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ORIGINAL RESEARCH

Nutritional and Phytochemical Compositions of *Peperomia pellucida* (L). Kunth from Bogor, West Java, Indonesia, and Its Hypoglycemic Effects in Normoglycemic Sprague-Dawley Rats Subjected to an Acute Glucose Load

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Background: *Peperomia pellucida* (L). Kunth, a perennial plant belonging to the Piperaceae family, grows mainly in wet tropical environments and has been reported to have various biological activities.

Purpose: This study aimed to evaluate the nutritional and phytochemical composition of an ethanol extract of the whole plant *Peperomia pellucida* (EEPP) collected in Bogor, West Java, Indonesia, and its hypoglycemic effects on normoglycemic rats subjected to an acute glucose load.

Methods: Nutritional composition of EEPP was assessed by proximate analysis, and vitamin C and quercetin levels were assessed using HPLC. Total phenols, flavonoids, and sterols were assessed using spectrophotometry, and the phytochemical profiles were assessed using UHPLC-HRMS/MS. The hypoglycemic effects of EEPP at doses of 125, 250, and 500 mg/kg body weight on acute glucose load were evaluated using an oral glucose tolerance test in normoglycemic Sprague-Dawley rats.

Results: EEPP contains high ash, carbohydrates, and protein, and low fat, with a total energy of 236.82 ± 1.15 kcal per 100 g extract. EEPP contains negligible levels of vitamin C and quercetin, a TPC of 15.62 mg GAE/100 g, a TFC of 8.00 mg QE/100 g, and total sterols of 2461.5 mg BSE/100 g. At least 50 metabolites, including flavonoids, flavonoid glycosides, alkaloids, sterols, fatty acid esters, chromenes, and coumarins, have been identified. EEPP demonstrated hypoglycemic properties by reducing 14.7–35.8% of blood glucose levels in rats subjected to an acute glucose load, but this was not statistically significant ($p > 0.05$) compared to the negative control group.

Conclusion: Because of its nutritional and phytochemical composition, *Peperomia pellucida* may have the potential to be developed into a nutraceutical supplement, particularly for maintaining blood glucose levels. However, further studies are needed to confirm this effect.

Keywords: flavonoids, pellucidin A, *Peperomia* sp, phytosterols, piperaceae, terpenoids

Introduction

Peperomia pellucida (L). Kunth (Piperaceae), a perennial plant native to Africa and South America, has been introduced to Asia and Australia. This plant is an epiphyte and grows mainly in wet tropical environments.[1] Ethnobotanical studies have been conducted in Singapore, India, Myanmar, Bangladesh, and Indonesia, revealing its use in managing respiratory diseases, cancer, and protecting the liver,[2–8] while in silico, in vitro, and in vivo pharmacological assays delineated antidiabetic (by inhibiting alpha-glucosidase and alpha-amylase), antihypertensive, anti-inflammatory, and antimicrobial activities,[8] which are attributed to its phytochemicals.

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Previous studies on the proximate, nutritional, and phytochemical composition of *P. pellucida* resulted in varied levels of proximate compositions due to different geographic settings, such as *P. pellucida* grown in Malaysia contained abundant carbohydrates and ash contents,[9] which are similar to those harvested at Nigeria,[10] however those harvested from South-Eastern Nigeria were low in protein, carbohydrates, and total ash levels.[11] *P. pellucida* collected at the Federal University of Pará in Brazil was reported to contain 16 compounds,[12] while the plant collected at Can Tho City in Vietnam was reported for its high total phenols and total flavonoids.[13] Thirty-two compounds were isolated from *P. pellucida* harvested in Tamil Nadu, India.[14] A compound known as 2-methyl-2-(4-methylpent-3-enyl)-6-(propan-2-ylidene)-3,4,6,7-tetrahydropyrano[4,3-g] chromen-9(2H)-one was successfully isolated from the leaves of *P. pellucida* collected in West Java, Indonesia,[15] while nonpolar compounds have been isolated from the aerial part of *P. pellucida* collected at Banten, Indonesia,[16] and three phenylpropanoids and two lignan derivatives were identified in the wild plant of *P. pellucida* collected at Cagak and Ciater Region, West Java, Indonesia.[17] In this regard, the present study was designed to determine the nutritional and phytochemical compositions of the whole plant of *P. pellucida* collected from Bogor, West Java, Indonesia, and its hypoglycemic effects on normoglycemic Sprague-Dawley rats subjected to an acute glucose load.

Methods

Plant Collection and Extraction

Plants were cultivated and harvested in October 2024 at the Indonesian Spices Medicinal and Aromatic Plants Instrument Standard Testing Institute (Bogor, West Java, Indonesia). The plant materials were taxonomically identified and authorized by Dr. Ratih Damayanti (https://www.scopus.com/authid/detail.uri?authorId=57213220550), a botanist at the Herbarium Bogoriense, and the Director of the Directorate of Scientific Collection Management, National Research and Innovation Agency. The plant materials were confirmed as *Peperomia pellucida* (L). Kunth of the family Piperaceae, with specimen number B-3873/2024. The plant is not categorized as an endangered species or protected heritage, and complies with the International Union for Conservation of Nature (IUCN) Red List Index (RLI).

