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New Antiglycative Compounds from Cumin (*Cuminum cyminum*) Spice

ABSTRACT: Cumin (*Cuminum cyminum* L.), a widely consumed food spice, has been reported to have antiglycative effects in vitro and in vivo, but there is a paucity of data on its bioactive compounds. Herein, we report the isolation and structure elucidation (by NMR, HRESIMS, and CD) of 21 (**1**−**21**) compounds from a methanol extract of cumin seeds. The isolates included five new compounds: two sesquiterpenoids, two pairs of monoterpeneoid epimers, and a chalcone, named cuminoids A−E, respectively. The isolates were evaluated for antiglycative effects using the bovine serum albumin−fructose intrinsic fluorescence assay. At equivalent concentrations, several of the isolates, including cuminoids C−E, were more potent inhibitors than the positive control, aminoguanidine, a synthetic antiglycative agent (>50 vs 35%, respectively).

KEYWORDS: *Cuminum cyminum, cumin, cuminoids, advanced glycation endproducts, antiglycative, bioactive*

INTRODUCTION

Advanced glycation endproducts (AGEs), formed from the nonenzymatic glycation of proteins, are linked with several health complications including type 2 diabetes and aging. Therefore, the search for compounds that can potentially mitigate the effects of AGE-related pathologies is necessary. Several synthetic compounds, such as aminoguanidine (AG) and tenilsetam, have been developed as antiglycative agents.[1] However, many of these synthetic agents, including AG, have failed in human clinical trials because of associated side effects leading to the search for natural antiglycative agents from plant foods and their derived products.[2,3]

Cumin (*Cuminum cyminum* L.) seeds are a widely consumed aromatic food spice with reported antiglycative and antidiabetic effects based on data accumulated from published in vitro and in vivo studies.[4−8] Studies in a streptozotocin-induced diabetic rat model suggest that cumin's flavor constituents, cuminaldehyde and cuminol, present in a nonpolar (petroleum ether) extract of its seeds, may play a potential role in these biological effects.[7] Interestingly, a polar (methanol) extract of cumin seeds has also been reported to have antiglycative effects in the same animal model, but no compounds were isolated or identified in that study.[8] Therefore, we conducted a phytochemical investigation of a methanol extract of cumin seeds, which led to the isolation and structure elucidation (by NMR, HRESIMS, and CD) of 21 compounds (**1**−**21**) (Figure 1). The isolates included five new compounds: two sesquiterpenoids (**1** and **2**), two pairs of inseparable monoterpenoid epimers (**3**/**3a** and **4**/**4a**), and a chalcone derivative (**5**), named cuminoids A−E, respectively. All of the isolates were evaluated for their in vitro antiglycative effects compared to the positive control, AG.

MATERIALS AND METHODS

Chemicals. Deuterated methanol (CD_3OD) was purchased from Cambridge Isotope Laboratories (Boston, MA, USA). Sephadex LH-20 resin, trifluoroacetic acid (TFA), bovine serum albumin (BSA), D-fructose, and aminoguanidine hydrochloride (AG) were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA).

General Experimental Procedures. All nuclear magnetic resonance (NMR) experiments were acquired either on a Bruker 300 MHz or on a Varian 500 MHz instrument. High-resolution electrospray ionization mass spectral (HRESIMS) data were acquired on a Synapt G2-S QTOF mass spectrometer (Waters, Milford, MA, USA). Optical rotations were recorded on a JASCO P-2000 automatic digital polarimeter. CD spectra were recorded on a JASCO J-810 spectropolarimeter. Analytical and reverse phase semipreparative high-performance liquid chromatography (RP-HPLC) were performed on a Hitachi Elite LaChrom system consisting of an L2130 pump, an L-2200 autosampler, and an L-2455 diode array detector, all operated by EZChrom Elite software. Medium-pressure liquid chromatography (MPLC) was carried out on a prepacked C18 column connected to a DLC-10/11 isocratic liquid chromatography pump (D-Star Instruments, Manassas, VA, USA).

