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

Yuliana Purwaningsih *, Mighfar Syukur, and Wulandari Wulandari

Department of Pharmacy, Semarang Pharmaceutical College
Jl. Letjend. Sarwo Edi Wibowo Km.1 Pucanggading-Semarang

* Correspondence: phone: (024) 6706147; email: y14purwaningsih@gmail.com

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ABSTRACT

Menthyl cinnamate was synthesized by Fischer esterification of cinnamic acid and menthol with the sulfuric acid catalyst at a temperature of 60°C within 4-6 hours. The synthesized compound is a yellow oil liquid with a sweet fruity aroma typical of cinnamic esters. The synthesized product is soluble in nonpolar solvents. Analysis by FTIR showed several functional groups such as C=O, C=C, C-O, C-H aliphatic. Analysis of the results of the synthesis 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 sulphate, cinnamic ester, menthol, menthyl cinnamate.*

INTRODUCTION

Diabetes mellitus is a metabolic disease caused by abnormalities in insulin secretion, insulin action, or both [1]. This disease is characterized by chronic hyperglycemia. 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].

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 that they are of great interest to researchers[3]. Cinnamic esters are derivatives of cinnamic acid by replacing the OH group in cinnamic acid with an alkyl group from alcohol. A cinnamic ester is a form of cinnamic acid derivative that is commonly found in nature. These compounds play an important role in various biological activities such as antidiabetic, anti-inflammatory[4], cytotoxicity, leishmanicidal activity [5], tyrosinase enzyme inhibitor [6], antioxidant [7], and antifungal [8]. Cinnamic esters are important compounds in the flavor, perfume, and pharmaceutical industries [9].

The antidiabetic activity of cinnamate esters was reported by several researchers [10],[11]. In vitro tests of glucose can be done using the anthrone-sulfate method. This method is one of the most commonly used

techniques for the determination of carbohydrate content by the colorimetric method [12].

One of the cinnamate ester compounds is menthyl cinnamate. This compound can be synthesized by Fischer esterification of cinnamic acid with menthol using an acid catalyst. Menthyl cinnamate has anti-inflammatory activity[13], and anti-fungal [14].

Based on the description above, this study aimed to synthesize menthyl cinnamate using Fischer esterification with time variations and to determine the activity of menthyl cinnamate as a glucose-lowering agent in vitro using anthrone-sulfate.

METHODS

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.

Procedures

Esterification of cinnamic acid with menthol

Menthyl cinnamate synthesis method using Fischer esterification. Cinnamic acid and menthol were weighed carefully with a mole ratio of 2:1. The mixture was put in a round bottom flask and added with 1 mL of H_2SO_4. The mixture was refluxed with time variations of 4, 5, and 6 hours at 60 °C. The result of reflux is added with saturated $NaHCO_3$ solution until neutral or until alkaline and extracted with ether as much as 2x 30 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 [15][16]. 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 [15].

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 with 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 results of the study, the operating time was obtained at 5 minutes and the maximum wavelength was 626 nm[17].

Sample Measurement

The synthesized compound was weighed at 100 mg and dissolved in 100 mL of ethanol to obtain a concentration of 1000 ppm. The concentration series of synthesis results were 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. The results of this treatment were allowed to stand for 5 minutes according to the OT and measured at the maximum wavelength.

RESULTS AND DISCUSSION

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 effluxed with time variations of 4, 5, and 6 hours at 60oC in ether solvent. If the esterification temperature is carried out above 60oC, then the hydrolysis reaction is easier to occur than the esterification reaction[18]. The ratio of cinnamic acid to menthol used is 2:1. The use of a larger mole of carboxylic acid than a mole of alcohol gives a larger % yield[19].

The reaction mechanism for the formation of menthyl cinnamate from cinnamic acid and alcohol begins with the protonation of cinnamic acid by a sulfuric acid catalyst. Cinnamic acid is an unreactive carboxylic acid, so it is not easy for alcohol to react with nucleophilic addition. Cinnamic acid requires a sulfuric acid catalyst to activate its carboxyl group. The protonation of carboxylic acids in cinnamic acid occurs at the carbonyl oxygen group. The addition of menthol to the protonated C carbonyl of cinnamic acid gives a tetrahedral intermediate. Dehydration of water molecules produces the compound menthyl cinnamate.

