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# Cuminaldehyde: Aldose Reductase and α-Glucosidase Inhibitor Derived from *Cuminum cyminum* L. Seeds

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The inhibitory activity of *Cuminum cyminum* seed-isolated component was evaluated against lens aldose reductase and α-glucosidase isolated from Sprague−Dawley male rats and compared to that of 11 commercially available components derived from *C. cyminum* seed oil, as well as quercitrin as an aldose reductase inhibitor and acarbose as an α-glucosidase inhibitor. The biologically active constituent of *C. cyminum* seed oil was characterized as cuminaldehyde by various spectral analyses. The $IC_{50}$ value of cuminaldehyde is 0.00085 mg/mL against aldose reductase and 0.5 mg/mL against α-glucosidase, respectively. Cuminaldehyde was about 1.8 and 1.6 times less in inhibitory activity than acarbose and quercitin, respectively. Nonetheless, cuminaldehyde may be useful as a lead compound and a new agent for antidiabetic therapeutics.

**KEYWORDS: Acarbose; aldose reductase; antidiabetic agent; antidiabetic complications; α-glucosidase; *Cuminum cyminum*; quercitrin**

## INTRODUCTION

Diabetes mellitus affects 300 million people worldwide and is the leading cause of blindness, kidney failure, heart attack, and amputation among adults (*1*). Achieving blood glucose levels as close to normal as possible has been considered as one of the major goals of therapy for those suffering from diabetes mellitus, as a high blood glucose level is implicated in the development of macro- and microvascular complications associated with diabetes (*2*). However, in clinical practices, normalizing blood glucose levels is a formidable challenge. Even more difficult is the control of postprandial hyperglycemia (*3*). Fortunately, both dietary and pharmacological tools are now available for its management. The pharmacological agents with the greatest effect on postprandial hyperglycemia include insulin lispro, amylin analogues, and α-glucosidase inhibitors (*4*−*10*). In hyperglycemia associated with diabetes, the use of aldose reductase inhibitors has been reported for the treatment of diabetic complications (*5*−*7*).

α-Glucosidase (EC 3.2.1.20) catalyzes the final step in the digestive process of carbohydrates. Its inhibitors can retard the uptake dietary carbohydrates and suppress postprandial hyperglycemia and could be useful for treating diabetic and/or obese patients (*4*). α-Glucosidase inhibitors such as acarbose, miglitol, and voglibose are known to reduce postprandial hyperglycemia primarily by interfering with the carbohydrate digesting enzymes and delaying glucose absorption. In addition, numerous α-glucosidase inhibitors have been screened from plants, some of which are of clinical importance (*7*−*11*). Although several drugs targeted for carbohydrate hydrolyzing enzyme are in clinical use, a large inhibitor pool is required as diabetic patients can develop resistance to current regimens.

Aldose reductase (EC 1.1.1.21) catalyzes the reduction of glucose to the corresponding sugar alcohol, sorbitol, which is subsequently metabolized to fructose by sorbitol dehydrogenase. Such a conversion of glucose into fructose constitutes the polyol pathway of glucose metabolism. Under normal physiological conditions, this pathway plays a minor role in the glucose metabolism of most tissues. In hyperglycemia associated with diabetes, however, cells undergoing insulin-independent uptake of glucose produce significant quantities of sorbitol due to the poor penetration by the sorbitol through the cellular membranes and its metabolism by sorbitol dehydrogenase. The resulting hyperosmotic stress to cells is postulated to be the primary cause for the development of such diabetic complications as retinopathy, cataracts, neuropathy, and nephropathy (*12*). These observations suggest that the inhibition of aldose reductase can be used as a novel, potentially direct pharmacological approach toward the treatment of certain diabetic complications (*13*).

