Esterification of Cinnamic Acid Anthrone

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ESTERIFICATION OF CINNAMIC ACID USING MENTHOL AND ITS ACTIVITY AS LOWERING GLUCOSE LEVELS USING ANTHRONE SULFATE

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ABSTRACT

This study aimed to synthesize menthyl cinnamate and its activity as a glucose-lowering agent. Synthesis of menthyl cinnamate using Fischer esterification of cinnamic acid and menthol with sulfuric acid as a catalyst using reflux at a temperature of 60°C with a synthesis time variation of 4,5 and 6 hours. Identification of synthesis results using FTIR spectrophotometry and GC-MS. Glucose lowering activity of the synthesis product using anthrone sulfate. The synthesized compound was a yellow oil liquid with a sweet fruity aroma typical of cinnamic esters with a yield % of 95.83%, 96.38, and 91.79%, respectively, at 4, 5, and 6 hours. The synthesized product was soluble in nonpolar solvents. Analysis by FTIR showed several functional groups such as C=O, C=C, C-O, and C-H aliphatic. Analysis of the synthesis results with GC-MS showed a retention time of 18.38 minutes for menthyl cinnamate with m/z = 286. Test with anthrone sulfate gave an optimum concentration of 300 ppm with a % decrease in the glucose of 48.62%. Based on these results, it can be concluded that menthyl cinnamate can be synthesized with optimum yield in 5 hours and has potential as an antidiabetic agent.

Keywords: *antidiabetic, anthrone sulfate, cinnamic ester, menthol, menthyl cinnamate.*

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease caused by abnormalities in insulin secretion, insulin action, or both [1]. This disease is characterized by chronic hyper-glycemia. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels [2].

People with diabetes in Indonesia showed a significant increase. For example, Riskesdas 2018 shows that DM's prevalence based on a doctor's diagnosis increased 2% compared to 2013 [3].

One class of compounds that can be used as antidiabetic agents is cinnamic acid derivatives in the form of esters. Cinnamic acid derivatives have low toxicity for humans, animals, and the environment, so these compounds are of great interest to researchers [4]. Cinnamic esters are cinnamic acid derivatives that replace the OH group in cinnamic acid with an alkyl group from alcohol. A cinnamic ester is a form of cinnamic acid derivative commonly found in

nature. These compounds play an important role in various biological activities such as antidiabetic, anti-inflammatory [5], cytotoxicity, leishmanicidal activity [6], tyrosinase enzyme inhibitor [7], antioxidant [8], and antifungal [9]. In addition, cinnamic esters are important compounds in the flavor, perfume, and pharmaceutical industries [10].

The antidiabetic activity of cinnamate esters was reported by several researchers [11-12]. Pharmacokinetic studies have shown that cinnamic acid and its derivatives are easily absorbed from the small intestine through various mechanisms [11]. Ethyl cinnamate synthesized from cinnamon oil was able to inhibit the enzyme alpha-glucosidase with IC_{50} at a concentration of 215.509 ppm [13]. One of the cinnamate ester compounds is menthyl cinnamate. Menthyl cinnamate has activity as an anti-inflammatory [14], and antifungal [15]. This compound can be synthesized using an acid catalyst by Fischer esterification of cinnamic acid with menthol [15].

Esterification of cinnamic acid using Fischer esterification with a sulfuric acid catalyst under reflux can be carried out for several hours. Reaction time is one of the important aspects of secondary alcohol esterification [16]. Synthesized menthyl cinnamate through Fischer esterification using reflux for 3-4 hours and gave 85-92% yield[15]. Synthesized amyl cinnamate for 6 hours with % a yield of 80.73% [17]. This research synthesized menthyl cinnamate with variations in reaction time, namely 4,5 and 6 hours.

In vitro, a glucose reduction test can be done using anthrone sulfate. The anthrone sulfate method is one of the most commonly used techniques for determining carbohydrate content by the colorimetric method[18]. The anthrone test has advantages in terms of sensitivity and a simple test. In addition, a small number of carbohydrates can provide a color that is detected using a visible spectro-photometer [19].

