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Original Research Article

Synthesis of some esters of cinnamic acid and evaluation of their in vitro antidiabetic and antioxidant properties

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Abstract

Purpose: *To synthesize various ester derivatives of cinnamic acid and to evaluate their in vitro antidiabetic and antioxidant properties.*
Methods: *Esters of cinnamic acid were synthesized by refluxing the parent compound (cinnamic acid) with different alcohols using concentrated sulphuric acid as a catalyst. Physicochemical analyses (solubility, boiling point, refractive index) and spectrophotometric analyses (ultraviolet-visible spectroscopy (UV-VIS), Fourier-transform infrared spectroscopy (FT-IR) and gas chromatography-mass spectroscopy (GC-MS)) were carried out on the synthesized products. The antioxidant inhibitory property, uptake of glucose by yeast, and haemoglobin glycosylation of the synthesized products were also evaluated using standard methods.*
Results: *The identities of methylcinnamate, ethylcinnamate, propylcinnamate, 2-propylcinnamate, butylcinnamate and 2-butylcinnamate were confirmed, at m/z ratios of (131,103,77 and M^+ of162), (131,103,77 and M^+ of 176), (147,103,77and M^+ of 190), (147,103,77 and M^+ of 204), (143, 103, 77 and M^+ of 190), and finally (147,103,77 and M^+ of 204) respectively. FT-IR results revealed the following important bonds for the synthesized compounds: C=O, C-C, C-O, C=H, C-H and adjacent H. The results for glucose uptake by yeast and of haemoglobin glycosylation test indicate that all the products facilitated the transport and detachment of glucose at varying concentrations, respectively. The DPPH scavenging activity of propylcinnamate, 2-butylcinnamate and methylcinnamate with the absorbance of 63.06, 56.85 and 53.06 at 50 µg/mL - 250 µg/mL, respectively, recorded the highest values when compared with the control (ascorbic acid).*
Conclusion: *The results reveal that the six ester derivatives of cinnamic acid exhibit a certain degree of antidiabetic activity by facilitating the uptake of glucose by yeast and reducing glycation of haemoglobin; thus, showing a reasonable level of inhibition against free radicals.*

Keywords: *Antidiabetic activity, Free-radicals, Antioxidant activity, Cinnamic acid, Esters*

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INTRODUCTION

Diabetes mellitus is a chronic, life-challenging and costly disorder arising from chronic hyperglycemia, caused by the inability of the body to produce insulin or efficiently utilize insulin. Chronic hyperglycaemia has the potential of damaging almost all the cells in the body [1].

This autoimmune and metabolic disorder has been a major concern in Africa and the world as a whole. The international diabetes federation (IDF) estimated three hundred and sixty-six million adults aged 20 - 79 suffer from diabetes mellitus. In 1985, over thirty million people were suffering from diabetes and by the end of 2006 the number had increased to two hundred and thirty million. (80 % of this number are from developing countries [2-5].

Various aryl substitutions of cinnamic acid, and their corresponding esters have been identified in *Iranian Propolis*, showing the minimum inhibitory concentration (MIC) values between 125 and 500 mg/L against diabetes, bacteria and fungi. Other studies have confirmed the antimicrobial potential of *propolis*. Although secondary metabolites such as flavonoids and sesquiterpenoids present in propolis may have antimicrobial property, cinnamic acids are likely to contribute to the observed effect [6].

Chlorogenic acids are a family of natural esters of hydroxycinnamic acids (coumaric, caffeic, ferulic and sinapic acids) with (−)-quinic acid. The most common chlorogenic acid is 5-*O*-caffeoylquinic acid, which is abundant in coffee, black tea and mate but is also present in apples, pears and cabbage [7].

The recent attention on plants is imperative because of toxicities encountered with the synthetic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG) and tertiary butylated hydroquinone (TBHQ) [8,9].

In the light of this reality, six ester derivatives of cinnamic acid were synthesized and screened for possible antioxidant and antidiabetic activity with the aim of obtaining templates with minimal or no toxicities. It is hoped that some, if not all of these synthesized esters may become beneficial to man in the treatment of diabetes and combating destructive reactive oxygenated species (ROS) that are responsible for disease conditions such as hypertension, premature aging, cancers, respiratory dysfunctions and vitamin deficiencies.