Extraction. *C. cyminum* (cumin) seeds (1 kg) were provided by Verdure Sciences (Noblesville, IN, USA). The seeds were authenticated by matching to internal monograph standards from Verdure, and a voucher specimen (VS-NSSP-001) has been deposited in the Heber-Youngken Herbarium and Greenhouse, College of Pharmacy, University of Rhode Island (Kingston, RI, USA). Air-dried ground cumin seed powder (950 g) was extracted with MeOH (4 L), and the dried methanol extract (105 g) was suspended in water and then successively partitioned with *n*-hexanes, EtOAc, and *n*-BuOH to yield their respective extracts.

Isolation of Compounds 1−5. Five new compounds (**1**−**5**) were isolated and identified from cumin seeds as follows. The dried EtOAc extract (11.2 g) was subjected to a silica gel column, eluted with chloroform/methanol (25:1, 15:1, 10:1, 5:1, 2:1, and 0:1, v/v), to yield nine fractions: A1−A9. Fraction A2 (1.1 g) was chromatographed on a Sephadex LH-20 column with MeOH/H_2O (8:2, v/v) and then further purified by reverse phase HPLC (RPHPLC) with MeOH/0.1% TFA in water (60:40, v/v) to yield compounds **1** (9.9 mg) and **2** (5.1 mg). Similarly, fraction A7 (1.2 g) was chromatographed on a Sephadex LH-20 column and then further purified by RP-HPLC with MeOH/0.1% TFA in water (40:60, v/v) to afford compound **5** (4.8 mg). The *n*-BuOH extract (18 g) was subjected to C18 MPLC eluted with MeOH/H_2O (10:90 to 100:0, v/v) to afford eight fractions, B1−B8. Fraction B2 (1.4 g) was chromatographed on a Sephadex LH-20 column and further purified by RP-HPLC with MeOH/0.1% TFA in water (29:71, v/v) to afford compounds **3** (118 mg) and **4** (10.9 mg). Acid hydrolysis of compounds **3**−**5** and sugar analysis by co-TLC was performed on the basis of method we previously reported (Supporting Information).[16]

Isolation and Identification of Compounds 6−21. Sixteen known compounds (**6**−**21**) were also isolated and identified from cumin seeds (Supporting Information).