The ethanol extract of *Peperomia pellucida*, abbreviated as EEPP, was prepared as follows: approximately 21.7 kg of fresh *P. pellucida* whole plants were sorted, separated from dirt, soil, and other contaminants, discarded rotten parts, then washed under tap water, resulting in 3.3 kg of wet plant material (see Figure 1a). The plant materials were cut and air-dried in a shady room for 14 days, followed by oven-drying at 40°C (Memmert UN55) for two hours, resulting in 1.57 kg of dried plants (52.42%). The dried plants were ground and passed through a 60-mesh sieve to yield 1.55 kg of plant powder. This powder was then cold-extracted using 70% technical-grade ethanol (Onemed). Ethanol (70%) was selected as the solvent owing to its capability to dissolve numerous phytochemicals. The excess ethanol solvent was removed using a rotary evaporator (Biobase RE-52C) at a fixed temperature of 45°C, speed of 70 rpm, using a rotor diameter of 24/28 mm, which yielded a 24.66% *w/w* concentrate extract (Figure 1b).

Proximate and Nutritional Analysis

The nutritional composition of EEPP was analyzed according to the Food Energy – Methods of Analysis and Conversion Factors for carbohydrate analysis,[18] while the Indonesian National Standard SNI 01–2891-1992 and the Official Methods of Analysis 2023 (https://www.aoac.org/official-methods-of-analysis/) were adopted for total ash, protein, fat, and water content analysis.[19–22] Additionally, a reversed-phase high-performance liquid chromatography (RP-HPLC; Shimadzu Prominence-I LC-2030C) with an Inertsil octadecylsilane (C18) column (150 × 4.6 mm; 5 µm) and an ultraviolet (UV) detector was employed for the determination of vitamin C and quercetin in EEPP, following previous methods with modifications.[23–25]

The total ash was determined based on the principle that organic substances decompose into water (H_2O) and carbon dioxide (CO_2). Approximately 6 g of EEPP was placed in a crucible, combusted in a furnace set at 550°C for 4 h for completion, cooled, and weighed. Water content was determined based on the weight loss of 10 g EEPP during heating at 105 ± 2°C in an oven for 5 h. Protein in 0.5 g EEPP was determined using the semi-micro Kjeldahl method, whereas fat was determined using the Soxhlet method. Carbohydrates were determined by subtracting the total percentages of water, ash, protein, and fat using the following formula:

$$\text{Carbohydrates}(\%) = 100\% - (\%\text{water} + \%\text{total ash} + \%\text{protein} + \%\text{fat})$$

Figure 1 (**a**) Wet plant material, and (**b**) concentrated ethanol extract of *Peperomia pellucida* of the family Piperaceae, obtained from the Indonesian Spices Medicinal and Aromatic Plants Instrument Standard Testing Institute, Bogor, Indonesia.

Determination of vitamin C in EEPP was carried out by following previous studies,[23–25] using an RP-HPLC (Shimadzu Prominence-I LC-2030C) with an octadecylsilane (C18) column (150 × 4.6 mm; 5 µm) for the stationary phase, and an isocratic elution mobile phase consisting of 30% HPLC-grade water, 0.1% high-purity trifluoroacetic acid, and 70% HPLC-grade methanol, at a flow rate of 0.8 mL/min, a column temperature of 25°C, injection volume of 10 µL, detection at 245 nm, and a total run time of 20 min. Initially, a series of vitamin C standard solutions was prepared in a 3% w/v analytical grade metaphosphoric acid solution and 1 mM analytical grade ethylenediamine tetraacetate (EDTA) to obtain two standard curves: one at low concentrations and one at high concentrations of standard vitamin C. The low vitamin C standard curve was prepared using the following concentrations of 0.21, 1.01, 1.84, 2.68, 3.52, 4.35, and 5.18 µg/mL, resulting in a linear regression equation of $y = 35{,}933.73x - 3084.07$, with an R^2 of 0.9999 (Figure 2a), and the high vitamin C standard curve was prepared using 5.33, 25.79, 51.80, 77.56, 103.23, 129.33, and 155.45 µg/mL, resulting in

a linear regression equation of y = 37,585.56x-17075.92, with an R^2 of 1.0000 (Figure 2b), each with a ± 3% residual. Approximately 5 g of EEPP was dissolved in 3% w/v analytical grade metaphosphoric acid solution and 1 mM analytical grade ethylenediamine tetraacetate (EDTA), sonicated for 15 min, diluted to 10 mL, centrifuged, filtered using a polytetrafluoroethylene (PTFE) 0.45 µm syringe filter, and transferred to an HPLC vial for immediate analysis.

Determination of quercetin in EEPP was carried out following a previous method of D'Mello et al (2011)[26] using a validated RP-HPLC with an Inertsil octadecylsilane (C18) column (150 × 4.6 mm; 5 µm) for the stationary phase, and an isocratic elution mobile phase consisting of 30% HPLC-grade water, 0.1% high-purity trifluoroacetic acid, and 70% HPLC-grade methanol, at a flow rate of 0.8 mL/min, a column temperature of 25°C, injection volume of 50 µL, detection at 254 nm, and a total run time of 20 min. Initially, a series of high-purity (99.0%) quercetin standard solutions was prepared in HPLC-grade methanol at concentrations of 1, 4, 10, and 60 µg/mL, resulting in a linear regression equation of y = 0.4909x + 1.005, with an R^2 of 0.9986 (Figure 2c). The method was validated, resulting in an intraday precision relative standard deviation of 0.80%, interday precision relative standard deviation of 0.62%, recovery of 96–105%, limit of detection (LOD) of 4.5 µg/mL, and limit of quantification (LOQ) of 12 µg/mL.

