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Research Article

Antihyperglycemic effects of apigenin-loaded self-nanoemulsifying drug delivery system (SNEDDS): Evidence from α-glucosidase inhibition and oral glucose tolerance test

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ABSTRACT

Apigenin, a naturally occurring flavonoid, exhibits promising antidiabetic activity; however, its clinical application is limited by poor aqueous solubility and low oral bioavailability. This study aimed to evaluate the antihyperglycemic potential of apigenin formulated in a self-nanoemulsifying drug delivery system (SNEDDS) using both *in vitro* α-glucosidase inhibition and *in vivo* oral glucose tolerance tests (OGTT). Based on our previous work, two SNEDDS formulations (A and B), each containing 0.5% (w/w) apigenin, were successfully developed and characterized, differing in the proportions of Gelucire® 44/14, Tween 80, and PEG 400 (25:37.5:37.5 and 30:35:35, respectively). In the present study, *in vitro* results showed that both formulations exhibited concentration-dependent α-glucosidase inhibitory activity, with similar IC_{50} values of 63.5 ± 17.0 and 58.0 ± 10.3 µg/mL for Formulations A and B, respectively, indicating approximately 10-fold greater potency than acarbose. The antihyperglycemic effect was further evaluated in streptozotocin (STZ)–nicotinamide (NA)-induced diabetic mice using an OGTT. Both SNEDDS formulations (50 mg/kg) significantly lowered postprandial blood glucose levels and reduced the area under the glucose concentration–time curve ($AUC_{0\text{-}120}$) compared to diabetic controls ($p < 0.05$). The glucose-lowering effects were similar to those of glibenclamide, with no significant differences between the two formulations. These results indicate that apigenin-loaded SNEDDS exhibit significant antihyperglycemic effects, likely mediated by enhanced oral absorption and inhibition of α-glucosidase. Overall, this study supports the favorable safety profile and therapeutic potential of apigenin-loaded SNEDDS and offers a strong preclinical foundation for further development as an oral antihyperglycemic treatment.

Keywords:
Apigenin; Self-nanoemulsifying drug delivery system (SNEDDS); Oral glucose tolerance test (OGTT); α-glucosidase inhibition; Antihyperglycemic activity

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders worldwide and constitutes a major global health burden. According to recent global health reports, the number of individuals affected by diabetes continues to rise substantially, leading to significant morbidity, mortality, and healthcare costs [1,2]. Effective glycemic control, particularly the management of postprandial hyperglycemia, is therefore

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in the small intestine, plays a crucial role in catalyzing the final step of carbohydrate digestion by converting oligosaccharides into absorbable monosaccharides [4]. Inhibition of α-glucosidase reduces the rate of glucose release and attenuates postprandial blood glucose excursions [5]. Accordingly, α-glucosidase inhibitors have been widely used as oral antidiabetic agents, offering effective glycemic control with a low risk of hypoglycemia [5,6]. The identification of novel α-glucosidase inhibitors, particularly from natural sources, therefore, remains an important focus in diabetes research [7].

Apigenin, a natural flavonoid widely found in fruits, vegetables, and herbs, has attracted considerable attention due to its diverse pharmacological activities [8,9]. Increasing evidence suggests that apigenin possesses promising antidiabetic potential through multiple mechanisms. Previous studies have reported that apigenin can inhibit carbohydrate-digesting enzymes such as α-glucosidase [10,11], thereby delaying carbohydrate digestion and reducing postprandial glucose absorption. Additionally, apigenin improves insulin sensitivity, potentiates glucose-stimulated insulin secretion, and enhances glucose utilization in peripheral tissues via pathways like GLUT4/AMPK/PI3K/Akt [12-15]. Its strong antioxidant and anti-inflammatory properties may also contribute to the protection of pancreatic β-cells and the attenuation of oxidative stress associated with diabetes progression [16,17]. Despite these promising biological activities, the therapeutic application of apigenin is limited by its poor aqueous solubility and low oral bioavailability, which restrict its systemic exposure and pharmacological effectiveness following oral administration [18].