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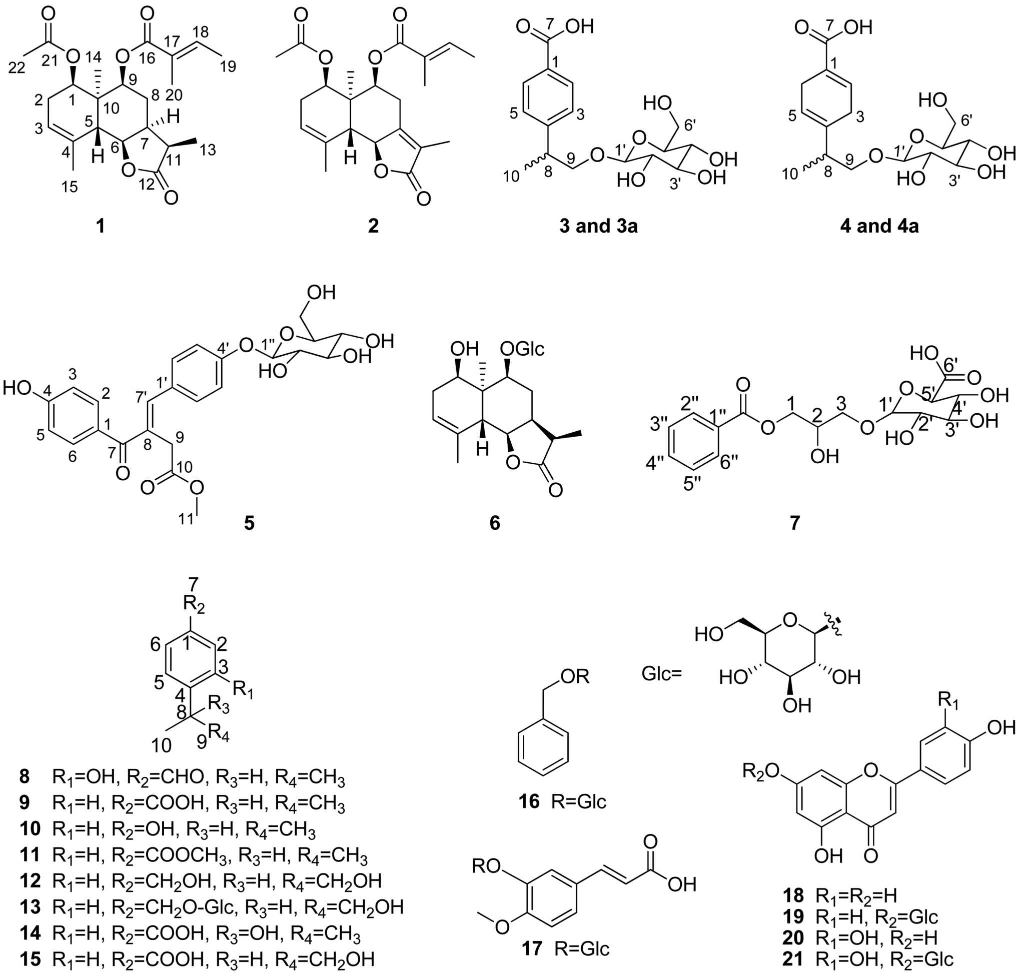


Figure 1. Structure of compounds **1**−**21**, including new compounds (**1**−**5**) cuminoids A−E, respectively, isolated and identified from *Cuminum cyminum* seeds.

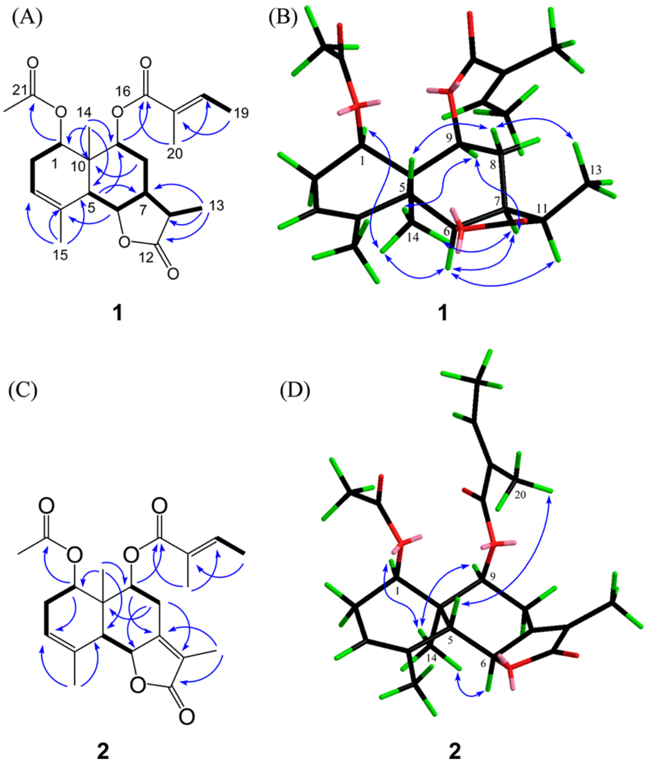
Antiglycative BSA−Fructose Intrinsic Fluorescence Assay. The inhibitory effects of the isolates on the formation of AGEs were evaluated as reported.[3,9] Briefly, 100 μM of each compound was added to reaction mixtures containing 10 mg/mL BSA and 100 mM D-fructose. Intrinsic fluorescence of AGEs was obtained with a Spectra Max M2 spectrometer (Molecular Devices, Sunnyvale, CA, USA) with excitation and emission wavelengths set at 340 and 430 nm, respectively. On the basis of the intrinsic fluorescent intensities, the percent inhibition of AGE formation was calculated using the following equation: % inhibition = [1 − (fluorescence intensity of solution with inhibitor/fluorescence intensity of control solution)] × 100%. The synthetic anti-AGE agent, AG, served as the positive control.

