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SOLVENT-FREE SYNTHESIS OF 4'-HYDROXY-4-HYDROXY CHALCONE AND ITS POTENTIAL AS AN ANTIBACTERIAL

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ABSTRACT

This study aimed to synthesize 4'-hydroxy-4-hydroxy chalcone from 4-hydroxy acetophenone and 4-hydroxybenzaldehyde by a solvent-free method using a grinding technique and determine its potential as an antibacterial against *Staphylococcus aureus* and *Escherichia coli*. Synthesis of 4'-hydroxy-4-hydroxy chalcone was conducted using the Claisen-Schmidt method of grinding for 30 minutes. The grinding results were then extracted with chloroform. The formed crystals were tested for purity by thin-layer chromatography (TLC), and recrystallization was carried out to purify the compound. FTIR, ^{1}H-NMR, and ^{13}C-NMR characterized the synthesized chalcone. The synthesized chalcone was determined for antibacterial activity using the disc method against *Staphylococcus aureus* and *Escherichia coli*. The results showed that 4'-hydroxy-4-hydroxy chalcone could be synthesized from 4-hydroxy acetophenone and 4-hydroxy benzaldehyde by grinding technique in orangish white crystals form (yield of 66.67%) and a melting point of 85-88°C. The synthesized chalcone has low antibacterial potential against *Staphylococcus aureus* and *Escherichia coli*.

Keywords: grinding, solvent-free, Claisen-Schmidt, chalcone, antibacterial, *Staphylococcus aureus*, *Escherichia coli*

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INTRODUCTION

Antibacterials are substances that can kill or inhibit bacteria growth. Antibacterials can only be used if they have selective toxic properties, meaning they can kill bacteria that cause disease but are not poisonous to the sufferer. The mechanisms of antibacterial action include inhibiting cell wall synthesis, inhibiting the bacterial cell integrity of wall permeability, inhibiting the action of enzymes, and inhibiting the synthesis of nucleic acids and proteins. The group of antibacterial compounds includes phenols, alcohols, halogens, heavy metals, detergents, and aldehydes. Phenol compounds are the most widely used because these compounds are found not only in synthetic antibiotics but also in natural compounds known as polyphenols. The specific superiority of the chalcone antibacterial is that the antibacterial activity varies with the various groups present in the aromatic ring of the chalcone. Molecular modification of chalcones can be carried out by changing the substituents present in the aromatic reactant system, namely acetophenone, and benzaldehyde, so that the potential of chalcones as antibacterials with the best activity can be determined.[1] Specifically, one of the compounds that can be used as an antibacterial is chalcone.[1-2] Chalcones with substitution of the hydroxy group at R1 in chalcones show antibacterial solid activity, like ((E)-3-(4-(Diethylamino)phenyl)-1-(2,4-dihydroxyphenyl)prop-2-en1-one) which showed MICs against MSSA (3.12 µg/mL) and MRSA (6.25 µg/mL), respectively. Chalcones and their derivatives have been widely used as antibacterial. However, substituted chalcones with two hydroxy groups at position 4 in rings A and B have not been identified against *Escherichia coli and Staphylococcus aureus*. Several chalcones can inhibit various pathways for the development of antibiotic resistance. Some chalcones are more active than conventional antibiotics, such as 2',4,4'- trihydroxy chalcone and 2',4,4'- trihydroxy-3-preny'-3'geranylchalcone.[3] The α,β unsaturation of chalcone structure was shown to be essential for antibacterial activity.[4] The chalcones with electron-donating groups (EDG) in ring B (C-3 and C-4), i.e., 3-methoxy-4-hydroxy chalcone, exhibit good activity to *Bacillus subtilis, Staphylococcus aureus*, *Klebsiella pneumonia*, and Enterobacter *cloacae*.[4]