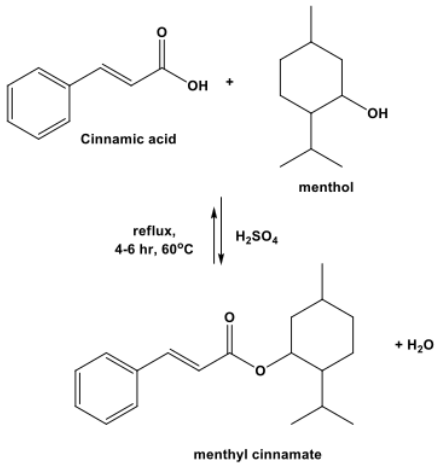


Figure 1. Synthesis of menthyl cinnamate

The reflux result is added with 10% sodium bicarbonate solution until it is neutral or basic. The function of adding this solution is to neutralize the acid contained in the mixture. The mixture is put in a separatory funnel, the ether phase and the aqueous phase are separated. The ether phase is added with anhydrous $MgSO_4$ to bind water[20]. 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.

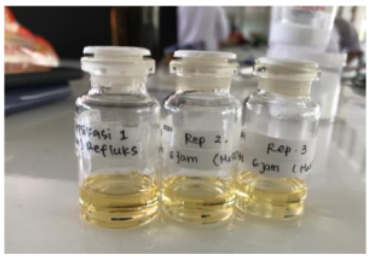


Figure 2. Synthesis product

Table 1. % yield of menthyl cinnamate

Synthesis time (hours)	% yield
4	95,83
5	96,38
6	91,79

The results of the synthesis showed that the time of 5 hours gave % optimal results compared to the time of 4 and 6 hours. The results of the synthesis showed an increase from 4 hours to 5 hours but decreased at 6 hours. This means that 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[21].

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.

Analysis of the synthesized compounds by FTIR obtained several functional groups indicating the presence of ester compounds in accordance with 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[16], and at 1167 cm-1 is the C-O ester [22].

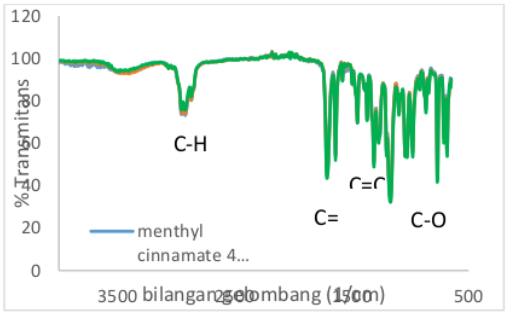


Figure 3. FTIR spectrum of synthesized mentyl cinnamate with variations in synthesis time

The overlay of the IR spectrum from the synthesis with its precursors, namely cinnamic acid and menthol, shows a different spectrum. Menthyl cinnamate does not have an OH-carboxylic acid group. The synthesized menthyl cinnamate also still contains -OH alcohol groups in the 3200-3500 cm-1 area, this group comes from its precursor, menthol. This indicates that the synthesized menthyl cinnamate is still not pure.

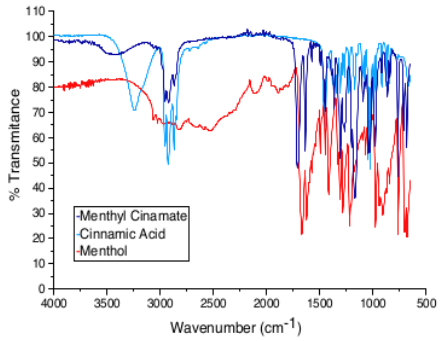
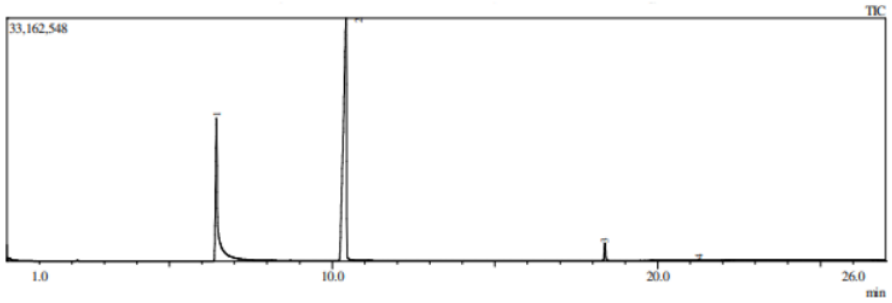


Figure 4. Overlay of menthyl cinnamate with its precursor



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

Based on the GC results for the synthesis results showed 4 peaks which indicated that the synthesis results were in the form of a mixture. Peak no. 1 with m/z 138 indicates menthol compound with % abundance 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%. The target compound appeared at retention time 18.38-38.92 minutes. This small percentage of abundance can be caused by menthol being a cyclic secondary alcohol compound so that the steric hindrance for the synthesis of menthyl cinnamate compounds is large [23].