■ RESULTS AND DISCUSSION

The isolates (Figure 1) included 5 new compounds (**1**−**5**), assigned the common names of cuminoids A−E, respectively, and 16 known compounds (**6**−**21**; Supporting Information) The structure elucidation of the new compounds is provided herein.

Compound **1**, a colorless amorphous powder, had a molecular formula of $C_{22}H_{30}O_6$ as determined by HRESIMS at *m*/*z* 413.1933 $[M + Na]^+$ (calcd for $C_{22}H_{30}O_6Na$), with 8 degrees of unsaturation. The ^1H NMR data (Supporting Information, Table S1) of **1** showed the signals of six methyl protons [δ_H 1.05 (3H, s, H_3-14), 1.10 (3H, d, J = 7.3 Hz, H_3-13), 1.77 (3H, s, H_3-20), 1.80 (3H, s, H_3-15), 1.85 (3H, d, J = 7.2 Hz, H_3-19), 1.88 (3H, s, H_3-22)], three oxygenated methine protons [δ_H 4.95 (1H, dd, J = 11.3 Hz, J = 6.3 Hz, H-9), 4.70 (1H, brs, H-1), 4.63 (1H, dd, J = 9.3 Hz, J = 6.3 Hz, H-6)], and two olefinic protons [δ_H 5.29 (1H, brs, H-3), 6.00 (1H, m, H-18)]. The ^{13}C NMR (Supporting Information, Table S1) and HSQC spectra of **1** displayed 22 carbon resonances assignable to 6 methyls (δ_C 10.3, 16.0, 20.8, 21.5, 21.9, and 22.3), 2 methylenes, 8 methines (including 2 olefinic and 2 oxygenated), and 6 quaternary carbons (including 3 ester carbonyls). On the basis of the NMR data, acetoxy (C-21 and C-22) and tigloyloxy (C-16 to C-20) groups were identified, respectively. Apart from these 2 moieties, the remaining 15 carbons suggested that compound **1** was most likely a sesquiterpene.

Further combined analysis of the COSY, HSQC, and HMBC spectra established the structure of compound **1**. The HSQC spectrum allowed for the assignment of all the protons attached to their corresponding carbons. Three spin systems labeled as bold in Figure 2A were determined by the $^1H-^1H$ COSY data. The HMBC correlations from H_3-13 to C-7 (36.9), C-11 (38.5), and C-12 (181.1), from H_3-14 to C-1 (73.0), C-5 (42.3), C-9 (77.9), and C-10 (40.2), and from H_3-15 to C-3 (120.2), C-4 (134.9), and C-5 (42.3) revealed that compound **1** possessed an eudesmanolide lactone skeleton with a double bond located at C-3 and C-4.[10] The aforementioned acetoxy and tigloyloxy moieties were located at C-1 and C-9,



1 1

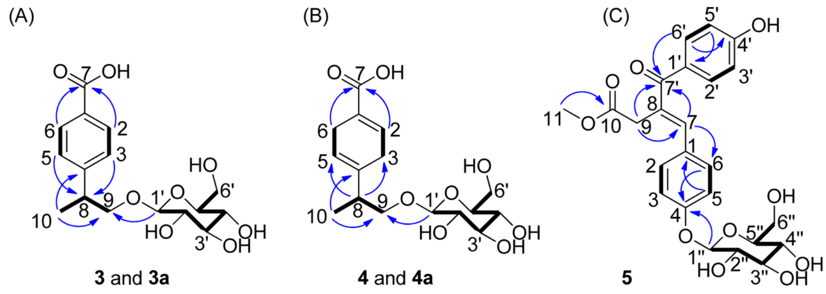
2 2

Figure 2. (A) ^{1}H−^{1}H COSY (——) and selected HMBC correlations (H → C) of cuminoid A (**1**). (B) Key NOESY correlations (H↔H) of cuminoid A (**1**). (C) ^{1}H−^{1}H COSY (——) and selected HMBC correlations (H → C) of cuminoid B (**2**). (D) Key NOESY correlations (H↔H) of cuminoid B (**2**).

