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ESTERIFICATION OF CINNAMIC ACID WITH OCTANOL USING ULTRASONIC WAVE ASSISTED BY COUPLING REAGENT AS ANTIERYTHEMA

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ABSTRACT

The n-octyl cinnamate compound, a cinnamate ester, is believed to have antierythema activity. This compound is naturally present in certain plant species; however, its quantity is limited. Steglich esterification can be used to produce n-octyl cinnamate, which involves the reaction of cinnamic acid with n-octanol using n,n'-dicyclohexylcarbodiimide (DCC) as a coupling reagent. Ultrasonic wave-assisted synthesis was performed to reduce the synthesis time and increase the yield of n-octyl cinnamate with time variations of 3, 4, and 5 hours at ± 2°C. The synthesized compounds were characterized by organoleptic properties, solubility, melting point, TLC, FTIR, and GC-MS tests. The synthetic compound occurred as a white powder, yielding 10.1% after an optimal duration of 4 hours. The compound was insoluble in distilled water but soluble in methanol, ethanol, chloroform, ether, and n-hexane. The compound has a melting range of 135.1-145.4°C, and the TLC results obtained different Rf values than the initial compound. FTIR test analysis showed the presence of C=C aromatic, C-H aromatic, C=O ester, C-O ester, C=C aliphatic, and C-H aliphatic group absorption by the n-octyl cinnamate compound. GC-MS analysis revealed a synthetic retention time of 17.193 minutes and an abundance of 35.40%. The antierythema activity of the synthesized n-octyl cinnamate compound was optimal at 100 ppm with a %TE of 1.661, classifying it as an extra protection category.

Keywords*: anti-erythema, esterification, ultrasonic waves, n-octyl cinnamate, time.*

INTRODUCTION

Erythema is a skin disorder characterized by redness, inflammation, pain, and burning sensation. It is caused by excessive exposure to ultraviolet (UV) radiation, resulting in skin damage. Sunscreens can help prevent this illness by absorbing and reflecting UV rays that hit the skin. The percentage of erythema transmission in the active chemicals used in sunscreen can be used to determine the effectiveness of antierythema. Cinnamate ester is an active chemical that can be used as an antierythema agent because it has a chromophore component, which is an aromatic core conjugated with a carbonyl group capable of absorbing UV light (Priastuti *et al.*, 2012). Cinnamate ester compounds can be found in several plants but in small amounts. Esterification synthesis is one approach to increase cinnamic acid derivative output (Kadidae *et al.*, 2020). Activator chemicals or coupling reagents are commonly used in esterification synthesis. Christensen (2001) employed n,n'-dicyclohexylcarbodiimide (DCC) as a coupling reagent in his esterification investigation. DCC is reactive, can occur at low temperatures, and can increase the yield to 97% after 12 hours. Mutiara *et al.* (2022b) discovered that one of the cinnamic acid derivatives that can be synthesized is n-octyl cinnamate, which is produced by esterification between carboxylic acid and alcohol using an acid catalyst and ultrasonic waves for 5 hours, yielding 23.02%. To obtain a greater yield of the synthetic product, the process must be improved. The synthesis of n-octyl cinnamate

compounds using coupling reagent compounds has never been done, so that synthesis will be carried out by Steglich esterification using DCC coupling reagents to obtain n-octyl cinnamate compounds with a high yield. The purpose of this study was to obtain n-octyl cinnamate compounds formed between cinnamic acid and octanol via Steglich esterification using DCC coupling reagents and ultrasonic waves at a temperature of ± 2°C to obtain the highest yield and optimum reaction time with time variations of 3, 4, and 5 hours. The produced compounds were then identified using organoleptic, solubility, and melting point assays as well as TLC. The synthesized compounds were then analyzed using FTIR-ATR spectroscopy and GC-MS to determine their structure, and their antierythema activity was tested in vitro using a UV spectrophotometer.

RESEARCH METHODS

Equipment

The tools used in this research were a volume pipette, beaker glass, Erlenmeyer, stative, clamp, porcelain cup, separating funnel, filter paper, oven, water bath, TLC plate, chamber, sonicator (B*ranson 1800*), melting-point apparatus, Fourier Transform Infrared Spectroscopy (*Agilent Cary 630*), *Gas Chromatography-Mass Spectrometry* (*Shimadzu QP 2010 SE*), and UV-Vis Spectrophotometer (*Shimadzu UV-1700 PharmaSpac*).