METHODS

1. Material and Instrument

The materials used in this synthesis were cinnamic acid from Sigma, menthol from Bratachem, sulfuric acid pa (Merck), ether, ethyl acetate, n-hexane, $MgSO_4.7H_2O$, and sodium bicarbonate. The instruments used in this study were ATR-FTIR Cary 630 from Agilent Technology and GC-MS QP 2010 SE from Shimadzu. The temperature of the GC column used is 80°C with column type Rtx-5MS. The injection temperature used is 250°C, and the carrier gas is Helium. Anthrone sulfate test using a double beam spectrophotometer with specs UV-1700 Pharma Spec UV-Vis Spectrophotometer from Shimadzu.

2. Procedures

a. Esterification of cinnamic acid with menthol

The method of synthesis of menthyl cinnamate in this research uses Fischer esterification. Cinnamic acid and menthol with a mole ratio of 2:1 were put into a round bottom flask, and 1 mL of H_2SO_4 was added. This mixture was refluxed with variations of 4, 5, and 6 hours at 60 oC. The result of reflux is added saturated $NaHCO_3$ solution until neutral or until alkaline and extracted with

ether as much as 2x30 mL. The ether phase was added with anhydrous $MgSO_4$ to bind the water. It was decanted, and the filtrate was evaporated using a vacuum evaporator. The results were weighed and characterized [20-21]. The characterization of the synthesis results was carried out based on the determination of physical properties, including color, aroma, and solubility, and analyzed by TLC, FT-IR, and GC-MS [20].

b. Glucose-Lowering Activity Test By Spectrophotometry Vis Using Anthrone Sulfate

Measurement of the level of glucose reduction was carried out using the anthrone sulfate method. The standard used is anhydrous glucose. Glucose was weighed at 100 mg and dissolved in 100 mL of distilled water to obtain a concentration of 1000 ppm. A series of standard glucose solutions were made with concentrations of 20 ppm, 35 ppm, 50 ppm, 65 ppm, and 80 ppm. 1 mL of standard glucose was pipetted and put in a test tube, added 5 mL of anthrone sulfate, and reacted at 100°C for 12 minutes. Measured operating time (OT) and the maximum wavelength of the solution. Based on the study results, the operating time was obtained at 5 minutes, and the maximum wavelength was 626 nm [22].

c. Glucose-lowering activity test using anthrone sulfate

The synthesized compound was weighed at 100 mg and dissolved in 100 mL of ethanol to obtain a concentration of 1000 ppm. The synthesis results' concentration series was made of 100, 200, 300, 400, and 500 ppm. Each concentration was pipetted 1 mL, added 1 mL of 80 ppm glucose and 5 mL of 1% anthrone sulfate. The mixture was shaken and heated at 100oC in a water bath for 12 minutes. According to the OT, the treatment results were allowed to stand for 5 minutes and measured at the maximum wavelength.

RESULTS AND DISCUSSION

1. Esterification of cinnamic acid with menthol

The procedure used in this synthesis is to react cinnamic acid with menthol, assisted by a sulfuric acid catalyst. The mixture was refluxed with time variations of 4, 5, and 6 hours at 60°C in ether solvent. If the esterification temperature exceeds 60oC, the hydrolysis reaction is easier to occur than the esterification reaction [23]. The ratio of cinnamic acid to menthol used is 2:1. A larger mole of carboxylic acid than a mole of alcohol gives a larger % yield [24].