Total Phenols and Total Flavonoids

Total phenols and flavonoids in EEPP were assayed using the procedures described by Tang et al (2020),[27] with some modifications.

For total phenols analysis, briefly, 25 µL of EEPP was reacted with 25 µL of Folin–Ciocâlteu reagent and 200 µL of water. The reaction mixture was incubated at room temperature for 5 min, after which 25 µL of 10% sodium carbonate was added. The mixture was then incubated for 60 min in the dark. The absorbance of the reaction mixture was measured at 765 nm. The total phenols in EEPP were quantified from a gallic acid curve prepared with high-purity gallic acid standard at various concentrations ranging from 15.63–125 µg/mL, resulting in a linear regression equation of y = 0.0087x - 0.0057, with an R^2 of 0.9948 (Figure 3a), and the result was expressed as mg of gallic acid equivalents (GAE) per g dry weight of EEPP, following a previous study.[28]

For total flavonoids analysis, 80 µL of EEPP was reacted with 80 µL of 2% analytical grade aluminum chloride in ethanol and 120 µL of 50 g/L analytical grade sodium acetate solution. The reaction mixture was incubated at room temperature for 2.5 h, and the absorbance of the mixture was measured at 440 nm. The total flavonoids were quantified from a quercetin curve prepared with high-purity (99.0%) quercetin standard at various concentrations ranging from 7.81–125 µg/mL, resulting in a linear regression equation of y = 0.0089x + 0.1079, with an R^2 of 0.9998 (Figure 3b), and the result was expressed as mg of quercetin equivalent (QE) per g of dry weight of EEPP, following a previous study.[28]

Total Sterols

Total sterols in EEPP were assayed using the procedure described by Poudel et al (2020)[29] with some modifications. Briefly, EEPP (0.5 g) was dissolved in 2000 µL of distilled water, and 1000 µL of chloroform was added. The reaction mixture was sonicated at room temperature for 20 min, and the chloroform phase was separated. This procedure was repeated three times, resulting in a total chloroform phase volume of 3 mL. EEPP samples (50, 100, 200, and 300 µL) were added with ethanol to obtain a total of 1 mL EEPP and reacted with the Lieberman-Burchard reagent. The absorbance of the mixture was measured at a wavelength of 625 nm. The total sterols in EEAP were quantified from a β-sitosterol curve prepared with a high-purity β-sitosterol standard reacted with the Lieberman-Burchard reagent at various concentrations ranging from 40–200 µg/mL, resulting in a linear regression equation of y = 0.0024x + 0.0079, with an R^2 of 0.9984 (Figure 3c), and the result was expressed as mg of β-sitosterol equivalent (BSE) per g of dry weight of EEPP, following a previous study.[29]

Metabolite Profiling by UHPLC-HRMS/MS

Metabolite profiling of EEPP was performed using a Thermo Scientific Vanquish UHPLC Binary Pump coupled with a high-resolution Orbitrap mass spectrometer (Thermo Scientific Q Exactive Hybrid Quadrupole-Orbitrap High Resolution Mass Spectrometer). Chromatographic separation was carried out on a Thermo Scientific Accucore Phenyl-Hexyl column (100 mm × 2.1 mm ID × 2.6 µm) maintained at 40°C. The mobile phases consisted of mass spectrometry-grade water with 0.1% analytical