Materials

The materials needed in the research are cinnamic acid (Merck, p.a.), n-octanol (Merck, p.a.), anhydrous magnesium sulfate (Merck, technical), anhydrous sodium bicarbonate (Merck, p.a.), n-hexane (Merck, p.a.), ethyl acetate (Merck, p.a.), methanol (Merck, p.a.).

Research Prosedure

1. **Step 1 : Synthesis of *n*-Octyl Cinnamate**

   n-Octyl cinnamate was synthesized with slight modifications to the method described by Mutiara *et al.* (2022a). Cinnamic acid, n-octanol, and DCC were weighed carefully. A total of 1.0934 grams (± 0.246 mol) of cinnamic acid and 11.76 mL of n-octanol (2.5 mol) and n,n'-dicyclohexylcarbodiimide (DCC) coupling reagent 0.9136 grams (0.1476 mol) were used. The mixture was sonicated at ±2°C for 3, 4, and 5 hours, respectively. The sonication process was followed by pH neutralization with the addition of anhydrous $NaHCO_3$ solution until the neutral atmosphere reached a pH of 7–8. The mixture was placed in a separatory funnel until the organic and water phases separated. The organic phase was mixed with anhydrous $MgSO_4$ and allowed to stand for 20 minutes. The $MgSO_4$ powder was filtered using filter paper. The mixture was evaporated in a water bath at 100°C until it was odorless, then oven at 70°C until the mixture became dry and had a powder texture.

2. **Step 2 : Identification of Synthesized n-Octyl Cinnamate**

   a. **Solubility Test**

      Water, methanol, ethanol, chloroform, ether, and n-hexane were among the solvents with varying polarity characteristics that were prepared and placed in a number of test tubes. Each tube contained a small quantity of the synthesized compound and its solubility was assessed.

   b. **Melting Point Test**

      A melting point apparatus, which uses the principle of observing the melting temperature of a solid sample turning into a liquid, was used to test the synthesized compound in a capillary tube at a temperature increase of 1°C/min. The temperature range in which the compound melted was observed.

   c. **Thin Layer Chromatography (TLC) Test**

      The eluent containing n-hexane, ethyl acetate, and methanol (80:15:5) was saturated in the chamber. Samples of the synthesized compounds were spotted on a TLC plate along with two reference compounds, n-octanol and cinnamic acid. Following the elution of the plate, a spot was observed in the UV spectrum at 254 and 366 nm.

d. Structural Identification using FTIR-ATR

The FTIR instrument (Agilent Cary 630) was blanked with air before testing the synthesized compounds and reference compounds (cinnamic acid and n-octanol). The obtained spectra showed the functional groups present in the compounds.

e. Structural Identification using GC-MS

The synthesized compound was dissolved in methanol and injected into a GC-MS instrument (Shimadzu QP 2010 SE) using an autoinjector syringe. The initial temperature of 80°C was increased to 300°C at a rate of 10°C/min and the flow rate was set at 0.46 mL/min. Chromatograms and mass spectrum of the compounds were obtained.

3. Step 3 : Activity of n-Octyl Cinnamate as Antierythema

For this purpose, 50 mg of n-octyl cinnamate was dissolved in 50 mL of methanol, resulting in a series of concentrations ranging from 60 to 100 ppm. The absorbance of the n-octyl cinnamate compound was measured using a UV-VIS spectrophotometer operating within a wavelength range of 290–320 nm at intervals of 5 nm. This allowed for calculation of the percentage of erythema transmission in vitro.

Data Analysis

The percentage yield of the synthesized n-octyl cinnamate was determined using the following equation:

$$Yield\ (\%) = \frac{\text{Weight of synthesized compounds (g)}}{\text{Theoretical weight of compound (g)}} \times 100\ \%$$

The synthesized compound was tested to evaluate its efficacy as an anti-erythema agent, and the percentage of Transmittance Erythema (TE) of the compound was determined. The transmittance value (T) was calculated with %TE using the following formula:

$$\%TE = \frac{Ee}{\sum Fe} = \frac{\sum(T\ x\ Fe)}{\sum Fe}$$

T : Transmission value
Fe : Erythema flux
Ee : $\sum(T\ x\ Fe)$ = Amount of erythema flux transmitted by sunscreen
$\sum Fe$: Total amount of UV light energy that causes erythema (Balsam & Sagarin, 1972).