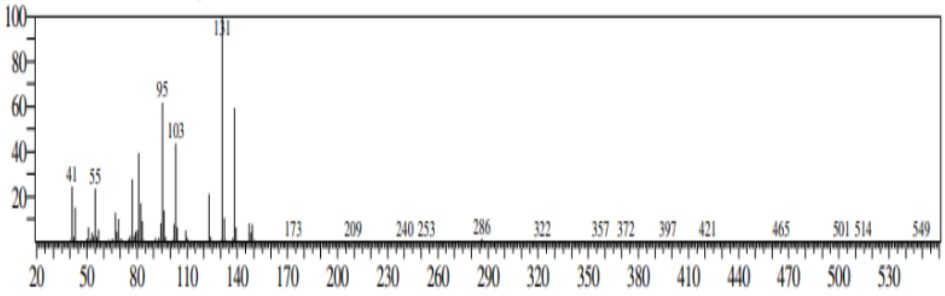


Figure 6. Mass Spectra of menthyl cinnamate

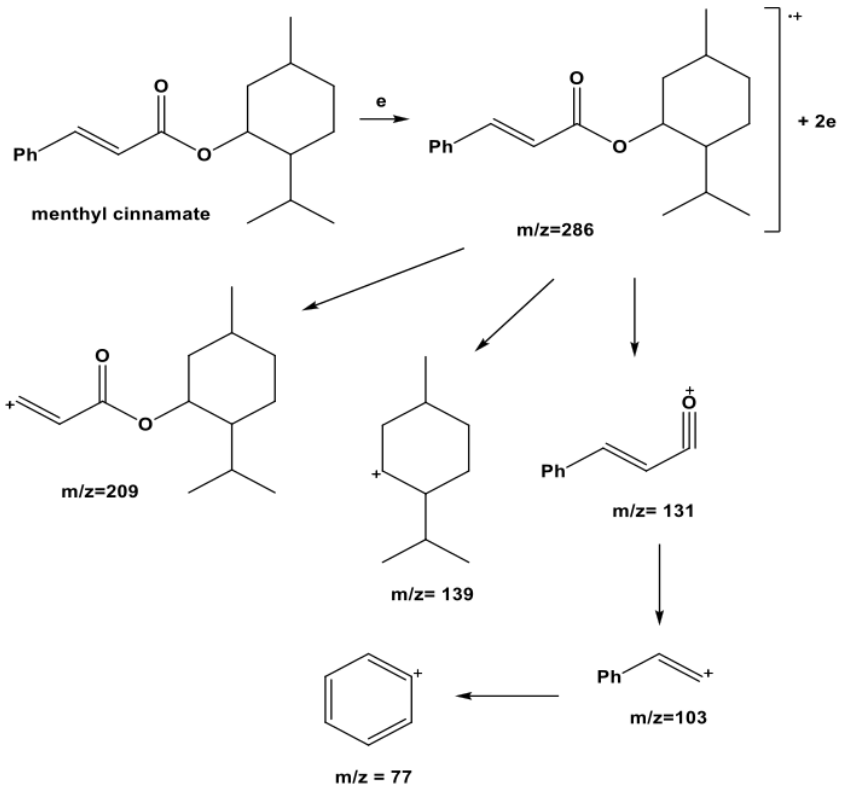


Figure 7. Fragmentation of synthesized menthyl cinnamate

Test The Activity Of Lowering Glucose Levels Using Anthrone Sulphate

The activity of reducing glucose levels by synthesized compounds using spectrophotometric methods with anthrone sulphate reagent. This method is very simple, relatively fast, easy to do, and precise for determining glucose levels[12]. 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 a wavelength of 626 nm [17].