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Chalcone $(C_{15}H_{12}O)_5$ in plants is very difficult to isolate due to the enzyme chalcone synthetase (CSH) content. The CSH enzyme plays a role in converting chalcone into flavanones. Chalcone is also one of the bioactive flavonoids with pharmacological potential as an anticancer, antioxidant, anti-inflammatory, antidiabetic, antimicrobial, antiparasitic, psychoactive, and neuroprotective agent.[5-6] This compound comprises one unsaturated α,β carbon atom, and two aromatic rings. The chalcone was synthesized using the Claisen-Schmidt condensation of benzaldehyde and acetophenone derivatives with alkaline or acid catalysts.[7] Several techniques for synthesizing chalcone in the laboratory include conventional techniques (solvent)[8], wave irradiation, and solvent-free synthesis such as grinding.[9] A facile synthesis of some novel 4-(Sub Phenyl)-1-phenyl 2-propen-1-ones has been achieved by intramolecular aldol condensation by a grinding technique using solid NaOH. The grinding technique is a simple, fast, efficient, and environmentally friendly chalcone synthesis procedure.[9] 2',6'-dihydroxy-3,4-dimethoxy chalcone has also been synthesized using a grinding using 2,6-dihydroxy acetophenone, 3,4-dimethoxybenzaldehyde, NaOH catalyst for 15 minutes at room temperature, and has given good results.[10] The grinding technique is more environmentally friendly (green synthesis) since it does not use organic solvents to reduce waste discharged into the environment. The advantages of the grinding technique are that the reaction time is shorter, the resulting product has good results, and it is straightforward.[10] Moreover, one of the pharmacological activities of chalcone is antibacterial.[6] Based on the results of previous studies, the 4-bromo-4'-methoxychalcone and 4-hydroxy-4'-methoxychalcone have been synthesized using grinding techniques and are active as antibacterials against *S. aureus* and *E. Coli.*[9] In addition, The synthesis of (Z)-1-(4-bromophenyl)-3-(pyridine-4-yl) prop-2en-1one and (Z)-1-(4-bromophenyl)-3-(pyridine-3-yl) prop-2en-1one has also been executed and has antibacterial activity against *S. aureus, B. subtilis*, and *E. Coli*.[7] However, this grinding technique has not been carried out to synthesize chalcone derivatives from 4-hydroxy acetophenone with 4-hydroxy benzaldehyde. The reaction reduces the use of volatile organic compounds (VOCs) and has a shorter reaction time.[11] 2′-hydroxy-chalcones synthesized by Claisen–Schmidt condensation and ultrasound-assisted reaction.[12-13] This research aims to develop active antibacterial compounds by modifying the chalcone molecule so that homologous compounds that most likely have the same or even better pharmacological properties can be obtained.

EXPERIMENTAL

Material and Methods

The materials utilized had analytical grade quality (E-Merck Germany), 4-hydroxy benzaldehyde, 4-hydroxyl acetophenone, NaOH, HCl, aquadest, ethyl acetate, ethanol, n-hexane, chloroform, and anhydrous sodium sulfate, Whatman paper, and TLC Plate. Instruments for the study were laboratory glassware Pirex, magnetic stirrer, desiccator, magnetic stirring plate, UV lamp (254 nm), ^{1}H-NMR (JEOL-MY500), and ^{13}C-NMR (125 MHz, JEOL-MY500).

General Procedure

Synthesis of Chalcone Grinding Technique

The chalcone was synthesized by grinding 4-hydroxybenzaldehyde (1.22g, 10mmol) with 4-hydroxyacetophenone (1.36g, 10mmol) at room temperature in a mortar and pestle for 30 minutes. Thin Layer Chromatography (TLC) monitored the reaction's completeness. The reaction mixture was diluted with cold water and then neutralized with HCl 10% (v/v, cold). The reaction product was collected by vacuum filtration and continued with ethanol recrystallization. The synthesized compound was measured in its melting point and characterized using FTIR, ^{1}H-NMR, and ^{13}C-NMR spectrophotometers.

