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Citronellyl Caffeate as a Novel α-Glucosidase Inhibitor with Potential Antidiabetic Activity

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ABSTRACT. Caffeic acid, a well-studied phenolic acid, has been extensively investigated for its diverse bioactivities, including antidiabetic, anti-inflammatory, antioxidant, antimicrobial, and antiviral properties. Esterification of caffeic acid has been explored to modulate its physicochemical and biological properties, however, optimization of lipophilicity while maintaining inhibitory activity remains a challenge. In this context, citronellyl caffeate was designed as a structurally optimized derivative that enhances α-glucosidase inhibition while improving lipophilicity and permeability. To enhance antidiabetic bioactivity through α-glucosidase inhibition, caffeic acid and citronellol were coupled using dicyclohexylcarbodiimide (DCC) as an activator and 4-dimethylaminopyridine (DMAP) as a catalyst with dimethylformamide (DMF) as the solvent. The synthesis was carried out under reflux conditions, followed by purification via liquid–liquid extraction and column chromatography, with thin-layer chromatography (TLC) used to confirm purity. The resulting compound, citronellyl caffeate, was characterized using ^{1}H NMR and ^{13}C NMR spectroscopy. Evaluation through α-glucosidase inhibition assays demonstrated that citronellyl caffeate showed enhanced α-glucosidase inhibitory activity (IC_{50} = 31.17 μg/mL) compared to its precursors, caffeic acid and citronellol, despite being less potent than quercetin (IC_{50} = 2.43 μg/mL), it demonstrates biologically relevant inhibition consistent with successful structural optimization.

Keywords: antidiabetic, caffeic acid, citronellol, glucosidase, synthesis

INTRODUCTION

The 10th edition of the IDF Diabetes Atlas reports that in 2021, over one in ten adults worldwide were living with diabetes, and projects that this number will rise substantially in the years ahead (Sun et al., 2022). Diabetes mellitus is a major global health challenge with rapidly rising prevalence and associated complications. Identifying novel compounds that can inhibit carbohydrate-hydrolyzing enzymes such as α-glucosidase to control postprandial blood glucose has emerged as a key strategy in antidiabetic drug discovery (Shah et al., 2025). Caffeic acid (CA) (**Figure 1**) is a metabolite of hydroxycinnamate and phenylpropanoid (Ekeuku et al., 2021), a by-product of the shikimate pathway and a polyphenol belonging to the hydroxycinnamic acid class (Maity et al., 2022).

The application of caffeic acid is constrained by its low aqueous solubility and limited oral bioavailability (Stasiłowicz-Krzemień et al., 2023) despite the fact that solubility and bioavailability are critical determinants of a compound's dissolution, absorption, and ultimately its effective dose delivery (Stanciauskaite et al., 2023). One potential approach is to incorporate caffeic acid and its derivatives into conjugates with other bioactive molecules (Khan et al., 2021). The synthesis of caffeic acid derivatives not only retains the parent compound's bioactivity but also enhances its functional versatility, highlighting the role of structural modification in expanding their applications (Peng et al., 2020). These modifications of caffeic acid through alkyl ester formation directly enhances its biological activity and broadens its potential (Salsabila et al., 2020), in which varying aromatic and alkyl chains enhances the antioxidant capacity of caffeic acid (Zheng et al., 2020).

Citronellol (3,7-dimethyl-6-octen-1-ol) is an acyclic monoterpenoid alcohol (**Figure 1**) within the essential oil constituents (Jiang et al., 2021) commonly produced by the vegetative organs of various plant species, including lemongrass (*Cymbopogon* spp.), lemon-scented gum (*Corymbia citriodora*), ginger (*Zingiber officinale*), and pelargonium (*Pelargonium* spp.) (Martinelli et al., 2024). Citronellol has been shown to exhibit moderate α-glucosidase inhibitory

activity and to significantly enhance glucose uptake in 3T3-L1 adipocytes by approximately 16% (Tan et al., 2016). The computational study of which citronellol, a major monoterpene in *Plectranthus neochilus* essential oil, interacts effectively with α-glucosidase, α-amylase, and DPP-4 which suggested that citronellol could play a significant role as a natural antidiabetic compound through multi-target enzyme inhibition mechanisms while maintaining good drug-likeness and safety characteristics (Mamoudou et al., 2025).

Previously reported caffeic acid derivatives have also demonstrated α-glucosidase inhibitory activity. Unmodified caffeic acid generally exhibits weak inhibition with IC_{50} 712.70 ± 7.11 (Subhan et al., 2025) while its derivatives, such as dicaffeoylquinic acid derivatives, have shown IC_{50} values in the range of ~50–60 μM, comparable to or slightly stronger than acarbose (60.91 ± 3.85 μM) under similar assay conditions (Lee et al., 2022). Recently, a series of caffeic acid derivatives isolated from *C. canephora* husk have demonstrated IC_{50} values in the low micromolar range (~2–50 μM) (Mai et al., 2024), highlighting the importance of structural modification in improving enzyme binding.