The sunscreen categories based on the percentage of erythema transmission can be seen in Table I.

Table I. Sunscreen Protection Categories Based on % Erythema Transmission

%TE	Category
<1.0	Total block
1-6	Extra protection
6-12	Suntah reguler
10-18	Fast tanning

RESULTS AND DISCUSSION

The synthesis of n-octyl cinnamate through esterification begins with the deprotonation of the H atom on the carboxylate group, which is attracted by the nitrogen atom on DCC to form cinnamate ions. The cinnamate ion then attacks the C atom on DCC, which is electron deficient, so that it is easily attacked by nucleophiles. Protonation occurs on DCC after the imide bond (-C=N-) binds to H ions that increase electrophilic properties, and the intermediate product O-acyliurea is formed, which has a carbon center atom (-C-) that lacks electrons. There is a double bond break, resulting in the rotation of the double bond of the N atom in the DCC (Nurjaya *et al*., 2019).

The intermediate product is highly reactive and reacts with alcohols. Octanol attacks the intermediate product O-acyliurea, which breaks the acyl-oxygen bond by releasing H+ atoms in the OH group of octanol and converting the carbon-nitrogen double bond of isourea (-N=C=N-) into a more stable carbonyl group; thus, the final result of the reaction, in addition to forming the ester n-octyl cinnamate, also formed DCU (1,3-dicyclohexylurea) as a by-product (Hasanah & Wirman, 2018).

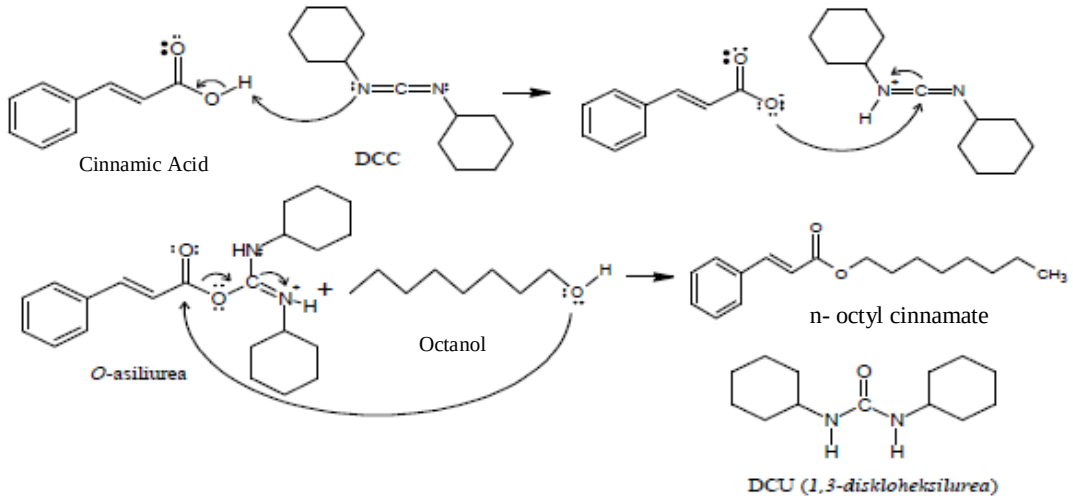

Figure 1. Steglich esterification reaction mechanism of n-octyl cinnamate compound (Nurjaya *et al.*, 2019)

The synthesized powder was tested organoleptically, including for color, shape, and odor, as compared to the literature. The synthesized compound, which appears as a white powder and is devoid of any odor, aligns with findings reported in the literature (Mutiara *et al.*, 2022a).

