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Synthesis of Some Distinct Curcumin-Based Pyrano [2,3-D] Pyrimidines with Barbituric Acid, Cinnamaldehyde, and Benzaldehyde

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Abstract

Curcumin is a powerful radical oxygen scavenger. The modification of of curcumin's α, β-unsaturated 1,3-diketone moiety can be carried out to improve its physicochemical stability and functionality. This research aimed to conduct a modification of curcumin structure and to study the antioxidant activity of the modified curcumin-based compound. The modified curcumin made from a combination of benzaldehyde and cinnamaldehyde, using barbituric acid and combination of citric acid as catalyst and ethanol as solvent. The combination of ethanol solvent and 20 mmol% citric acid catalyst produce the highest yield of curcumin product which has a yield of 99.3581±0.2873% and was chosen as the best combination for the next modification using different β-diketone compounds. In the following stage, the mixture was reacted with either benzaldehyde or cinnamaldehyde. Yield, TLC, and antioxidant activity parameters were assessed for all modified products and were accompanied by their characterization using UV-Vis spectrophotometry. This study showed that curcumin cinnamaldehyde had a yield of 47.4831±2.7032%, a maximum wavelength of 416 nm, and antioxidant activity of IC50 18.2130±2.8766 mg/L with a molecular mass of 594 m/z.

Keywords: antioxidant activity; benzaldehyde; cinnamaldehyde; curcumin; dimedone; modification

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INTRODUCTION

Curcumin, is a major yellow pigment mainly found in the rhizome of *Curcuma longa* Linn. While most of the antioxidants present have either a phenolic functional group or a β-diketone group, curcumin is a unique antioxidant that contains a variety of functional groups, such as β-diketone group, carbon-carbon double bonds, and phenyl rings containing hydroxyl and methoxy substituents (Mbese et al., 2019). Hence, curcumin is a potential scavenger of a variety of reactive oxygen species such as peroxide anion free radical, hydroxyl radical, singlet oxygen, and nitrogen-centered free radical. This biomolecule is also known to have protection activity various organic molecules, especially hemoglobin, and DNA against oxidative degradation as well as inhibition of several tumor cancer growths. Naturally, curcumin has several derivates, namely pure curcumin, demethderivatesmin (DMC), and bisdemethoxycurcumin (BDMC) three of which made curcuminoids, a group of polyphenol in

turmeric plant with curcumin comprise the majority compound (77% (Elburki et al., 2017). Despite its superior functional properties, curcumin is susceptible to hydrolysis under basic and neutral environment and high tendency to crystallize out from its acidic solution. An attempt has been developed to improve curcumin stability by encapsulating it into an emulsion which was reported to successfully preserve 85% of its contain (Kharat et al., 2017).

Consider that curcumin has a distinct structure that made it easier to undergo chemical modifications, such as hydrogen donation, nucleophilic addition, hydrolysis, and enzymatic degradation, many efforts have been carried out to enhance curcumin stability by producing its synthetic derivatives (Priyadarsini, 2014). A modification of curcumin's α,β-unsaturated 1,3-diketone moiety as semicarbazone and pyrazole derivatives have been reported with an increased antioxidant and anti-inflammatory properties compared to the native curcumin (Anselmo et al., 2021). Meanwhile, another modification of curcumin has been found to have profound anti-inflammatory (Elburki et al., 2017).