Purification and Characterization

Purification was carried out by recrystallization, followed by determining its melting point. The synthesized chalcone was, at that point, characterized by utilizing ^{1}H- and ^{13}C-NMR spectrometers.

Antibacterial Activity

The channel paper circle spread strategy was utilized to select the antibacterial potential of the synthesized chalcone. The antibacterial test of chalcone was carried out against E. coli and S. aureus.

The bacterial culture is blended with a sterile NaCl course of activity until a turbidity of around 0.5 CFU/mL (colony-forming units per milliliter) is obtained. Petri dishes containing 20 mL MH agar were utilized as a bacterial test medium. The inoculum was spread onto the surface of the serious media. Whatman circle channel paper was streamed with 20ÂµL of the synthesized chalcone and, after that, set on the surface of the plate. Tetracycline (5ÂµL/disc) was used as a positive control, though DMSO was used as a negative control. Bacteria-inoculated were brought forth at 37Â°C for 24 hours. The restriction zone breadth illustrated positive prevention by forming a clear zone of more than 2 mm around the channel paper.[14]

RESULTS AND DISCUSSION

The synthesis of 4'-hydroxy-4-hydroxy chalcone was carried out by solvent-free method using the grinding process 4-hydroxy benzaldehyde, 4-hydroxy acetophenone, and NaOH (Fig.-1). The synthesis process in the absence of any solvent in mortar and pestle for 30 minutes. The compounds synthesized were white-orange crystals that looked shiny. Then, the crystals were weighed utilizing an analytical balance, and crystals of 1.6 grams were obtained from the synthesis results. Based on the theory, the weight of the 4'-hydroxy-4-hydroxy chalcone is 2.4 grams. Afterward, yield calculations were carried out, resulting in 66.67%. The results obtained from this synthesis method were lower compared to other studies. Sreedhar has synthesized 4-hydroxychalcone using PEG-400, quickly producing good to excellent yields (75-85%) without forming any by-products.[11] The Claisen-Schmidt aldol condensation is carried out in alkaline conditions to ensure the reaction is more stable because keto-enol tautomerization can occur in acidic conditions. NaOH is a commonly utilized base catalyst. KOH (yield 88-94%), $Ba(OH)_2$ (yield 88-98 %), and NaOH (yield 90-96 %) have all been utilized as catalysts within the Claisen-Schmidt reaction.[15]

