR sprctrophotometry analysis

Functional Group	Benzaldehyde Wave Number (cm–1)	Product Wave Number (cm–1)	References (cm–1)
N-H	-	3244,56	3240,41
C-H	2850,90	3117,65	3116,97
CH=O	2883,5 & 2740,34	-	-
CH_3	-	2979,93	2978,09
C=O	1702,44	1705,83	1705,85
C=C	1655,12	1647,10	1643,35
C=C	1455,62	1465,58	1465,90
CH_2	-	1421,81	1419,61
C-O	-	1294,29	1288

The results of the FTIR sprctrophotometry analysis on the wave number indicated as an N-H group in the range of 3750-3000 cm-1. The stretching C-H group is in the range of 3300-2900 cm^{-1}. The CH3 group stretches in the range of 3000-2850 cm-1. C=O buckling is in the range of 1740-1705 cm-1. The functional group C=C for stretched alkenes is in the range of 1680-1600 cm^{-1} . The aromatic C=C group is in the range of 1500-1450 cm-1. The CH2 group is in the range of 1480-1400 cm-1. The stretching C-O functional group is in the range of 1300-1000 cm-1. Based on the results of the FTIR data test, 3,4-dihydropyrimidine-2-(1H)-one was formed with the type of compound 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2(1H)-one. Synthesis of 3,4-dihydropyrimidine-2-(1H)-one compound using benzaldehyde as a substrate. The results of the synthesis of dihydropyrimidine compounds are characterized by the presence of NH with the appearance of an atomic absorption band at a wavelength of 3244.56 cm-1 which indicates the presence of a secondary amine group and an atomic absorption band at a wavelength of 1705.83 indicates the presence of a C=O group, this indicates the presence of an NH amide group. -C=O which is a characteristic of the 3,4-dihydropyrimidine-2-(1H)-on functional group and in the product a reaction occurs with the loss of the aldehyde functional group at wave numbers 2883.5 & 2740.34 cm-1. Based on the results of the FTIR analysis, it showed conformity with the functional groups contained in the dihydropyrimidine compound.

The results of the FTIR analysis only found functional groups present in the synthesized compounds, therefore more specific characterization was needed to determine the structure of the compounds produced. Compound of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2(1H)-one with the results of 1H-NMR (60 MHz, CDCl3): 9,663 (1H); 6,444 (5H); 5,033 (2H); 3,374 (1H); 2,301 (3H). The integration of the resulting dihydropyrimidine compound with a magnetic field resonance of 60 MHz is not visible but the peak of the chemical shift is close to the reference.

Antibacterial test

Antibacterial testing was carried out by the diffusion method which aims to determine the area of the inhibition zone formed in the form of a clear zone formed around the paper disc placed on the agar medium as a benchmark for the strength of the inhibition against bacteria. The synthesized compound dihydropyrimidine was tested on gram-positive (*S. aureus*) and gram-negative (*E. coli*) bacteria. The synthesized compound was dissolved in DMSO with antibacterial test concentrations of 10%, 30% and 75%. Antibacterial activity was shown by measuring the clear zone formed after incubation at 37ºC. The results of the measurement of the diameter of the inhibition zone of dihydropyrimidine compounds against *S. aureus* and *E. coli* bacteria can be seen as follows:

Bacteria	Concentration (ppm)	Inhibition zone (mm)
Staphylococcus Aureus	10	2,82
	30	3,00
	75	6,72
	C(+)	48,84
	C(-)	-
Escherichia Coli	30	0,12
	75	1,02
	C(+)	43,47
	C(-)	43,47

The results of the synthesis of dihydropyrimidine compounds have performance as antibacterial which is indicated by the formation of a clear zone in the comparison dish Amoxilin as control (+) and DMSO as control (-). According to David and Stout (1971) antibacterial inhibition based on the diameter of the inhibition zone is divided

into very strong (inhibition zone more than 20 mm), strong (inhibition zone 10-20 mm), moderate (inhibition zone 5-10 mm) and weak (inhibition zone). less than 5mm). The results of the antibacterial activity test of the dihydropyrimidine compound against Staphylococcus aureus showed that at concentrations of 10 and 30 ppm it was categorized as weak with a zone yield of 2.82 mm and 3 mm respectively, while at a concentration of 75 ppm it was categorized as moderate with a zone of moderate inhibition. The activity of dihydropyrimidine compounds against e.coli bacteria showed that at concentrations of 30 and 75 ppm it was categorized as weak with results of 0.12 and 1.02 ppm, respectively. The increase in concentration used gives a larger clear zone diameter, this is in accordance with the opinion of Munthe *et al.*, (2015) which states that the higher the concentration in a sample, the higher the antibacterial activity. Staphylococcus aureus bacteria have a single layered cell wall so that the results of the synthesis of dihydropyrimidine compounds easily enter the bacterial cell membrane while E.coli bacteria have a three-layered cell wall that can protect bacteria from antibiotic substances.

Previous research conducted by Fauziyah (2015) using modified benzaldehyde, urea and ethyl acetoacetate using pineapple juice as a catalyst with low concentrations (0.1%, 0.2%, and 0.4%) showed no antibacterial activity against S. aureus and E. coli bacteria. Research conducted by Padmasali (2019) using a benzohydrazide substrate using sulfuric acid as a catalyst, antibacterial activity was obtained in S. aureus bacteria with concentrations of 50µg/L and 100µg/L, respectively, 11 mm and 16 mm, while in E.coli it was 10 mm. and 14 mm. Therefore, it is necessary to replace the substrate that can increase the value of antibacterial activity by using compounds derived from benzaldehyde such as benzohydrazide.

The mechanism of action of the antibacterial compound dihydropyrimidine by disrupting the peptidoglycan component in the bacterial cell wall. The amine group in a dihydropyrimidine compound in an acid solution will be protonated into ammonium ion. This ammonium ion group is an active group that can be used to inhibit bacterial growth through the interaction between polycationic ammonium and negative ionic charges in bacterial cells. The amine group in dihydropyrimidine compounds can interfere with the components of the peptidoglycan component in bacterial cells, therefore the cell wall layer cannot be fully formed so that it can cause cell death. The amine and protein groups will form hydrogen bonds and can damage the protein structure. Antibacterial agents, especially those with ammonium ions, interact with cell walls containing proteins and peptidoglycans (Pramita, 2011). Alkyl groups and phenyl groups can affect the interaction of compounds against bacteria. The alkyl and phenyl groups are hydrophobic chains that play a role in forming hydrophobic interactions with bacterial membrane lipids. Damage to the membrane results in leakage in the cell which is followed by the release of intracellular material (Pramita, 2011).

Conclusion

Based on the results of the study, the optimum results of the synthesis of dihydropyrimidine compounds using the water of kelubi (*Eleiodoxa conferta*) as catalyst were 0.3 ml of catalyst, 50ºC temperature and 4 hours reaction time with yield value of 46.75% and antibacterial activity of dihydropyrimidine compounds against *Stapylococcus aureus* bacteria in concentration of 75 ppm is included in the medium category. Antibacterial activity against Eschericia coli bacteria at concentrations of 30 ppm and 75 ppm was categorized as weak.

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