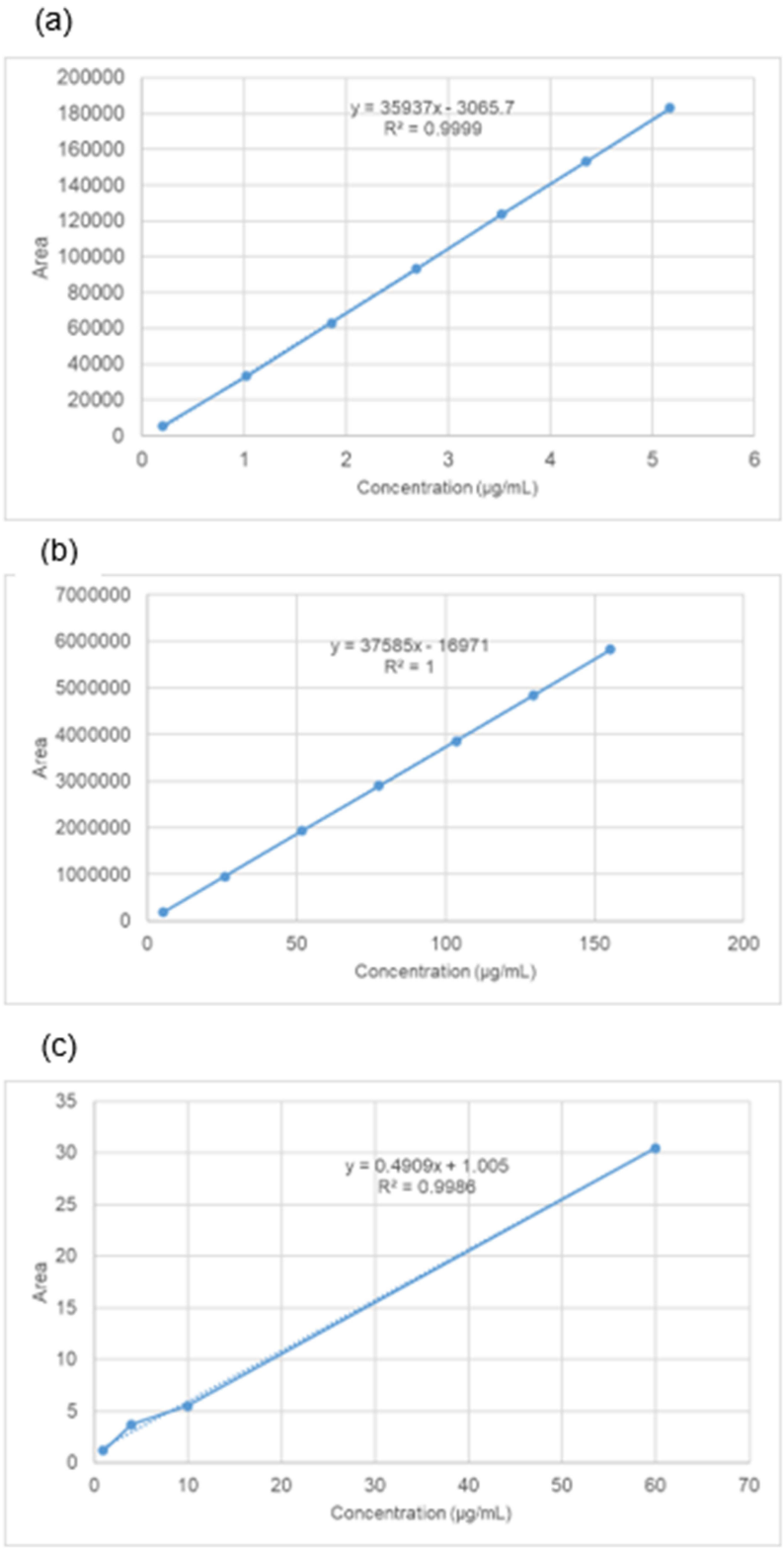

Figure 2 HPLC analysis of (**a**) vitamin C, showing the low vitamin C standard curve (prepared using a series of concentrations of 0.21 µg/mL, 1.01 µg/mL, 1.84 µg/mL, 2.68 µg/mL, 3.52 µg/mL, 4.35 µg/mL, and 5.18 µg/mL, resulting in a linear regression equation of $y = 35{,}933.73x - 3084.07$, with an R^2 of 0.9999); (**b**) vitamin C, showing the high vitamin C standard curve (prepared using a series of concentrations of 5.33 µg/mL, 25.79 µg/mL, 51.80 µg/mL, 77.56 µg/mL, 103.23 µg/mL, 129.33 µg/mL, and 155.45 µg/mL, resulting in a linear regression equation of $y = 37{,}585.56x - 17{,}075.92$, with an R^2 of 1.0000); and (**c**) quercetin, showing the quercetin standard curve (prepared using a series of concentrations of 1 µg/mL, 4 µg/mL, 10 µg/mL, and 60 µg/mL, resulting in a linear regression equation of $y = 0.4909x + 1.005$, with an R^2 of 0.9986).

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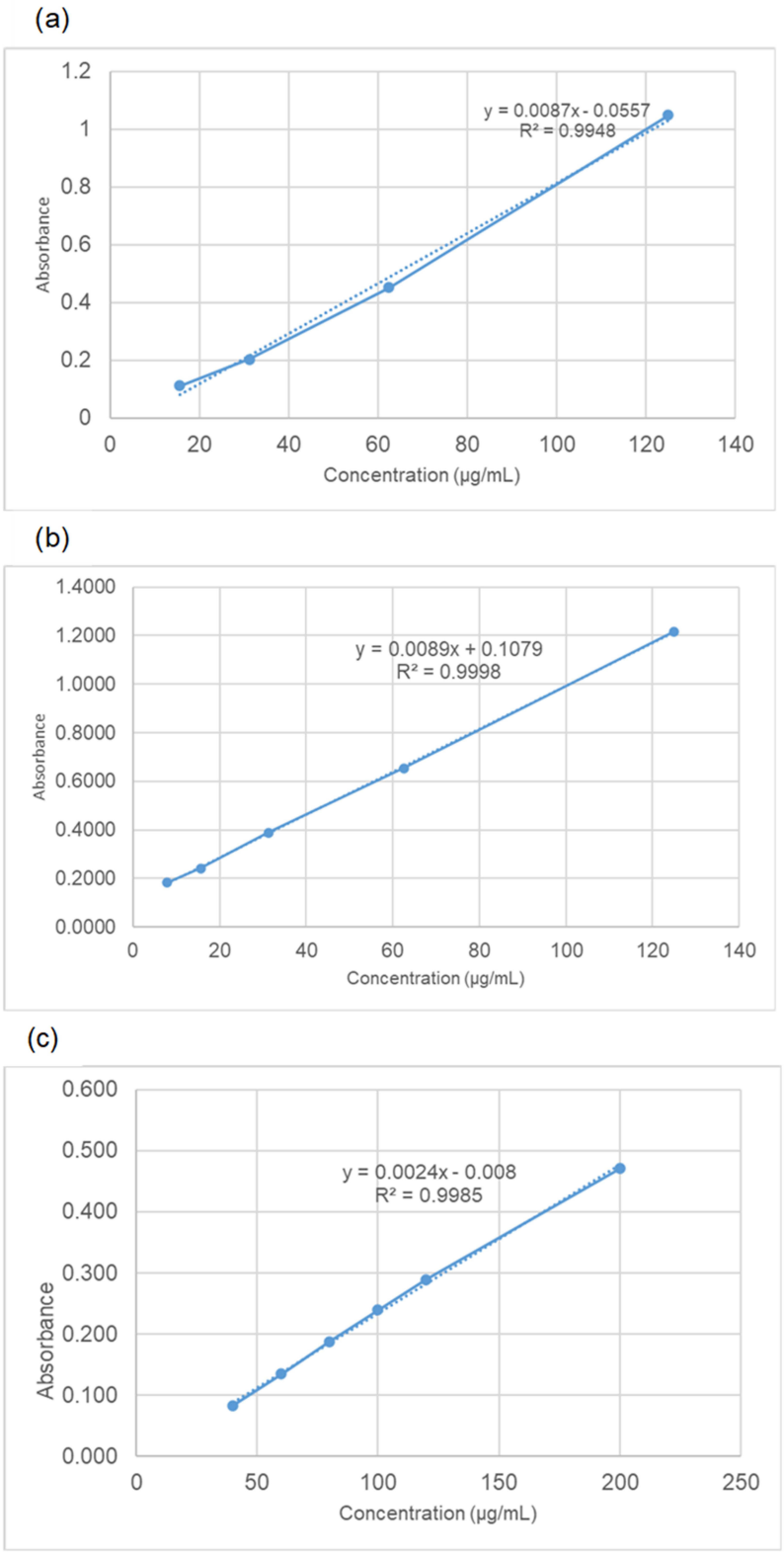