Table II. Percent (%) Yield of Synthesized n-Octyl Cinnamate

Replication	Time Variation (hours)		
	3	4	5
1	8.12 %	9.17 %	10.36 %
2	4.78 %	10.92 %	6.86 %
3	11.78 %	10.21 %	8.11 %
Mean ± SD	8.23 ± 3.50 %	10.10 ± 0.88 %	8.44 ± 1.77 %

As shown in Table II,**Table *II*** the percentage yield of n-octyl cinnamate fluctuated over time. The n-octyl cinnamate compound, subjected to sonication for 3 hours, achieved a yield of 8.23 ± 3.50 %. This indicates that the esterification reaction did not proceed optimally. However, extending the treatment time to 4 hours resulted in an increased yield of 10.10 ± 0.88 %. Conversely, a 5-hour sonication treatment led to a decrease in yield, which may be attributed to the hydrolysis of the esterification reaction, as this process is inherently reversible (Purwaningsih *et al.*, 2022).

Because there is very little information on the characteristics of n-octyl cinnamate, a solubility test was conducted to identify the synthetic compound. The results of this test can be used to select an eluent for use in the TLC test. Solubility tests indicated that the synthesized compound n-octyl cinnamate was not soluble in distilled water; however, it was soluble in methanol, ethanol, acetone, ether, ethyl acetate, chloroform, and n-hexane. These solubility results reflect the polarity characteristics of the compounds in different solvents, suggesting that they possess a semipolar to nonpolar nature.

Table III. The Temperature Range at Which A Compound Melts

Replication	Melting Point		
	3	4	5
1	138.2 – 144.6°C	135.2 – 146.6°C	138.2 – 144.6°C
2	135.2 – 144.5°C	136.4 – 145.2°C	135.2 – 144.5°C
3	135.8 – 144.4°C	135.1 – 145.4°C	133.1 – 152.4°C
Range Temperature	6.4 – 8.6°C	9.4 – 10.3°C	18.9 – 21.3°C

The goal of determining the melting point of a compound was to assess its purity. The purity of a compound ranges from ± 2°C to its melting point (Hasanah and Wirman, 2018). The melting point of the synthesized compound is lower than the melting point of the n-octyl cinnamate compound according to the literature, which is 242.1–244.2°C (Mutiara *et al*., 2022a). Based on the n-octyl cinnamate compound obtained, it was still a mixture because it had a melting point distance of more than ± 2°C for all replications.

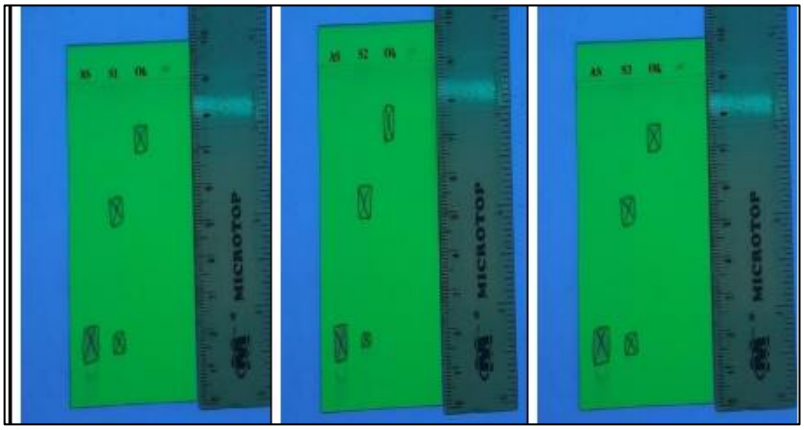

Figure 2. The results of the identification test using TLC for the compound n-octyl cinnamate (S1-S3), a synthetic compound with cinnamic acid (AS) and n-octanol (Ok) as a comparison.

As shown in Figure 2, the synthesized compound was identified using KLT, and two stains were created. The first stain had an Rf value of 0.25–0.30, which is close to the Rf value of cinnamic acid. The second stain was formed with an Rf value of 0.70–0.74, which is estimated to be the target compound. The longer structure of n-octyl cinnamate makes it more non-polar than cinnamic acid, which is why the target compound has a higher Rf value than cinnamic acid.

The results of the synthesis of the n-octyl cinnamate compounds were tested for functional group characterization using an FTIR spectrophotometer. The FTIR spectrum showed that it was different from the initial compound, with the disappearance of acidic OH groups at wave numbers 3200–2200 cm^{-1}, OH groups from alcohol, namely octanol at 3300 cm^{-1}, and the formation of C-O ester groups at wave numbers 1228 cm^{-1}.