EXPERIMENTAL

All reagents were purchased from JDH India (methanol, ethanol, propanol 2-propanol butanol and 2-butanol). Glucose, DPPH and powdered haemoglobin were bought from Sigma Aldrich USA. Baker's yeast was purchased from local market in Nigeria.

Synthesis of esters of cinnamic acid

Five grams (5 g) of cinnamic acid were measured using electronic analytical balance and dissolved in 50 mL of methanol. Sulphuric acid (3 mL) was added to the mixture as a catalyst in a 250 mL round bottom flask. The mixture refluxed under heat with regular stirring. The mixture was allowed to cool and transferred into a separating funnel. Cold water (100 mL) was added to the solution and the aqueous layer discarded. Ten (10) mL of $NaHCO_3$ was added and finally 10 mL of NaCl, discarding the aqueous layer respectively in each case. Water was removed using anhydrous Na_2SO_4. The crude esters were dried and the products purified using column chromatography. The procedure above was used to synthesize, ethylcinnamate, propylcinnamate, 2-propylcinnamae, butylcinnamate and 2-butylcinnamate.

Separation and purification of the synthesized products

The separation was carried out using preparatory TLC glass plate (20 x 20) coated with a 0.7 mm silica gel 60 F which was activated prior to use at 120^{o}C for 30 min to 45 min, while purification was done by simple recrystallization. A solution of each of the synthesized compounds alongside with the substrate was spotted on an imaginary line on the glass plate and developed using a solvent system of ethyl acetate and chloroform in the ratio of 5:5 with a drop of acetic acid. After development, the separated products were viewed under UV lamp.

Determination of physicochemical properties of the synthesized compounds

The boiling points of the synthesized compounds were determined using Siwoloboff method. The refractive index and solubility was determined using of a refractometer and by dissolving the compounds in various solvents respectively.

Spectrophotometric analysis of the synthesized compounds

The Ultraviolet Spectrophotometric analysis (UV) of the products were carried out using 0.1 mL of the test samples in 2 mL of dichloromethane and absorbance was read at 200 - 400 nm using spectrometer (UV-Visible UH4100). The Fourier Transform infrared spectrophotometric analysis (FTIR) of the synthesized compounds was carried out using Digilab (Model FTS-14). Five milligram each of synthesized compounds was analysed using GC-MS equipment (MS-Agilent 7890) for molecular weight elucidation with the

following acquisition parameters: Oven temperature program (temperature and hold time, 70 and 280 °C, 0 and 5 min, respectively); Column flow (1.80 mL/min); Total flow (40.8 mL/min); purge flow (3 mL/min); washing volume (8 µL); ion source temperature (200 °C); MS (start time, 3 min, end time, 24 min, event time, 0.50 sec). The identities of the compounds were suggested by the NIST library.

Preparation of calibration curve for DPPH reagent

DPPH (4 mg) was weighed out and dissolved in methanol (100 mL) to produce the stock solution (0.004 w/v). Serial dilutions were done to obtain the following concentrations; 0.0004, 0.0008, 0.0012, 0.0016, 0.0020, 0.0024, 0.0028, 0.0032 and 0.0036 w/v. The absorbance of each of the samples were read at λ_{max} of 512 nm using ultra-violet spectrophotometer (UV-Visible, UH4100). The machine was zeroed after an absorbance had been taken by a solution of methanol without DPPH used as the blank.

Evaluation of DPPH-radical scavenging property of synthesized compounds

Solution of DPPH (0.1 mm) was prepared in methanol and 0.5 mL of this solution added to 1.5 mL of test sample in ethanol at different concentrations (50 - 250 mg/mL). The solutions were vortexed thoroughly and incubated in the dark for about 30 min. The absorbance was read at 517 nm against blank samples. Low absorbance by the sample mean higher DPPH scavenging activity. Inhibition (H) of free radical DPPH was calculated as in Eq 1.

$$(H) = [(A_{blank} - A_{sample})/ A_{blank}] \times 100 \ldots\ldots\ldots (1)$$

A_{blank} is the absorbance of the control reaction (DPPH solution without the test sample) and A_{sample} is the absorbance of DPPH incubated with the synthesized samples or standard anti-oxidant drug. The (IC_{50}) of the synthesized compounds and standard antioxidant drug, was calculated by plotting a a graph of percentage inhibition against the concentration of both the synthesized compound and standard antioxidant drug respectively.