Figure 3 Spectrophotometric analysis of (**a**) phenols, showing the gallic acid standard curve (prepared using a series of concentrations ranging from 15.63–125 µg/mL), resulting in a linear regression equation of $y = 0.0087x - 0.0057$, with an R^2 of 0.9948); (**b**) flavonoids, showing the quercetin standard curve (prepared using a series of concentrations ranging from 7.81–125 µg/mL), resulting in a linear regression equation of $y = 0.0089x + 0.1079$, with an R^2 of 0.9998); and (**c**) sterols, showing the β-sitosterol standard curve (prepared using a series of concentrations ranging from 40–200 µg/mL), resulting in a linear regression equation of $y = 0.0024x + 0.0079$, with an R^2 of 0.9984).

grade formic acid (A) and mass spectrometry-grade methanol with 0.1% analytical grade formic acid (B). The gradient program started at 5% B, gradually increased to 90% B within 16 min, held at 90% for 4 min, and then returned to the initial condition (5% B) for 25 min. The flow rate was set at 0.3 mL/min, with an injection volume of 3 µL. The analyzed sample was EEPP prepared at 1 mg/mL in 96% methanol. Mass spectrometric detection was performed using electrospray ionization (ESI) in positive mode, with a capillary voltage of 3.30 kV, capillary temperature of 320°C, and a scan range of m/z 66.7–1000. Data were acquired in the full-scan mode, followed by MS/MS fragmentation for structural elucidation. Metabolite identification was achieved by matching the experimental spectra against online databases, such as ChemSpider (https://www.chemspider.com/) and PubChem (https://pubchem.ncbi.nlm.nih.gov/).

Hypoglycemic Effects of EEPP in Normoglycemic Sprague-Dawley Rats Subjected to an Acute Glucose Load

The protocol for animal handling was approved on 17 April 2025 by the Research Ethics Committee of Universitas Padjadjaran, Indonesia (https://kep.unpad.ac.id/; approval document number 324/UN6.KEP/EC/2025, signed by Dr. Muhammad Hasan Bashari). The procedure was carried out by strictly adhering to The Guide for the Care and Use of Laboratory Animals (NRC 2011; eighth edition) (https://grants.nih.gov/grants/olaw/guide-for-the-care-and-use-of-laboratory-animals.pdf) (Guide for the Care and Use of Laboratory Animals. 2011),[30] and The ARRIVE guidelines 2.0 Animal Research: Reporting of In Vivo Experiments (https://arriveguidelines.org/arrive-guidelines). The procedures were carried out at the Pharmacology Laboratory, Faculty of Pharmacy, National Institute of Science and Technology, Jakarta, Indonesia.

Total animals needed for the experiments were calculated using G*Power version 3.1.9.7 with one-way analysis of variance (ANOVA) at fixed-effect, α set at 0.05, power at 0.80, and the number of groups at 6, and an effect size of 0.80,[31] resulting in a minimum ideal sample of 30 rats (or 5 rats per group).

Thirty healthy normoglycemic male Sprague-Dawley rats aged 2–3 months, weighing 180 ± 220 g, were purchased from an animal breeding house in Bogor, West Java, Indonesia, and used for the acute glucose load test. The rats were acclimatized in husk-based polypropylene cages (30 × 25×10 cm^3) with standard environmental conditions of 25–26°C, a 12-h light and 12-h dark cycle, and a relative humidity of 55 ± 2%, at the animal house of Pharmacology Laboratory, Faculty of Pharmacy, National Institute of Science and Technology, Jakarta, Indonesia, for 5 days before the experiment. The cages were cleaned, and the husks were replaced every three days to ensure animal welfare. The rats were fed daily with a standard diet consisting of 15% protein, 8% water, 14% raw fiber, 14% ash, a minimum 2% of raw fat, 0.8% calcium, 0.5% phosphorus, and a digestible energy equivalent to 2400 kcal/kg or 2 g/rat/day. Rats were included in the experiment after the acclimatization, if they did not lose more than 20% of their body weight. In this study, all rats were included in the experiments because they showed normal, healthy behavior.