Although numerous caffeic acid esters have been developed to enhance bioavailability and biological activity, no study has specifically investigated the conjugation of caffeic acid with ±-citronellol as a strategy to improve α-glucosidase inhibition. Given the moderate inhibitory activity and favorable lipophilicity of ±-citronellol, we hypothesized that esterification with caffeic acid could generate a derivative with enhanced inhibitory potency and improved membrane permeability to explore the potential antidiabetic activity. Conventional Fischer esterification under acidic reflux conditions was avoided since caffeic acid contains phenolic hydroxyl groups and a conjugated system that may be unstable under strong acid and elevated temperatures (Rahim, 2023). In addition, Fischer esterification is equilibrium-controlled and requires water removal to achieve high conversion (Fernandes, 2022). Therefore, Steglich esterification using DCC/DMAP was selected to enable efficient ester formation under mild, anhydrous conditions. This study aimed to synthesize citronellyl caffeate via the Steglich esterification method and evaluate its α-glucosidase inhibitory activity as a structurally optimized derivative.

EXPERIMENTAL SECTION

Materials

For synthesis, caffeic acid was purchased from Tokyo Chemical Industry, ±-citronellol, dimethyl formamide (DMF), dicyclohexylcarbo-diimide (DCC), 4-dimethylaminopyridine (DMAP) were all purchased from Sigma-Aldrich. For thin layer chromatography, TLC silica gel sheet 60 F254 aluminium sheets (Merck, 1.05554.0001) was used. Column chromatography was performed using distilled *n*-hexane:ethyl acetate (9:1, v/v), and the polarity was gradually increased before final washing with methanol which loaded with silica gel 60 (63–200 μm, 70–230 mesh) purchased from Merck. Sodium bicarbonate ($NaHCO_3$) and sodium sulfate Na_2SO_4 from Merck were used to purify the product. For α-glucosidase inhibition assay, dimethyl sulfoxide (DMSO), p-Nitrophenyl β-D-glucopyranoside (PNPG), and sodium phosphate were all purchased from Sigma-Aldrich. For α-glucosidase assay, yeast α-glucosidase (0.35 U/mL) is used. The structure of the synthesized derivative was determined by ^1H NMR and ^{13}C NMR using Bruker AVANCE NEO 700 MHz.

Synthesis of Caffeic Acid Citronellol Derivate

Into a 100 mL capacity of round bottom flask were 0.25 mmol (45 mg) caffeic acid, 0.375 mmol (58 mg) citronellol, 0.25 mmol (51 mg) DCC, 0.25 mmol (30.54 mg) DMAP, and 2 mL of DMF. After reflux for 6 hours, a brown liquid was obtained and filtered to remove by 1,3-dicyclohexyl urea (DCU) before evaporating the rest of the solvent. The produced result was a dark brown solid.

Before purifying it with liquid-liquid extraction method, the product was diluted in 1-2 mL of distilled methanol before water was added then ethyl acetate to form 2 layers. The top layer containing the non-polar compounds including the ester product in ethyl acetate was separated. The next step was to wash the organic layer with $NaHCO_3$, separate the top layer before drying the product using Na_2SO_4. Filtered the finished product and dried it in the oven.

After TLC analysis, the crude product was further purified by column chromatography. A total of 38 mg of crude extract was loaded onto a silica gel column. Elution was initially carried out using *n*-hexane:ethyl acetate (9:1, v/v), and the polarity was gradually increased before final washing with methanol. This purification process isolated 11 mg of the final compound.

Analysis of Thin Layer Chromatography (TLC)

Thin Layer Chromatography analysis was conducted to monitor the reaction progress and assess product purity. Aluminum-backed silica gel plates were employed as the stationary phase, while a mixture of *n*-hexane and ethyl acetate served as the mobile phase (eluent). The sample was carefully

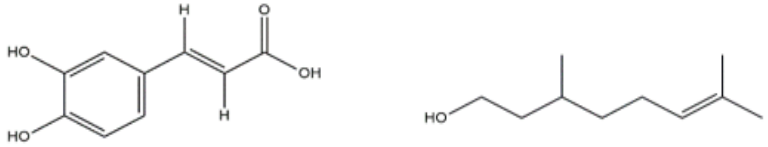

Figure 1. Structure of caffeic acid and citronellol.

Figure 2. Thin-layer chromatography (TLC) analysis of the fraction containing citronellyl caffeate after column chromatography using n-hexane:ethyl acetate (9:1, v/v) as the solvent system. From left to right: (1) caffeic acid, (2) citronellol, and (3) citronellyl caffeate.

spotted approximately 0.7 cm from the bottom edge of the plate, air-dried, and subsequently placed in a developing chamber containing the eluent n-hexane and ethyl acetate with 3:1 ratio. Upon completion of the development (with the solvent front reaching approximately 0.5 cm from the top edge), the plate was removed and dried. The resulting spots were visualized under UV light at wavelengths of 254 nm to identify and compare the components. **Figure 2** shows the TLC profile of the fourth fraction obtained after column chromatography, which was presumed to contain citronellyl caffeate. The observed Rf values were 0.06 for caffeic acid, 0.31 for citronellol, and 0.42 for citronellyl caffeate.