Plants constitute a rich source of bioactive chemicals (*11*−*16*). Because many of them are largely free from adverse effects and have excellent pharmacological actions, they could lead to the development of new classes of possibly safer antidiabetic agents and antidiabetic complication. Additionally, some flavonoids and polyphenols as well as sugar derivatives are found to be effective on the inhibitory activities of α-glucosidase and aldose reductase (*5*−*8*, *10*). Therefore, much effort has been focused on the plants for potentially useful products as commercial α-glucosidase inhibitors and aldose reductase inhibitors or as lead compounds. Relatively little work has been done on antidiabetic effect of the compound isolated from *Cuminum cyminum* seeds despite its excellent pharmacological action such

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as an antimicrobial activity, a food spice, a fungicide, and a tyrosinase inhibitor (*17*−*19*). Active compounds isolated from *C. cyminum* seeds may be a good source for lead compounds as alternatives for antidiabetic agents currently used. The importance of finding effective antidiabetic therapeutics led me to further investigate natural compounds.

## MATERIALS AND METHODS

**Chemicals.** Bovine serum albumin, 3-carene, β-caryophyllene, *p*-cymene, DL-glyceraldehyde, imidazole, lithium sulfate, β-myrcene, NADPH, α-phellandrene, phenylmethylsolfonyl fluoride, α-pinene, β-pinene, quercitrin, sabinene, γ-terpinene, and thymol were purchased from Sigma Chemical (St. Louis, MO). Coomassie Blue reagent was purchased from Bio-Rad (Hercules, CA). Sprague−Dawley male rats were purchased from Dong Nam Laboratory Animal Research Center Co. (Chonju, Chonbuk, South Korea), and all other chemicals were of reagent grade.

**Isolation and Identification.** The oil (yield 9.8%) of *C. cyminum* seeds (500 g) was extracted by steam distillation as previously described by Sung et al. (*14*). A preparative high-performance liquid chromatograph (HPLC) (Spectra System P2000, Thermo Separation Products) was used for separation of the biologically active constituent from the oil (221 mg). The column was μPorasil (20 mm i.d. × 500 mm, Waters) using hexane/ethyl acetate (7:3) at a flow rate of 1.5 mL/min and detected at 260 nm. In this step, five fractions (P1, P2, P3, P4, and P5) were obtained and bioassayed as described below. The active P3 fraction (113 mg) was rechromatographed under the same condition. Finally, an active compound (65 mg) at the retention of 9.8 min was isolated. The structure of the active isolate was determined by spectroscopic analyses. $^1$H and $^{13}$C NMR spectra were recorded in deuteriochloroform with a JNM-LA 400F7 spectrometer at 400 and 100 MHz, respectively. UV spectra were obtained in methanol with a Jasco V-550 spectrometer and EI-MS spectra on a JEOL GSX 400 spectrometer.

**Gas Chromatography−Mass Spectrometry (GC-MS).** The oil of *C. cyminum* seeds was analyzed on a gas chromatograph (HP 6890)−mass spectrometer (JMS-600W, JEOL). The GC column was a 60 m × 0.25 mm i.d. DB-WAX (0.25 μm film) fused silica capillary column (J&W Scientific, Folsom, CA). The GC conditions were as follows: injector temperature, 210 °C; column temperature, isothermal at 50 °C for 15 min and then programmed to 200 °C at 2°C/min and held at this temperature for 15 min; and ion source temperature, 200 °C. Helium was used as the carrier gas at the rate of 0.8 mL/min. The effluent of the GC column was introduced directly into the source of the MS. Spectra were obtained in the EI mode with 70 eV of ionization energy. The sector mass analyzer was set to scan from 50 to 800 amu for 2 s. Compounds such as 3-carene, β-caryophyllene, cuminaldehyde, *p*-cymene, β-myrcene, α-phellandrene, α-pinene, β-pinene, sabinene, γ-terpinene, and thymol were identified by comparison with retention times and the mass spectra obtained with the authentic standards on the GC-MS system used for analysis. When an authentic sample was not available, the identification was carried out by comparison of mass spectra with those in the mass spectra library (The Wiley Registry of Mass Spectral Data, 6th ed.).

