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

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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
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 dicafeoylquinic acid derivatives (Fig. 1) on α-glucosidase inhibitory activity were compared, and it was also confirmed whether the dicafeoylquinic 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 chemicals

The dried aerial parts of *Saussurea grandifolia* were extracted with methanol under reflux. 1,4-Di-O-cafeoylquinic acid (1,4-DCQA) and 1,5-di-O-cafeoylquinic acid (1,5-DCQA) were isolated from *S. grandifolia*. Dicafeoylquinic acid derivatives such as 3,4-di-O-cafeoylquinic acid (3,4-DCQA), 4,5-di-O-cafeoylquinic acid (4,5-DCQA), and 3,5-di-O-cafeoylquinic acid (3,5-DCQA) were isolated from *Acanthopanax henryi* and obtained Natural Product Institute (RPMI 1640 medium (Cellgro, Manassas, VA, USA) supplemented with 1 mM sodium pyruvate, 2.8 mM glucose, 2 mM L-glutamine, and 10% fetal bovine serum (FBS), 1% penicillin/streptomycin (Invitrogen Co., Grand Island, NY, USA) under 5% CO₂ and 95% humidity at 37 °C. To determine the non-toxic dose ranges of dicafeoylquinic acid derivatives, INS-1 cells were seeded at 10⁴ cell per well in 96-well plates. After 24 h of incubation, cells were treated with gliclazide and dicafeoylquinic 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 (%) = [(Ablank-A sample)/A blank] × 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). We used the Cell Titer 96 AQueous One Solution Cell Proliferation Assay (Promega, Madison, WI, USA) to measure cell viability. The assay is based on the conversion of a tetrazolium salt into a formazan dye by mitochondrial NADH dehydrogenase. The amount of formazan is proportional to the number of living cells in the sample. In brief, cells were seeded at 10³ cell per well in 96-well plates. After 24 h of incubation, cells were treated with gliclazide and dicafeoylquinic 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 dicafeoylquinic 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 con-
centration 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 pro-
tease inhibitor. The concentration of protein in the
lysates was determined using the Pierce BCA protein
assay kit (Thermo Scientific, Rockford, IL, USA). Sam-
ples 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 com-
parisons 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 filtrate was
concentrated to dryness, suspended in water, and then
partitioned and ethyl acetate fraction was further chro-
matographed 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
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**

Dicafeoylquinic 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).
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 (IC$_{50}$ = 130 μM), and 3,5-DCQA (IC$_{50}$ = 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$_{50}$
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. 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 compared 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/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 effects. 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.

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Authors’ contributions
Conceptualization: SL, and KSK; methodology, DHL, H‑DL, and HLL; investigation, GSH, HUK, 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.

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Availability of data and materials
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Declarations
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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 there are no competing interests.

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