Lee *et al. Applied Biological Chemistry* 2022, **65**(1):22
https://doi.org/10.1186/s13765-022-00688-9

KSABC
The Korean Society for Applied Biological Chemistry

ARTICLE Open Access

Insulin secretion and α-glucosidase inhibitory effects of dicaffeoylquinic acid derivatives

Dahae Lee[1], Hak-Dong Lee[2], Hyukjin Kwon[3], Hye Lim Lee[4], Gwi Seo Hwang[1], Sungyeol Choi[1], Hyun Young Kim[5], Sanghyun Lee[2*] and Ki Sung Kang[1*]

Abstract

In this study, we investigated the effects of dicaffeoylquinic acid derivatives, including 1,4-di-O-caffeoylquinic acid (1,4-DCQA), 3,4-di-O-caffeoylquinic acid (3,4-DCQA), 3,5-di-O-caffeoylquinic acid (3,5-DCQA), 4,5-di-O-caffeoylquinic acid (4,5-DCQA), and 1,5-di-O-caffeoylquinic acid (1,5-DCQA) on glucose-stimulated insulin secretion (GSIS) activity and α-glucosidase activity were compared in rat INS-1 pancreatic β-cells. The α-glucosidase inhibitory activities of dicaffeoylquinic acid derivatives were as follows: 1,4-DCQA > 1,5-DCQA > 3,4-DCQA > 4,5-DCQA > 3,5-DCQA. In INS-1 cells, dicaffeoylquinic acid derivatives showed no cytotoxic effect at any concentration (2.5–10 μM). In addition, the GSIS activities of dicaffeoylquinic acid derivatives were as follows: 4,5-DCQA > 3,4-DCQA > 1,4-DCQA > 3,5-DCQA > 1,5-DCQA. Treatment of INS-1 cells with 4,5-DCQA resulted in a marked increase in protein expression of extracellular signal-regulated protein kinases (ERK), insulin receptor substrate-2 (P-IRS-2), Akt, phosphoinositide 3-kinase (P-PI3K), and pancreatic and duodenal homeobox-1 (PDX-1), which might be related to its GSIS activity in INS-1 cells. These findings indicate that the location of the dicaffeoyl functional group influences the anti-diabetic activity of quinic acid.

Keywords: Dicaffeoylquinic acid derivatives, Glucose-stimulated insulin secretion, PDX-1

Introduction

Diabetes mellitus (DM) is metabolic endocrine disorder in the world associated with abnormal compromised lipid and carbohydrate metabolism. One approach for the treatment of type 2 DM is using α-glucosidase inhibitors as an oral anti-hyperglycemic drug [1]. α-Glucosidase inhibitors has its own mechanism of action that diminish the levels of postprandial blood glucose. It can help in retarding the absorption of carbohydrates by decreasing α-glucosidase activity in the epithelium of small intestine [2]. Acarbose, miglitol, and voglibose are clinically approved as α-glucosidase inhibitors [3]. These three α-glucosidase inhibitors are sugars or its derivatives, which can induce gastrointestinal side effects [3]. A range of chemical compounds isolated from natural products have been reported to be effective in inhibiting the α-glucosidase activity. Most of the chemical compounds reported as α-glucosidase inhibitors in previous studies are secondary metabolites including flavonoids, alkaloids, anthocyanins, terpenoids, and phenolic acids [4].

Caffeoylquinic acid derivatives have been claimed to have various biological effects including neuroprotective activity [5, 6], anti-oxidant effect [7, 8], anti-inflammatory activity [9, 10], anti-viral effect [11, 12], anti-cancer activity [13], and anti-hepatotoxic activity [14]. Furthermore, their inhibitory effects on α-glucosidase activity have been scientifically evaluated in the previous many reports [15–17]. However, little is known concerning their effect on glucose-stimulated insulin secretion (GSIS). Another

*Correspondence: slee@cau.ac.kr; kkang@gachon.ac.kr
[1] College of Korean Medicine, Gachon University, Seongnam 13120, Republic of Korea
[2] Department of Plant Science and Technology, Chung-Ang University, Anseong 17546, Republic of Korea
Full list of author information is available at the end of the article
The original article was revised: Affiliation 5 has been updated

Springer Open

© The Author(s) 2022, corrected publication 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

approach for the treatment of type 2 DM is an increase in GSIS. GSIS had been considered the exclusive mechanism of insulin regulation [18]. Defective insulin secretion is a characteristic of pancreatic β cell dysfunction, which develops early and gets worse further in T2D [19]. Sulfonylureas known as oral insulinotropic agents to treat T2DM promote insulin secretion by closing K^+ATP channels at the plasma membrane, while medicines in this group are known to often lead to hypoglycemia. This is because it continuously stimulates insulin secretion, regardless of plasma glucose levels [20]. Thus, identification of potential compounds that stimulate GSIS is highly desirable. Therefore, in this study, the inhibitory effects of dicaffeoylquinic acid derivatives (Fig. 1) on α-glucosidase inhibitory were compared, and it was also confirmed whether the dicaffeoylquinic acid derivatives enhance insulin secretion in pancreatic β cells using only stimulatory glucose. In addition, the corresponding mechanisms were investigated.

Materials and methods

Plant materials and chemiclas

The dried aerial parts of *Saussurea grandifolia* were extracted with methanol under reflux. 1,4-Di-O-caffeoylquinic acid (1,4-DCQA) and 1,5-di-*O*-caffeoylquinic acid (1,5-DCQA) was isolated from *S. grandifolia*. Dicaffeoylquinic acid derivatives such as 3,4-di-O-caffeoylquinic acid (3,4-DCQA), 4,5-di-O-caffeoylquinic acid (4,5-DCQA), and 3,5-di-O-caffeoylquinic acid (3,5-DCQA) were isolated from *Acanthopanax henryi* and obtained Natural Product Institute of Science and Technology (www.nist.re.kr, Anseong, Korea).

NMR data of dicaffeoylquinic acid derivatives

1,4-DCQA (purity: 99.7%): ^{1}H-NMR (DMSO-*d6*, 500 MHz) δ: 7.51 (2H, d, *J* = 15.5 Hz, H-7′, 7″), 7.02 (2H, br s, H-2′, 2″), 6.98 (2H, d, H-6′, 6″), 6.76 (2H, dd, H-5′, H-5″), 6.24 (2H, d, *J* = 15.5 Hz, H-8′, 8″), 5.05 (1H, br s, H-3), 4.75 (1H, br s, H-4), 4.16 (1H, br s, H-5), 2.20 (3H, m, H-6a, 6b, 2a), 1.80 (1H, br s, H-2b).