**Isolation of Aldose Reductase and α-Glucosidase from Sprague−Dawley Rats.** α-Glucosidase was prepared from the small intestines of 4 week old rats each weighing 180−200 g. Sprague−Dawley male rats were starved for 16−18 h prior to the study but were allowed access to water ad libitum. The small intestinal brush border was removed from Sprague−Dawley male rats and carefully homogenized for 5 min in 5 volumes (w/v) of 5 mM ethylenediaminetetraacetic acid (EDTA) (pH 7.0) containing 0.5 M NaCl and 0.5 M KCl using a Potter-Elvehjem homogenizer (Wheaton Co., United States). The homogenate was centrifuged at 20000*g* for 30 min. The precipitate was then dissolved with 5 mM EDTA (pH 7.0) and centrifuged at 20000*g* for 30 min. The precipitate was then redissolved with 5 volumes of 0.9% NaCl and centrifuged at 1000*g* for 30 min. The supernatant was retained as an enzyme preparation. All of the procedures were carried out at 4 °C.

Crude aldose reductase was prepared from rat lenses. Lenses were removed from the eyes of 8 week old Sprague−Dawley male rats each weighing 100−150 g and were homogenized in 12 volumes of 135 mM Na, K-phosphate buffer (pH 7.0) containing 0.5 mM phenylmethylsolfonyl fluoride, and 10 mM 2-mercaptoethanol. The homogenate was centrifuged at 100000*g* for 30 min, and the resulting supernatant was retained as an enzyme preparation. All procedures were carried out at 4 °C. The activity of this preparation was determined by measuring the amount of NADP converted from NADPH per unit time at 37 °C and pH 7.0 (*5*). One unit (U) of activity is defined as the amount of the enzyme catalyzing the oxidation of 1 μmol of NADPH per minute under our experimental conditions.

**Table 1.** α-Glucosidase and Aldose Reductase Inhibitory Activity of *C. cyminum* Seed Oil and Antidiabetic Agents

| | α-glucosidase | | aldose reductase | |
|---|---|---|---|---|
| sample tested | final concn (mg/mL) | inhibition (%) | final concn (mg/mL) | inhibition (%) |
| *C. cyminum* seed oil | 1 | 85 | 1 | 100 |
| | 0.5 | 37 | 0.5 | 100 |
| acarbose | 1 | 100 | | |
| | 0.5 | 68 | | |
| quercitrin | | | 1 | 100 |
| | | | 0.5 | 100 |

**Enzyme Inhibitory Assay.** The aldose reductase activity was assayed according to the method described by Lee and Kim (*5*). The incubation mixture contained 135 mM Na, K-phosphate buffer (pH 7.0), 100 mM lithium sulfate, 0.03 mM NADPH, 0.04 mM DL-glyceraldehyde, and 50 μL of an enzyme preparation, with or without a sample, at a total volume of 1.0 mL. Each plant extract was dissolved in dimethyl sulfoxide, which was found to have no effect on the enzyme activity at less than 1%. Appropriate blanks contained all of the above-mentioned compounds, except dl-glyceraldehyde. The reaction (5−10 min) was initiated by adding NADPH at 37 °C and stopped by adding 0.5 N hydrochloric acid (0.3 mL). Subsequently, 6 N NaOH (1 mL) containing 10 mM imidazole was added, and the mixture was incubated at 60 °C for 10 min to convert NADP into a fluorescent product. The fluorescence was measured at room temperature with a spectrofluorophotometer (Aminco Bowman series 2, Spectronic Instruments, Rochester, NY) with an excitation wavelength of 360 nm and an emission wavelength of 460 nm. Standards of NADP (0.1−5 μM) were treated in the same manner. All determinations were performed in triplicates. The concentration of each test sample giving 50% inhibition of the enzyme activity ($IC_{50}$) was estimated from the least-squares regression line of the logarithmic concentration plotted against the remaining activity. The protein content of the enzyme preparation was 0.021 g/L, and the aldose reductase activity in the preparation was 7.38 U/L or 370.1 U/g of protein at 37 °C. The protein content of the enzyme preparation was determined using Coomassie Blue reagent (Bio-Rad) according to the manufacturer's instructions, with bovine serum albumin as a standard.