Self-nanoemulsifying drug delivery systems (SNEDDS) have emerged as an effective strategy for improving the dissolution, oral absorption, and therapeutic performance of poorly water-soluble compounds. Recent studies have demonstrated the successful application of SNEDDS and related nano-delivery systems to enhance the solubility, bioavailability, and biological activity of hydrophobic drugs, including apalutamide [19] and andrographolide [20]. In addition, SNEDDS have been extensively recognized as an advanced oral delivery platform for improving the biopharmaceutical properties of poorly water-soluble compounds [21]. These findings further support the potential of SNEDDS as a promising formulation approach for enhancing the oral delivery and therapeutic performance of bioactive compounds such as apigenin. In our previous study [22,23], apigenin was successfully formulated into a SNEDDS, an effective formulation approach for improving the oral delivery of poorly water-soluble compounds. Apigenin-loaded SNEDDS, composed of Gelucire® 44/14, Tween 80, and PEG 400 and containing 0.5% (w/w) apigenin, spontaneously form nano-sized emulsions upon dilution in aqueous media. *In vitro* dissolution studies demonstrated that apigenin released from the SNEDDS was markedly higher than that from the coarse powder across various physiological pH conditions, indicating a significant improvement in dissolution performance. In addition, *in vitro* permeability in Caco-2 cells and *in vivo* pharmacokinetic performance highlighted apigenin's potential to improve its biopharmaceutical properties for oral delivery [22,23]. Despite these promising findings regarding the physicochemical characteristics, improved dissolution and oral bioavailability performance of apigenin-loaded SNEDDS, the pharmacodynamic antihyperglycemic efficacy of this delivery system of apigenin has not yet been fully investigated. It remains unclear whether the improved oral bioavailability of apigenin provided by the SNEDDS formulation could translate into enhanced glucose-lowering activity.

Therefore, this study aimed to evaluate the antihyperglycemic potential of apigenin-loaded SNEDDS by assessing α-glucosidase inhibitory activity and *in vivo* glucose tolerance in streptozotocin (STZ)-nicotinamide (NA)-induced diabetic (DM) mice. By integrating *in vitro* enzymatic assays with *in vivo* pharmacological evaluation, this work further elucidates the potential of SNEDDS as an effective oral delivery system of apigenin in the management of hyperglycemia.

2. MATERIALS AND METHODS

2.1. Materials

2.1.1. Chemicals

Acarbose, α-glucosidase from *S. cerevisiae*, *p*-nitrophenyl-α-D-glucopyranoside (pNPG), *p*-nitrophenyl, streptozotocin, and nicotinamide were purchased from Sigma Aldrich Chemical Co. (St. Louis, MO, USA). Tween 80 (polyoxyethylene sorbitan monooleate) was obtained from Ajax Finechem, Australia, and PEG 400 from Krungthepchemi, Thailand. Glibenclamide (Daonil®) was obtained from Sano-Aventis (Indonesia), and apigenin from Xian Neo Biotech (Xian, China). Gelucire® 44/14 (lauroyl polyoxyl-32 glycerides) was kindly supplied by Gattefossé, France. All other chemical reagents were of analytical grade and used without further purification.

2.1.2. Animals

ICR mice (6-8 weeks old; initial body weight 30-35 g) were purchased from Nomura Siam International Co., Ltd. (Bangkok, Thailand) and divided a critical component of diabetes treatment strategies [3]. In this context, α-glucosidase, a brush-border enzyme into two batches for distinct experimental purposes. The first batch consisted of non-pregnant female mice

used for the acute oral toxicity study, while the second batch comprised male mice used for the oral glucose tolerance test. Mice were acclimatized for 1 week under a constant 12 h light-dark cycle at a controlled temperature (23 ± 2 °C) and humidity (40–70%), with free access to food and water ad libitum, prior to experimentation. All procedures involving animals were approved by the Institutional Animal Care and Use Committee (IACUC), Faculty of Pharmacy, Mahidol University (Approval No. PYR007/2023).