1,5-DCQA (purity: 99.7%): ^{1}H-NMR (DMSO-*d6*, 500 MHz) δ: 7.40 (2H, t, *J* = 16.5 Hz, H-7′,7″), 7.00 (2H, br s, H-2′, 2″), 6.88 (2H, dd, *J* = 8.0 Hz, H-6′, 6″), 6.66 (2H, d, *J* = 8.5 Hz, H-5′, H-5″), 6.21 (1H, d, *J* = 16.0 Hz, H-8″), 6.06 (1H, d, *J* = 16.0 Hz, H-8′), 5.28 (1H, dd, *J* = 7.5 Hz, H-5), 3.99 (1H, br s, H-3), 3.49 (1H, br s, H-4), 1.71–2.51 (4H, m, H_2-2, H_2-6).

3,4-DCQA (purity: 98.4%): ^{1}H-NMR (DMSO-*d6*, 500 MHz) δ: 7.45 (2H, m, H-7′, 7″), 7.03 (2H, dd, *J* = 10.0 Hz H-2′, 2″), 6.95 (2H, m, H-6′, 6″), 6.73 (2H, d, *J* = 8.5 Hz, H-5′, H-5″), 6.20 (1H, m, H-8′, H-8″), 5.42 (1H, br s, H-3), 4.94 (1H, br s, H-4), 4.05 (1H, br s, H-5), 1.91–2.11 (4H, m, H_2-2, H_2-6).

3,5-DCQA (purity: 98.7%): ^{1}H-NMR (DMSO-*d6*, 500 MHz) δ: 7.47 (2H, t, *J* = 16.5 Hz, H-7′, H-7″), 7.05 (2H, dd, *J* = 8.5 Hz, H-2′, H-2″), 6.99 (2H, m, H-6′, 6″), 6.77 (2H, dd, *J* = 8.0 Hz, H-5′, H-5″), 6.25 (1H, d, *J* = 16.0 Hz, H-8″), 6.16 (1H, d, *J* = 15.5 Hz, H- 8′), 5.20 (1H, m, H-3), 5.11 (1H, br s, H-5), 3.84 (1H, br s, H-4), 1.91–2.17 (4H, m, H_2-2, H_2-6).

4,5-DCQA (purity: 99.9%): ^{1}H-NMR (DMSO-*d6*, 500 MHz) δ: 7.49 (1H, d, *J* = 16.0 Hz, H-7″), 7.42 (1H, d, *J* = 16.0 Hz, H-7′), 7.02 (2H, dd, *J* = 4.5 Hz, H-2′, 2″), 6.97 (2H, m, H-6′, 6″), 6.74 (2H, dd, *J* = 8.0 Hz, H-5′, H-5″), 6.24 (1H, d, *J* = 16.0 Hz, H-8″), 6.14 (1H, d, *J* = 16.0 Hz, H-8′), 5.35 (1H, br s, H-5), 4.96 (1H, dd, *J* = 7.5 Hz, H-4), 4.17 (1H, br s, H-3), 1.87–2.18 (4H, m, H_2-2, H_2-6).

α-Glucosidase-inhibitory activity assay

Dicaffeoylquinic acid derivatives were assessed for α-glucosidase-inhibitory activity as described previously, with slight modifications [21, 22]. In brief, acarbose and dicaffeoylquinic acid derivatives (80 μL) at varying concentrations (12.5 to 100 μM) in 120 μL of 0.1 M phosphate buffer (pH 6.8) were incubated with 100 μL of 0.5 U/mL α-glucosidase at 37 °C. Enzyme activity was calculated as: α-glucosidase-inhibitory activity (%) = $[(A_{blank}\text{-}A_{sample})/A_{blank}] \times 100$.

Cell culture and determination of cell viability

Rat pancreatic INS-1 line (Biohermes, Shanghai, China) was maintained routinely in the Roswell Park Memorial Institute (RPMI) 1640 medium (Cellgro, Manassas, VA, USA) supplemented with 1 mM sodium pyruvate, 0.05 mM 2-mercaptoethanol, 10 mM HEPES, 11 mM D-glucose, 2 mM L-glutamine, and 10% fetal bovine serum (FBS), 1% penicillin/streptomycin (Invitrogen Co., Grand Island, NY, USA) under 5% CO_2 and 95% humidity at 37 °C. To determine the non-toxic dose ranges of dicaffeoylquinic acid derivatives, INS-1 cells were seeded at 10^4 cell per well in 96-well plates. After 24 h of incubation, cells were treated with gliclazide and dicaffeoylquinic acid derivatives (100 μL) at varying concentrations (2.5 to 10 μM) for 24 h. The cells were then incubated for 2 h with 10 μL of Ez-Cytox reagent (Daeil Lab Service Co., Seoul, Korea) as described in published methods [23].

GSIS assay

INS-1 cells plated on 12-well plates for 24 h were used to measure the effects of dicaffeoylquinic acid derivatives on GSIS. To this end, INS-1 cells were kept in Krebs–Ringer bicarbonate HEPES buffer (KRBB) supplemented with 2.8 mM glucose for 2 h. Thereafter

the INS-1 cells were incubated for 1 h in the fresh KRBB with the denoted glucose concentrations (2.8 or 16.7 mM glucose) and test agents (gliclazide and dicaffeoylquinic acid derivatives). Glucose stimulated index (GSI) was calculated by dividing the insulin concentration that had accumulated during exposure to 16.7 mM glucose by the insulin accumulated during exposure to 2.8 mM glucose. After incubation a cell culture supernatant was analyzed using a rat insulin ELISA kit (Gentaur, Shibayagi Co. Ltd., Shibukawa, Gunma, Japan) as recommended by the producer to measure the GSIS.

Western blot analysis

In the Western blot analysis, INS-1 cells plated on 12-well plates for 24 h were used to measure the effect of 4,5-DCQA on protein expression changes of PI3K, Akt, P-IRS-2 (Ser731), IRS-2, P-ERK, ERK, P-PI3K, P-Akt (Ser473), and PDX-1. To this end, the cells were treated with 4,5-DCQA for 24 h. The cells were lysed on ice for 20 min in radioimmunoprecipitation assay buffer (Cell Signaling, Danvers, MA, USA) with protease inhibitor. The concentration of protein in the lysates was determined using the Pierce BCA protein assay kit (Thermo Scientific, Rockford, IL, USA). Samples containing 20 μg concentration of protein were subsequently transferred onto polyvinylidene difluoride membranes. The membranes were incubated treated with first and second antibodies against PI3K, Akt, P-IRS-2 (Ser731), IRS-2, P-ERK, ERK, P-PI3K, P-Akt (Ser473), PDX-1, and glyceraldehyde 3-phosphate dehydrogenase (GAPDH).