The protonation of cinnamic acid begins with the reaction mechanism of synthesizing mentyl cinnamate from cinnamic acid and alcohol by a sulfuric acid catalyst. Cinnamic acid is a carboxylic acid that is not reactive, so the alcohol does not react easily by nucleophilic addition. Cinnamic acid requires a sulfuric acid catalyst to activate its carboxyl group. The protonation of carboxylic acids in cinnamic acid occurs in the carbonyl oxygen group. The addition of menthol to the protonated C carbonyl of cinnamic acid gives a tetrahedral intermediate. Transferring a proton from one oxygen atom to another produces a second cation tetrahedral intermediate and converts the OH group into a good leaving group (H_2O^+). The release of protons and dehydration of water molecules

regenerates the sulfuric acid catalyst and produces the menthyl cinnamate compound [25]. The esterification reaction is reversible, so the reaction equilibrium must be shifted to the ester side. One way is to make one of the reactants in excess so that in this study, the moles of cinnamic acid were made twice the moles of menthol. Another way is to remove the side-product water [26].

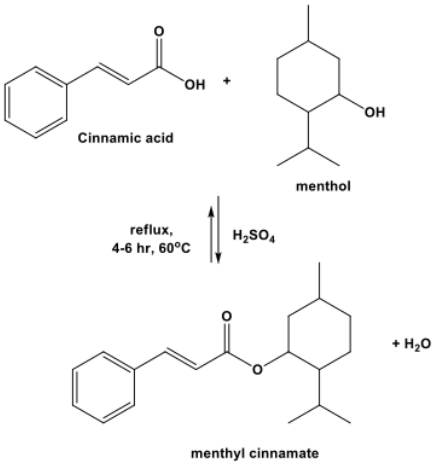


Figure 1. Synthesis of menthyl cinnamate

The reflux result was added with 10% sodium bicarbonate solution until it was neutral or basic. Adding this solution was to neutralize the acid contained in the mixture. Next, the mixture was put in a separatory funnel, and the ether and aqueous phases were separated. Next, the ether phase was added with anhydrous $MgSO_4$ to bind water[26]. The ether phase filtration yields a filtrate containing menthyl cinnamate. Evaporation of the ether filtrate using a vacuum evaporator removes the ether solvent and produces a clear yellow solution with a characteristic sweet-smelling oil texture.

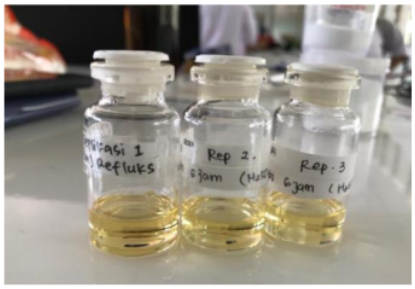


Figure 2. Synthesis product

Table 1. % yield of menthyl cinnamate

Synthesis time (hours)	% yield
4	95.83
5	96.38
6	91.79

The synthesis results showed that the time of 5 hours gave % optimal results compared to the time of 4 and 6 hours. The synthesized increased from 4 hours to 5 hours but decreased at 6 hours. At 4 hours, the esterification reaction has not occurred optimally, while at 6 hours, it is suspected that there is the hydrolysis of the synthesized compound. Esterification is a reversible reaction so that the ester obtained can be returned to its constituent compounds [27]. Esterification is a reversible reaction so that the ester obtained can be returned to its constituent compounds. Reaction time significantly affects the product obtained, the longer the reaction time. The greater the product obtained because the opportunity for collisions between the reactant molecules is greater. However, if an equilibrium state has been reached, the addition of time will no longer be profitable or not proportional to the product [28].

Menthyl cinnamate is a clear yellow liquid with an oily texture with a sweet aroma typical of cinnamic esters. The synthesized product was soluble in methanol, DMSO, ethanol, ether, chloroform, and n-hexane but insoluble in distilled water. This compound is semipolar when viewed from its solubility according to the principle like dissolves like.