α-Glucosidase activity was assayed according to the method described by Lee and Kim (*5*) with slight modifications. α-Glucosidase (0.6 U) was dissolved in 100 mM phosphate buffer (pH 7.0) containing 2 g/L bovine serum albumin and 0.2 g/L $NaN_3$ and used as an enzyme solution. *p*-Nitrophenyl-α-D-glucopyranoside (5 mM) in the same buffer (pH 7.0) was used as a substrate solution. The enzyme solution (50 μL) and test extracts (10 μL) dissolved in dimethyl sulfoxide at a concentration of 5 mg/mL were mixed in a well of a microtiter plate and measured for titer (Abs 405 nm) at zero time using a microplate reader (model 550, Bio-Rad). After incubation for 5 min, the substrate solution (50 μL) was added and incubated for additional 5 min at room temperature. The increase in absorbance from zero time was measured. The inhibitory activity was expressed as 10 minus relative absorbance difference (%) of test compounds to absorbance change of the control where test solution was replaced by carrier solvent. All determinations were performed in triplicate.

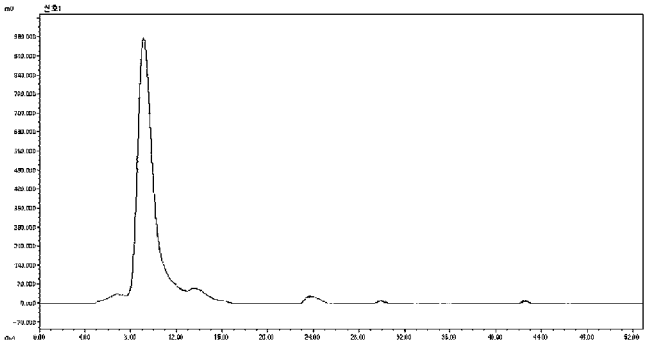

**Figure 1.** HPLC chromagram of cuminaldehyde. Conditions: wavelength, 260 nm; column, $\mu$Porasil (20 mm i.d. × 500 mm).