The curcumin can be modified as pyrimidine derivative; a pyranopyrimidine that is formed from the fusion of pyrimidine and pyran rings together from a reaction of curcumin together with aldehyde molecules and barbituric acid (Ghaffarian et al., 2019). In this research, solvent-free modification was proposed to minimize harmful waste as well as to make an easier and faster modification technique (Stepanova et al., 2022; Zangade & Patil, 2019). In general, a catalyst is required to accelerate the chemical reaction. This research employed citric acid as the catalyst (Panahi et al., 2017). Citric acid is a compound natural found in citrus fruits, and thus can be considered as an eco-friendly catalyst. The aldehyde was selected from natural origin, namely cinnamaldehyde and benzaldehyde. This new combination of curcumin containing pyrimidine subdivision is of great interest because many of them exhibit increase biological activities and thus clinical applications, which bring the interest in researching further regarding modification of curcumin as a pyrimidine derivative (Liu et al., 2017; Yousefi et al., 2015)

RESEARCH METHODOLOGY

Materials and Equipment

Materials used in this research were commercial curcumin powder "Merck", dimedone "Sigma Aldrich", cinnamaldehyde "Sigma Aldrich", benzaldehyde "Sigma Aldrich", barbituric acid "Sigma Aldrich", and citric acid in form of citric acid monohydrate "Sigma Aldrich". Reagents used for experiment and analysis were ethanol p.a. "Merck", NaOH solution, distilled water, ethyl acetate p.a. "Merck", n-hexane p.a. "Merck", DPPH solution, and methanol p.a. "PT. Smart Lab Indonesia".

Equipment used in this research consisted of mortar and pestle, glassware, analytical balance, hot plate stirrer "Barnstead Thermolyne Cimarec", reflux apparatus, thermometer, TLC plate "Merck", capillary glass tube, UV lamp machine, filter paper Whatman No.1, evaporating dish, cuvette, micropipette, UV-Vis spectrophotometer "Hitachi U-1800", and LC-MS "UPLC Acquity SDS-XEVO G2QTOF".

Research Method

Curcumin was modified using cinnamaldehyde and benzaldehyde with barbituric acid as a reagent and citric acid 5, 10, 20, and 25 mmol% (mmol/mmol substrate) as the catalyst. The pH of the reaction is controlled with addition of sodium hydroxide solution (Ghaffarian et al., 2019). The reaction was done with and without additional solvent. Different citric acid concentrations were added to find the optimum concentration of catalyst. The second stage was done by reacting the modified curcumin with cinnamaldehyde and benzaldehyde. The result of the synthesis was identified using TLC, whereas the spectrum and mass spectral characteristics were conducted using analysis using UV-vis Spectrophotometer and LC-MS, respectively.

Research Stage I

The procedure of curcumin modification in research stage I was carried out using the method developed by Yousefi *et al.* (2015) with necessary modification. The efficiency of reaction with and without solvent as well as the concentration of catalyst was observed through a simple reaction between 1 mmol curcumin (Mr: 368.385 g/mol) added into a 2 mL 10 mM sodium hydroxide solution reacted together with 1 mmol benzaldehyde (Mr: 106.124 g/mol) and 1 mmol barbituric acid (Mr: 128.087 g/mol). Different citric acid concentrations, e.g., 5, 10, 20, or 25 mmol% (mmol substrate rate) (Mr: 210.138 g/mol) were added and the mixture was ground and crushed using a pestle for 1 h at room temperature. The reactions were done with and without hot ethanol addition. After 1 hour, re-precipitation was done using water and the precipitate is washed and filtered. The dried modified curcumin was recrystallized using hot ethanol (78°C) and then weighed to determine the percentage of yield. Accordingly, the dried modified curcumin was analyzed using TLC.

Research Stage II

The chosen process from stage 1 was then used to react curcumin with two different aldehydes. A carefully prepared 1 mm of cinnamaldehyde or benzaldehyde was added to the mixture hence resulting in two products of modified curcumin. The modified products were analyzed for their yields, TLC results, antioxidant activities using the DPPH method, as well as their UV-Vis characteristics using a UV-Vis spectrophotometer to determine UV-Vis wavelength at maximum absorbance and mass spectra using original curcumin as a comparison.