2.2. Preparation of apigenin-loaded SNEDDS formulations

Two optimized SNEDDS formulations incorporating 0.5% (w/w) apigenin were prepared, according to the method described previously [22,23]: Formulation A (Gelucire® 44/14, Tween 80, and PEG 400 at a ratio of 25:37.5:37.5, w/w/w) and Formulation B (30:35:35, w/w/w). Briefly, blank SNEDDS were prepared by mixing Gelucire® 44/14 with Tween 80 and PEG 400 according to the specified formulation ratios. Apigenin (0.5%, w/w) was then incorporated into the blank SNEDDS and stirred continuously at 40°C for 30 min to obtain a homogeneous system. Any excess undissolved apigenin was removed to yield a clear formulation. These two formulations were selected from 16 formulations for enhanced drug dissolution and good thermodynamic stability [22] and were further employed in this study.

2.3. Acute oral toxicity test in mice

To ensure formulation safety prior to evaluating its *in vivo* glucose-lowering effect in STZ–NA-induced diabetic mice, an acute oral toxicity study was performed in non-pregnant female ICR mice in accordance with the Organization for Economic Cooperation and Development (OECD) guideline 425 (up-and-down procedure) [24]. Briefly, a total of 15 mice were randomly divided into three groups (n = 5 mice per group): control, Formulation A, and Formulation B. Before the experiment, the mice were fasted for 3-4 hours with free access to water. At the start of the experiment, the first mouse in each test group received a single oral dose of apigenin-loaded SNEDDS formulations (Formulation A or B) at 2,000 mg/kg body weight, or water in the control group. Animals were closely observed for signs of toxicity and behavioral changes within the first hour after administration. If no signs of toxicity were observed in the first animal, the remaining four animals in each group were subsequently administered under the same conditions. Following administration, all animals were observed for clinical signs of toxicity, behavioral changes, and mortality at 4 and 6 h post-dose and subsequently monitored daily for 14 days. Body weight was recorded throughout the study period. If three or more animals survived in each group, the formulation was considered safe, and the median lethal dose (LD_{50}) was estimated to be greater than 2,000 mg/kg.

2.4. α-Glucosidase inhibition assay *in vitro*

The α-glucosidase inhibitory activity of apigenin-loaded SNEDDS was evaluated *in vitro* using a method described previously [25] with slight modifications. All samples were diluted in DMSO to obtain equivalent apigenin concentrations (0-500 µg/mL), with the final DMSO concentration not exceeding 0.1% (v/v). Briefly, 10 µL of each test sample was mixed with 40 µL of α-glucosidase solution (0.1 U/mL) prepared in 0.1 M phosphate buffer (pH 6.9) in a 96-well microplate. The mixture was gently shaken and pre-incubated at 37 °C for 20 min. Subsequently, 50 µL of 2 mM pNPG, as the enzyme substrate, was added to initiate the reaction. The reaction mixture was further incubated at 37 °C for 20 min. The enzymatic reaction was terminated by adding 100 µL of 1 M sodium carbonate solution. The amount of *p*-nitrophenol released was measured at 405 nm using a microplate reader. Acarbose was used as a positive control. All experiments were performed in triplicate with replicate measurements in each experiment. The percentage of α-glucosidase inhibitory activity was calculated as follows [25]:

$$\% \text{ α-glucosidase inhibitory activity} = \left(\frac{A_C - A_S}{A_C}\right) \times 100 \quad \text{Eq. 1}$$

where A_C and A_S represent the absorbance of the control group and the test sample, respectively. The half-maximal inhibitory concentration (IC_{50}) values were determined by plotting percentage inhibition against log concentrations of apigenin from each formulation and calculating the concentration required to inhibit 50% of enzyme activity.

2.5. Induction of diabetic mice

Male ICR mice (6–8 weeks old) were used to induce experimental type 2 diabetes using a STZ–NA model, as previously described [26,27]. Briefly, following an overnight fast (12 h), mice received an intraperitoneal injection of nicotinamide dissolved in normal saline solution (NSS) at a dose of 120 mg/kg. After 15 min, streptozotocin, freshly prepared in 0.1 M citrate buffer (pH 4.5), was administered intraperitoneally at a dose of 180 mg/kg. After 21-28 days, fasting blood glucose (FBG) levels were measured in tail-vein blood using a glucometer (Accu-Chek®, Roche, Thailand). Mice with FBG levels greater than 200 mg/dL were

considered diabetic and selected for subsequent oral glucose tolerance testing.