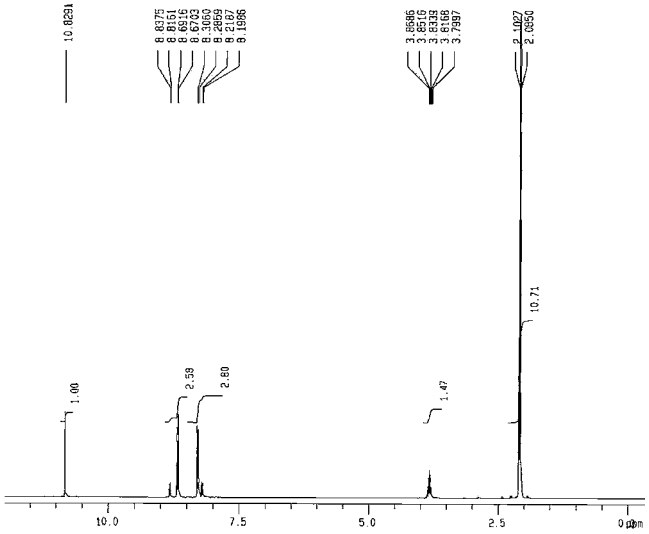

**Figure 2.** $^1$H NMR spectra of cuminaldehyde isolated from *C. cyminum* L. seeds.

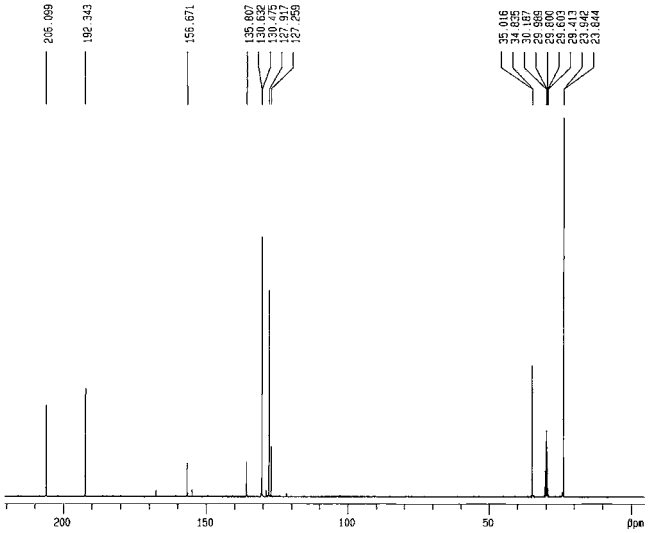

**Figure 3.** $^{13}$C NMR spectra of cuminaldehyde isolated from *C. cyminum* L. seeds.

## RESULTS AND DISCUSSION

The oil obtained from *C. cyminum* seeds was determined for the inhibitory activity against lens aldose reductase and α-glucosidase isolated from Sprague−Dawley male rats (**Table 1**). At 1 and 0.5 mg/mL, the oil showed 85 and 37% inhibition against α-glucosidase, and 100 and 100% against aldose reductase, respectively. The oil of *C. cyminum* seeds showed about 1.8 times less inhibitory activity than acarbose against α-glucosidase at 0.5 mg/mL, whereas the inhibitory activity of *C. cyminum* oil was similar to that of quercitrin against aldose reductase at 0.5 mg/mL. α-Glucosidase inhibitors including acarbose and miglitol are at present available for the treatment of patients with type II diabetes mellitus, and quercitrin and tolrestat as aldose reductase inhibitors are commonly used oral agents for good penetration of sorbitol (*12*). Because of the strong activity of the oil, purification of the biologically active compound was repeatedly done by HPLC, and the isolate was bioassayed (**Figure 1**). One active principle was isolated from the oil. Structural determination of the isolate was made by spectroscopic methods including EI-MS and NMR and by direct comparison with authentic reference compound, and it was characterized as cuminaldehyde. The $^{13}$C and $^1$H NMR spectra of cuminaldehyde (**Figures 2** and **3**) were found to be the same as those for cuminaldehyde isolated from cumin (*19*, *20*).

**Table 2.** α-Glucosidase and Aldose Reductase Inhibitory Activity of Cuminaldehyde Isolated from *C. cyminum* Seed Oil and Antidiabetic Agents

| compound | final concn (mg/mL) | α-glucosidase inhibition (%) | $IC_{50}$ (mg/mL) | final concn (mg/mL) | aldose reductase inhibition (%) | $IC_{50}$ (mg/mL) |
|---|---|---|---|---|---|---|
| cuminaldehyde | 1 | 100 | 0.50 | 0.1 | 100 | 0.00080 |
| | 0.8 | 74 | | 0.05 | 100 | |
| | 0.5 | 51 | | 0.01 | 100 | |
| | 0.3 | 29 | | 0.005 | 77 | |
| | 0.1 | 16 | | 0.001 | 64 | |
| | | | | 0.0005 | 40 | |
| | | | | 0.0001 | 23 | |
| quercitrin | | | | 0.1 | 100 | 0.00051 |
| | | | | 0.05 | 100 | |
| | | | | 0.01 | 89 | |
| | | | | 0.005 | 83 | |
| | | | | 0.001 | 68 | |
| | | | | 0.0005 | 49 | |
| | | | | 0.0001 | 32 | |
| acarbose | 1 | 100 | 0.28 | | | |
| | 0.8 | 76 | | | | |
| | 0.5 | 68 | | | | |
| | 0.3 | 53 | | | | |
| | 0.1 | 36 | | | | |
| | 0.05 | 18 | | | | |