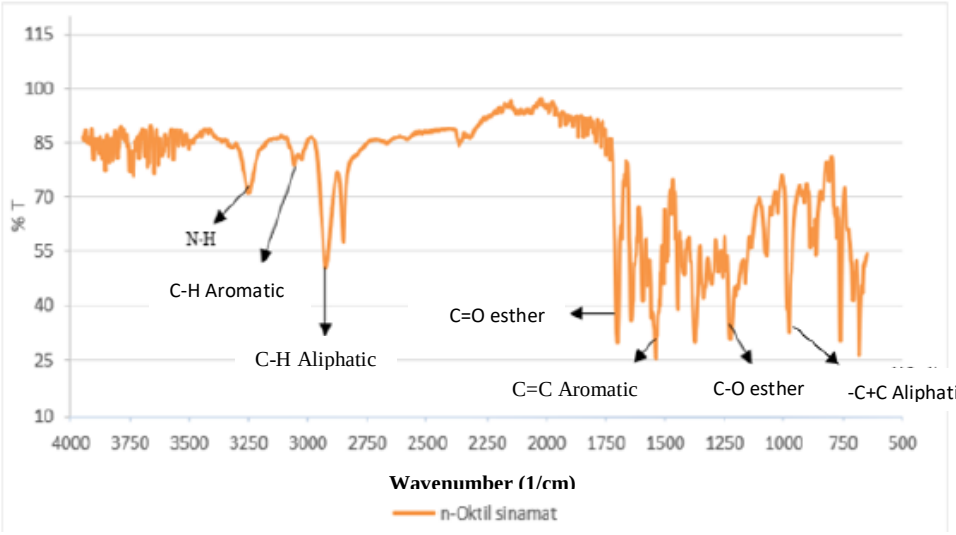

Figure 3. IR spectrum of synthesized n-octyl cinnamate

Figure 3 shows the presence of aromatic groups (C=C) at wavenumber 1541 cm^{-1}. The n-octyl cinnamate compound has a (C=O) ester bond appearing at wavenumber 1702 cm^{-1}. The aromatic (C=C) bond in the benzene ring has an absorption peak at 1541 cm^{-1} and the aromatic C-H bond appears at 3134 cm^{-1}. The n-octyl cinnamate compound has an aliphatic C=C bond with an absorption that appears with a value of 987 cm^{-1}, CH3 methyl bond appears at 1375 cm^{-1}, CH2 methylene appears at 1420 cm^{-1} and the N-H group is formed which is shown at wave number 3252 cm^{-1}. The appearance of the N-H group spectrum is due to the residual reaction between DCC and cinnamic acid which forms 1,3- disicyclohexylurea (DCU) (Dachriyanus, 2004).

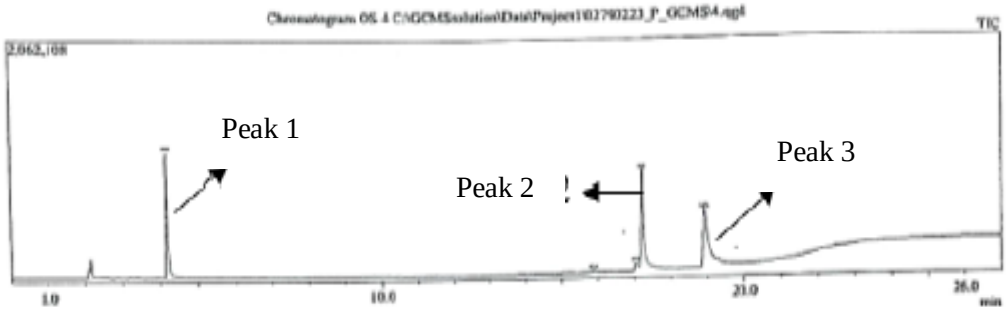

Figure 4. Chromatogram of n-octyl cinnamate compound

Figure 4 illustrates the chromatogram obtained from the Gas Chromatography (GC) analysis, which displays three distinct peaks. This indicates that the n-octyl cinnamate compound was not yet pure. The n-octyl cinnamate compound was identified at peak 2, corresponding to a reaction time of 17.19 minutes and a percentage abundance of 35.40%.