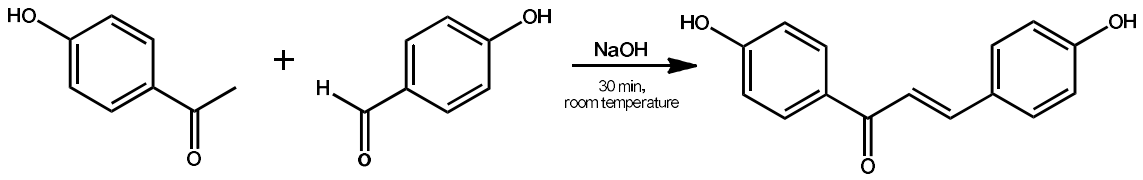

Fig.-1: Reaction to Produce the Chalcones

The advantage of the solvent-free method using a grinding technique is that it uses simple and inexpensive equipment. The reaction process is shorter. The grinding technique does not use organic solvents, so it is environmentally friendly. Synthesis using this method applies one of the principles of green chemistry, namely the removal of reaction solvent. By removing the solvent, we create a much more complex reaction environment, an environment in which interactions usually ignored in solution chemistry, e.g., product-reactant interactions, may now play an important role in the final outcome. The solubility of reactants and products in a particular solvent does not need to be considered. The reaction starts from grinding, with small amounts of energy through the starter, generating local heat when grinding crystal substrates and reagents with a mortar and pestle. The synthesis uses milling, low base concentration, shorter reaction time (15 minutes), and higher yields (70-84%). The disadvantage of the grinding technique is that the grinding is done manually, so the grinding process depends on a person's physical strength and grinding speed. Manual grinding is also greatly influenced by the stability and direction of the grinding rotation. The rate of speed also depends on the force applied. Fast and stable grinding produces products in a much shorter time compared to slow milling. The recrystallization process was conducted by preparing 5 ml of ethanol and putting it into a beaker that already contained the crystals of the synthesis. Then, it was stirred at 80°C until the crystals dissolved. The results were obtained in a clear solution, which stood for one hour and was covered with filter paper that was given a hole sealed with rubber. Then, the solution was stood until the ethanol evaporated and crystals formed again. The time required for the ethanol to evaporate and the crystals to dry ultimately was 6-8 days. Recrystallized crystals were white and slightly shiny orange. The crystal mass obtained after this recrystallization process was 1.54 grams. The difference in the resulting crystal mass was not too significant with the crystal mass before recrystallization. The crystal recrystallization results of the 4'-

hydroxy-4-hydroxy chalcone were then tested for purity by TLC. The TLC chromatogram showed one spot (Rf 0.76), indicating that the synthesized chalcone was pure.

Characterization of 4'-hydroxy-4-hydroxy Chalcone

The synthesized 4'-hydroxy-4-hydroxy chalcone was tested for melting point. After testing, the melting point of the 4'-hydroxy-4-hydroxy chalcone was 85-88^{0}C. This melting point was measured when the 4'-hydroxy-4-hydroxy chalcone changed its state from crystal to liquid. Using FTIR, characterization was performed to determine the functional groups in the synthesized 4'-hydroxy-4-hydroxy chalcone (Fig.-2). Asymmetric and symmetric stretching vibrations within the chalcone's aromatic C–H were recognized in the IR range by two low-intensity bands at 3120–3080 cm^{-1} and 3060–3040 cm^{-1}. In the interim, the C–H band in the =C–H group is observed at 3030–3010 cm^{-1}. The band at 1610–1570 cm^{-1} is the vibration of the aromatic ring, whereas, at 1460–1430 cm$^{-1,}$ the wide weak band is the deformation of the =C–H bond plane. The strain vibration for enone (=C–C=O) can be found at 1650-1685 cm^{-1}. The functional groups contained in the 4'-hydroxy-4-hydroxy chalcone were carbonyl groups (C=O), hydroxy groups (OH), aromatic groups, and alkene groups (C=C). The results obtained were in the form of a spectrum, such as a graph. The results of these FTIR spectra can be seen in Fig.-2.