respectively, on the basis of the HMBC correlations from H-1 to C-21 (172.0) and from H-9 to C-16 (169.7), respectively. The planar structure of compound **1** was thus identified as depicted (Figure 2A). The relative configuration of compound **1** was established by NOESY data (Figure 2B), in which the correlations from H_3-14 to H-1, H-6, H-7, and H-9, from H-6 to H-7 and H-11, and from H-7 to H-9 indicated that they were cofacial and, thus, they were arbitrarily assigned as an *α*-configuration. Similarly, the NOESY correlations of H-5/H-8*β* and H-8*β*/H_3-13 revealed that they were in a *β*-orientation. The absolute configuration of compound **1** was assigned by considering the empirical Klyne's lactone sector rule.[11,12] On the basis of CD analyses (Supporting Information), the positive Cotton effect at 242 nm revealed that position 11 was in the *R* configuration. Therefore, on the basis of the relative configurations deduced from the NOESY correlations, the other chiral centers of compound **1** were assigned as 1*R*, 5*S*, 6*R*, 7*S*, 9*S*, and 10*R*. The structure of compound **1** was established as depicted (Figure 1) and assigned the common name cuminoid A.

Compound **2** was isolated as a white amorphous powder with a molecular formula of $C_{22}H_{28}O_6$ as established by HRESIMS at *m*/*z* 389.1966 $[M + H]^+$ (calcd for $C_{22}H_{29}O_6$). The ^{1}H and ^{13}C NMR data (Supporting Information, Table S1) of compound **2** showed marked similarities to compound **1**. The primary differences were that compound **2** contained an additional double bond (δ_C 124.5, 161.5) and a methyl (Me-13) group, which was shifted farther downfield compared to that in compound **1**. The key HMBC (Figure 2C) correlations from H_3-13 (δ_H 1.72) to C-7 (δ_C 161.5), C-11 (124.5), and C-12 (δ_C 176.1) situated the double bond between C-7 and C-11. Similar to compound **1**, the relative stereochemistry of **2** was determined by the NOESY data (Figure 2D) based on correlations from H_3-14 to H-1, H-6, and H-9 and the correlation from H-5 to H_3-20. The 6*S* absolute configuration was assigned on the basis of a positive Cotton effect at 218 nm (CD data shown in the Supporting Information), which was within the 205−235 nm region of *α*,*β*-unsaturated *γ*-lactones and has previously been employed to determine the absolute configuration of *γ*-carbon atoms.[13−15] Thus, the structure of compound **2** was established with an absolute configuration of 1*R*, 5*S*, 6*S*, 9*S*, 10*R* as depicted (Figure 1) and assigned the trivial name cuminoid B.