Method of Analysis

Yield Percentage (YP)

Yield percentage (%) was calculated by taking the ratio between the actual yield which was the mass of product gained and the theoretical yield which was the mass of product that should be generated from the chemical reaction based on the stoichiometry of the balanced equation, by following this equation (Isac-García et al., 2016) :

$$YP\ (\%) = \frac{\text{actual yield}}{\text{theoretical yield}} \times 100\% \qquad (1)$$

Thin Layer Chromatography

Thin layer chromatography (TLC) was used to monitor whether the synthesized compound existed. The TLC method was done using ethyl acetate: n-hexane (1: 1) as a mobile phase (Setyaningsih et al., 2016). Samples were spotted on the TLC plates by using capillary glass tubes. The plate was then developed in a glass chamber via mobile phase elution. The bands of compounds were visualized using a UV lamp machine. The R_F, a standard measure of retention, was obtained and compared with the spot of all the original reagents.

Antioxidant Activity

The antioxidant activity of the curcumin product was analyzed following the DPPH Methods (Sökmen & Khan, 2016). The reaction mixture consisted of a 0.8 mL sample and 1 mL DPPH radical solution of 0.2 mM in methanol. The reaction is read at 517 nm using a UV-Vis spectrophotometer. The free radical scavenging capacity was determined by:

$$\text{Inhibition (\%)} = ((A_0 - A_1)/A_0) \times 100\% \qquad (2)$$

where A_0 and A_1 were respectively the absorbance of the control and sample. The IC_{50} (concentration providing 50% inhibition) value was then calculated using the concentration inhibition curve plotting the sample concentration and percentage of inhibition in a linear equation.

Bathochromic Shift.

The wavelength shift of the Curcumin-based products was analyzed using a UV-vis spectrophotometer (Octa et al., 2021). The difference between the bathochromic and hypochromic curves indicates maximum wavelength shifting while the change in hyperchromic and hypochromic curves indicates the intensity of concentration. The analysis was done by dilution of 5 mg sample with methanol to obtain a 50 µg/mL concentration. The samples were then placed in a cuvette and measured in UV visible wavelength (λ 200-800 nm) spectrophotometer to determine the wavelength where maximum absorbance of each sample occurred.

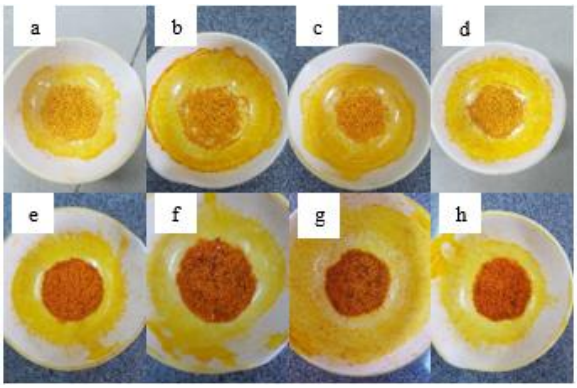
Liquid Chromatography-Mass Spectrometry

LC-MS ESI ion positive was used to analyze the synthesized product(Kunati et al., 2018). The LC used was a UPLC-QToF-MS/MS System with UPLC Acquity SDS and MS XEVO-G2QTOF was used as the instrumentation with data processing using MassLynk 4.1 software. The solvent carrier used was a mixture of water: acetonitrile (19:1).

RESULTS AND DISCUSSION

Effect of Solvent and Catalyst Concentration

Figure 1 shows the color differences of curcumin upon reaction with citric acid.



Note: (a-d) no solvent with 5 mmol%,10 mmol%,20 mmol%, 25 mmol% respectively
(e-g) with ethanol solvent, with 5 mmol%,10 mmol%,20 mmol%, 25 mmol% respectively

Figure.1 Products from different use of solvent and catalyst concentration

There is prominence color difference observed between modified products from the without solvent method (yellowish orange) and products from the solvent method (reddish orange). The use of solvent help solubilizes the curcumin thus increasing their reaction capacity. Curcumin is insoluble in water, but readily soluble in an organic solvent, such as ethanol that indicates its susceptibility toward chemical reactions in their soluble form (Priyadarsini, 2014). The use of ethanol also greatly decreases reaction and increases the yields of reaction compared to the aprotic solvent or nonsolvent option (Ghaffarian et al., 2019). The success of the reaction was further observed in the yield and TLC spots.