Evaluation of DPPH-radical scavenging property of standard antioxidant drugs

A stock solution of the standard antioxidant drug, vitamin C (Greenfield)was prepared by dissolving 10 mg of ascorbic acid in 10 mL of water. One (1) mL was taken in test tubes and diluted with same solvent up to 10 mL. A control sample was prepared containing same volume with neither the synthesized compounds nor ascorbic acid. The solution was left in the dark for 30 min. The DPPH- free radical was measured as in Eq 1.

Evaluation of glucose uptake by yeast

One millimeter (1.0 mL) of glucose solution at different concentrations (20 µg/mL, 40 µg/mL, 60 µg/mL, 80 µg/mL and 100 µg/mL) was transferred to various test tubes containing 4 mL 10 v/v suspension of yeast solution prepared by repeatedly washing yeast with distilled water and centrifuging at 3000 rpm for 5 min. The solution was incubated in a dark cupboard for one hour. 1 mL of the test solution was transferred to the test tubes containing glucose and yeast solution mixture, the solution mixture was vortexed and further incubated at 37 °C for 60 min. The percentages increase in glucose uptake by yeast cells was calculated as in Eq 1. (Cirillo, 2008).

$$(\%) = \left(\frac{Ac - As}{Ac}\right) \times \frac{100}{1} \ldots\ldots\ldots (2)$$

where *Ac* is absorbance of the control which does not contain the sample and *As* is absorbance containing the different samples.

Determination of haemoglobin glycosylation

Haemoglobin (1 mL) each was transferred into three test tubes, containing 1 mL solution of different concentrations (10 µg/mL, 20 µg/mL, and 30 µg/mL) of glucose prepared in 0.01 M phosphate buffer at pH 7.4. The contents were incubated at room temperature for 72 h. A blank solution in which glucose was omitted was used as control. One milligram of each of the test sample was added to the test tubes containing different glucose concentrations. The degrees of glycosylation of haemoglobin were estimated using UV at 540 nm at different incubation periods of 24, 48 and 72 h [10].

RESULTS

Regression data for the regression equation derived from the inhibitory activities

Regression equation: A = bc + d ……. (1)

where slope, b = 0.0093, intercept, d = 0.0023, and correlation coefficient = 0.9996

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Antioxidant activity of the synthesized products

The DPPH radical scavenging activities of the synthesized products are shown in Table 1.

In-vitro antidiabetic property

The antidiabetic property of the synthesized products using two different models (glucose uptake by yeast and haemoglobin glycosylation over the period 72 h) is presented in Table 2 -5. Considering the percentage increase in glucose uptake and significant ability to detach glycated glucose, three out of the six synthesized compounds can be classified as having promising activity.

Table 1: DPPH inhibitory activity of the synthesized products

Concentration (g/mL)	Inhibition (%)						
	MC	***EC***	***PC***	***2PC***	***BC***	***2BC***	***AC***
50	53.6	43.58	63.06	47.73	55.34	56.85	94.61
100	6.43	52.87	72.43	55.26	56.61	56.98	95.04
150	77.83	59.79	77.83	57.18	57.47	58.75	95.01
200	79.96	64.43	81.96	63.34	58.38	58.81	97.07
250	81.92	70.01	89.92	68.47	61.01	62.18	95.29

Key: MC = methylcinnamate, EC = ethylcinnamate, PC = propylcinnamate, 2PC = 2-propylcinnamate, BC = buthylcinnamate, 2BC = 2- Buthylcinnamate, AC = ascorbic acid

Table 2: Increase in glucose uptake by the synthesized products

Concentration (µg/mL)	Increase in glucose uptake (%)						
	MC	***EC***	***PC***	***2-PC***	***BC***	***2-BC***	***G+Y***
20	33.0	43.0	49.0	32.0	42.0	34.0	32.4
40	36.0	52.0	52.0	34.2	44.0	35.3	32.8
60	40.0	59.0	55.0	34.7	48.0	36.3	33.6
80	43.0	64.0	57.0	35.8	50.0	36.4	34.8
100	45.0	47.0	59.0	38.0	53.0	36.8	35.1