Statistical analysis

All analyses were conducted using SPSS Statistics ver. 19.0 (SPSS Inc., Chicago, IL, USA). Nonparametric comparisons of samples were conducted with the Kruskal–Wallis test to analyze the results. Statistical significance was set at $p < 0.05$.

Results

Identification of dicaffeoylquinic acid derivatives

The dried aerial parts of *Saussurea grandifolia* were extracted with methanol under reflux. The filterate was concentrated to dryness, suspended in water, and then partitioned and ethyl acetate fraction was further chromatographed on a silica gel to afford 1,5-DCQA with spectra analysis as reported previously [24]. 3,5-DCQA, 4,5-DCQA, 1,4-DCQA, and 3,4-DCQA were identified by spectral analysis [25] (Fig. 1).

α-Glucosidase inhibitory activities of dicaffeoylquinic acid derivatives

Dicaffeoylquinic acid derivatives were assessed for their α-glucosidase inhibitory activity. It was observed that 3,5-DCQA exhibited 60.65 ± 1.97% inhibitory activity at 50 μM (Fig. 2A). The 4,5-DCQA, 1,4-DCQA, 3,4-DCQA, and 1,5-DCQA exhibited 58.83 ± 2.71, 23.66 ± 2.81, 52.18 ± 2.67, 50.92 ± 2.37% activity at 100 μM