2.6. Oral glucose tolerance test (OGTT) in normal and diabetic mice

Following randomization, diabetic mice were allocated into five experimental groups. Test samples were orally administered 30 min prior to glucose loading (2 g/kg body weight). Each group (n = 8) was defined as follows:

- Group 1 (Normal control): non-diabetic receiving distilled water
- Group 2 (Negative control): diabetic mice receiving distilled water
- Group 3 (Positive control): diabetic mice receiving glibenclamide (5 mg/kg)
- Group 4 (Treatment 1): diabetic mice receiving Formulation A (50 mg/kg), followed by distilled water (1 mL/kg)
- Group 5 (Treatment 2): diabetic mice receiving Formulation B (50 mg/kg), followed by distilled water (1 mL/kg)

Subsequently, a glucose solution (2 g/kg) was administered via oral gavage. Blood samples were collected from the tail vein at 0 (baseline), 30, 60, 90, and 120 min after glucose administration. Blood glucose levels were measured using a glucometer (Accu-Chek®) with compatible test strips.

The mean blood glucose levels for each group were calculated and plotted against time. The area under the glucose concentration–time curve from 0 to 120 min ($AUC_{0\text{-}120}$) was determined using a trapezoidal method as follows [28]:

$$AUC_{0-120}=\frac{[C_0+C_{30}]\times[t_{30}-t_0]}{2}+\frac{[C_{30}+C_{60}]\times[t_{60}-t_{30}]}{2}+\frac{[C_{60}+C_{90}]\times[t_{90}-t_{60}]}{2}+\frac{[C_{90}+C_{120}]\times[t_{120}-t_{90}]}{2} \quad \text{Eq. 2}$$

where C_0, C_{30}, C_{60}, C_{90}, and C_{120} represent blood glucose levels (mg/dL) measured at 0, 30, 60, 90, and 120 min, respectively, and t_0, t_{30}, t_{60}, t_{90}, and t_{120} represent the corresponding time points (min).

2.7. Statistical analysis

Data are presented as mean ± standard error of the mean (SEM) for *in vivo* studies and mean ± standard deviation (SD) for *in vitro* experiments. Statistical analyses were performed using GraphPad Prism version 10.0.0 (GraphPad Software, La Jolla, CA, USA). Differences among multiple groups were evaluated using one-way analysis of variance (ANOVA), followed by appropriate post hoc multiple-comparison tests. Differences were considered statistically significant at $p < 0.05$.

3. RESULTS

Apigenin has attracted considerable attention as a natural flavonoid with promising antidiabetic activity. However, its clinical application is limited by poor aqueous solubility and low oral bioavailability. To address these limitations, SNEDDS have been developed as a novel formulation strategy to enhance solubility and improve oral absorption [22,23]. In our previous study, apigenin-loaded SNEDDS demonstrated improved pharmacokinetic properties in rats, including enhanced absorption and increased systemic exposure [23]. Building on these findings, the present study was conducted to further evaluate the pharmacodynamic effects of apigenin-loaded SNEDDS and to assess antihyperglycemic activity in STZ-NA-induced diabetic mice. The acute oral toxicity of apigenin-loaded SNEDDS formulations (Formulations A and B) at a high apigenin dose of 2,000 mg/kg showed no mortality in any treatment group during the 14-day observation period, indicating that both formulations were well tolerated at the administered dose. In addition, body weight increased progressively in all groups throughout the study, with comparable initial values and no significant differences among the control and treatment groups on days 7 and 14 ($p > 0.05$). No abnormal clinical signs or behavioral changes were observed. These results support a favorable safety profile following acute oral administration, demonstrating that apigenin-loaded SNEDDS are safe and well tolerated under the conditions of this study. From a translational perspective, this safety profile supports the potential of apigenin-loaded SNEDDS as an oral delivery system for further development in diabetes management [24].

3.1. α-Glucosidase inhibition assay *in vitro*

As shown in Figure 1, apigenin in SNEDDS Formulations A and B exhibited concentration-dependent inhibition of α-glucosidase activity, with greater inhibition observed at higher concentrations. The IC_{50} values for Formulations A and B were comparable, at 63.5 ± 17.0 and 58.0 ± 10.3 µg/mL, respectively. Notably, apigenin-loaded SNEDDS demonstrated markedly greater inhibitory potency than acarbose, with the IC_{50} values (approximately 60 µg/mL) being 10-fold lower than that of acarbose (IC_{50} of 700 ± 49 µg/mL).