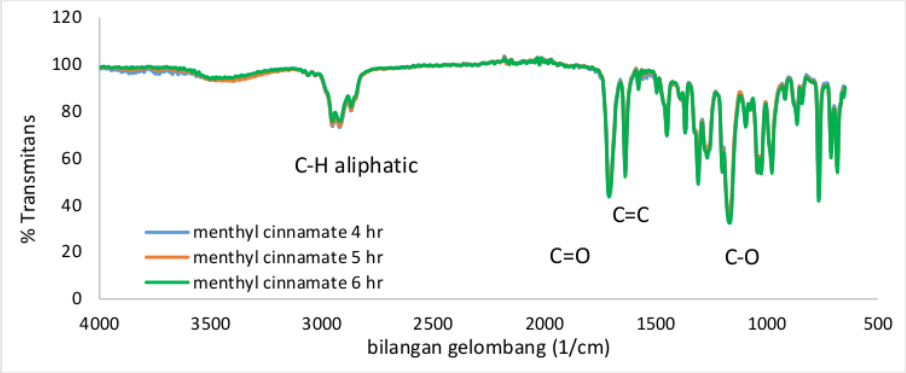


Figure 3. FTIR spectrum of synthesized mentyl cinnamate with variations in reaction time

Analysis of the synthesized compounds by FTIR (Figure 3) obtained several functional groups indicating the presence of ester compounds by the target compound. The functional groups are C=O ester at a wavenumber of 1711 cm^{-1}, the area at 1636 cm^{-1} is a C=C aromatic group [21], and at 1167 cm^{-1} is the C-O ester [29].

The overlay of the IR spectrum (Figure 4) from the synthesis with its precursors, namely cinnamic acid and menthol, showed a different spectrum. Menthyl cinnamate does not have an OH-carboxylic acid group. However, the synthesized menthyl cinnamate contains -OH alcohol groups in the 3200-3500 cm^{-1} area; this group comes from its precursor, menthol. Indicates that the synthesized menthyl cinnamate was still not pure because it contains menthol.

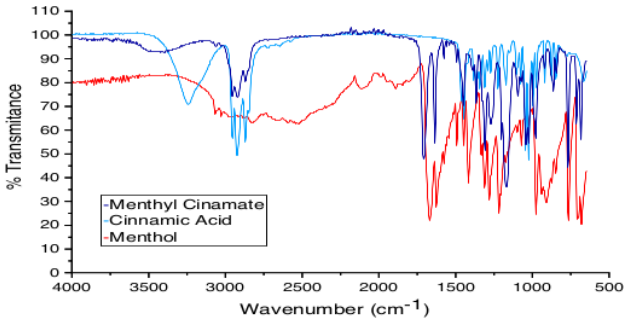
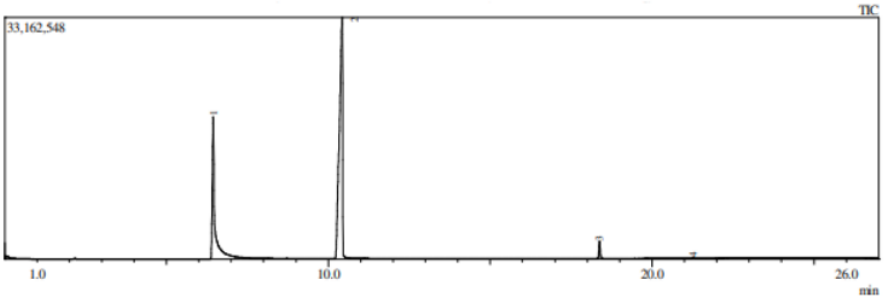


Figure 4. Overlay of menthyl cinnamate with its precursor

The GC results (Figure 5) for the synthesis results showed four peaks which indicated that the synthesis results were in the form of a mixture. Peak no. 1 with m/z 138 indicates a menthol compound with a % abundance of 30.02%-35.42%. Peak no 2 with m/z 176 with an abundance of 62.08-67.77 % indicates ethyl cinnamate compound. The third peak is the target compound, namely menthyl cinnamate with m/z 286 with an abundance of 2.11-2.44%.