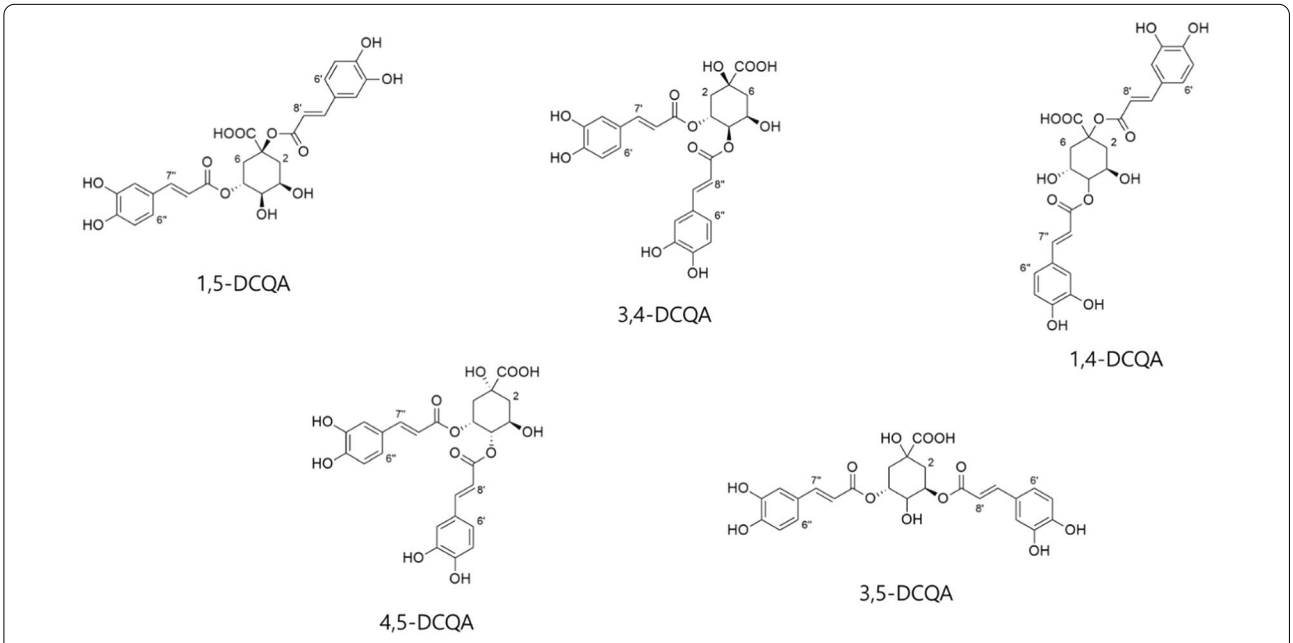

Fig. 1 Chemical structures of dicaffeoylquinic acid derivatives

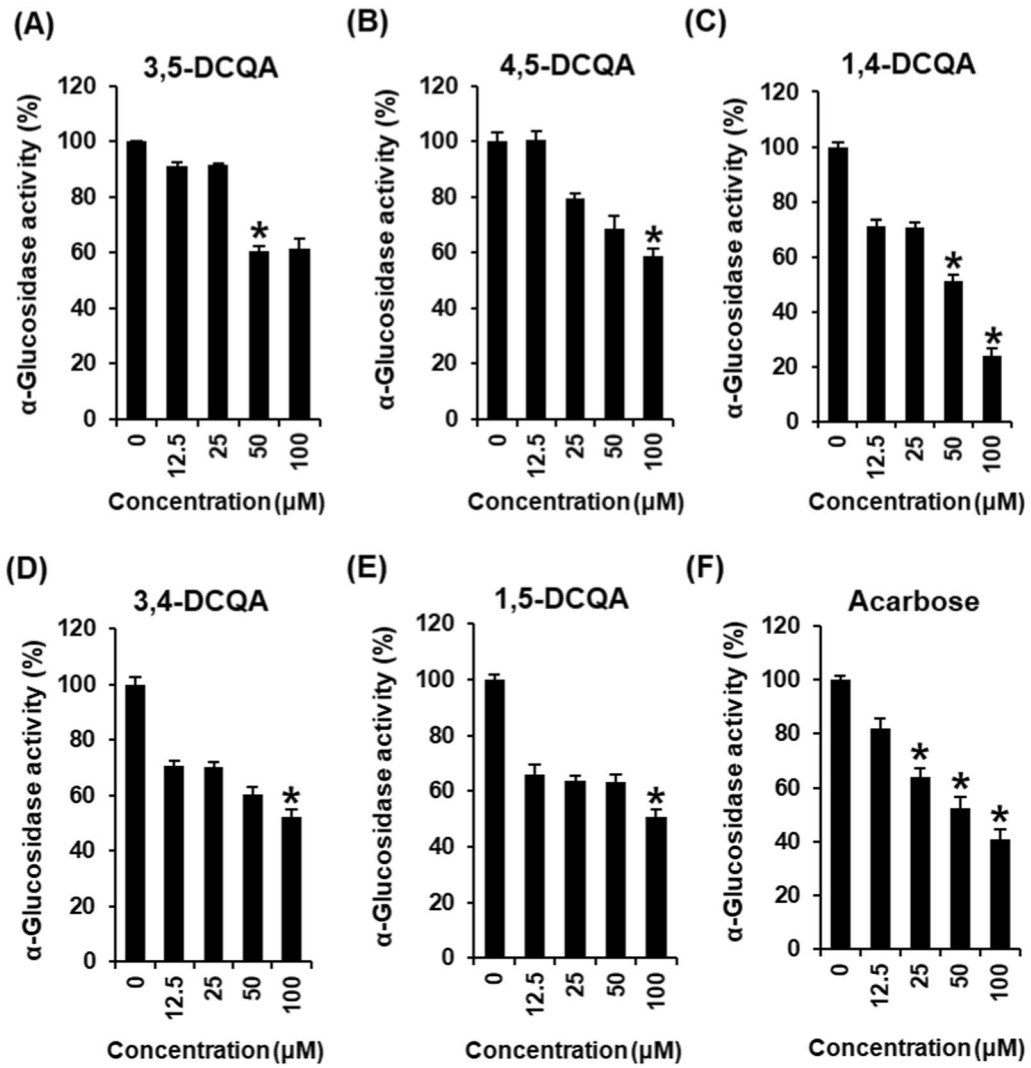

Fig. 2 Inhibitory effects of the dicaffeoylquinic acid derivatives on α-glucosidase inhibitory activities. Effect of **A** 3, 5-DCQA, **B** 4, 5-DCQA, **C** 1, 4-DCQA, **D** 3, 4-DCQA, **E** 1, 5-DCQA, and **F** acarbose (positive control) on the α-glucosidase inhibitory activities, compared with that of the control (0 μM), as determined by the α-glucosidase assay ($n = 3$ independent experiments). The data are presented as the mean ± SEM. *$P < 0.05$ compare with not-treated group

respectively (Fig. 2B–E). Among the dicaffeoylquinic acid derivatives, 1,4-DCQA exhibited maximum inhibitory activity with IC50 51.75 ± 0.32 μM better than the activity shown by positive control (acarbose) with IC50 60.91 ± 3.85 μM (Fig. 2F).

Effects of dicaffeoylquinic acid derivatives on GSIS

Dicaffeoylquinic acid derivatives were evaluated for their GSIS activity. Since none of dicaffeoylquinic acid derivatives were toxic at all concentrations (2.5 to 10 μM), those concentrations were used in the GSIS assay (Fig. 3A–F). Dicaffeoylquinic acid derivatives led to an increase in GSI in a concentration-dependent manner. The GSI level was 3.59 ± 0.02 for 3,5-DCQA at 10 μM (Fig. 4A). The GSI levels were 4.39 ± 0.08 and 5.42 ± 0.07 for 4,5-DCQA at 5 μM and 10 μM, respectively (Fig. 4B). The GSI levels were 3.84 ± 0.11, 4.28 ± 0.13, and 3.51 ± 0.06 for 1,4-DCQA, 3,4-DCQA, and 1,5-DCQA at 10 μM, respectively (Fig. 4C–E). The GSI levels were 3.71 ± 0.19 and 6.41 ± 0.22 for gliclazide (positive control) at 5 μM and 10 μM, respectively (Fig. 4F). Although the GSIS activity of 4,5-DCQA was not superior to that of the same concentration of gliclazide, it is important that the GSI was increased approximately 5 times compared with control (0 μM).

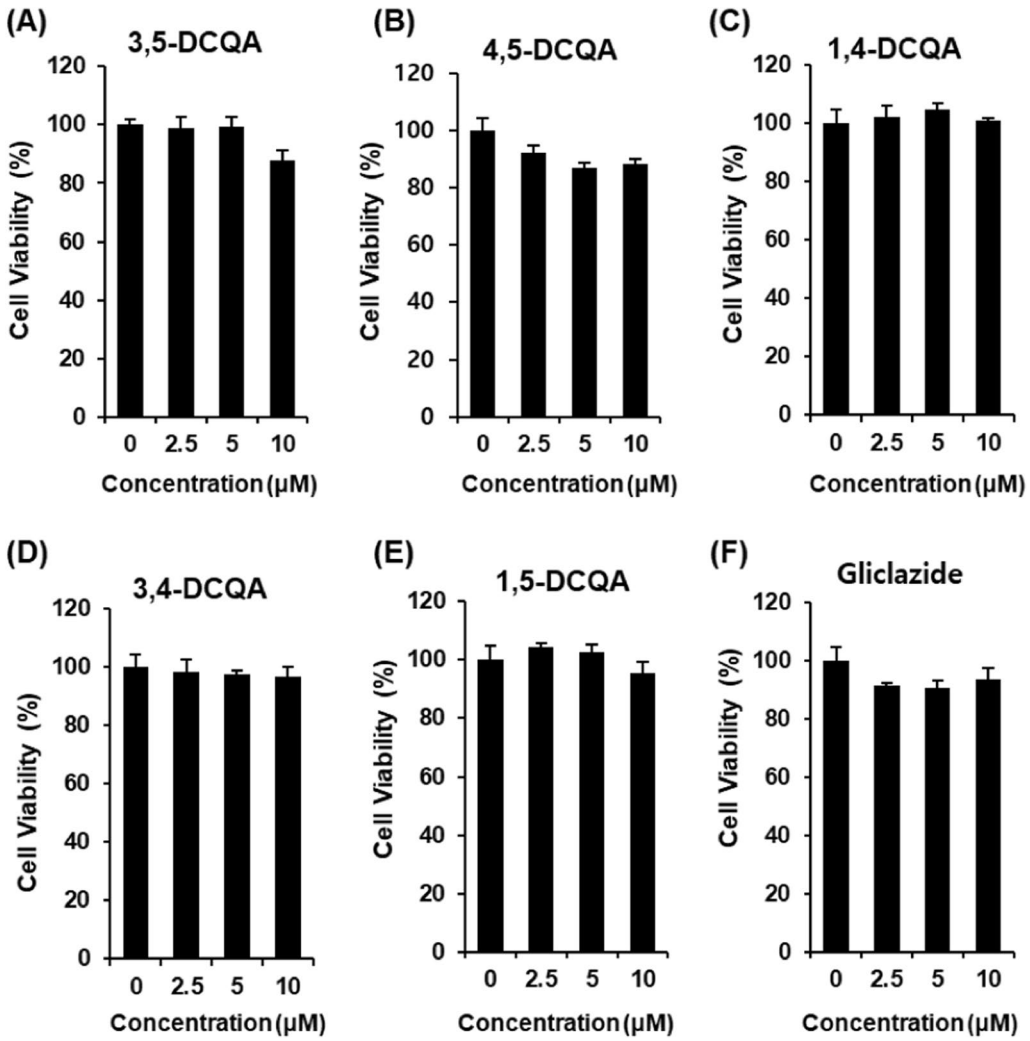

Fig. 3 Effect of the dicaffeoylquinic acid derivatives on the viability of pancreatic INS-1 cells. Effect of **A** 3, 5-DCQA, **B** 4, 5-DCQA, **C** 1, 4-DCQA, **D** 3, 4-DCQA, **E** 1, 5-DCQA, and **F** gliclazide (positive control) on the viability of INS-1 cells following 24 h of treatment, compared with the control (0 μM). The data are presented as the mean ± SEM