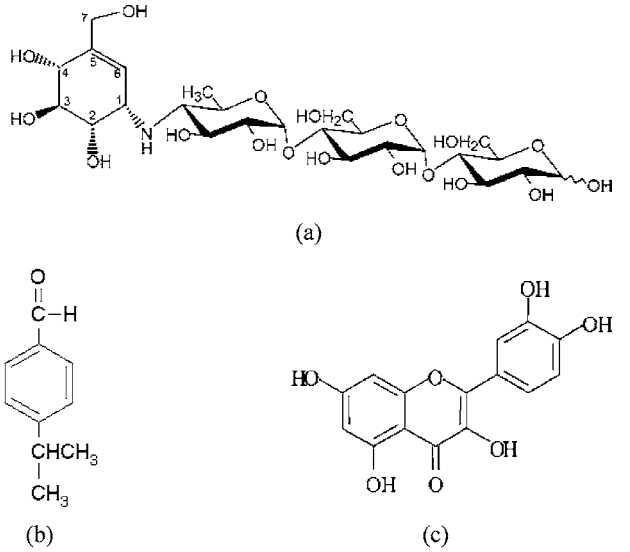

**Figure 4.** Structures of acarbose (**a**), cuminaldehyde (**b**), and quercetin (**c**).

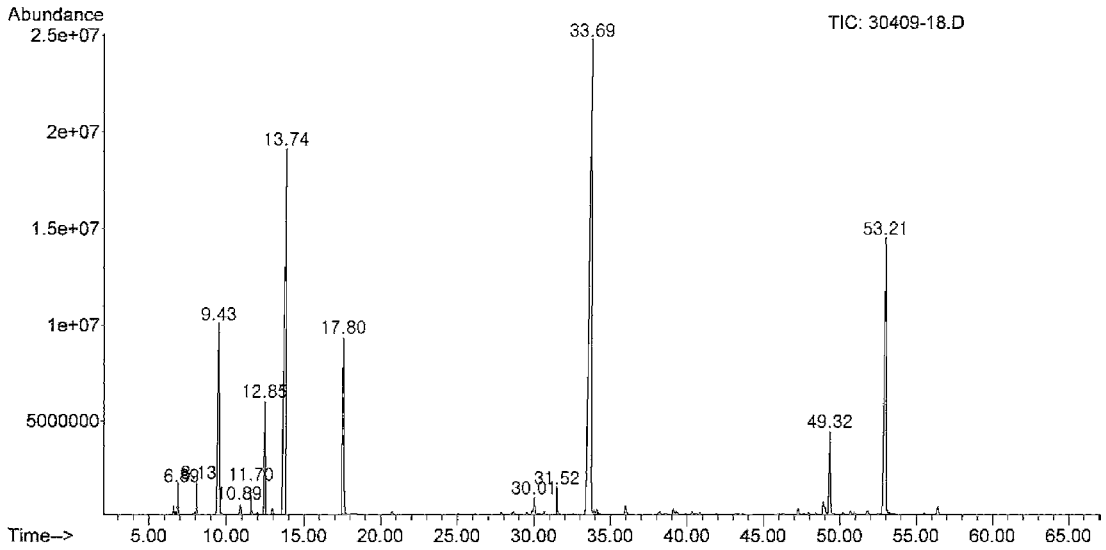


**Figure 5.** GC-MS of *C. cyminum* L. seed oil.

The inhibitory activity of cuminaldehyde against aldose reductase and α-glucosidase was compared to quercitrin as a potent aldose reductase inhibitor and acarbose as α-glucosidase inhibitor in vitro (**Table 2** and **Figure 4**). The inhibitory response of cuminaldehyde varied with the concentrations tested. At 0.1 and 0.05 mg/mL, cuminaldehyde produced significant inhibition (100%) against aldose reductase. On the basis of the effective inhibitory activity of cuminaldehyde, the effect was determined as the concentration of compound was decreased step by step. The $IC_{50}$ value of cuminaldehyde is 0.0008 mg/mL. Furthermore, the inhibitory effect of cuminaldehyde is approximately 1.6 times lower than that of quercitrin as an aldose reductase inhibitor. Against α-glucosidase, cuminaldehyde showed 100 and 74% at 1 and 0.8 mg/mL, respectively. The inhibitory effect of cuminaldehyde is approximately 1.8 times lower than that of acarbose as an α-glucosidase inhibitor. The substances of *C. cyminum* oil are identified by GC-MS (**Figure 5**). The main constituents were acoradiene (14.3%), 3-carene (5.3%), caryophyllene (4.6%), cuminaldehyde (24.3%), *p*-cymene (19.1%), *β*-myrcene (0.3%), α-phellandrene (1.1%), α-pinene (1.4%), *β*-pinene (7.9%), pulegone (0.5%), sabinene (1.5%), *γ*-terpinene (7.4%), and thymol (1.3%) presented by relative percentage. Except for cuminaldehyde, 11 commercially available components derived from *C. cyminum* oil exhibited weak or no inhibition against aldose reductase and α-glucosidase.

It has been well-acknowledged that plant-derived extracts and phytochemicals are potential alternatives to synthetic inhibitors against aldose reductase and α-glucosidase (*5*−*8*, *11*, *13*, *21*). Currently, the compounds isolated from plants as aldose reductase inhibitors and α-glucosidase inhibitors are classified in diterpene-, triterpene-, and flavonoid-related compounds. These include kotalanol 16-acetate isolated from *Salaia oblonga* (*7*), myrciacitrin I and myrciaphenone from *Myrcia