The rats were randomly assigned to six groups (five rats per group per cage) using a stratified randomization technique, which involves first categorizing animals into subgroups (strata) based on their aggressiveness, and then randomly assigning each rat within its subgroup to a control group or treatment, as follows: the normal control group (treated with 0.5% sodium carboxymethyl cellulose), negative control group (treated with 0.5% sodium carboxymethyl cellulose), positive control group (sitagliptin, a DPP-4 inhibitor, at a dose of 2.5 mg per rat, dispersed in 0.5% sodium carboxymethyl cellulose), and three extract groups, which were treated with EEPP 125 mg/kg body weight, 250 mg/kg body weight, or 500 mg/kg body weight dispersed in 0.5% sodium carboxymethyl cellulose. Rats were subjected to food privation for eight hours (06.00 am to 02.00 pm) before the experiments. The rats in all groups, except the normal control group, were administered a glucose solution containing 2 g glucose/kg body weight by oral gavage. Acarbose or EEPP dispersed in 0.5% sodium carboxymethyl cellulose was administered in a mixture with glucose. Blood, approximately 0.5 µL, was taken from the lateral vein using the tail vein puncture technique. Blood glucose levels were measured using an Easy Touch blood glucose meter at T0 (approximately 5 min after sitagliptin or EEPP intervention mixed with glucose, representing the baseline of each group), T30 (30 min after glucose load), T60 (60 min after glucose load), and T120 (120 min after glucose load).[32–34] The total area under the curve (AUC), which represents blood glucose levels, was calculated using the trapezoid rule.[34–36]

$$AUC = \Sigma\ [(C_n - C_o)\ +\ (C_{n+1} - C_0)]\ \times\ (t_{n+1} - t_0)]$$

To further investigate the hypoglycemic effects of EEPP, we performed a similar assessment on another group of rats, using a different drug control, namely acarbose at a dose of 2.5 mg per rat, and blood glucose was measured at T0, T30, T60, and T120.

At the end of the study, the rats were euthanized by a cervical dislocation technique performed by a trained individual, and death was confirmed when there was no respiration for one minute, no heartbeat, and no eye response to stimuli. The remains were wrapped in medical waste plastics and buried in an animal waste burial.

Statistical Analysis

IBM SPSS Statistics version 25.0 for Windows was used to analyze the data. Significant differences between groups were analyzed using one-way analysis of variance (ANOVA) followed by the least significant difference (LSD) test for multiple comparisons. If the data were not normally distributed, a non-parametric Mann–Whitney test was performed. All data are presented as an average ± SD; $p < 0.05$ indicates a significant result.

Results

Proximate and Nutritional Composition in EEPP

Determination of proximate and nutritional composition of the ethanol extract of the whole plant of *P. pellucida* cultivated in Bogor, West Java, Indonesia (EEPP) in triplicate resulted in a total ash level of 29.39 ± 0.21%, water of 14.38 ± 0.12%, carbohydrates of 39.44 ± 0.59%, proteins of 14.40 ± 0.22%, fat of 2.36 ± 0.03%, and a total energy of 236.82 ± 1.15 kcal per 100 g extract. Moreover, the extract contains negligible levels of vitamin C and quercetin, at 1.17 mg/100 g and 0.01 mg/100 g, respectively, calculated using the standard curves.

Total Phenols, Flavonoids, and Sterols in EEPP

The total phenols (TPC) of EEPP were calculated using the gallic acid standard curve, resulting in 15.62 mg GAE/100 g dry EEPP. The total flavonoids (TFC) were calculated using the quercetin standard curve, resulting in 8.00 mg QE/100 g dry EEPP. The total sterols were calculated using the β-sitosterol standard curve, resulting in 2461.5 mg BSE/100 g dry EEPP.

Metabolite Profiling by UHPLC-HRMS/MS

Eventually, we further analyzed the metabolite profile of the extract using UHPLC-HRMS/MS and identified 50 metabolites (summarized in Table 1). The chromatograms of the metabolites are shown in Figure 4. Of these 50 metabolites, only three flavonoid glucosides were identified, which explains the low TFC value. The flavonoids in EEPP were present in their glycoside structure, namely corymboside (a flavonoid apigenin-6-arabinoside-8-glucoside), schaftoside (a flavonoid apigenin-6-glucoside-8-arabinoside), and rutin (a flavonoid quercetin 3-O-glucoside), with relative abundances of 8.06%, 4.96%, and 1.78%, respectively. Moreover, only eight metabolites were confirmed to have antidiabetic activity: corymboside,[37] quassin,[38] α-eleostearic acid,[39] schaftoside,[40] rutin,[41,42] syringic acid,[43,44] and glycitein.[45] EEPP contains alkaloids, sterols such as ergosta-3,5-diene (synonym: 24-methylcholesta-3,5-diene), fatty acid esters, chromenes, coumarins, and other metabolites.

Hypoglycemic Effects of EEPP on Normoglycemic Sprague-Dawley Rats Subjected to an Acute Glucose Load

The hypoglycemic effects of EEPP on normoglycemic Sprague-Dawley rats subjected to an acute glucose load are presented in Tables 2–4 for the sitagliptin set and Tables 5–7 for the acarbose set.