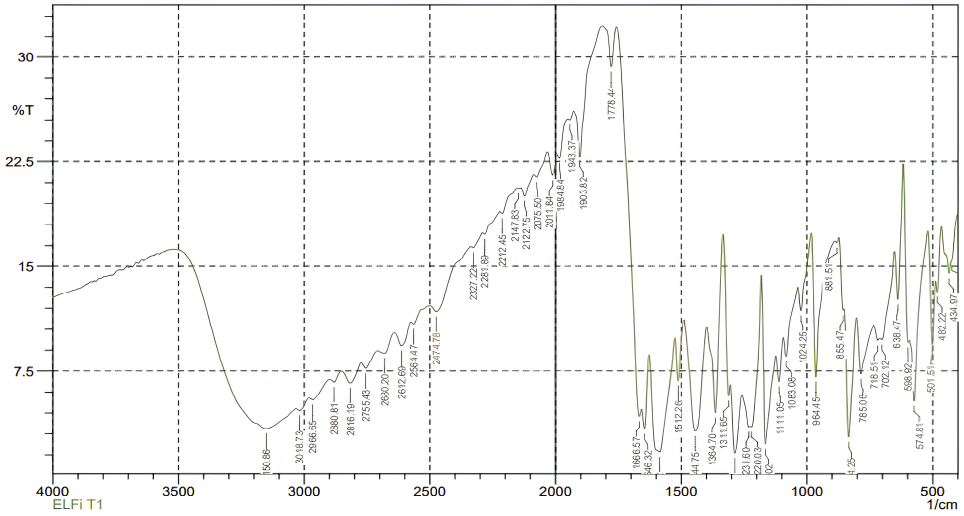

Fig.-2: FT-IR Spectra of Chalcone Synthesized

The spectrum that could be interpreted is that at the wave number 3150.86 cm^{-1}, there was a wide peak. This broad peak indicates the presence of an O-H. At wave number 3018.73 cm^{-1}, there was a weak peak, indicating the presence of an aromatic C-H group. The sharp peak at the wave number of 1586.52 cm^{-1} means a sharp peak strengthens the aromatic C=C group at 1444.75 cm^{-1}. At 1646.32 cm^{-1}, a sharp peak indicated the presence of the C=C group. The sharp peak at wave number 1666.57 cm^{-1} indicates the C=O (carbonyl) group, strengthened by a weak peak at 2755.43 cm^{-1}. It is in by the groups contained in the 4'-hydroxy-4-hydroxy chalcone.

The synthesized chalcone was then characterized by ^{1}H-NMR. This ^{1}H-NMR spectrometer measures the resonance of protons or hydrogen atoms, where the chemical environment of each proton distinguishes the results. The ^{1}H-NMR spectrometer also provides information on the protons in organic compounds. The protons are surrounded by not always the same electrons, so a different chemical shift will be produced. Chemical shift is symbolized by (delta) and is usually used in ppm. Chemical shift is also a number showing the proton resonance shift of the TMS in ppm concerning the frequency spectrometer. In addition, the chemical shift value (δ) for the ^{1}H-NMR spectrometer ranges from 0-12 ppm. The ^{1}H-NMR spectra of 4'-hydroxy-4-hydroxy are shown in Fig.-3.

The spectra in Fig.-3 illustrate the number of proton types in the 4'-hydroxy-4-hydroxy. The number of signals generated was eight proton signals. Figure-3 provides information about the signals that appeared with each group's chemical shift value. The absorption band at the chemical shift (δ) of 6.85 ppm (8.75 Hz) indicates aromatic CH=CH or aromatic protons, H-3 and H5. A chemical shift (δ) of 6.93 ppm (8.55

Hz) suggests the absorption of aromatic protons, H-3' and H-5'. Absorption also appeared at a chemical shift (δ) of 7.75 ppm (8.75 Hz), indicating aromatic protons H-2 and H-6. A chemical shift (δ) of 7.82 ppm denotes proton absorption of H-2' and H-6'.

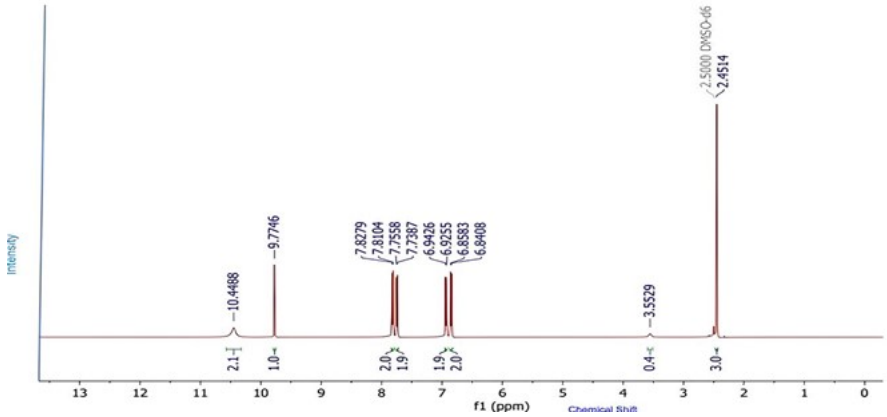

Fig.-3: [1]H-NMR Spectra of 4'-hydroxy-4-hydroxy Chalcone (DMSO as Solvent)