3.2. OGTT in normal and diabetic mice

Following induction of type 2 diabetes using STZ-NA, diabetic mice exhibited significantly elevated

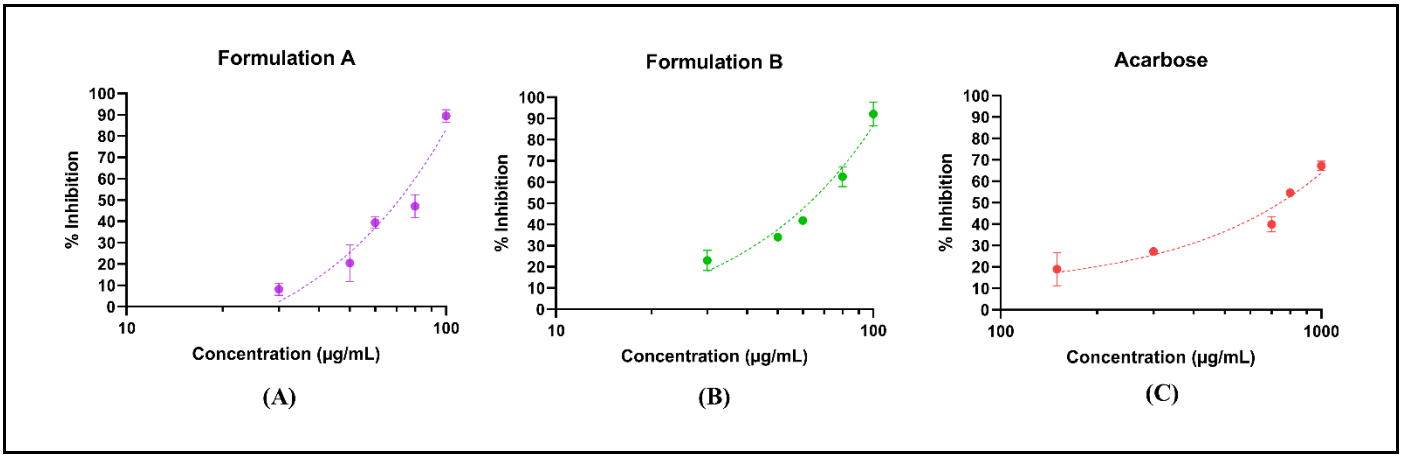

Figure 1. Percentage inhibition of α-glucosidase activity vs. log concentration of apigenin-loaded SNEDDS Formulation A (A), Formulation B (B), and acarbose (C). Data are presented as mean ± SD (n = 3).

blood glucose levels compared with the normal control group ($p < 0.05$). In addition, STZ-NA-induced diabetic mice displayed characteristic symptoms, including body weight loss, increased food intake, and polyuria. After induction, STZ-NA-induced diabetic mice were randomly divided into experimental groups, with no significant differences in baseline blood glucose levels among the diabetic groups.

In the OGTT study, test samples were administered 30 min prior to oral glucose loading (2 g/kg). For comparison, baseline glucose levels (0 min) were normalized by subtracting the initial values from subsequent time points (30, 60, 90, and 120 min), and the changes in blood glucose levels over time are presented in Figure 2. The diabetic negative control group exhibited significantly higher blood glucose levels than the normal control group at all time points ($p < 0.01$). In contrast, treatment with apigenin-loaded SNEDDS (Formulations A and B) significantly reduced blood glucose levels over the 60 to 120 min period compared with the diabetic negative control group ($p < 0.05$). The glucose-lowering effects of all apigenin formulations were comparable to those observed in the glibenclamide-treated group, with no significant differences observed among the formulations.