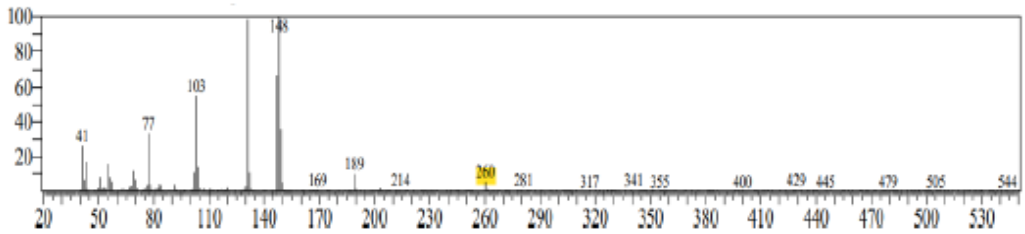

Figure 5. Mass spectra of n-octyl cinnamate

The mass spectrum illustrated in Figure 5 displays a peak corresponding to the molecular ion at 260 m/z, indicative of the molecular weight of the n-octyl cinnamate compound. Fragmentation of this compound resulted in the emergence of peaks at 260, 189, 148, 131, 103, 77, and 41 m/z.

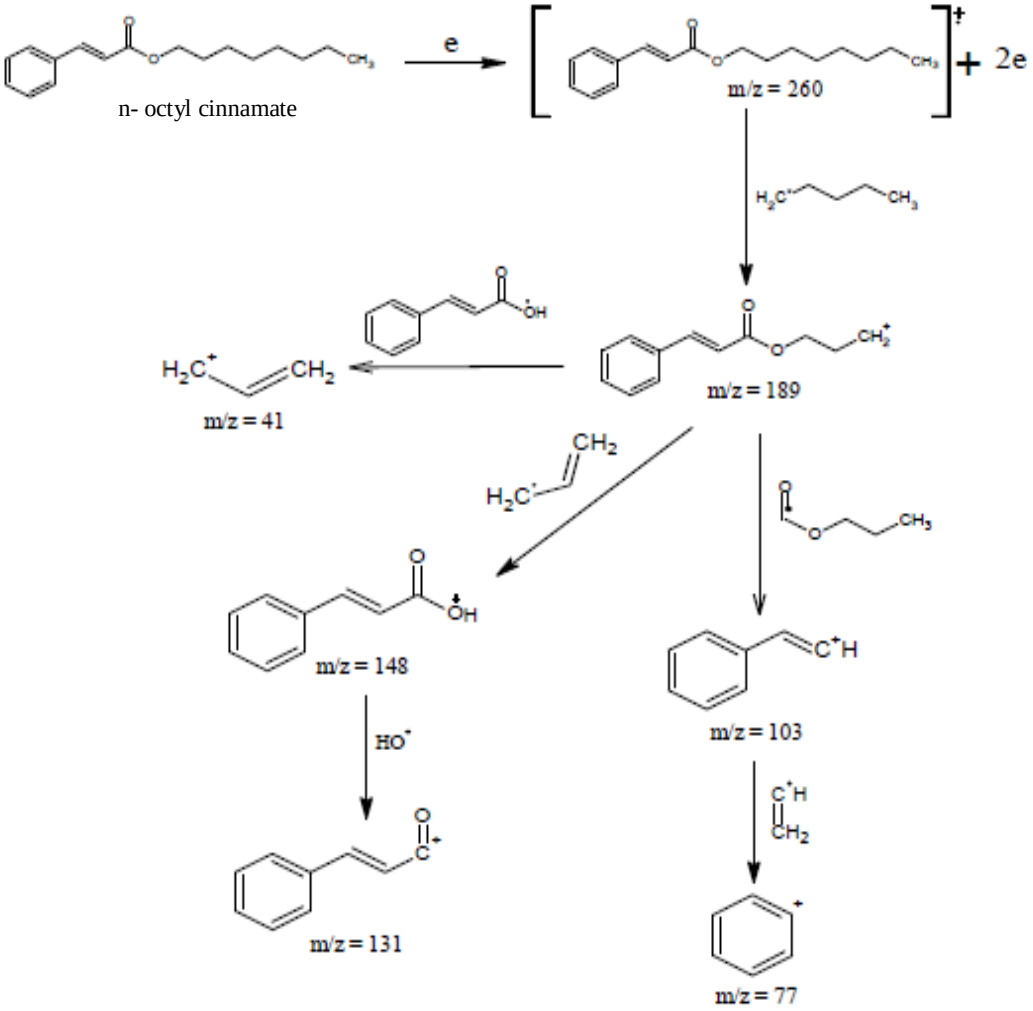

Figure 6. Fragmentation pattern of n-octyl cinnamate compound

The first fragmentation pattern involved molecular ions that emitted pentyl radicals, resulting in a peak at 189 m/z. This process subsequently releases three radicals, with the first generation of cinnamic acid radicals yielding a peak at 41 m/z. The second fragmentation pattern involved the release of the allyl radical, leading to a peak at 148 m/z, which corresponded to the cinnamic acid ion. Cinnamic acid ions further release hydroxyl radicals, producing a peak for cinnamoyl ions at 131 m/z, and also emit isopropyl carbonyl radicals, resulting in a peak at 103 m/z. Finally, the phenylethylenilium cation released the vinyl radical, which generated a peak at 77 m/z, identified as the phenyl cation.

Antierythema activity was carried out by determining %TE (percent erythema transmission) in vitro using a UV spectrophotometer. The percentage of erythema transmission shows the amount of sunlight reflected after striking the sunscreen ingredient, which can result in skin redness. Accordingly, a lower %TE value indicates higher potential for effective