In this case, the chemical shift value is the same for several protons of an aromatic group because they have the same proton environment, so the spectrum will appear in almost the same area. This is because the 1H-NMR spectrum of chalcone double bonds is seen at 5.4 and 6.1 ppm, while aromatic C-H is observed at 6.9–8.1 ppm.[4] The proton absorption of the H-β alkene (CH=CH) appeared at a chemical shift of 9.77 ppm. The chemical shifts at 7.15-8.23 ppm and 7.45-8.07 ppm are H-α and H-β. Suppose the coupling constants value is JHα-Hβ=8 Hz, which indicates the cis configuration of the vinylic system. The coupling constants value is JHα-Hβ=15-16.1 Hz, which points out the trans configuration of the vinylic system. Based on the H-NMR characterization results, the chalcone synthesized from the research results is suspected to have a cis configuration. The absorption for the proton O-H also appeared at a chemical shift of 10.45 ppm. The shift was farthest from the DMSO standard due to the influence of an electronegative oxygen element. Oxygen pulled the electron density away from the carbon atom and thus affected the electron density of the proton. Therefore, the protons in the hydroxyl group were de-shielded. Based on the interpretation of the spectral data, it can be seen that these signals indicate a proton signal from the 4'-hydroxy-4-hydroxy chalcone. Absorption at 2.5 ppm in the HNMR spectra shows that there are still impurities, presumably from reactants that have not entirely reacted. A ^{13}C-NMR then characterized the synthesized chalcone. ^{13}C-NMR is a spectrophotometer used to analyze the carbon atoms in a compound, such as the number of atoms, the type of atom, or the environment of the carbon atoms. The ^{13}C-NMR spectrometer is also needed to determine the number of carbon atoms in organic compounds or molecules. The area, which is the chemical shift of the ^{13}C atom of organic molecules, is 10-210 ppm. The ^{13}C-NMR spectra resulting from the characterization of the compound 4'-hydroxy-4-hydroxy chalcone can be seen in Fig.-4.