For the sitagliptin set: At T0, glucose levels ranged from the lowest at 81.8 ± 8.7 mg/dL (in the normal control group) to the highest at 482.8 ±133.3 mg/dL (in the negative control group). At this time point, there was a significant difference between the groups ($p = 0.000$ in Table 3), and a significant difference between all groups compared with the negative control ($p < 0.05$ in Table 4). At T30, glucose levels ranged from the lowest at 85.8 ± 9.9 mg/dL (in the normal control group) to the highest at 332.0 ± 61.9 mg/dL (in the negative control group). At this time point, there was a significant difference between the groups ($p = 0.021$ in Table 3), and a significant difference between the normal control, EEPP 125 mg/kg body weight, and EEPP 500 mg/kg body weight compared to the negative control ($p < 0.05$ in Table 4),

Table 1 UHPLC-HRMS/MS Data of Metabolites in the Ethanol Extract of *Peperomia pellucida* L. Kunth

No	Name of Compound [Class of Metabolite]	Molecular Formula	$[M+H]^+$ m/z		Retention Time (min)	Δ Mass (ppm)	Main Product IONS (MS/MS, m/z)	Area (Max)	Relative Abundance (%)	Antidiabetic-Related Biological Activity [Reference]
			Calculated Mass (Da)	Accurate Mass (Da)						
1	Corymboside [Flavonoid apigenin-6-arabinoside-8-glucoside]	$C_{26}H_{28}O_{14}$ [PubChem CID 13644660]	564.147	565.154	5.28	−2.16	121.028, 295.060, 307.059, 321.076, 325.069, 337.070, 363.085, 379.080, 409.090, 427.103	8.896×10^8	8.06	Antioxidant and anti-inflammatory [37]
2	5,7-Dihydroxy-2-(4-hydroxyphenyl)-6,8-bis [3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yl]-4H-chromen -4-one	$C_{27}H_{30}O_{15}$ [PubChem CID 3084407]	594.157	595.163	4.68	−3.09	189.018, 295.059, 307.059, 325.069, 335.089, 379.080, 427.101, 457.112, 523.123	8.736×10^8	7.92	N/A
3	SB236057A [Indole–piperidine–oxadiazole derivative]	$C_{33}H_{34}ClN_4O_3$ [PubChem CID 10483134]	534.262	535.269	14.80	−1.68	91.1990, 92.2054, 226.869, 315.084, 405.207, 419.224, 435.254, 447.213, 535.269	8.048×10^8	7.30	N/A
4	Quassin [Triterpene lactone]	$C_{22}H_{28}O_6$ [PubChem CID 65571]	388.188	389.194	11.89	−2.81	371.185, 353.175, 325.164	7.069×10^8	6.41	Antidiabetic [38]
5	1-Stearoylglycerol [Monoacylglycerol, An ester of a fatty acid]	$C_{21}H_{42}O_4$ [PubChem CID 22035687]	358.308	359.314	15.34	−1.76	57.0703, 71.0859, 85.1014, 123.116, 213.230, 249.256, 267.268, 285.277, 341.304	6.846×10^8	6.21	N/A
6	Stearamide [Fatty acid amide]	$C_{18}H_{37}NO$ [PubChem CID 31292]	283.287	284.293	15.63	−2.83	57.0703, 72.0447, 102.091, 116.107, 144.138, 243.047, 248.242, 284.294	6.385×10^8	5.79	N/A
7	α-Eleostearic acid [Conjugated fatty acid]	$C_{18}H_{30}O_2$ [PubChem CID 5281115]	278.224	279.231	12.51	−2.44	67.0545, 81.0701, 95.0856, 109.101, 123.116, 137.132, 173.132, 261.221, 279.231	5.566×10^8	5.04	Antidiabetic [39]

(*Continued*)

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Table 1 (Continued).

No	Name of Compound [Class of Metabolite]	Molecular Formula	$[M+H]^+$ m/z		Retention Time (min)	Δ Mass (ppm)	Main Product IONS (MS/MS, m/z)	Area (Max)	Relative Abundance (%)	Antidiabetic-Related Biological Activity [Reference]
			Calculated Mass (Da)	Accurate Mass (Da)						
8	9-Oxo-10(E),12(E)-octadecadienoic acid [Fatty acid]	$C_{18}H_{30}O_3$ [PubChem CID 24775]	294.219	333.181	12.85	−2.65	71.0859, 93.0701, 95.0857, 107.085, 179.142, 240.082, 259.205, 277.216	5.554×10^8	5.04	N/A
9	Schaftoside [Flavonoid apigenin-6-glucoside-8-arabinoside]	$C_{26}H_{28}O_{14}$ [PubChem CID 5283011]	564.147	565.154	4.96	−2.11	35[illegible]087, 311.07[illegible], 283.061	5.474×10^8	4.96	Antidiabetic [40]
10	NP-000465	$C_{17}H_{14}O_6$ [PubChem CID 2724360]	314.078	315.085	10.23	−3.34	76.8573, 109.028, 121.064, 178.057, 243.065, 267.044, 272.067, 300.062, 315.085	5.373×10^8	4.87	N/A
11	Rutin [Flavonoid quercetin 3-O-glucoside]	$C_{27}H_{30}O_{16}$ [PubChem CID 5280805]	610.152	611.159	4.24	−1.78	85.0284, 311.054, 323.054, 325.068, 341.064, 353.064, 365.064, 443.096, 473.107, 491.107	1.969×10^8	1.78	Antidiabetic [41,42]
12	Methyl palmitate [Methyl ester of palmitic acid]	$C_{17}H_{34}O_2$ [PubChem CID 8181]	270.256	271.262	16.90	−0.56	57.0703, 103.075, 117.090, 121.101, 219.210, 230.246, 271.262	1.629×10^8	1.48	N/A
13	2,4,5-Trimethoxybenzaldehyde [Aromatic aldehyde]	$C_{10}H_{12}O_4$ [PubChem CID 20525]	196.073	197.080	7.19	−2.15	109.064, 107.085, 111.044, 123.044, 138.067, 139.038, 154.062, 169.085, 197.080	1.569×10^8	1.42	N/A
14	NP-016582	$C_{20}H_{35}NO$ [PubChem CID 104033]	305.271	306.278	14.86	−3.8	67.0546, 81.0701, 95.0857, 109.101, 154.122, 204.583, 268.955, 306.278	1.539×10^8	1.40	N/A
15	Araadenosine [Synonym: vidarabine or arabinosyladenine]	$C_{10}H_{13}N_5O_4$ [PubChem CID 60961]	267.097	268.103	1.03	−1.01	85.0285, 119.035, 136.061, 137.045, 152.056, 268.103	1.434×10^8	1.30	N/A