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height
1	6.447	6.360	7.085	99960373	30.02	19438531
2	10.424	10.195	10.640	225665671	67.77	33019733
3	18.380	18.305	18.490	7047156	2.12	2393908
4	21.271	21.215	21.345	327000	0.10	109916
				333000200	100.00	54962088

Figure 5. Chromatogram of the synthesized compound using Gas chromatography

The target compound appeared at a retention time of 18.38-38.92 minutes. This small percentage of abundance can be caused by menthol being a cyclic secondary alcohol compound, so the steric hindrance for synthesizing menthyl cinnamate compounds is large [16].

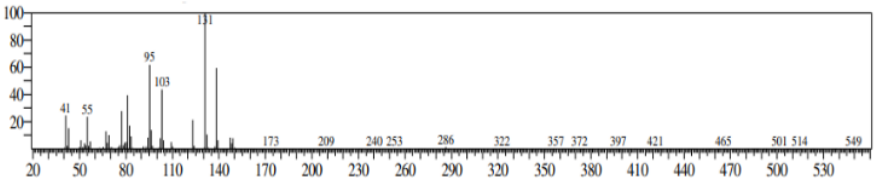


Figure 6. Mass Spectra of menthyl cinnamate

The results of the third MS peak (Figure 6) and the fragmentation in Figure 7 showed that the third peak has the same fragmentation pattern as mentyl cinnamate with a base peak of cinnamoyl cations at m/z 131. The release of CO radicals gives styrene cations. Fragment with m/z 209 indicated a mentyl cinnamate compound that loses a phenyl radical. The fragment with m/z 139 was a mentyl cation, while the phenyl ion was indicated by m/z 77.

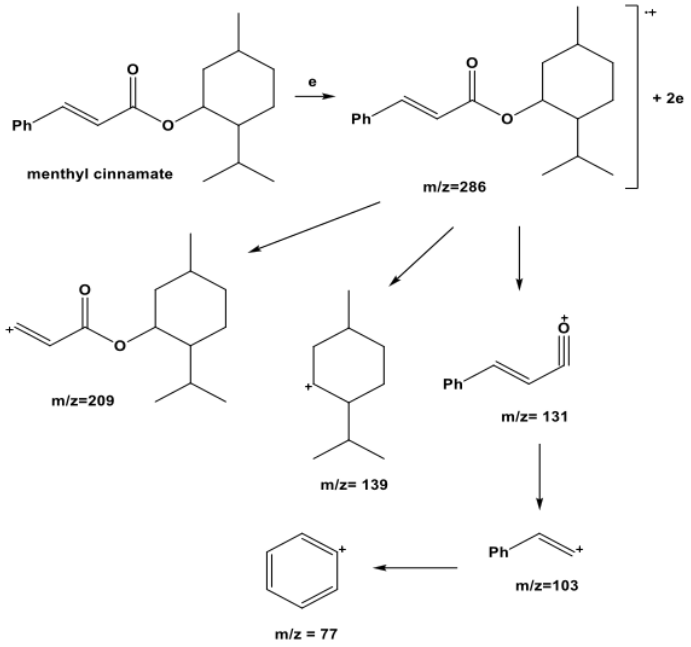


Figure 7. Fragmentation of synthesized menthyl cinnamate

2. Test The Activity of Lowering Glucose Levels Using Anthrone Sulfate

The activity of reducing glucose levels by synthesizing compounds using the spectrophotometric method using anthrone sulfate reagent. This method is very simple, relatively fast, easy to do, and precise for determining glucose levels[18]. The principle of determining glucose levels using the anthrone sulfate method is the hydrolysis of carbohydrates into monosaccharides by sulfuric acid, which will then be hydrated to furfural. Furfural compounds react with anthrone to form a greenish-blue complex whose absorbance can be measured at the maximum wavelength [22]. The maximum wavelength used in this study was 626 nm, which was the same as the literature (623.80 nm) [30].