Thin layer chromatography (TLC) was used to monitor whether the expected modified compound existed or not. When the modified products showed additional TLC spots that were not seen on their building blocks' TLC result or that they had different R_F compared to their building blocks, it could be assumed that the modification was successful. TLC results of modified curcumin products using no solvent method and ethanol method with different catalyst concentrations can be seen in Table 1.

As shown in Table 1, all the reactions using ethanol as a solvent carrier showed four additional TLC spots observed compared to commercial curcumin at all concentrations of catalyst. R_F values of

spot 1, spot 2, spot 3, and spot 4 at all catalyst concentrations were 0.26, 0.40, 0.54, and 0.79, respectively. These showed the formation of new compounds different from curcumin which was 0.97 as shown in Table 1, while other reactants; Benzaldehyde and barbituric acid did not produce any spot on the TLC plate. During the pyrimidine synthesis there are several possibilities of intermediate Schiff based compound formed (Stepanova et al., 2022). During the synthesis of curcumin using vanillin and ethyl acetone and butyl amine, formation of several intermediate compound with different electrophilicity than the original compound was reported. The appearance intermediate compounds were also found as an additional spots during a synthesize of curcumin analog using vanillin and cyclopentane (Martha et al., 2022). This observation proves the formation of additional spots on the TLC.

Table 1. TLC Result: R_F Values of Modified Products from Solventless and Ethanol Method with Different Catalyst Concentrations

Treatment	TLC spot/ Rf
Curcumin	0.97
Benzaldehyde	No spot
Barbituric acid	No spot
Ethanol (5 mmol %)	4 spots (0.26; 0.4; 0.54; 0.79)
Ethanol (10 mmol %)	4 spots (0.26; 0.4; 0.54; 0.79)
Ethanol (20 mmol %)	4 spots (0.26; 0.4; 0.54; 0.79)
Ethanol (25 mmol %)	4 spots (0.26; 0.4; 0.54; 0.79)
Solventless	1 spot (0.95)

This result is following the previous research, in which the synthesis of curcumin using ethanol as a solvent produces a higher efficiency (Priyadarsini, 2014). For a molecule to react, they need to meet in the exact active sites. Without solvent, the molecule probably did not distribute enough at the molecular level thus hindering the successful interaction between substrates. In solventless system, using the grinding technique, the reaction of molecules is accelerated through the formation of heat energy generated through friction using mortar and pestle. This heat is obtained through grinding the crystals of substrate and reagent in a mortar (Zangade & Patil, 2019). The non-solvent methods usually require rigorous grinding and a longer period to succeed in which explains the failure in this experiment. Probably, the grinding process was not done rigorously enough to produce a sufficient reaction.

The efficiency of citric acid concentration will then be observed at the amount of crystallized product. Based on statistical analysis there was a significant effect ($p < 0.05$) of the use of solvent factor as well as a significant effect ($p < 0.05$) of catalyst concentration factor on the yield of modified products. Also, there was an interaction found between the use of solvent and catalyst concentration.

Based on the yield percentage, it can be seen that the use of 20 mmol% catalyst concentration showed the highest percentage of yield compared to the other three concentrations, hence the best combination of solvent and catalyst concentration for research stage II in terms of yield was the ethanol method with 20 mmol% catalyst concentration. Acid-based catalyst has been known to successfully enhance the modification reaction of curcumin, the presence of an acidic side will help the reaction to move forward (Panahi et al., 2017; Yousefi et al., 2015).