Chemical Shift of Citronellyl Caffeate

The ^{1}H and ^{13}C NMR spectral data below are citronellyl caffeate obtained in this study as well as the same structure synthesized using different method from Oufensou, et al. (2021). The results were in good agreement with previously reported values with comparable chemical shifts and coupling constants, thereby confirming the successful synthesis and structural assignment of the compound.

From our experiment, citronellyl caffeate, brown solid, ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.57 (1H, d, J = 15.89 Hz), 7.09 (1H, d, J = 1.89 Hz), 7.01 (1H, dd, J = 1.89; J = 8.26 Hz), 6.87 (1H, d, J = 8.26 Hz), 6.27 (1H, d, J= 15.82 Hz), 5.09 (1H, t, J = 7.07 Hz), 4.2 (2H, m), 2.00 (2H, m), 1.75 (2H, m), 1.7 (2H, m), 1.68 (3H, s), 1.61 (3H, s), 1.51 (1H, m), 0.95 (3H, d, J = 6.72 Hz). ^{13}C NMR (175 MHz, $CDCl_3$): δ 167.85, 146.28, 144.76, 143.80, 131.37, 127.56, 124.46, 122. 37, 115.73, 115.45, 114.33, 63.23, 36.99, 35.49, 29.54, 25.70, 25.38, 19.44, 17.65.

Citronellyl caffeate synthesized with a different method from (Oufensou et al., 2021). (E)-3,7-Dimethyloct-6-en-1-yl 3-(3,4-dihydrophenyl) acrylate: brown solid; 47%; mp 100–101 ◦C; [α]$D_2$0 2.9 (c = 0.4, $CHCl_3$); 1H-NMR δ 0.93 (d, J = 6.4 Hz, 3H), 1.21 (m, 1H), 1.36 (m, 1H), 1.52 (m, 1H), 1.59 (m, 1H), 1.60 (s, 3H), 1.67 (s, 3H), 1.74 (m, 1H), 1.99 (m, 2H), 4.30 (m, 2H), 5.09 (m, 1H), 6.28 (d, J = 15.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, Ar, 1H), 6.99 (dd, J = 2.1, 8.4 Hz, Ar, 1H), 7.12 (d, J = 2.1 Hz, Ar, 1H), 7.59 (d, J = 15.6 Hz, 1H); 13C-NMR δ 17.66, 19.42, 25.37, 25.72, 29.51, 35.42, 36.97, 63.61, 114.44, 115.14, 115.46, 122.46, 124.52, 127.17, 131.42, 144.03, 145.56, 146.78, 168.69; Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; Found: C, 71.60; H, 8.26.

α-Glucosidase Inhibition Assay

Antidiabetic activity was evaluated using the α-glucosidase inhibition assay based on method by Dea Firdaus et al. (2021). Samples were serially diluted to concentrations of 100, 50, 25, 12.5, and 6.25 ppm. Briefly, 5 μL of each sample was mixed with 5 μL of DMSO and 45 μL of phosphate buffer. Subsequently, 25 μL of substrate solution was added, followed by incubation for 5 min. Thereafter, 25 μL of yeast α-glucosidase (0.35 U/mL) was introduced and the mixture was incubated for an additional 15 min. The reaction was terminated by adding 100 μL of 0.2 M sodium bicarbonate. Quercetin was used as a positive control under identical experimental conditions to validate the assay performance. Enzyme activity was determined by measuring the absorbance of the released *p*-nitrophenol at 400 nm using a Varioskan Flash microplate reader (Thermo Fisher Scientific, Massachusetts, USA). The percentage inhibition was

calculated using the absorbance values of sample (s1), background sample (s0), blank (b1), and background blank (b0) according to the following formula:

$$\%Inhibition = \frac{[(A_{b1} - A_{b0}) - (A_{s1} - A_{s0})]}{(A_{b1} - A_{b0})} \times 100\%$$

The resulting inhibition values were plotted to generate a dose–response curve, from which the IC_{50} of the antidiabetic activity was determined using linear regression analysis. Each sample concentration was analyzed in triplicate.

RESULTS AND DISCUSSION

The compound citronellyl caffeate was synthesized from caffeic and citronellol using dicyclohexylcarbodiimide (DCC) as activator and 4-dimethylaminopyridine (DMAP) as catalyst used with dimethylformamide (DMF) as the solvent. **Figure 3** illustrates the synthetic route for the preparation of citronellyl caffeate via esterification.