Effect of 4,5-Dicaffeoylquinic acid on the protein expression of P-IRS-2, IRS-2, P-PI3K, P-ERK, ERK, PI3K, P-Akt (Ser473), and Akt, PDX-1

Treatment with 4,5-DCQA at 5 μM and 10 μM increased the protein expressions of extracellular signal-regulated protein kinases (ERK), insulin receptor substrate-2 (P-IRS-2), Akt, phosphoinositide 3-kinase (P-PI3K), and pancreatic and duodenal homeobox-1 (PDX-1) compared to untreated controls in INS-1 cells (Fig. 5).

Discussion

Inhibitory effect of dicaffeoylquinic acid derivatives on α-glucosidase activity have been scientifically evaluated in the previous many studies [26–28]. In previous studies, 3,4-DCQA ($IC_{50} = 128$ μM), 4,5-DCQA (IC50 = 130 μM), and 3,5-DCQA (IC50 = 1166 μM) inhibit the α-glucosidase activity by 50% at a relatively high concentration [26, 28]. Our study showed similar results to previously reported data. In the present study, the effects of dicaffeoylquinic acid derivatives including 3,5-DCQA, 4,5-DCQA, 1,4-DCQA, 3,4-DCQA, and 1,5-DCQA on α-glucosidase activity were compared, and all exhibit inhibitory activity. α-Glucosidase inhibitory activities of dicaffeoylquinic acid derivatives are as follows 1,4-DCQA > 1,5-DCQA > 3,4-DCQA > 4,5-DCQA > 3,5-DCQA. 1,4-DCQA exhibited maximum inhibitory activity with IC_{50} of 51.75 ± 0.32 μM better than the activity shown by acarbose (positive control) with IC_{50}

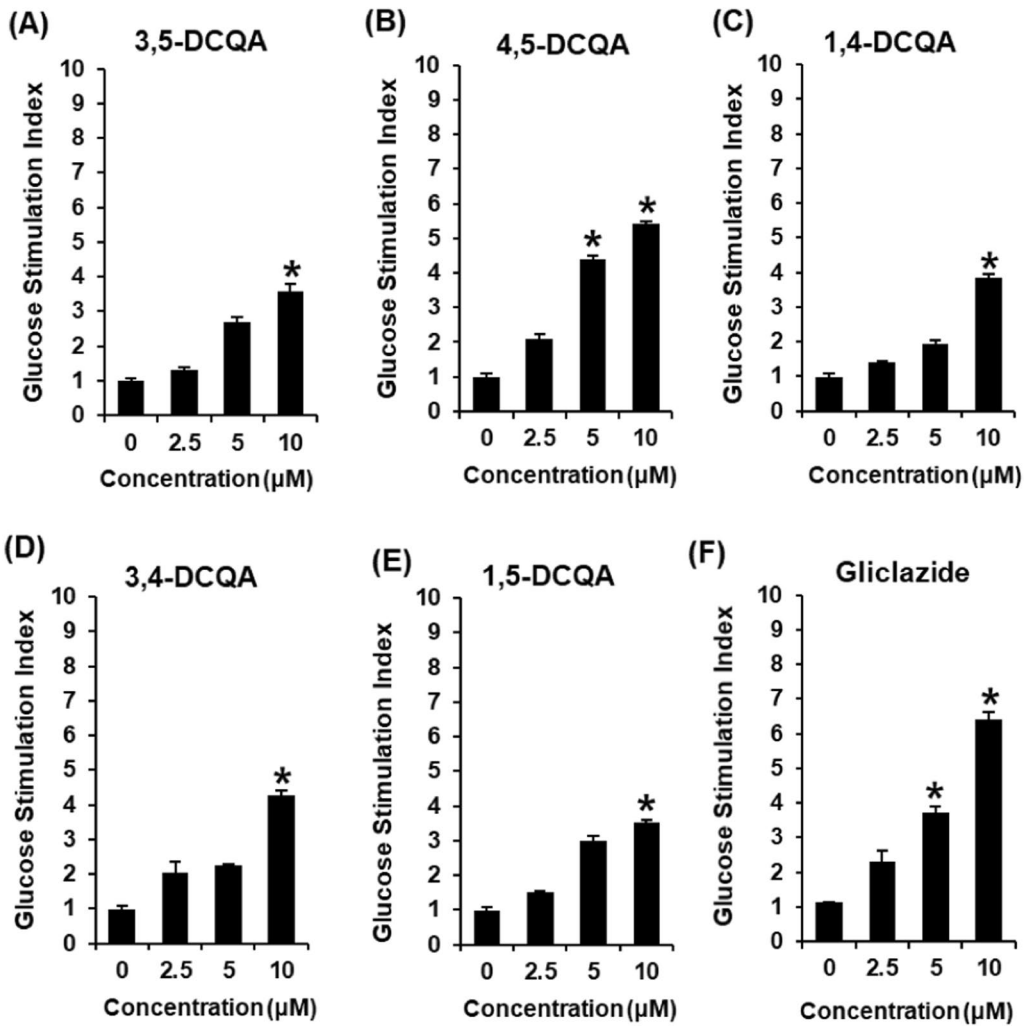

Fig. 4 Effect of the dicaffeoylquinic acid derivatives on the GSIS in INS-1 cells. Effect of **A** 3, 5-DCQA, **B** 4, 5-DCQA, **C** 1, 4-DCQA, **D** 3, 4-DCQA, **E** 1, 5-DCQA, and **F** gliclazide (positive control) on the GSIS in INS-1 cells following 1 h of treatment, compared with the control (0 μM). The data are presented as the mean ± SEM ($n = 3$). *$P < 0.05$ compare with not-treated group

of 60.91 ± 3.85 μM. Among the dicaffeoylquinic acid derivatives, less has been reported for effect of 1,4-DCQA on α-glucosidase activity [29]. It has been reported that 1,4-DCQA inhibits production of tumor necrosis factor-α (TNF-α) and nitric oxide considered as major inflammation marker in lipopolysaccharide-activated murine macrophage RAW 264.7 cells, whereas 1,5-DCQA and 3,5-DCQA have no inhibitory effect on TNF-α production [29]. The DCQA derivatives used in our study differ only in the arrangement of dicaffeoylquinic acid in the same quinic acid structure. When considering these results, the position of caffeoyl group at the quinic acid moiety might attribute their biological activity.