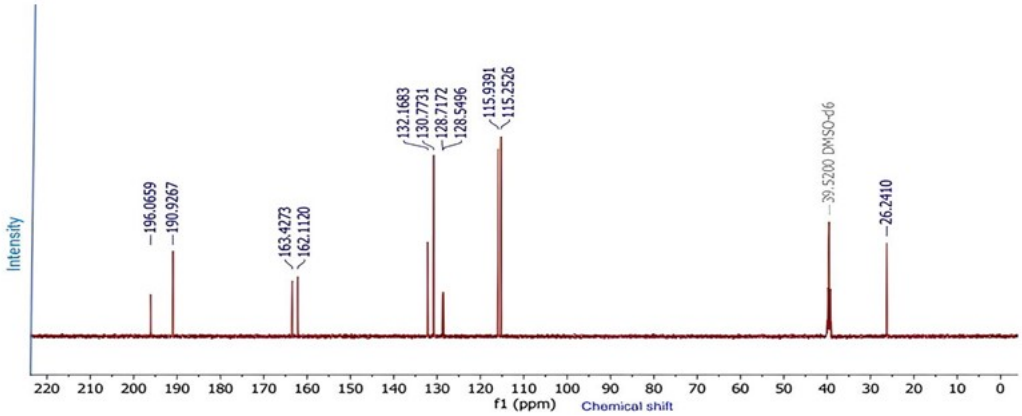

Fig.-4: ^{13}C-NMR Spectra of 4'-hydroxy-4-hydroxy Chalcone in DMSO

Figure-4 shows that the signals that appeared were 11 carbon atom signals. The smallest chemical shift value was 26.24 ppm, and the most significant value was 196.06 ppm. Each carbon atom also had a different chemical shift value. Figure 4 illustrates the number of signals that appeared in the C-NMR characterization of 4'-hydroxy-4-hydroxy chalcone. The signal at the chemical shift of 115.25 ppm is the signal shift area for the carbon atoms in the aromatic ring, namely C-3 and C-5. Meanwhile, the chemical shift of 115.94 ppm indicates C-3' and C-5' carbon atoms. Then, the signal that appeared in the chemical shift (δ) of 128.55 ppm signifies the signal of the C- alpha carbon atom in the chalcone, which is double bonded to the C-β atom. Meanwhile, the chemical shift (δ) 128.72 ppm indicates the signal of the C- carbon atom, one aromatic ring. As a rule, the carbonyl carbon of chalcone usually appears between δ 186.6 and 196.8 within the ^{13}C-NMR spectrum. The α- and β- carbon of the carbonyl group give characteristic signals between δ 116.1–128.1 ppm and δ 136.9–145.4 ppm separately. In addition, a chemical shift (δ) of 130.77 ppm denotes a signal of carbon atoms, namely C-1', C-2, and C-6, which are in the aromatic ring.

The signal that appeared on the shift was three signals, and this is because the signals were close together and had a higher intensity compared to other signals. The chemical shift (δ) of 132.16 ppm is the signal shift area for the C-2' carbon atom. The signal on the chemical shift (δ) of 162.11 ppm shows the signal of the C-β carbon atom double bonded to C-α (alkene). The chemical shift of 163.42 ppm is the signal shift area for the C-4 carbon atom, where this carbon atom is in the aromatic ring. Besides, the chemical shift of 196.06 ppm was the highest signal, indicating the presence of a carbonyl group (C=O) in the chalcone. The carbonyl group had the most significant chemical shift value because it was influenced by electronegative atoms, namely oxygen (O) and double bonds. Based on the interpretation of the C-NMR spectral data, the signals that appeared were signals of carbon atoms in the 4'-hydroxy-4-hydroxy chalcone. Further, based on the characterization, it was found that the chalcone compound had been synthesized from 4-hydroxy acetophenone and 4-hydroxy benzaldehyde using the grinding technique. Using simple equipment and good results, synthesizing chalcone by grinding was a solvent-free chalcone synthesis method.

Antibacterial Activity of 4'-hydroxy-4-hydroxy Chalcone

Antibacterials are substances that can kill or inhibit bacteria growth. Antibacterials are known as antibiotics in the pharmaceutical field, chemical substances produced by microorganisms that can kill or impede the growth of other microorganisms.[1] In this study, the 4'-hydroxy-4-hydroxy chalcone was tested for antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*. The test results shown demonstrate that the 4'-hydroxy-4-hydroxy chalcone has antibacterial activity. Tests on both bacteria formed a clear zone, which indicated that the 4'-hydroxy-4-hydroxy chalcone could inhibit bacteria. The results on *S. aureus* bacteria (gram-positive) formed a clear zone of 10.34 mm. It suggests that the antibacterial activity of *S. aureus* was relatively weak. The E. coli (gram-negative) results showed that the clear zone formed was 7.81 mm, and the antibacterial activity level was fragile (Fig.-5).

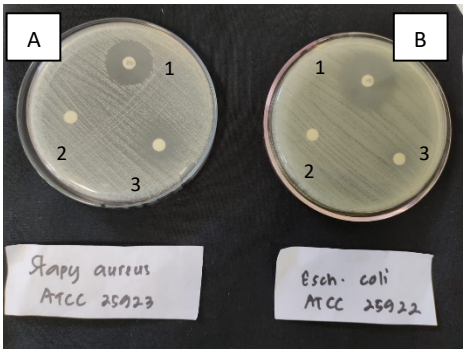

Fig.-5: Clear Zones formed Around Bacterial Extracts after 24 h Incubation at 37°C. 1. + Control = Chloramphenicol, 2. -Control = DMSO, 3. Chalcone Synthesized) A. against *S. aureus*. B. against *E. coli*