Using 1% anthrone in this test resulted in the highest absorbance. The anthrone solution of more than 1% showed a decrease in absorbance[18]. The synthesized compound binds to glucose. The remaining glucose, which is not bound by menthol cinnamate, is dehydrated by sulfuric acid to form 5-hydroxymethylfurfural. This dehydration results in double bonds and ring formation [22]. The compound 5-hydroxymethyl furfural reacts with anthrone to form a compound (anthracene-9-yloxy) (5-(hydroxymethyl) furan-2-yl) methanol which is blue-green, which can be measured through its absorption at a wavelength of 626 nm [30]. The anthrone sulfate test reaction can be seen in Figure 8.

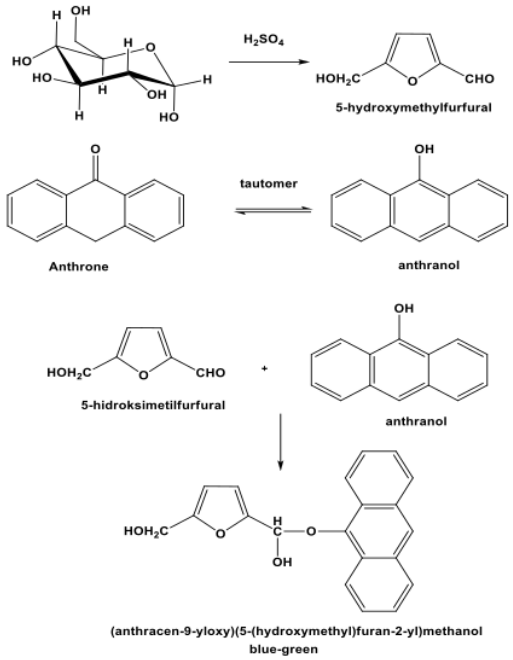


Figure 8. The reaction of anthrone sulfate test on glucose [30]

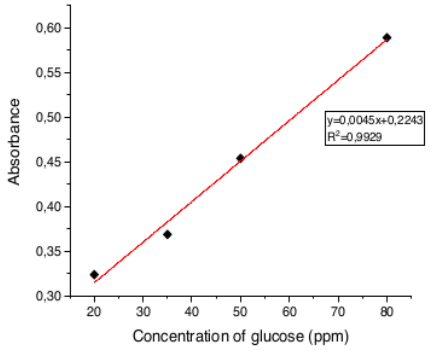


Figure 9. standard curve of glucose with anthrone sulfate

Figure 10 shows that the synthesized compound produces an optimum % decrease in glucose by 48.62% at a concentration of 300 ppm. The synthesized compound has the potential as an antidiabetic agent. Menthyl cinnamate compound can be used as an antidiabetic because it has a phenylacrylate group (Ph-CH=CH-CO-) or a cinnamic moiety [31-32].

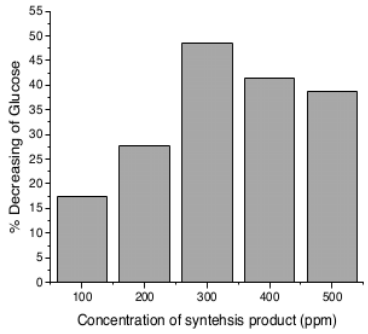


Figure 10. Graph of the decrease in glucose levels by synthesis results

Based on the literature that menthol [33] and ethyl cinnamate [13] can lower

glucose levels. In addition, Menthyl cinnamate is an ester, as it is known that the ester can act as an antidiabetic. Therefore, this study's ability to reduce glucose levels was caused by these compounds: menthyl cinnamate and menthol and ethyl cinnamate.

CONCLUSION

Fischer esterification of cinnamic acid by menthol using sulfuric acid catalyst can produce menthol cinnamate with good yields but low purity. The optimum time for this reaction was reached at 5 hours. The synthesized compound could reduce glucose levels by 48.62% at a concentration of 300 ppm using the anthrone sulfate method. It is necessary to carry out other methods to synthesize mentyl cinnamate compounds to produce a large % abundance.

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Esterification of Cinnamic Acid Anthrone

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