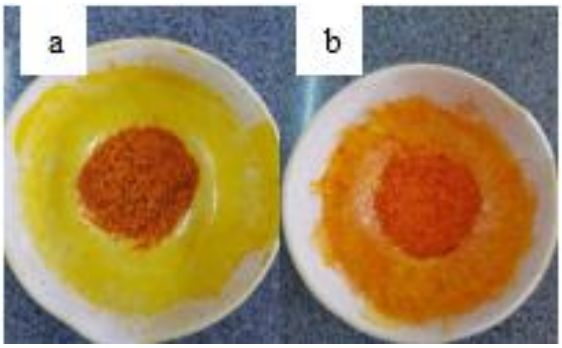
Table 2 Yield Percentage of Products Obtained from Different Use of Solvent and Catalyst Concentration

Treatment	Yield
Solventless (5 mmol %)	51.38%^{g}
Solventless (10 mmol %)	54.26%^{f}
Solventless (20 mmol %)	65.91%^{d}
Solventless (25 mmol %)	58.69%^{e}
Ethanol (5 mmol %)	94.82%^{c}
Ethanol (10 mmol %)	96,63%^{b}
Ethanol (20 mmol %)	99.36%^{a}
Ethanol (25 mmol %)	97.99%^{ab}

Note: Different superscript notation indicates a significant difference between samples ($p<0.05$)

Effect of different aldehydes

After determining the use of ethanol as a solvent carrier and the addition of 20mm% citric acid as the catalyst. The reactions were then carried out to analyze the effect of different aldehydes used; benzaldehyde and cinnamaldehyde. Benzaldehyde and cinnamaldehyde were both an aldehyde which possessed structural differences: cinnamaldehyde possessed a conjugated double bond while benzaldehyde did not.



Note: (a) curcumin benzaldehyde (b) curcumin cinnamaldehyde

Figure 2 Products from different types of aldehydes

The resulting product of curcumin synthesize of benzaldehyde showed a yellowish green color

similar to the color reported by Martha et al. (2022). While the curcumin synthesized with cinnamaldehyde produce a deep orange color shown in Figure 2. The yield percentage of the modified curcumin products obtained from different types of β-diketone compounds (curcumin and dimedone) and different types of aldehydes (benzaldehyde and cinnamaldehyde) were recorded and shown in Table 3.

Table 3 The Yield Percentage of Products from Different Types of Aldehydes

Treatment	Yield
Benzaldehyde	98.78%[a]
Cinnamaldehyde	45.48%[b]

Note: Different superscript notation indicates a significant difference between samples ($p<0.05$)

As shown in Table 3, a higher yield percentage was achieved when curcumin was reacted with benzaldehyde than cinnamaldehyde. This observation is to the similar preceding experiments where curcumin derivatives gave a good yield between 63-99% (Anselmo et al., 2021; Yousefi et al., 2015) benzaldehyde was the most common one to be used in this type of synthesis. Curcumin and benzaldehyde combination has also been associated with the antimalarial activity. Pyrazole analog of curcumin exhibited seven to ninefold higher anti-malarial potency (Dohutia et al., 2018). Several research has been attempted to combine curcumin with cinnamaldehyde. Curcumin and cinnamaldehyde by themselves have lower stability, however, the hybrid proves to have better stability and increase functional activity. Curcumin cinnamaldehyde hybrid has been associated with their antiproliferative activity and inhibition against a-glucosidase (Panahi et al., 2017).

TLC results of modified curcumin and dimedone products using, two different aldehydes, benzaldehyde, and cinnamaldehyde as seen in table 4. As shown in Table 4, modified curcumin products had three and two additional TLC spots observed compared to commercial curcumin for benzaldehyde and cinnamaldehyde respectively. R_F values of spot 1, spot 2, and spot 3 resulting from curcumin benzaldehyde were 0.29, 0.49, and 0.71 respectively while R_F values of spot 1 and spot 2 resulting from curcumin cinnamaldehyde were 0.06 and 0.20 respectively. Those R_F values from both curcumin benzaldehyde and curcumin cinnamaldehyde were different from the R_F value of curcumin which was 0.97. This different spot indicate the presence of several intermediate compound with different electrophilicity than the original compound (Martha et al., 2022; Stepanova et al., 2022). The presence of intermediate compound and also product is shown by the shift in the ultraviolet adsorption of the compound.