Key: MC = methylcinnamate, EC = ethylcinnamate, PC = propylcinnamate, 2-PC = 2-propylcinnamate, BC = buthylcinnamate, 2-BC = 2- Buthylcinnamate, G+Y = ascorbic acid

Table 3: Comparative effects of synthesized products on haemoglobin glycosylation at physiological glucose concentration after 24 h of incubation (values are expressed as mean ± SEM, n = 3)

Concentration (µg/mL)	Absorbance (nm)						
	MC	***EC***	***PC***	***2-PC***	***BC***	***2-BC***	***ACB***
10	0.170	0.109	0.157	0.657	0.162	0.362	0.823
20	0.233	0.117	0.187	0.724	0.212	0.452	0.900
30	0.311	0.178	0.205	0.924	0.412	0.600	0.986

Key: MC = methylcinnamate, EC = ethylcinnamate, PC = propylcinnamate, 2PC = 2-propylcinnamate, BC = buthylcinnamate, 2BC = 2- Buthylcinnamate, ACB = ascorbic acid

Table 4: Comparative effects of synthesized products on haemoglobin glycosylation at physiological glucose concentration after 48 h of incubation (mean ± SEM, n = 3)

Concentration (µg/mL)	Absorbance (nm)						
	MC	***EC***	***PC***	***2-PC***	***BC***	***2-BC***	***ACB***
10	0.321	0.198	0.217	0.722	0.263	0.523	0.923
20	0.501	0.235	0.300	0.824	0.345	0.610	1.056
30	0.771	0.318	0.393	1.086	0.523	0.721	1.098

Table 5: Comparative effects of synthesized products on haemoglobin glycosylation at physiological glucose concentration after 72 h of incubation (values are expressed as mean ± SEM, n = 3)

Concentration (µg/mL)	Absorbance (nm)						
	MC	***EC***	***PC***	***2-PC***	***BC***	***2-BC***	***ACB***
10	0.590	0.243	0.315	0.789	0.365	0.589	0.987
20	0.654	0.312	0.421	0.867	0.432	0.710	1.087
30	0.749	0.378	0.467	1.021	0.5601	0.765	1.130

Spectral characteristics

The physicochemical (yield, refractive index and boiling point) and spectrophotometric results of the synthesized products are shown below.

Methylcinnamate

Percentage yield =2 %, Refractive index (R.I), 1.600; Boiling point, 259-ºC, λmax in chloroform and absorbance (300.00nm,0.123); IR absorption: 2020.72 (C=C stretch (Aromatic)), 1638.48 (C=H stretch), 1419.84 (C-H def. (CH_3CH_2), 1276.19 (C-O (Ester)), 846.71 (adjacent H). Formula: $C_9H_8O_2$. Mol Weight: 148. GCMS Fragmentation: m/z ratios of (131,103, 77, 29, 15 and M^+ of 162).

Ethylcinnamate

Percentage yield = 26 %**,** RI, 1.5520; Boiling point 271-273ºC; λmax in chloroform and absorbance (325.00 nm, 0.153); IR absorption: 2832.00 (O=C-H stretch (Aromatic)), 1626.57 (C=H stretch), 1415.34 (C-H def. (CH_3CH_2), 1283.25 (C-O (Ester)), 764.84 (3 adjacent H). Formula: $C_{10}H_{10}O_2$. Mol Weight: 162. GC-MS Fragmentation: m/z ratios of (131,103, 77, 15 and M^+ of 176).

Propylylcinnamate

Percentage yield = 18 %**,** R.I, 1.5521; Boiling point 281-283ºC; λmax in chloroform and absorbance (290.00 nm, 0.122); IR absorption: 3057.88 (C-H stretch (Aromatic)), 1711.53 (CC=O) 1638.20 (C=C stretch), Aromatic)), 1458.20 (C=H def. (CH_3CH_2), 1178.20 (C-O (Ester)), 865.39 (adjacent H). Formula: $C_{11}H_{12}O_2$. Mol Weight: 176. GC-MS Fragmentation: m/z ratios of (147, 103, 77, 29, 15 and M^+ of 190).