The strength of antibacterial activity can be seen from the clear zone resulting from the disc method test, i.e., the activity is classified as vital if the clear zone has a diameter of > 20mm; the activity is classified

as moderate if it has a clear zone diameter of 16-20 mm; the activity is classified as moderate if it has a clear zone diameter of 16-20 mm; it is classified as weak if the diameter of the clear zone is 10-15 mm; the activity is classified as very weak if the clear zone is <10 mm in diameter.[17]

The 4'-hydroxy-4-hydroxy chalcone is thought to have pharmacological activity due to the presence of a carbonyl group (C=O) and an alkene group (C=C) on the α,β-unsaturated carbon atom bond. Molecules possessing such systems have relatively low redox potentials and are more likely to undergo electron transfer reactions.[25] Avila HP's research results (2008) explained that the OH group at C2 is essential due to its intramolecular interactions with the C=O group, and the OH group at C4 activates a region that includes the neighboring OH group at C2, and the unsaturated carbonyl groups α,β. Existence The OH group at C4 is essential for antibacterial activity. This may be the reason for the low activity of dihydrochalcone against MSSA strains and no activity against isolated MRSA because it does not have a hydroxyl group at this position or a double bond.[14] The clear zone in this test's results revealed how large the inhibition zone for the antibacterial compound was. The clear zone or the antibacterial inhibition zone against *E. coli* was smaller than the inhibition zone for *S. aureus* bacteria. This is because gram-negative bacteria have higher resistance to an antibacterial compound. The cell wall composition in gram-negative bacteria is more complex than in gram-positive bacteria, so the resistance to antibacterial is higher or better. Gram-negative bacteria also have cell wall structures, namely lipid-protein, lipopolysaccharide, and peptidoglycan. The peptidoglycan level in gram-negative bacteria's cell walls is only slightly around 5% - 10%. In addition, intermolecular cationic cross-links in the lipopolysaccharide layer make the cell wall solid and sturdy. The robust cell wall makes penetrating antibacterial compounds more complex.[15] Research on chalcone, which has antibacterial activity, has been widely reported. Prasad *et al.* (2008) synthesized 12 chalcone derivatives, and the results of their research show that chalcones with methoxy and hydroxy groups have better antibacterial activity than chalcones without these groups.[17] (E)-2′-hydroxy chalcone with a hydroxyl group on the B-ring shows good antibacterial activity against eight bacterial strains, namely *S. aureus*, *S. epidermidis*, *E. faecalis*, *M. flavus*, *M. luteus*, *B. subtilis*, *K. pneumoniae,* and *P. aeruginosa* with MIC values ranged from 0.052-2.10 Mm.[6] Chalcone with two hydroxy groups on ring B and no other substituents on ring A showed good antibacterial activity (MIC value 50 µg/mL) against *S. aureus*.[16] Based on the test results, it can be concluded that the 4'-hydroxy-4-hydroxy chalcone has antibacterial activity with a weak group on *Staphylococcus aureus* bacteria and a very weak one on *Escherichia coli* bacteria. The 4'-hydroxy-4-hydroxy chalcone also has antibacterial activity due to the presence of an ethylene keto group (-CO-CH=CH-), which is reactive, causing the chalcone to have pharmacological activity as an antibacterial.

CONCLUSION

4'-hydroxy-4-hydroxy chalcone has been synthesized from 4-hydroxy benzaldehyde and 4-hydroxy acetophenone by the solvent-free method using grinding techniques. The synthesized chalcone compound obtained was white-orange crystals with a yield of 66.67% and a melting point of 85-88^{0}C. 4'-hydroxy-4-hydroxy chalcone has weak antibacterial activity against *Staphylococcus aureus* and weak against *Escherichia coli.*

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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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[RJC-8889/2024]