The reaction mechanism of the Steglich method begins with the protonation of DMAP, in which the nitrogen group takes a hydrogen ion from the carboxyl group of caffeic acid. The resulting carboxylate anion then nucleophilically attacks the central carbon of DCC, forming an O-acylurea intermediate. This intermediate subsequently transfers a hydrogen ion to the positively charged nitrogen of DMAP. DMAP then attacks the carbonyl carbon of caffeic acid to form an acylpyridinium ion. This interaction induces electron rearrangement within the compound, leading to the release of dicyclohexylurea (DCU) as a byproduct. Citronellol then attacks the carbonyl carbon of the acylpyridinium ion, causing the bond with DMAP to dissociate and producing citronellyl caffeate, while DMAP is regenerated as a catalyst.

Figure 4 illustrates the proposed reaction mechanism between caffeic acid and citronellol using DCC and DMAP as catalysts, based on previously reported reaction mechanisms in related studies (Kart & Sari, 2020). In addition to the desired esterification pathway, carbodiimide-mediated coupling is known to generate N-acylurea through O→N acyl migration of the O-acylisourea intermediate. This rearranged by-product is unreactive toward nucleophilic substitution and may reduce the effective yield of the ester. Although, DMAP facilitates rapid formation of the reactive acylpyridinium intermediate and suppresses this rearrangement. Competitive N-acylurea formation cannot be completely excluded and may contribute to incomplete conversion observed in the reaction which partially accounts for the presence of unreacted starting material observed in TLC analysis.

Characterization of Citronellyl Caffeate

Figures 5 shows the ^{1}H and ^{13}C NMR spectra of citronellyl caffeate, the x-axis represents the chemical shift (δ, ppm), and the y-axis represents signal intensity. ^{1}H NMR (700 MHz, $CDCl_3$) and ^{13}C NMR (175 MHz, $CDCl_3$) spectra were recorded on a Bruker AVANCE NEO spectrometer. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal of $CDCl_3$ (δH = 7.26 ppm; δC = 77.16 ppm). The ^{1}H-NMR spectrum exhibited characteristic signals corresponding to the aromatic protons of the caffeic acid moiety, appearing as an ABX system at δH 7.09 (d, J = 1.89 Hz), 7.01 (dd, J = 1.89; 8.26 Hz), and 6.87 (d, J = 8.26 Hz). The trans-olefinic protons of caffeic acid were observed at δH 7.57 (d, J = 15.89 Hz) and 6.27 (d, J = 15.82 Hz), confirming the presence of a trans-coupled double bond. A signal at δH 5.09 (m) was attributed to the double bond proton of the citronellol moiety. The methylene protons (CH_2–CH_2) of citronellol appeared as multiplets at δH 4.20 (m), 2.00 (m), 1.76 (m), and 1.23 (m). The methyl groups of citronellol were identified at δH 1.68 (s), 1.61 (s), and 0.95 (d, J = 6.72 Hz).

The ^{13}C-NMR spectrum exhibited characteristic signals corresponding to the aromatic carbons of the caffeic acid moiety, observed at δC 127.56, 122.37, 115.73, and 114.33. Additionally, the two hydroxyl-substituted aromatic carbons appeared further downfield at δC 144.76 and 146.28, consistent with the deshielding effect of the attached hydroxyl groups. The olefinic carbons of the caffeic acid moiety were identified at δC 143.80 and 115.45, corresponding to the conjugated double bond. A slight downfield shift of the carbonyl carbon was observed, from δC 165.58 in free caffeic acid to δC 167.85 in the product, indicating ester bond formation. Similarly, the hydroxyl-bearing carbon of citronellol, originally appearing at δC 62.75, exhibited a minor shift to δC 63.23, further supporting successful esterification between caffeic acid and citronellol. The aliphatic carbons (C–H single bonds) of the citronellol moiety were observed at δC 36.99, 35.49, 29.54, and 25.38. The carbon corresponded to the C=C double bond appeared at δC 124.56, while the tri-substituted carbon at the other end of the double bond was detected at δC 131.37. Furthermore, the methyl carbons of citronellol were identified at δC and 25.70, 19.44, and 17.65, consistent with the characteristic signals of citronellol.

Figure 6 show the ^{1}H and ^{13}C NMR spectra together with the annotated structure of citronellyl caffeate. The observed chemical shifts, multiplicities, and carbon signals are in agreement with the proposed structure, confirming the successful synthesis of the target ester. **Table 1** compares the ^{1}H and ^{13}C NMR spectral data obtained in this study with those previously reported in the literature for citronellyl caffeate synthesized via a different method (Oufensou et al., 2021). The literature values were used as a reference to confirm the structural identity of the synthesized compound.