2-Propylcinnamate

Percentage yield = 26**,** R.I, 1.6030; Boiling point, 269-271ºC; λmax in chloroform and absorbance (300.00 nm, 0.05); IR absorption: 3059.23 (C-H (Aromatic weak)), 1708.11 ((C-C=O) Aliphatic ketone) 1637.98 (C=C stretch), 1456.51 (C-H def. (CH_3CH_2), 1182.00 (C-O (Ester)), 865.54 (adjacent H). Formula: $C_{12}H_{14}O_2$. Mol Weight: 204. GCMS Fragmentation: m/z ratios of (147, 103, 77, 29, 15 and M^+ of 204).

Butylcinnamate

Percentage yield = 18 %**,** R.I, 1.5519. Boiling point, 287-289 ºC; λmax in chloroform and absorbance (340.00 nm, 0.123); IR absorption: 2968.00 (C-O ester), 1683.00 (C-H Aromatic (weak)), 1627.00 (C - C = O (aliphatic ketone)), 1497.40, (C =C stretch (Aromatic)), 1081.00 (C =H def (CH_3CH_2)) 764.59 (Adjacent H). Formula: $C_{13}H_{16}O_2$. Mol Weight: 218. GCMS Fragmentation: m/z ratios o3 (147, 103, 77, 29, 15 and M^+ of 195).

2-Butylcinnamate

Percentage yield 19%**,** R.I, 1.5522); Boiling point, 279-280ºC; λmax in chloroform and absorbance (300.00 nm, 0.006); IR absorption: 3024.48 (C-H stretch); 1626.06 (C=C stretch (aromatic)), 1497.44 (C-H def. (CH_3CH_2), 1282.72 (C-O (Ester)), 764.42 (adjacent H). Formula: $C_{14}H_{18}O_2$. Mol Weight: 323. GCMS Fragmentation: m/z ratios of (149, 103, 75, 29, 15 and M^+ of 208).

DISCUSSION

One of the most important aspects of pharmaceutical Chemistry is drug synthesis. It is very necessary that every chemotherapeutic agent that is synthesized is tested for biological activity. *In vitro* testing involves the biological test done outside a living organism or system.

Diabetes mellitus is a chronic, life challenging and costly disorder arising from chronic hyperglycemia, caused by the inability of the body to produce insulin or efficiently utilize available insulin [1].

Insulin regulates the glucose transporters that are responsible in transporting glucose into the cells. For example, GLUT4 is responsible in transporting glucose into the muscles and adipose tissues in anabolic conditions. Type-2 diabetes (insulin dependent) is characterized by hyperglycemia, dyslipidemia and protein metabolism due to insulin resistance, impaired insulin signaling, and β-cell dysfunction. Thus, drugs or synthetic products that can mimic the function of insulin in regulating GLUT4 transporters can be of good use in the treatment of this hyperglycemic disorder.

However, oral hypoglycemic agents like sulfonylureas (Glyuride, glipizide and tolazamide) have been used in the treatment of diabetes but could produce severe hypoglycemia, weight gain, and gastrointestinal disturbances. Hence there is a growing interest in discovering new and effective hypoglycemic agents with minimal or less side effects, readily available and affordable [2]. The results of this research suggest that the synthesized products do not only inhibit the binding of glucose to haemoglobin, but also facilitated the uptake of glucose by yeast cells. Ethylcinnamate, Propylcinnamatre and

Butylcinnamate having the highest activity. This may be as a result of the presence of ester group attached to the parent compound and subsequently the increase in carbon chain.

The antioxidant activity revealed that propylcinnamate, 2-butylcinnamate and methylcinnamate with absorbance of 63.06, 56.85 and 53.06 at 50 µg/mL, respectively, have the highest antioxidant activity similar to the control ascorbic acid.

Literature has shown that m- hydroxo or p-hydroxo residues of cinnamic acid where significantly important as an insulin releasing agent both *in vivo* and *in vitro* [11].

Furthermore, Sova and Chen confirmed the anti-diabetic and antioxidant properties of cinnamic acid ester derivatives, which is in accordance to these results obtained in this study [12,13].

CONCLUSION

The results show that the esterification of cinnamic acid by given alcohols improves the activity of the compound by significantly increasing the uptake of glucose by yeast and reducing the glycosylation of haemoglobin by glucose. Thus, it can be reasonably deduced that the ester derivatives of cinnamic acid are potential novel antidiabetic drugs.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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