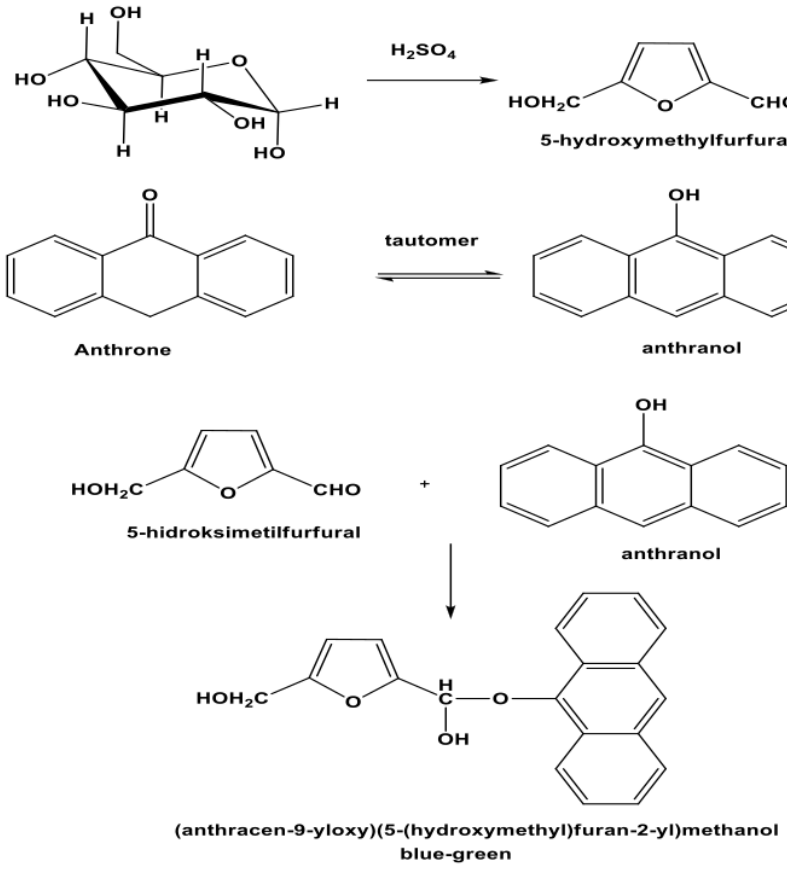


Figure 8. The reaction of anthrone sulfate test on glucose [24]

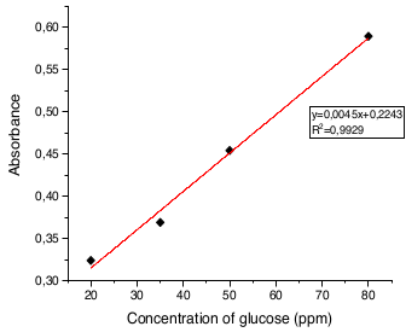


Figure 9. standard curve of glucose with anthrone sulfate

The use of 1% anthrone in this test resulted in the highest absorbance. The use of anthrone solution of more than 1% showed a decrease in absorbance [12]. The synthesized compound binds to glucose and the remaining glucose is dehydrated to form furfural which then reacts with anthrone sulfate to form a compound with a turquoise color whose absorption can be measured at a wavelength of 626 nm (Figure 8).

Figure 10 shows that the synthesized compound produces an optimum % decrease in glucose by 48.62% at a concentration of 300 ppm. This means that the synthesized compound has the potential as an antidiabetic agent.

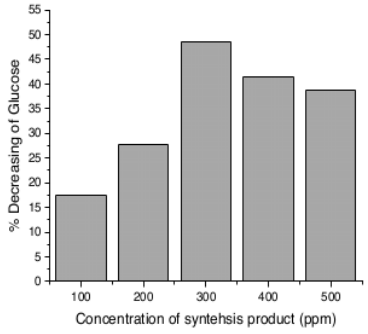


Figure 10. Graph of the decrease in glucose levels by synthesis results

Based on the literature that menthol [25] and ethyl cinnamate [26] can lower glucose levels. Menthyl cinnamate is an ester, as it is known that the ester can act as an antidiabetic. Based on this, the ability to reduce glucose levels in this study was caused by these three compounds, not only menthyl cinnamate but also menthol and ethyl cinnamate.

CONCLUSION

Fischer esterification of cinnamic acid by menthol using sulfuric acid catalyst can produce menthyl cinnamate with good yield with optimum time reached at 5 hours. The test compound can act as an antidiabetic agent using the anthrone sulfate method. It is necessary to do other methods for this synthesis to produce a large % abundance.

ACKNOLEDGEMENT

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