Little is known about effects of dicaffeoylquinic acid derivatives on insulin secretion compared to their α-glucosidase activities in the in vivo and in vitro models of type 2 DM. Although it has been suggested that *Gynura divaricata* rich in 4,5-DCQA restore pancreatic function in type 2 DM mice [30], the effect on 4,5-DCQA itself has not been investigated yet. In the present study, we compared the effects of dicaffeoylquinic acid derivatives including 3,5-DCQA, 4,5-DCQA, 1,4-DCQA, 3,4-DCQA, and 1,5-DCQA on GSIS activity, and all exhibit inhibitory activity without toxicity in INS-1 cells. GSIS activities of dicaffeoylquinic acid derivatives are as follows 4,5-DCQA > 3,4-DCQA > 1,4-DCQA > 3,5-DCQA > 1,5-DCQA.

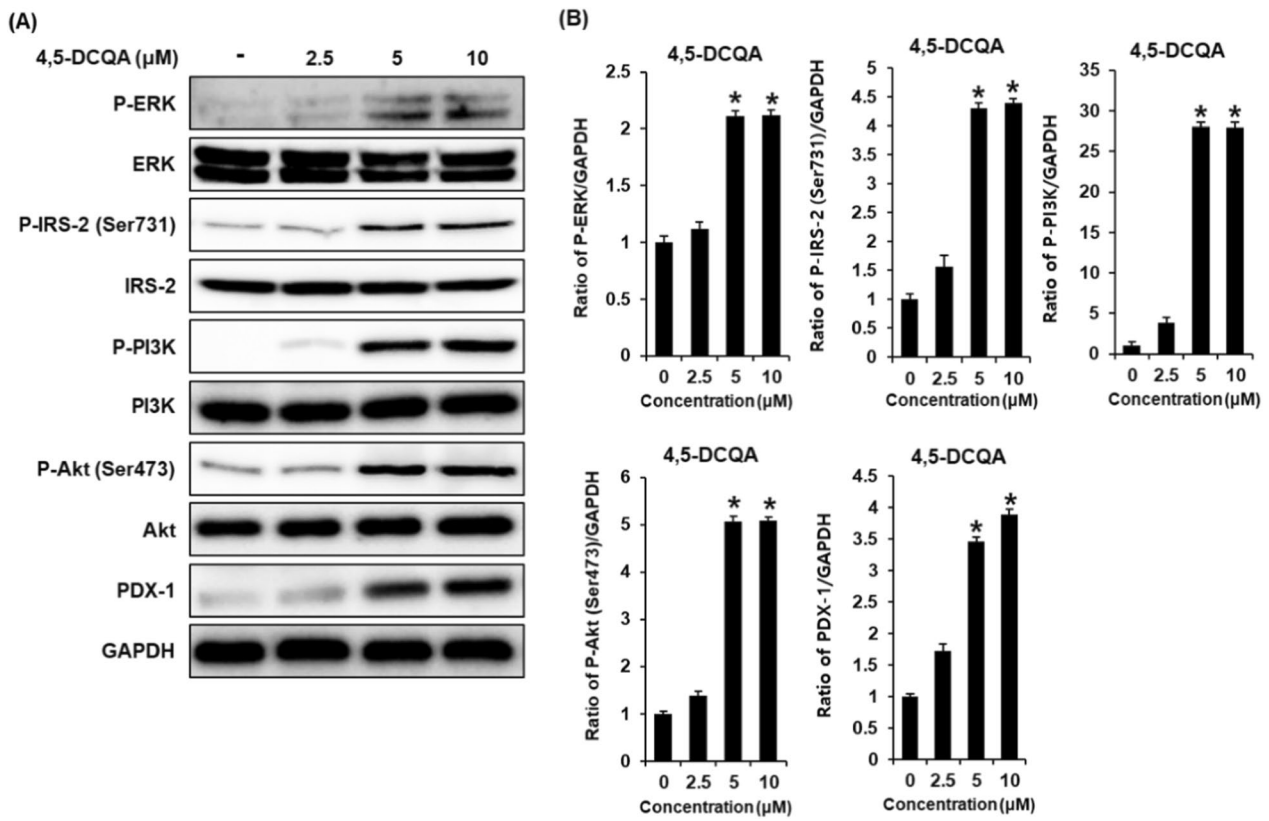

Fig. 5 Effect of 4,5-Dicaffeoylquinic acid (4,5-DCQA) on the expression levels of phospho-Akt (P-Akt) (Ser473), Akt, phospho-extracellular signal-regulated protein kinases (ERK), ERK, phospho-insulin receptor substrate-2 (P-IRS-2), (Ser731), IRS-2, phospho-phosphoinositide 3-kinase (P-PI3K), PI3K, and pancreatic and duodenal homeobox-1 (PDX-1) proteins in INS-1 cells. **A** The expression levels of P-ERK, ERK, P-IRS-2 (Ser731), IRS-2, P-PI3K, PI3K, P-Akt (Ser473), Akt, PDX-1, and GAPDH proteins in INS-1 cells treated or untreated with 4,5-DCQA at concentrations of 2.5, 5 and 10 μM for 24 h. **B** Densitometric quantification graphs of the Western blotting bands ($n = 3$ independent experiments). The data are presented as the mean ± SEM. *$P < 0.05$ compare with not-treated group

4,5-DCQA exhibited maximum activity. These findings indicate that the location of the dicaffeoyl functional group influences the anti-diabetic activity of quinic acid. However, we could not speculate the importance of the number of caffeoyl groups at the quinic acid moiety responsible for biological activity of DCQAs, and need for further studies in our future studies.