sunscreen protection. In the erythema spectrum, the number of erythema effectiveness factors at each wavelength of 290–320 nm with a 5-nm interval on UV-B rays for %TE was correlated with the amount of UV light energy transmitted by the sunscreen preparation. Antierythema was measured using a concentration series of 60, 70, 80, 90, and 100 ppm of n-octyl cinnamate without using a standard solution.

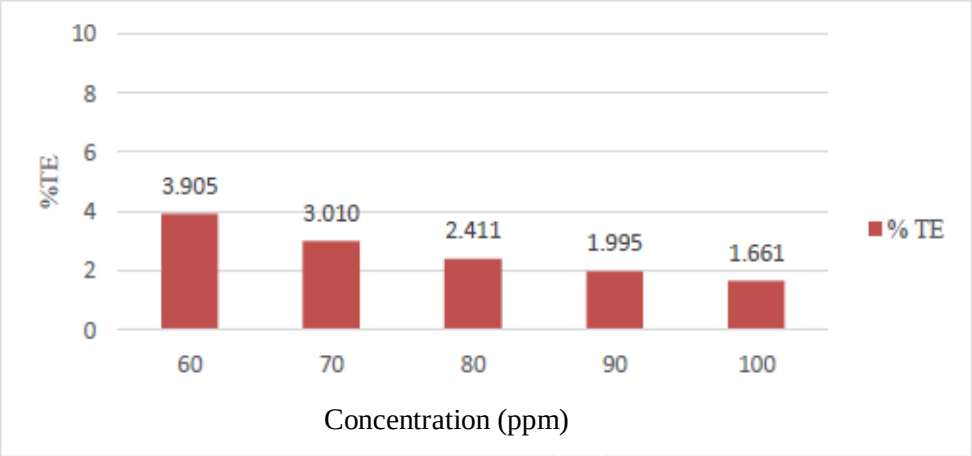

Figure 7. %TE value of n-octyl cinnamate compound

The results from the %TE measurement indicated that an optimal concentration of 100 ppm was achieved and categorized under extra protection. This level of extra protection effectively protects against erythema by absorbing less than 85% of UV-B radiation, thereby preventing pigmentation. Consequently, when the skin is exposed to sunlight, it may experience only mild erythema or redness without accompanying pain while also inhibiting skin darkening. These results demonstrate that as the concentration increases, the %TE value decreases; a lower transmittance value signifies greater light absorption by the sample, thereby enhancing the sunscreen's efficacy as an antierythema agent.

CONCLUSIONS

The optimum time variation for the synthesis of n-octyl cinnamate was sonication for 4 hours with an average yield of 10.1%. The n-octyl cinnamate compound with an optimal concentration of 100 ppm has potential as an antierythema agent with an extra protection category *in vitro*.

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