Compounds **3** and **3a** were obtained as an inseparable pair of epimers in a 1:1 ratio based on the NMR data. Exhaustive efforts to separate the mixture using different chromatographic resins were unsuccessful. Thus, structure elucidation was performed on the epimeric mixture. A molecular formula of $C_{16}H_{22}O_8$ was assigned from the quasi-molecular positive ion at *m*/*z* 365.1213 $[M + Na]^+$ (calcd for $C_{16}H_{22}O_8$Na). The NMR spectra (Supporting Information, Table S2) showed duplication of several signals supporting the presence of epimers. A para-substituted benzene ring [δ_H 7.96 (2H, d, *J* = 8.1 Hz), 7.40 (2H, d, *J* = 8.1 Hz)] and a sugar moiety (δ_C 103.31/103.01, 73.67, 76.71/76.69, 70.23/70.21, 76.56/76.53, 61.38/61.34) were readily identified from the ^{1}H and ^{13}C NMR data. The anomeric proton signal at δ_H 4.31/4.27 (d, *J* = 7.9/7.7 Hz) indicated a *β*-orientation of the glucopyranose moiety. Two isolated proton spin systems corresponding to the C-10/C-8/C-9 and a hexose moiety, C-1′−C-6′, were established on the basis of ^{1}H−^{1}H COSY spectra and confirmed by HMBC correlations (Figure 3A). The HMBC correlations from H-2 and H-6 to C-7 (168.52), from H-3 and H-5 to C-8 (40.00/39.89), and from H-1′ to C-9 (74.45/74.26) indicated that carboxyl and C-10/C-8/C-9 subunits were attached to C-1 and C-4 of a benzene ring, respectively, and that the glucopyranose



3 and **3a** **4** and **4a** **5**

Figure 3. (A) ^{1}H−^{1}H COSY (——) and selected HMBC correlations (H → C) of cuminoid C (**3**/**3a**). (B) ^{1}H−^{1}H COSY (——) and selected HMBC correlations (H → C) of cumioid D (**4**/**4a**). (C) ^{1}H−^{1}H COSY (——) and selected HMBC correlations (H → C) of cuminoid E (**5**).

moiety was linked to C-9. Thus, the planar structures of the mixture of epimers of **3**/**3a** were determined as depicted (Figure 3A). The epimeric mixture of **3**/**3a** was subjected to acid hydrolysis, and the released glucose was identified as being in the D-configuration by co-TLC and comparison of its optical rotation to an authentic sample of D-glucose as previously reported.[16] Therefore, this indicated that compounds **3**/**3a** differed only in configuration at C-8, and they were assigned the common name cuminoid C (**3**/**3a**).

Similar to compounds **3**/**3a**, a second pair of inseparable epimers, namely, compounds **4** and **4a**, were isolated. The HRESIMS gave a $[M + Na]^+$ ion at m/z 367.1375 (calcd for $C_{16}H_{24}O_8Na$, 367.1369) corresponding to the molecular formula $C_{16}H_{24}O_8$. The ^1H and ^{13}C NMR data (Supporting Information, Table S2) of compounds **4**/**4a** revealed the presence of a carboxyl group (δ_C 169.01), a C-10/C-8/C-9 subunit, and a *β*-glucopyranose moiety, in which the anomeric proton resonated at δ_H 4.27/4.26 (d, J = 7.6/7.7 Hz). The $^1H-^1H$ COSY data (Figure 3B) revealed the attachment of C-2 (136.91/136.86)/C-3 (27.76/27.56), and C-5 (118.44/118.42)/C-6 (25.54), and the HMBC correlations (Figure 3B) from H-2 to C-4 and C-6, from H-5 to C-3 and C-1, from H-3 to C-5 and C-1, and from H-6 to C-2 and C-4 allowed for the construction of the ring system of C-1−C-6. Similarly, the carboxyl group, C-10/C-8/C-9 subunit, and the glucopyranose moiety were assigned to C-1, C-4, and C-9, respectively, by the HMBC correlations from H-2 and H-6 to C-1, from H-3 and H-5 to C-8, and from H-1′ to C-9. Similar to compounds **3** and **3a**, acid hydrolysis of compounds **4** and **4a** yielded glucose in the D-configuration, suggesting that compounds **4** and **4a** are also C-8 epimers. Therefore, the structure of compounds **4** and **4a** was elucidated as depicted (Figure 1) and given the common name cuminoid D.