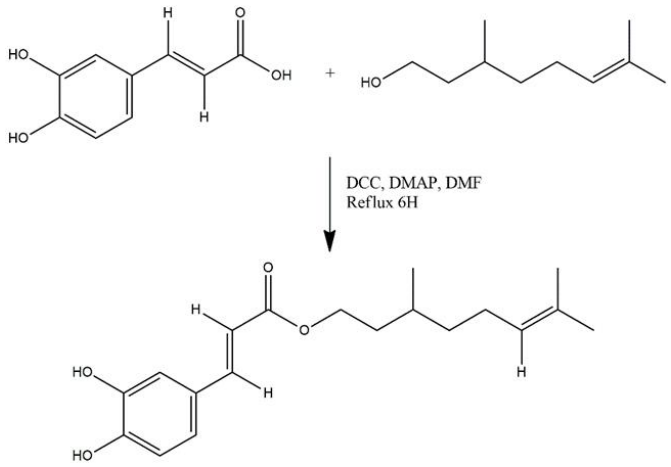

Figure 3. Reaction for synthesis of citronellyl caffeate using 0.25 mmol DCC and 0.25 mmol DMAP.

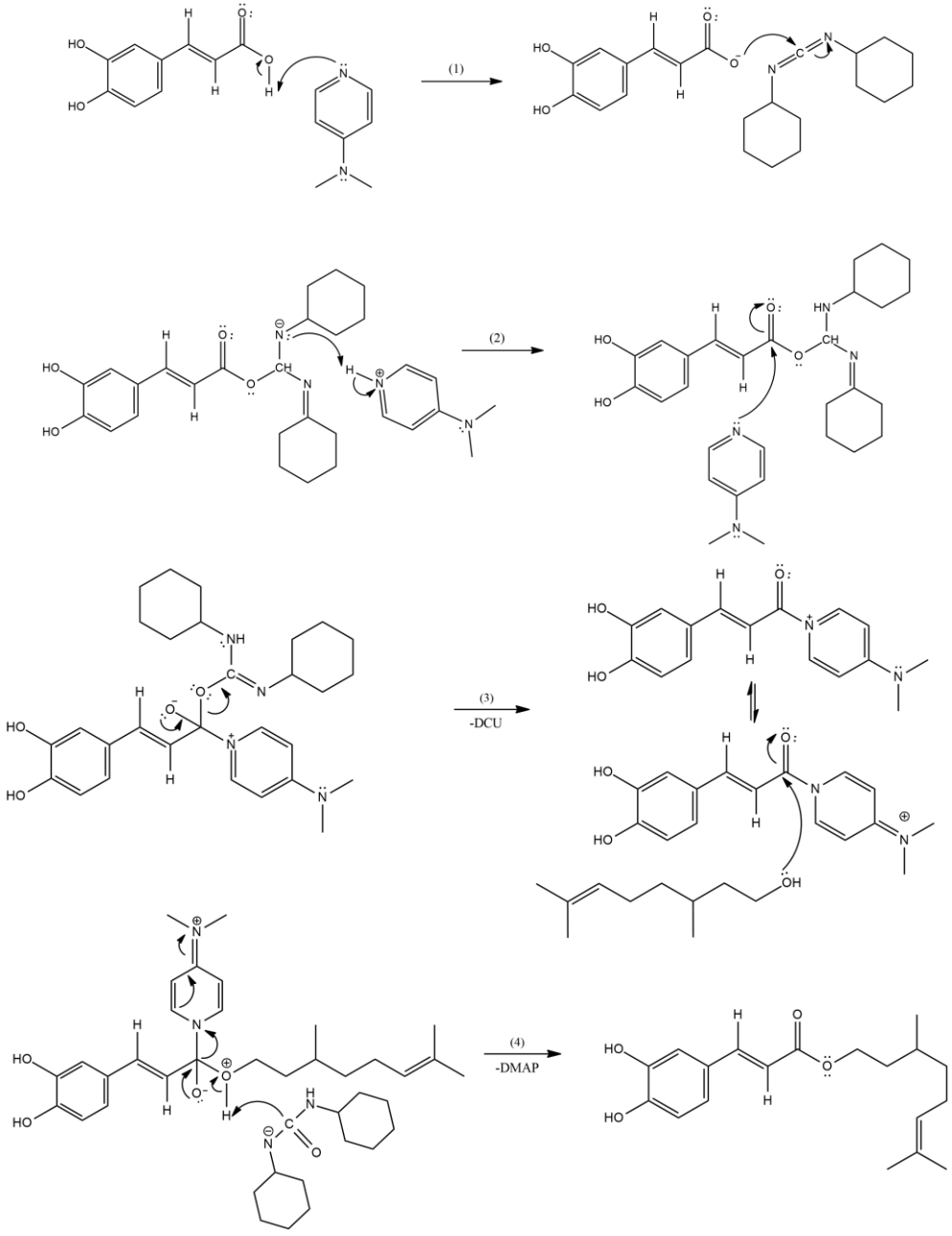

Figure 4. Mechanism of Steglich reaction, (**1**) protonation followed by attachment of DCC, (**2**) intermediate activated by DMAP, creating acylpyridinium ion, (**3**) the release of DCU continued with insertion of citronellol, (**4**) DMAP was regenerated prior to the formation of citronellyl caffeate.