multiflora* DC. (*8*), and dihydroflavonol rhamnosides and quercitrin 3-rhamnoside from *Engelhardtia chrysolepis* (*21*). In this study, the active component isolated from *C. cyminum* seeds against aldose reductase and α-glucosidase was identified as cuminaldehyde, although the inhibitory responses varied with concentrations tested. It has been reported that *C. cyminum* seed-derived materials have antimicrobial activity, a food spice, a fungicide, and a tyrosinase inhibitor (*17*−*20*). It might be expected then that the active component isolated from *C. cyminum* seeds has a range of pharmacological actions for antidiabetic therapeutics.

α-Glucosidase inhibitors are currently the most commonly used oral agents for improving postprandial hyperglycemia due to the lack of a hypoglycemic threat, and, more importantly, the prospect of blood glucose control without hyperinsulinemia and body weight gain (*3*). Inhibition of α-glucosidase and amylase should result in delayed carbohydrate digestion and glucose absorption with attenuation of postprandial hyperglycemic excursions. It has been reported that α-glucosidase inhibitors usually do not alter the total amount of carbohydrate absorbed and, therefore, do not cause any net nutritional caloric loss although they slow carbohydrate digestion. Quercitrin and tolrestat are oral agents for good penetration of sorbitol through cellular membranes, fast metabolism of sorbitol by sorbitol dehydrogenase, and, more importantly, the therapeutic prospect of patient treatment associated with such diabetic complications as retinopathy, cataracts, neuropathy, and nephropathy (*12*). In this regard, cuminaldehyde may be used as a lead compound for the development of antidiabetic therapeutics, although the inhibitory activity of cuminaldehyde was lower than that of acarbose and quercitrin.

In conclusion, these results indicate that *C. cyminum* seed-derived materials have an inhibitory effect in vitro against rat lens aldose reductase and α-glucosidase. Upon the basis of my limited data and some earlier findings, the inhibitory action of *C. cyminum* seed-derived cuminaldehyde confirms their potential utility as an antidiabetic therapeutic.

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