Compound **5** was isolated as a white amorphous powder with a molecular formula of $C_{24}H_{26}O_{10}$ as established by the HRESIMS at m/z 475.1614 $[M + H]^+$ (calcd for $C_{24}H_{27}O_{10}$, 475.1604). The ^1H and ^{13}C NMR data of compound **5** revealed the presence of two para-substituted aromatic rings [δ_C 164.1, 159.6, 131.9 (2 × C), 131.6 (2 × C), 130.4, 129.6, 117.7 (2 × C), and 116.3 (2 × C); δ_H 7.89 (2H, d, J = 8.9 Hz), 7.20 (2H, d, J = 8.7 Hz), 7.03 (2H, d, J = 8.7 Hz), 6.79 (2H, d, J = 8.9 Hz)] and a trisubstituted double bond (δ_C 127.0, 142.7; δ_H 7.86 (1H, s). Six oxygenated carbon signals at δ_C 101.9, 78.1, 77.9, 74.8, 71.3, and 62.4 observed in the ^{13}C NMR spectrum indicated the presence of a sugar moiety, and several proton signals at δ_H 3.29−3.81 and an anomeric proton that resonated at δ_H 4.85 (d, J = 7.5 Hz, H-1′) supported the presence of a *β*-glucopyranose moiety. Two carbonyl carbons signals at δ_C 198.2 and 169.8, a methoxyl at δ_C 52.6, and a methylene at δ_C 38.7 were also observed in the ^{13}C NMR spectrum. Further combined analysis of the $^1H-^1H$ COSY, HSQC, and HMBC spectra allowed for the establishment of the structure of compound **5**. From the $^1H-^1H$ COSY spectrum, a hexose moiety (C-1−C-6) (Figure 3C) could be proposed. A broad singlet at δ_H 7.86 (H-7) showed HMBC correlations (Figure 3C) to C-2,6 (δ_C 131.6), C-7′ (δ_C 198.2), and C-9 (δ_C 38.7), as well as to an olefinic carbon at δ_C 127.0 (C-8), which suggested an *α*,*β*-unsaturated ketone moiety was connected to C-1. The HMBC correlations from H-2′,6′ (δ_H 7.89) to C-7′ indicated C-7′ was linked at C-1′. The HMBC correlations from H-9 (δ_H 4.16) to C-7 (δ_C 142.7), C-8, C-7′, and C-10 (δ_C 169.8) and from H-11 (δ_H 3.70) to C-10 suggested that a methoxycarbonylmethyl group was connected to C-8. The HMBC correlations from H-1″ to C-4 (δ_C 159.6) indicated the *β*-glucopyranose moiety was linked at C-4. The NOESY correlation (Supporting Information) from H-2 (δ_H 7.20) to H-9 (δ_H 4.16) established the *E*-type $\Delta^{7,8}$ double bond.[17] Therefore, compound **5** was elucidated as a chalcone derivative and was named cuminoid E (**5**). It is possible that compound **5** is naturally found as a free carboxylic acid but was isolated as the methyl ester given that methanol solvent was used during the extraction and isolation scheme.

Sixteen known compounds (**6**−**21**) were identified as (1*R*,5*R*,6*S*,7*S*,9*S*,10*S*,11*R*)-1,9-dihydroxyeudesm-3-ene-12,6-olide 9-*O*-*β*-D-glucopyranoside (**6**),[18] glycerol 1-*O*-*α*-D-glucuronide 3-*O*-benzoyl ester (**7**),[19] 3-hydroxy-1-(4-methylethyl)-benzaldehyde (**8**), 1-(4-methylethyl)-benzoic acid (**9**),[20] 1-(4-methylethyl)-phenol (**10**),[21] 1-(4-methylethyl)-benzoic acid methyl ester (**11**),[22] 1-hydroxymethyl-*β*-methyl-benzeneethanol (**12**),[23] (8*R*)-9-hydroxycuminyl *β*-D-glucopyranoside (**13**),[24] 1-(8-hydroxy-4-methylethyl)-benzoic acid (**14**),[25] 1-(9-hydroxy-4-methylethyl)-benzoic acid (**15**),[25] benzyl *β*-D-glucopyranoside (**16**),[26] (*E*)-isoferulic acid-3-*O*-*β*-D-glucopyranoside (**17**),[27] apigenin (**18**),[28] apigenin 7-*O*-*β*-D-glucoside (**19**),[29] luteolin (**20**),[30] and luteolin 7-*O*-*β*-D-glucoside (**21**)[31] on the basis of their NMR and mass spectral data and by comparison to literature data (Supporting Information). Notably the NMR data for compound **8** are being reported herein for the first time (Supporting Information).