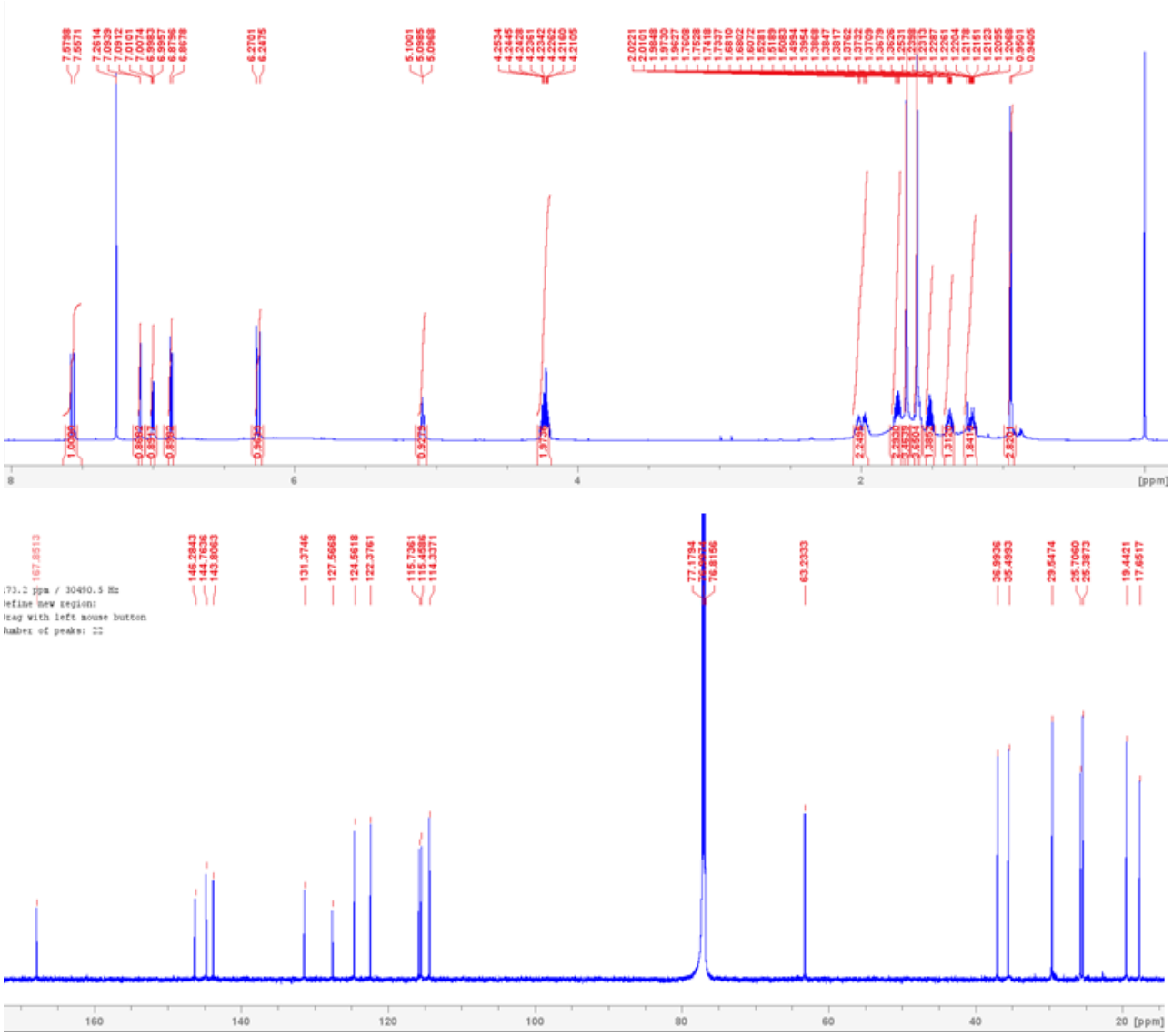

Figure 5. ^{1}H-NMR and ^{13}C-NMR spectra of citronellyl caffeate.

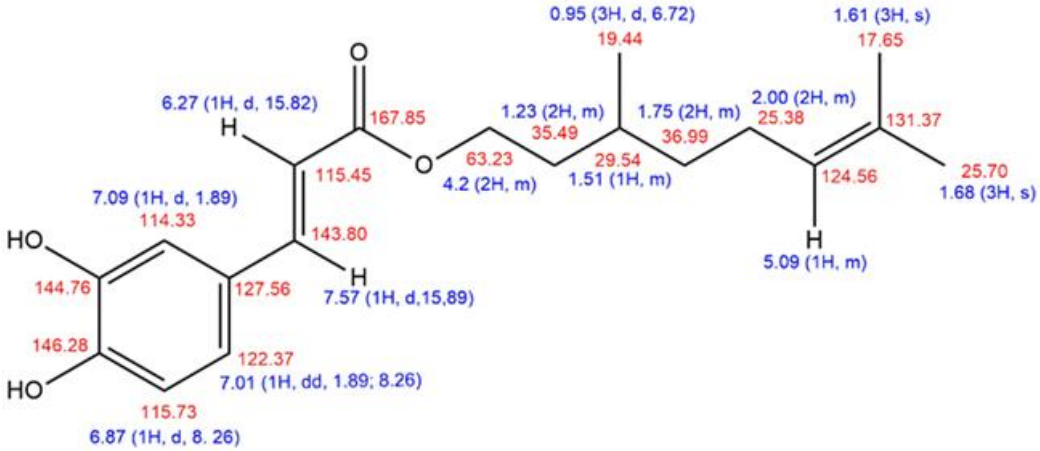

Figure 6. Structure of citronellyl caffeate.