The isolated compounds were then analyzed using UV-Vis spectrophotometry, to help determine the chemical structure of compounds using ultraviolet radiation and visible light. Different UV-Vis spectrums indicated different chemical structures. The ultraviolet region of the electromagnetic spectrum corresponded to the wavelength of 200-400 nm while the visible region corresponded to 400-800 nm (Johnson, 1999). Table 5 shows the maximum wavelength of modified products and Figure 3 shows the UV-Vis spectrophotometry graph of curcumin benzaldehyde and curcumin cinnamaldehyde.

Table 4. R_F Values of Products from Different Types Of B-Diketone Compounds and Types of Aldehydes

Type of β-diketone compound	Type of aldehyde	Additional spot	R_F
Curcumin	Benzaldehyde	Spot 1	0.29
		Spot 2	0.49
		Spot 3	0.71
	Cinnamaldehyde	Spot 1	0.06
		Spot 2	0.20
Curcumin		Spot 1	0.97

Table 5 Maximum wavelength of modified products of curcumin and dimedone

Type of Compound	Maximum wavelength (nm)
Curcumin Benzaldehyde	404
Curcumin Cinnamaldehyde	416
Curcumin	424
Benzaldehyde	304
Cinnamaldehyde	330

Curcumin will react with aldehyde compound, via aldol condensation in the presence of acid or alkali catalyst(Anselmo et al., 2021). As shown in Table 5. the maximum wavelength of curcumin benzaldehyde, curcumin cinnamaldehyde, dimedone benzaldehyde, and dimedone cinnamaldehyde were 404 nm, 416 nm, 312 nm, and 372 nm respectively. Those wavelengths were different from the maximum wavelength of their building blocks such as curcumin (424 nm), benzaldehyde (304 nm), and cinnamaldehyde (330 nm), Thus, it could be inferred that all modifications were successful since different UV-Vis spectrums indicated different chemical structures (Panahi et al., 2017; Setyaningsih et al., 2016)

There were two phenomena found regarding UV-Vis spectrophotometry which were bathochromic shift and hypsochromic shift. Bathochromic shift was a shift of absorption maximum to a longer wavelength while the hypsochromic shift was a shift towards a shorter wavelength. Extension of conjugation in a carbon chain or more conjugation of double bonds would lead to a shift to a longer wavelength (bathochromic shift). As shown in Table 4.4, both modified products of curcumin using cinnamaldehyde were longer in wavelength compared to products using benzaldehyde. Cinnamaldehyde had more double

bonds compared to benzaldehyde, as seen from their chemical structures. Cinnamaldehyde even possessed a conjugated double bond while benzaldehyde did not. The conjugation of double bonds would lead to a shift to a longer wavelength (bathochromic shift).

Both modification products of curcumin which were curcumin benzaldehyde (404 nm) and curcumin cinnamaldehyde (416 nm) also underwent hypsochromic shift or a shift towards shorter wavelength when compared with commercial curcumin (424 nm) while also underwent bathochromic shift or a shift of absorption maximum to a longer wavelength when compared with benzaldehyde (304 nm) or cinnamaldehyde (330 nm).

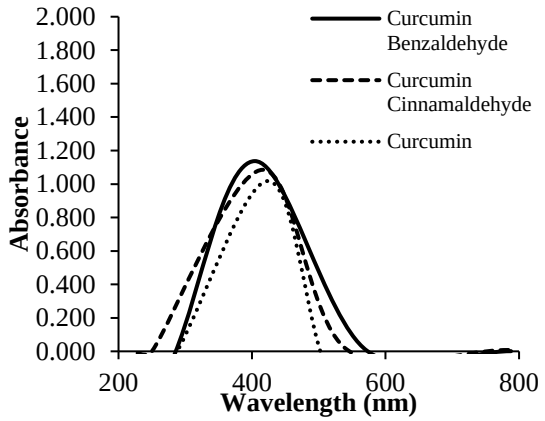


Figure 3. UV-Vis spectrophotometry graph of modified curcumin products

Antioxidant activity of modified products resulted from different types of β-diketone compounds (curcumin and dimedone) with different types of aldehydes (benzaldehyde and cinnamaldehyde) were measured to determine which modified product possessed the highest antioxidant activity.