The new compounds, cuminoids C−E (**3**, **4**, **5**), and known phenolic derivatives **14**, **15**, **18**, **20**, and **21** reduced the formation of advanced glycation endproducts >50%. At an equivalent test concentration, the positive control, AG, showed 34.1% antiglycative effects as previously reported.[3] Among all of the isolates, the most potent antiglycative effects were observed with the flavonoids **20** (79.0%), **21** (71.0%), and **18** (66.2%), which was in agreement with published studies.[32,33] These were followed by the new monoterpenoid **4** and the new chalcone **5** (66.0 and 64.5%, respectively). Notably, the new sesquiterpenoids, compounds **1** and **2**, as well as the phenolic derivatives, compounds **7**, **8**, and **10**, showed similar antiglycative activity compared to AG. Compounds **6**, **9**, **13**, and **17** also reduced the formation of advanced glycation endproducts but were less potent than AG. No inhibitory effects were observed for compounds **11**, **12**, **16**, and **19** (Figure 4).

In summary, an anti-AGE bioassay-guided strategy yielded 5 new compounds along with 16 known compounds from a

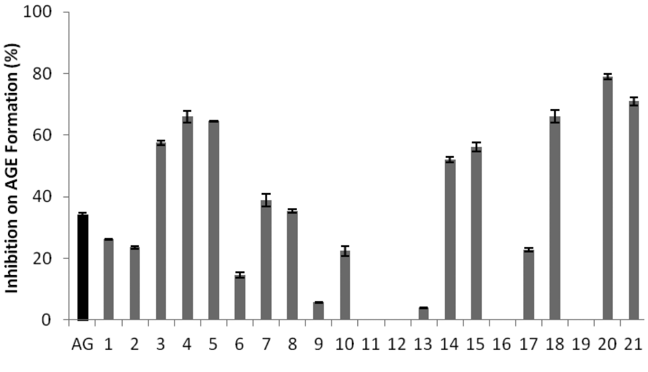


Figure 4. Inhibitory effects of compounds **1**−**21** on the formation of advanced glycation end products (AGE) in the BSA−fructose assay. All data points represent the average value ± SD for triplicate measurements. Aminoguanidine (AG) served as positive control. The compounds and AG were evaluated at equivalent test concentrations.

methanol extract of cumin seeds. The compounds showed various levels of antiglycative effects and, thus, could contribute toward the antiglycative effects previously reported for a methanol extract of cumin seeds in vivo.[8] Although it was difficult to make structure–activity-related (SAR) conclusions based on the diverse structural features and stereochemistry of the isolates, the "flavonoid-type compounds" showed the most potent antiglycative effects. It is possible that the combined effects of all of the compounds reported herein, with others previously reported from cumin, including cuminaldehyde and cuminol,[7] in toto would impart biological effects to the whole food greater than any single compound alone. However, further studies would be required to confirm this. Nevertheless, the current study adds to the growing body of data supporting the biological effects of this popularly consumed food spice.

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ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jafc.5b04796.

> Original NMR, CD, and mass spectra of compounds **1**–**5** (Figures S1–S34); ^{1}H and ^{13}C NMR data of compounds **1**–**5** (Tables S1–S3); general experimental procedures; extraction and isolation of compounds **1**–**21**; physiochemical properties of **1**–**5**; NMR data of compound **8**; acid hydrolysis of compounds **3**–**5** and sugar analysis (PDF)

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Notes

The authors declare no competing financial interest.

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