Table 1. Chemical Shift data of NMR comparison of citronellyl caffeate from this study and reference.

	From this study Citronellyl caffeate (700 MHz in $CDCl_3$)		Reference (Oufensou et al., 2021) Citronellyl caffeate (700 MHz in $CDCl_3$)	
No.	δC	δH (m, J in Hz)	δC	δH (m, J in Hz)
1	127.56		127.17	
2	114.33	7.09 (1H, d, 1.89)	114.44	7.12 (1H, d, 2.1)
3	144.76		145.56	
4	146.28		146.78	
5	115.73	6.87 (1H, d, 8.26)	115.46	6.88 (1H, d, 8.4)
6	122.37	7.01 (1H, dd, 1.89; 8.26)	122.46	6.99 (1H, dd, 2.1; 8.4)
7	143.80	7.57 (1H, d, 15.89)	144.03	7.59 (1H, d, 15.6)
8	115.45	6.27 (1H, d, 15.82)	115.14	6.28 (1H, d, 15.6)
9	167.85		168.69	
1′	63.23	4.2 (2H, m)	63.61	4.3 (2H, m)
2′	35.49	1.23 (2H, m)	35.42	1.21 (1H, m)
3′	29.54	1.52 (1H, m)	29.51	1.52 (1H, m)
4′	36.99	1.76 (2H, m)	36.97	1.74 (1H, m)
5′	25.38	2.00 (2H, m)	25.37	1.99 (2H, m)
6′	124.46	5.09 (1H, m)	124.52	5.09 (1H, m)
7′	131.37		131.42	
8′	25.70	1.68 (3H, s)	25.72	1.67 (3H, s)
	19.44	0.95 (3, d, 6.72)	19.42	0.93 (3H, d, 6.4)
	17.65	1.61 (3H, s)	17.66	1.60 (3H, s)

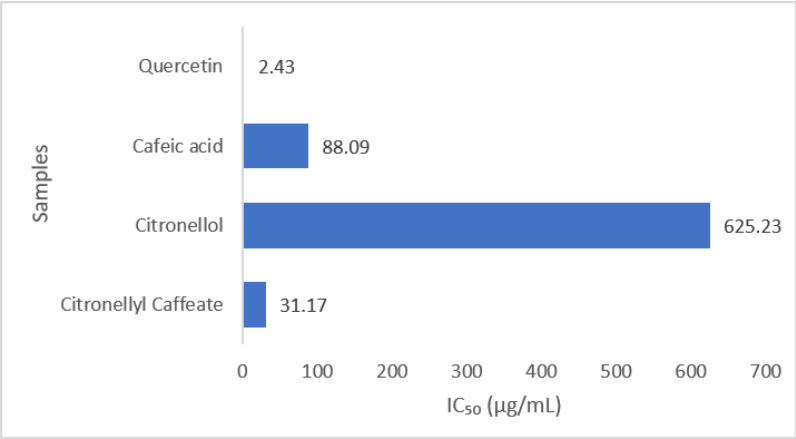

Figure 7. $IC5_0$ value of α-glucosidase inhibitory activity of quercetin, caffeic acid, citronellol, and citronellyl caffeate

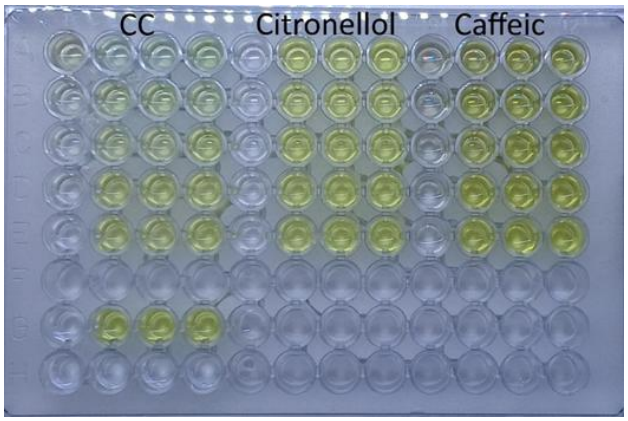

Figure 8. Result of α-glucosidase inhibition assay, consecutively from left to right, citronellyl caffeate, citronellol, and caffeic acid.