Table 6. Antioxidant Activity of Curcumin Cinnamaldehyde and Commercial Curcumin

Type of Compound	IC50 mg/L
Curcumin Benzaldehyde	18.2130 ± 2.8766^{b}
Curcumin Cinnamaldehyde	39.8205 ± 1.7094^{c}
Curcumin	11.4477 ± 1.4661^{a}

Note: Different superscript notation indicates a significant difference between samples ($p < 0.05$)

Based on the t-test analysis commercial curcumin was significantly ($p < 0.05$) lower in IC_{50} value commercial curcumin had higher antioxidant activity than their curcumin derivates. The antioxidant activity was related to the presence of phenolic groups in ortho and/or para positions of the curcumin aromatic rings (Sökmen & Khan, 2016), the more phenolic groups, the higher antioxidant activity calculated. From this study, Curcumin cinnamaldehyde possessed a significantly lower IC_{50} value (higher antioxidant activity) compared to the one using benzaldehyde. This might be caused by the difference in the structure of cinnamaldehyde and benzaldehyde where cinnamaldehyde possessed a conjugated double bond. However, despite the difference, all modifications are considered to possess a very strong antioxidant ($IC_{50} < 50$ ppm), which can be assumed that this type of modification did not change their properties, even have the possibility of an increase in their value (Dohutia et al., 2018; Elburki et al., 2017; Mbese et al., 2019; Qiu et al., 2013).

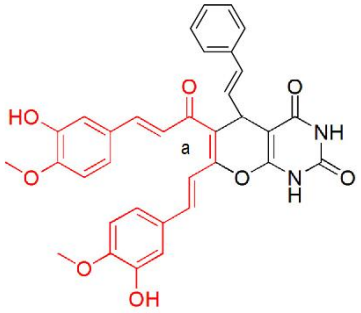


Figure 4. Predicted chemical structure of the expected curcumin cinnamaldehyde (Panahi et al., 2017; Yousefi et al., 2015).

The predicted structure of Curcumin cinnamaldehyde was predicted from a literature study. There are several possible positions of condensation, however, most reaction of C-alkylation and condensation reactions happened in position a (Yousefi et al., 2015) above is the proposed structure of curcumin modification using barbituric acid and cinnamaldehyde using ethanol and an acid catalyst which might be similar with the resulting component synthesized in this research. To confirm the predicted structure, the modified product was further characterized using LC-MS in which LC-MS provided molecular weight (m/z) information of the sample.

The expected curcumin cinnamaldehyde shown in Figure 4 had a molecular weight of 592 m/z. Based on the LC-MS result shown in Figure 5. curcumin cinnamaldehyde was found at a retention time of 4.247 mins in which a peak of 593.9973 m/z was observed, and once again at 7.929 mins in which a peak with 594.0139 m/z was found. Those two peaks showed a molecular weight close to 594 m/z which only had a 2 m/z difference from the expected molecular weight of curcumin cinnamaldehyde. Thus, it could be inferred that the modification was successful and the slight difference in m/z might be caused by the presence of hydrogen.