Furthermore, the area under the glucose concentration–time curve ($AUC_{0\text{-}120}$) was analyzed, as shown in Figure 3. Mice treated with Formulations A and B exhibited significantly lower $AUC_{0\text{-}120}$ values than the diabetic negative control group ($p < 0.01$ and $p < 0.05$, respectively). Glibenclamide significantly reduced $AUC_{0\text{-}120}$ relative to negative-control diabetic mice ($p < 0.01$), with no significant differences compared to Formulations A and B.

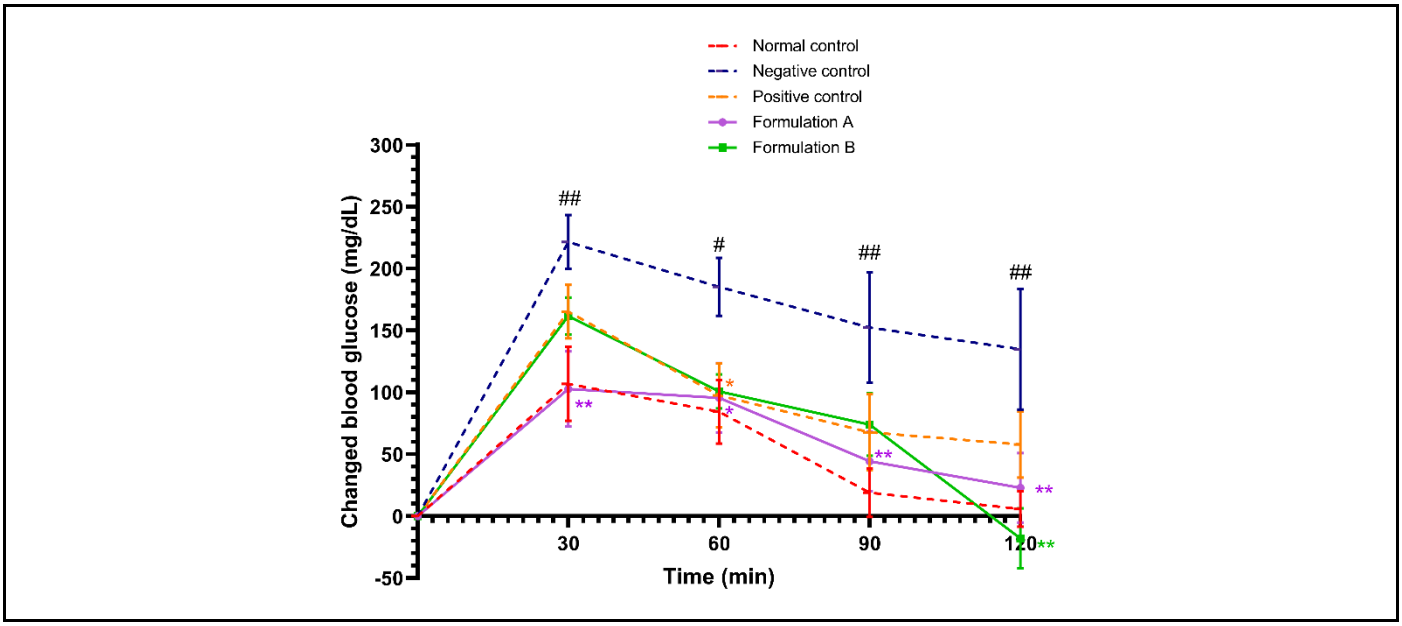

Figure 2. Changes in blood glucose levels during the OGTT following treatment with Formulation A (apigenin 50 mg/kg, purple), Formulation B (apigenin 50 mg/kg, green), glibenclamide (5 mg/kg, orange), diabetic control (blue), and normal control (red). Data are presented as mean ± SEM (n = 8 per group). *p < 0.05 and **p < 0.01 vs. diabetic control; #p < 0.05 and ##p < 0.01 vs. normal control.