Table 2. IC50 value of α-glucosidase inhibitory activity of quercetin, caffeic acid, citronellol, and citronellyl caffeate.

Samples	IC_{50} (μg/mL)
Citronellyl Caffeate	31.17
Citronellol	625.23
Caffeic acid	88.09
Quercetin	2.43

α-Glucosidase Inhibition Assay

The α-glucosidase inhibition assay demonstrated that citronellyl caffeate significantly inhibited the enzyme activity, as evidenced by the reduction in yellow coloration. A lower color intensity corresponds to greater inhibitory activity as shown in **Figure 8**. The percentage inhibition values of the three tested compounds were calculated and subsequently analyzed using linear regression to determine the IC_{50} values, which are presented in **Table 2**. As expected, caffeic acid exhibited notable antidiabetic activity with an IC_{50} of 88.09 μg/mL, whereas citronellol showed minimal inhibitory effect, with an IC_{50} of 625.23 μg/mL. In contrast, the synthesized citronellyl caffeate displayed markedly stronger activity than its precursors, with an IC_{50} of 31.17 μg/mL. Although citronellyl caffeate exhibited significant inhibitory activity, it was still less potent than the reference standard, quercetin, which recorded an IC_{50} value of 2.43 μg/mL. **Figure 7** shows the comparative α-glucosidase inhibitory activity of quercetin, caffeic acid, citronellol, and citronellyl caffeate expressed as IC_{50} values. Quercetin exhibited the strongest inhibition (IC_{50} = 2.43 μg/mL), serving as the reference compound. Among the tested compounds, citronellyl caffeate demonstrated significantly improved inhibitory activity (IC_{50} = 31.17 μg/mL) compared to its precursors, caffeic acid (IC_{50} = 88.09 μg/mL) and citronellol (IC_{50} = 625.23 μg/mL). The substantial reduction in IC_{50} value following esterification indicates that conjugation of caffeic acid with citronellol enhances α-glucosidase inhibitory potency, supporting the rationale for structural optimization.

The enhanced antidiabetic activity of citronellyl caffeate compared to its precursors, citronellol and caffeic acid, may be attributed to a synergistic combination of their structural features and improved molecular properties. However, this mechanistic explanation remains a hypothesis based on in silico and structure–activity considerations and requires further experimental validation. Citronellol contributes anti-inflammatory and glucose uptake–enhancing effects, while caffeic acid provides potent antioxidant and α-glucosidase inhibitory activity. Lipophilization of phenolic acids through esterification with linear alcohols yields compounds that are more biologically active than their parent acids (Zieniuk et al., 2020). When esterified, the resulting compound of citronellyl caffeate exhibited increased lipophilicity similar to the formation of caffeic acid phenethyl ester (CAPE), which highlight the importance of esterification for carboxylic group with a phenethyl moiety, resulting in a marked decrease in molecular polarity and a significant increase in lipophilicity, thereby enhancing the compound's membrane permeability (Shao et al., 2021). This modification facilitates easier interaction with enzyme active sites, such as that of α-glucosidase, potentially enhancing its inhibitory effect, which further supports the notion that esterification serves as one of the effective strategies for improving inhibitory activity against α-glucosidase (Liu et al., 2022).

The production of reactive oxygen species (ROS) is a major factor contributing to the onset and progression of type 2 diabetes mellitus (T2DM) (Shrivastav et al., 2023), the increasing ROS production can damage blood vessels, promote inflammatory responses which collectively contribute to the development and progression of diabetic vascular complications (Caturano et al., 2023) to which strong antioxidant properties may help reduce diabetic complications by effectively lowering oxidative stress and minimizing cellular damage (Mallik et al., 2024). Esterified derivatives of caffeic acid have been reported to exhibit enhanced antioxidant activity compared to the parent compound, likely due to a synergistic stabilization effect (Lu et al., 2022). This structural modification not only enhances stability and bioavailability but also protects the phenolic core of caffeic acid from rapid degradation, thereby prolonging its biological activity. These combined biochemical and structural advantages may explain why citronellyl caffeate demonstrates stronger and more sustained antidiabetic potential than either citronellol or caffeic acid alone.

CONCLUSIONS

The present study demonstrated that citronellyl caffeate exhibited remarkable inhibitory activity against the α-glucosidase enzyme, indicating its potential as an antidiabetic agent. The compound was successfully synthesized from citronellol and caffeic acid via Steglich esterification. α-Glucosidase inhibition assays revealed that citronellyl caffeate possessed significantly stronger inhibitory activity, with an IC_{50} value of 31.17 μg/mL, compared to its precursors, citronellol and caffeic acid. These results suggest that the synthesized derivative not only retains the intrinsic bioactivities of its parent compounds but also exhibits enhanced

potency. The esterification process increases lipophilicity, thereby improving membrane permeability and facilitating more effective interactions with enzyme active sites. Moreover, the modification enhances structural stability, protecting the compound from degradation. Overall, these findings underscore citronellyl caffeate's potential as a promising antidiabetic candidate.

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