In addition, treatment with 4,5-DCQA increased protein expressions of ERK, IRS-2, PDX-1, Akt, and PI3K compared to untreated controls in INS-1 cells. These results indicated that GSIS activity of 4,5-DCQA might be partly related to PDX-1 expression via IRS-2/Akt/PI3K signaling pathway and ERK expression. ERK belongs to the mitogen-activated protein kinases (MAPK) family and plays an essential role in regulating not only cellular apoptosis and proliferation, but also differentiation. Earlier study indicates that the MAPK inhibitor PD98059 inhibit ERK phosphorylation and GSIS in β-TC6 mouse pancreatic cells [31].

Similar results are observed with U0126, a specific MAPK/ERK kinase inhibitor, reduces GSIS in mice pancreatic islets. ERK appears to regulate pancreatic β-cell survival and expression of insulin gene [32]. Many studies have shown that phosphorylated IRS-2 triggers PI3K/Akt pathway activation, and the participation of IRS-2/PI3K/Akt signaling in the regulation of maintenance of β-cell mass and normal pancreatic β-cell function is demonstrated [33]. In addition, IRS-2/PI3K/Akt signaling is known as the upstream of PDX-1. It has been reported that administration of *Gynura divaricata* rich in 4,5-DCQA enhances the PDX-1 expression in the pancreatic tissue of diabetic mice, thus retaining mature β-cell function [30]. PDX-1 is a vital transcription factor in the development of pancreas and transactivates insulin gene. Moreover, impaired GSIS is observed in PDX-1-deficient mice [34, 35]. Our current study suggested that treatment with 4,5-DCQA increased the PDX-1 expression via IRS-2/Akt/PI3K signaling pathway and ERK1/2

expression. These results supported the possibility of application of 4,5-DCQA as an antidiabetic agent that can ameliorate GSIS.

Based on the results, we reported the potent α-glucosidase inhibitory potential of dicaffeoylquinic acid derivatives and their GSIS effect. All dicaffeoylquinic acid derivatives exerted promising α-glucosidase inhibitory effects. 1,4-DCQA among dicaffeoylquinic acid derivatives exhibited maximum inhibitory effcets. Further, GSIS assay supported potentiation effect on GSIS shown by the dicaffeoylquinic acid derivatives. In addition, GSIS effect of 4,5-DCQA was supported by increased protein expressions of ERK, IRS-2, Akt, PI3K, and PDX-1. Our study provided partial evidence for the applicability of dicaffeoylquinic acid derivatives as candidates in the treatment of diabetes. However, further study including effect in animal models of T2D and in human islets are necessary.

Acknowledgements
We have no acknowledgement to declare.

Authors' contributions
Conceptualization: SL, and KSK; methodology, DHL, H-DL, and HLL; investigation, GSH, HJK, SC and HYL; writing—original draft preparation, DHL and KSK; writing—review and editing, KSK; project administration, KSK. All authors read and approved the final manuscript.

Funding
This research was supported by UNDBIO Co. Ltd. This research was also supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by Ministry of Science & ICT (2020M3A9E4104380).

Availability of data and materials
All data analysed or generated in this study are included in this published.

Declarations

Ethics approval and consent to participate
Ethics approval is not applicable. All authors have agreed to participate to the works described in this manuscript.

Consent for publication
All authors have read and agreed to the published version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]College of Korean Medicine, Gachon University, Seongnam 13120, Republic of Korea. [2]Department of Plant Science and Technology, Chung-Ang University, Anseong 17546, Republic of Korea. [3]UNDBIO Co. Ltd., Uijeongbu 11622, Republic of Korea. [4]Department of Pediatrics, College of Korean Medicine, Daejeon University, Daejeon 34520, Republic of Korea. [5]Department of Food science and nutrition, Gyeongsang National University, Jinju 52725, Republic of Korea.

Received: 30 December 2021 Accepted: 12 March 2022
Published: 29 March 2022

Published online: 29 March 2022

References

1. van de Laar FA (2008) Alpha-glucosidase inhibitors in the early treatment of type 2 diabetes. Vasc Health Risk Manag 4:1189
2. Cai X, Han X, Luo Y, Ji L (2013) Comparisons of the efficacy of alpha glucosidase inhibitors on type 2 diabetes patients between Asian and Caucasian. PloS One 8:e79421
3. Sugihara H, Nagao M, Harada T, Nakajima Y, Tanimura-Inagaki K, Okajima F, Tamura H, Inazawa T, Otonari T, Kawakami M, Oikawa S (2014) Comparison of three α-glucosidase inhibitors for glycemic control and bodyweight reduction in Japanese patients with obese type 2 diabetes. J Diabetes Investig 5:206–212
4. Assefa ST, Yang E-Y, Chae S-Y, Song M, Lee J, Cho M-C, Jang S (2020) Alpha glucosidase inhibitory activities of plants with focus on common vegetables. Plants 9:2
5. Nakajima Y, Shimazawa M, Mishima S, Hara H (2007) Water extract of propolis and its main constituents, caffeoylquinic acid derivatives, exert neuroprotective effects via antioxidant actions. Life sci 80:370–377
6. Yang P-F, Feng Z-M, Yang Y-N, Jiang J-S, Zhang P-C (2017) Neuroprotective caffeoylquinic acid derivatives from the flowers of *Chrysanthemum morifolium*. J Nat Prod 80:1028–1033
7. Maruta Y, Kawabata J, Niki R (1995) Antioxidative caffeoylquinic acid derivatives in the roots of burdock (*Arctium lappa* L.). J Agric Food Chem 43:2592–2595
8. Jiang X-W, Bai J-P, Zhang Q, Hu X-L, Tian X, Zhu J, Liu J, Meng W-H, Zhao Q-C (2016) Caffeoylquinic acid derivatives from the roots of *Arctium lappa* L. (burdock) and their structure–activity relationships (SARs) of free radical scavenging activities. Phytochem Lett 15:159–163
9. Santos MDd, Chen G, Almeida MC, Soares DM, de Souza GEP, Lopes NP, Lantz RC (2010) Effects of caffeoylquinic acid derivatives and C-flavonoid from *Lychnophora ericoides* on in vitro inflammatory mediator production. Nat Prod Commun 5:733–740
10. Abdel Motaal A, Ezzat SM, Tadros MG, El-Askary HI (2016) In vivo anti-inflammatory activity of caffeoylquinic acid derivatives from *Solidago virgaurea* in rats. Pharm Biol 54:2864–2870
11. Ge L, Wan H, Tang S, Chen H, Li J, Zhang K, Zhou B, Fei J, Wu S, Zeng X (2018) Novel caffeoylquinic acid derivatives from *Lonicera japonica* Thunb. flower buds exert pronounced anti-HBV activities. RSC Adv 8:35374–35385
12. Li Y, But PP, Ooi VE (2005) Antiviral activity and mode of action of caffeoylquinic acids from *Schefflera heptaphylla* (L.) Frodin. Antiviral Res 68:1–9
13. Jafari N, Zargar SJ, Delnavazi M-R, Yassa N (2018) Cell cycle arrest and apoptosis induction of phloroacetophenone glycosides and caffeoylquinic acid derivatives in gastric adenocarcinoma (AGS) cells. Anticancer Agents Med Chem 18:610–616
14. Nagaoka T, Banskota AH, Xiong Q, Tezuka Y, Kadota S (2001) Synthesis and antihepatotoxic and antiproliferative activities of di-and tri-O-caffeoylquinic acid derivatives. J Tradit Med 18:183–190
15. Vongsak B, Kongkiatpaiboon S, Jaisamut S, Konsap K (2018) Comparison of active constituents, antioxidant capacity, and α-glucosidase inhibition in *Pluchea indica* leaf extracts at different maturity stages. Food Biosci 25:68–73
16. Chen Y, Geng S, Liu B (2020) Three common caffeoylquinic acids as potential hypoglycemic nutraceuticals: evaluation of α-glucosidase inhibitory activity and glucose consumption in HepG2 cells. J Food Biochem 44:e13361
17. Gao H, Huang Y-N, Gao B, Xu P-Y, Inagaki C, Kawabata J (2008) α-Glucosidase inhibitory effect by the flower buds of *Tussilago farfara* L. Food chem 106:1195–1201
18. Komatsu M, Takei M, Ishii H, Sato Y (2013) Glucose-stimulated insulin secretion: a newer perspective. J Diabetes Investig 4:511–516
19. Cohrs CM, Panzer JK, Drotar DM, Enos SJ, Kipke N, Chen C, Bozsak R, Schöniger E, Ehehalt F, Distler M, Brennand A, Bornstein SR, Weitz J, Solimena M, Speier S (2020) Dysfunction of persisting β cells is a key feature of early type 2 diabetes pathogenesis. Cell Rep 31:107469
20. Sola D, Rossi L, Schianca GPC, Maffioli P, Bigliocca M, Mella R, Corlianò F, Fra GP, Bartoli E, Derosa G (2015) Sulfonylureas and their use in clinical practice. Arch Med Sci 11:840
21. Nguyen DH, Le DD, Ma ES, Min BS, Woo MH (2020) Development and Validation of an HPLC-PDA Method for Quantitation of Ten Marker Compounds from *Eclipta prostrata* (L.) and Evaluation of Their Protein Tyrosine