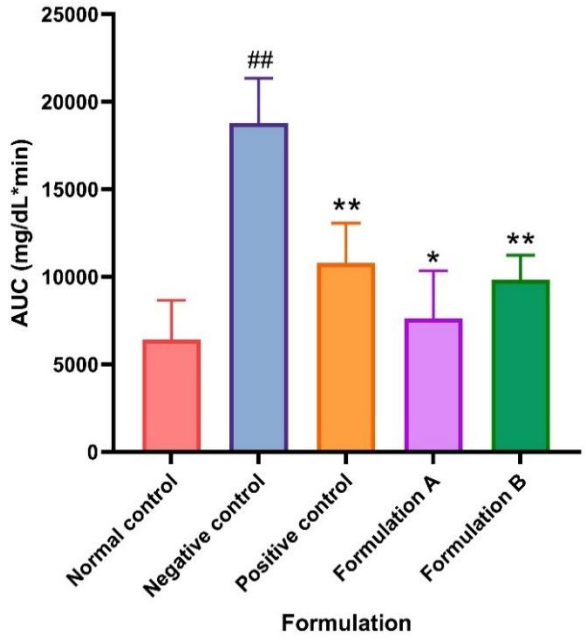

Figure 3. Area under the blood glucose concentration-time curve (AUC0-120) during the OGTT following treatment with Formulation A (apigenin 50 mg/kg, purple), Formulation B (apigenin 50 mg/kg, green), glibenclamide (5 mg/kg, orange), diabetic control (blue), and normal control (red). Data are presented as mean ± SEM (n = 8 per group). *p < 0.05 and **p < 0.01 vs. diabetic control; ##p < 0.01 vs. normal control.

4. DISCUSSION

In the *in vivo* antihyperglycemic evaluation, apigenin, administered as SNEDDS Formulations A and B at 50 mg/kg, significantly reduced postprandial blood glucose levels in STZ-NA-induced diabetic mice, as assessed by the OGTT. Both formulations exhibited comparable glucose-lowering effects, with no statistically significant differences between them. This similarity in pharmacodynamic response is likely attributable to their comparable physicochemical characteristics, including nano-sized droplet formation and efficient drug solubilization, which contribute to similar absorption profiles [23].

The antihyperglycemic effects observed *in vivo* are consistent with *in vitro* findings, in which apigenin from both SNEDDS formulations exhibited comparable α-glucosidase inhibitory activity, with the IC_{50} values being approximately 60 µg/mL (Figures 1A and 1B). On the other hand, acarbose, a standard oral α-glucosidase inhibitor used in the management of type 2 diabetes, exhibited an IC_{50} of approximately 700 µg/mL (Figure 1C), which is comparable to the previously reported value (IC_{50} = 884 µg/mL) [29]. Moreover, the present *in vitro* results are consistent with previous studies demonstrating that apigenin and its analogs possess significant α-glucosidase inhibitory activity. Liu et al. reported that apigenin derivatives exhibit potent inhibitory effects against α-glucosidase [11], while Zeng et al. demonstrated that apigenin inhibits α-glucosidase through a mixed-type inhibition mechanism involving interactions at the enzyme active site [10]. Taken together, these findings support the role of apigenin in modulating carbohydrate digestion and reducing postprandial glucose levels.

This study demonstrated that apigenin-loaded SNEDDS produced a glucose-lowering effect comparable to that of the commercially available antidiabetic drug glibenclamide in mice. However, the observed *in vivo* effects are likely not solely attributable to α-glucosidase inhibition, but also to other multiple mechanisms of apigenin's actions, including enhancement of insulin sensitivity, activation of AMP-activated protein kinase (AMPK) signaling, suppression of hepatic gluconeogenesis, and antioxidant and anti-inflammatory activities [12–15]. Collectively, these pleiotropic effects may contribute to the overall antihyperglycemic activity observed in the present study.

The antihyperglycemic effects observed in the present study are consistent with previous reports demonstrating the antidiabetic activity of free (non-formulated) apigenin. Ren et al. reported that oral administration of free apigenin (50-100 mg/kg/day) for six weeks significantly improved glucose tolerance in type 2 diabetic rats, resulting in a 34-36% reduction in glucose AUC during the OGTT compared with diabetic control [15]. In contrast, apigenin-loaded SNEDDS in the present study produced a greater reduction in glucose $AUC_{0\text{-}120}$ (approximately 49-60%) following a single

oral dose of 50 mg/kg. Although direct comparison should be interpreted with caution due to differences in animal models, dosing regimens, and OGTT protocols, the greater reduction in blood glucose level observed in the present study suggests that incorporation of apigenin into the SNEDDS may enhance its pharmacological efficacy. This interpretation is supported by our previous pharmacokinetic study, which demonstrated significantly improved intestinal permeability, systemic exposure, and oral bioavailability of apigenin following SNEDDS administration [23]. Therefore, the improved antihyperglycemic activity observed in the present study may result not only from the intrinsic biological activity of apigenin but also from enhanced oral delivery achieved through the SNEDDS formulation.