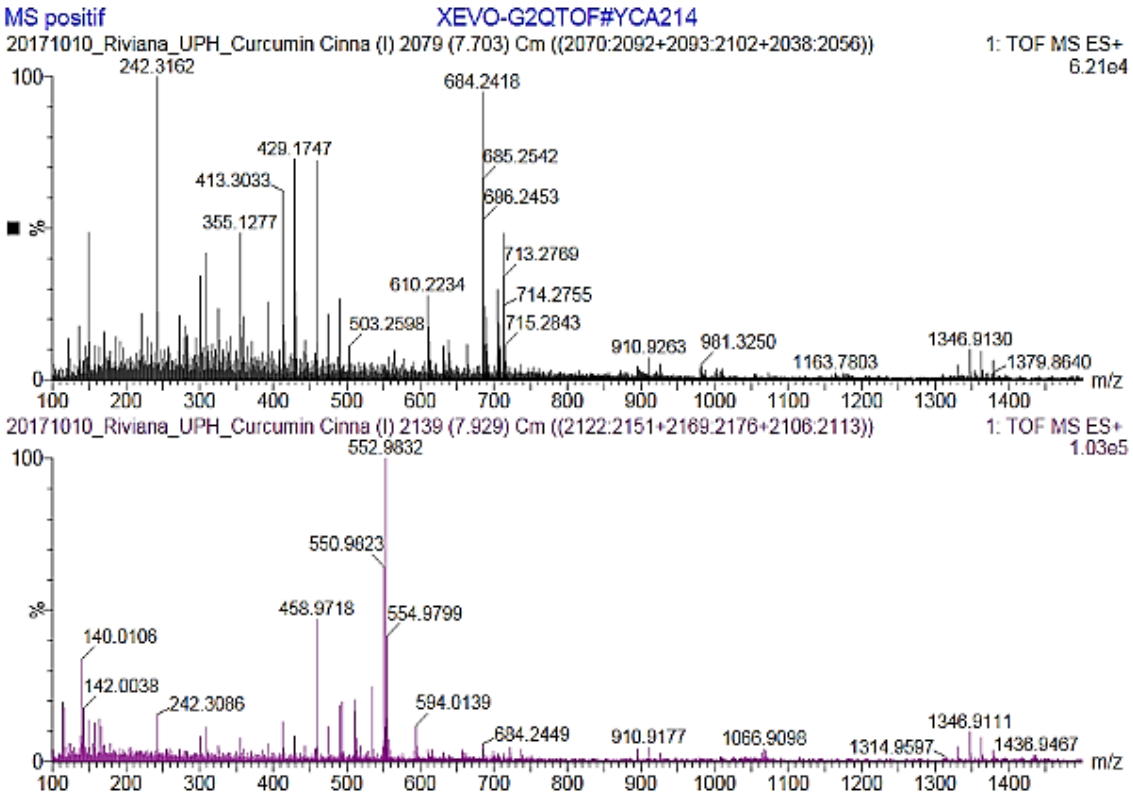


Figure 5. Mass spectrum of curcumin cinnamaldehyde

CONCLUSION

The solvent method using ethanol as solvent with 20 mmol% citric acid catalyst concentration and benzaldehyde and barbituric acid as the modifying agent was chosen as the best method to produce modified curcumin with the highest yield percentage of and good TLC result. Modification of curcumin with benzaldehyde and cinnamaldehyde using the ethanol method and 20 mmol% catalyst concentration also showed successful TLC results with curcumin benzaldehyde generating the highest yield percentage. Curcumin cinnamaldehyde possessed the highest antioxidant activity (18.2130±2.8766 mg/L) and the longest maximum wavelength using Hitachi-800 spectrophotometer (416 nm) has a predicted mass spectrum showing 594 m/z from UPLC Acquity SDS-XEVO G2QTOF.

Suggestions

As the antioxidant activity of the modified curcumin was still lower than commercial curcumin, different catalyst, longer reflux time, and more enhanced purification method may be tested in the future research for the better reaction performance. Other biological activities and clinical applications such as antidiabetic and anticarcinogenic should be explored in the future research as the modified curcumin may have a higher potential than as antioxidants. To investigate the changes in chemical structure, the FTIR or NMR analysis may be used for a more accurate analysis.

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