Phosphatase 1B, α-Glucosidase, and Acetylcholinesterase Inhibitory Activities. Nat Prod Sci 26:326–333
22. Park S-J, Lee D, Kim D, Lee M, In G, Han S-T, Kim SW, Lee M-H, Kim O-K, Lee J (2020) The non-saponin fraction of Korean Red Ginseng (KGC05P0) decreases glucose uptake and transport in vitro and modulates glucose production via down-regulation of the PI3K/AKT pathway in vivo. J Ginseng Res 44:362–372
23. Park MY, Han SJ, Moon D, Kwon S, Lee J-W, Kim KS (2020) Effects of red ginseng on the elastic properties of human skin. J Ginseng Res 44:738–746
24. Kim HM, Lee DG, Lee S (2015) Plant-derived molecules from Saussurea grandifolia as inhibitors of aldose reductase. J Appl Biol Chem 58:365–371
25. Li X-J (2018) Studies on the Anti-inflammatory Constituents of *Acanthopanax henryi* (Oliv.) Harms. Dissertation, Wonkwang University.
26. Chen J, Mangelinckx S, Ma L, Wang Z, Li W, De Kimpe N (2014) Caffeoylquinic acid derivatives isolated from the aerial parts of *Gynura divaricata* and their yeast α-glucosidase and PTP1B inhibitory activity. Fitoterapia 99:1–6
27. Xu D, Wang Q, Zhang W, Hu B, Zhou L, Zeng X, Sun Y (2015) Inhibitory activities of caffeoylquinic acid derivatives from Ilex kudingcha CJ Tseng on α-glucosidase from *Saccharomyces cerevisiae*. J Agric Food Chem 63:3694–3703
28. Arsiningtyas IS, Gunawan-Puteri MD, Kato E, Kawabata J (2014) Identification of α-glucosidase inhibitors from the leaves of *Pluchea indica* (L.) Less., a traditional Indonesian herb: promotion of natural product use. Nat Prod Res 28:1350–1353
29. Yoo S-R, Seo C-S, Lee N-R, Shin H-K, Jeong S-J (2015) Phytochemical analysis on quantification and the inhibitory effects on inflammatory responses from the fruit of *xanthii fructus*. Pharmacogn Mag 11:S585
30. Yin X-L, Xu B-Q, Zhang Y-Q (2018) *Gynura divaricata* rich in 3, 5—/4, 5-dicaffeoylquinic acid and chlorogenic acid reduces islet cell apoptosis and improves pancreatic function in type 2 diabetic mice. Nutr Metab 15:1–12
31. Niu B, Liu L, Su H, Xia X, He Q, Feng Y, Xue Y, Yan X (2016) Role of extracellular signal-regulated kinase 1/2 signal transduction pathway in insulin secretion by β-TC6 cells. Mol Med Rep 13:4451–4454
32. Lawrence M, Shao C, Duan L, McGlynn K, Cobb M (2008) The protein kinases ERK1/2 and their roles in pancreatic beta cells. Acta Physiol 192:11–17
33. Balcazar Morales N, Aguilar de Plata C (2012) Role of AKT/mTORC1 pathway in pancreatic β-cell proliferation. Colomb 43:235–243
34. Brissova M, Shiota M, Nicholson WE, Gannon M, Knobel SM, Piston DW, Wright CVE, Powers AC (2002) Reduction in pancreatic transcription factor PDX-1 impairs glucose-stimulated insulin secretion. J Biol Chem 277:11225–11232
35. Gauthier BR, Wiederkehr A, Baquié M, Dai C, Powers AC, Kerr-Conte J, Pattou F, MacDonald RJ, Ferrer J, Wollheim CB (2009) PDX1 deficiency causes mitochondrial dysfunction and defective insulin secretion through TFAM suppression. Cell metab 10:110–118

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen journal and benefit from:

- ► Convenient online submission
- ► Rigorous peer review
- ► Open access: articles freely available online
- ► High visibility within the field
- ► Retaining the copyright to your article

Submit your next manuscript at ► springeropen.com