It is important to consider the OGTT experimental design, which involves a single-dose administration followed by glucose loading and short-term monitoring of blood glucose levels (up to 120 min). As α-glucosidase is primarily localized on the apical surface of enterocytes in the small intestine, a temporal discrepancy may exist between the attainment of peak drug concentrations at the site of action (intestinal wall) and in the systemic circulation (plasma). This acute model is particularly sensitive to intestinal mechanisms regulating glucose absorption but may not fully capture systemic pharmacodynamic effects that emerge after repeated dosing. It is important to notice that apigenin undergoes enterohepatic recycling following oral administration [23,30], resulting in a characteristic double-peak plasma concentration profile in rats, with $T_{peak,1}$ and $T_{peak,2}$ occurring at approximately 1 h and 6 h post-dose, respectively [23]. This pharmacokinetic behavior may contribute to a delayed antihyperglycemic effect, suggesting the need to monitor blood glucose for a longer period. Previous studies have demonstrated that the antihyperglycemic effects of apigenin are typically associated with sustained systemic exposure and longer treatment duration. Therefore, further investigations involving repeated dosing and extended evaluation of glycemic control are warranted.

Despite the promising antihyperglycemic activity observed in the present study, some limitations should be considered before further clinical development of the apigenin-loaded SNEDDS formulations. The current study evaluated only the acute effects following a single oral administration, and the long-term safety of repeated exposure to the formulations remains unknown. Therefore, sub-chronic and chronic toxicity studies are necessary to assess potential toxicological effects associated with prolonged administration. In addition, the antihyperglycemic activity was assessed only in an acute oral glucose tolerance test model. Further investigations in diabetic animal models and under repeated-dose regimens are warranted to verify the long-term therapeutic efficacy and safety of the formulations prior to clinical evaluation.

5. CONCLUSIONS

In conclusion, apigenin-loaded SNEDDS formulations (Formulations A and B) demonstrated favorable safety profiles and significant antihyperglycemic activity in diabetic mice. Both formulations, optimized to enhance dissolution, stability, and oral delivery of apigenin, exhibited glucose-lowering effects comparable to those of glibenclamide. Based on the findings of the present study, the antihyperglycemic activity of apigenin-loaded SNEDDS is likely mediated, at least in part, through inhibition of α-glucosidase, as evidenced by the potent *in vitro* α-glucosidase inhibitory activity and the significant attenuation of postprandial glucose excursions during the oral glucose tolerance test. Importantly, the present findings, together with our previous pharmacokinetic studies demonstrating enhanced intestinal absorption and oral bioavailability of apigenin, suggest that the improved biopharmaceutical performance achieved by SNEDDS can translate into enhanced pharmacodynamic efficacy. These results highlight the potential of SNEDDS as an effective oral delivery strategy for overcoming the poor aqueous solubility and limited bioavailability of apigenin, thereby maximizing its therapeutic potential in the management of postprandial hyperglycemia. Nevertheless, further studies are warranted to evaluate the long-term efficacy, safety, and clinical applicability of apigenin-loaded SNEDDS.

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Author contribution

Boontida Morakul: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing; Funding acquisition; Project administration. Vilasinee Hirunpanich Sato: Data curation; Formal analysis; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing. Veerawat Teeranachaideekul: Data curation; Formal analysis; Investigation; Methodology; Validation; Writing – review & editing. Jannarin Nontakham and Manaw Sangfuang: *In vivo* Methodology. Varaporn Buraphacheep Junyaprasert

and Hitoshi Sato: Conceptualization; Supervision; Writing – review & editing.

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Conflict of interest
None to declare.

Ethics approval
All procedures involving animals were approved by the Institutional Animal Care and Use Committee (IACUC), Faculty of Pharmacy, Mahidol University (Approval No. PYR007/2023).

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