16	L-Phenylalanine [Amino acid]	$C_9H_{11}NO_2$ [PubChem CID 6140]	165.079	166.086	1.38	−1.28	79.0545, 93.0700, 103.054, 107.049, 120.080, 131.049, 149.059, 166.086	1.030×10^8	0.93	N/A
17	(-)-Caryophyllene oxide [Sesquiterpene oxide]	$C_{15}H_{24}O$ [PubChem CID 1742210]	220.182	221.189	13.04	−1.63	95.0857, 105.070, 119.085, 147.116, 203.179, 221.044	9.502×10^7	0.86	N/A
18	Syringic acid [Dimethoxybenzene derivative of gallic acid]	$C_9H_{10}O_5$ [PubChem CID 10742]	198.052	199.059	4.96	−2.48	53.0390, 67.0545, 95.0493, 123.044, 140.046, 155.070, 181.049, 199.180, 199.060	9.428×10^7	0.85	Antidiabetic [43,44]
19	5-hydroxy-3-(4-methoxyphenyl)-7-[(3,4,5-trihydroxy-6-{[(3,4,5-trihydroxy-6-methyloxan-2-yl) oxy] methyl} oxan-2-yl) oxy]-4H-chromen-4-one	$C_{28}H_{32}O_{14}$ [PubChem CID 45782929]	592.179	593.186	5.88	−0.55	85.0287, 267.064, 270.051, 285.075, 297.074, 327.085, 447.127, 496.070, 593.186	8.725×10^7	0.79	N/A
20	Tonkinelin [Acetogenin compound]	$C_{37}H_{70}O_4$ [PubChem CID 3083512]	578.526	579.533	21.62	−2.88	57.0704, 67.0545, 159.145, 348.470, 426.768, 579.534, 590.885	8.487×10^7	0.77	N/A
21	12-Oxo phytodienoic acid [Carboxylic acid]	$C_{18}H_{28}O_3$ [PubChem CID 5280411]	292.203	293.210	12.39	−1.48	79.0545, 107.085, 145.101, 147.116, 149.095, 219.174, 229.194, 275.200	6.336×10^7	0.57	N/A
22	Erucamide [Fatty acid amide]	$C_{22}H_{43}NO$ [PubChem CID 5365371]	337.333	338.341	17.08	−3.18	57.0703, 72.0811, 97.1012, 134.096, 303.303, 321.314, 338.284, 338.340	6.320×10^7	0.57	N/A
23	Acridine-9(10H)-thione [Heteroaromatic alkaloid derivative]	$C_{13}H_9NS$ [PubChem CID 2818474]	211.045	212.052	11.77	−2.92	65.0388, 88.9525, 109.010, 152.078, 169.081, 180.073, 212.052	5.560×10^7	0.50	N/A
24	Methyl isonicotinate [Methyl ester of nicotinic acid]	$C_7H_7NO_2$ [PubChem CID 227]	137.048	138.055	0.82	−0.28	93.0699, 92.0496, 94.0652, 96.0445, 110.060, 121.064, 133.054, 138.054	5.453×10^7	0.49	N/A

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Table 1 (Continued).

No	Name of Compound [Class of Metabolite]	Molecular Formula	$[M+H]^+$ m/z		Retention Time (min)	Δ Mass (ppm)	Main Product IONS (MS/MS, m/z)	Area (Max)	Relative Abundance (%)	Antidiabetic-Related Biological Activity [Reference]
			Calculated Mass (Da)	Accurate Mass (Da)						
25	Bis-2-ethylhexyl-adipate [Ester of adipic acid]	$C_{22}H_{42}O_4$ [PubChem CID 227085]	370.308	371.315	17.09	−0.13	111.044, 147.065, 163.409, 241.180, 263.268, 268.264, 336.760	5.012×10^7	0.45	N/A
26	6-Methylquinoline [Quinoline]	$C_{10}H_9N$ [PubChem CID 7059]	143.073	144.080	3.44	−1.68	56.9652, 70.0008, 85.9600, 98.0602, 102.970, 143.072, 144.080	4.114×10^7	0.37	N/A
27	Hexadecanamide [Fatty acid amide]	$C_{16}H_{33}NO$ [PubChem CID 69421]	255.256	256.263	14.47	−1.21	57.0703, 88.0758, 102.091, 116.107, 130.122, 156.009, 215.016, 256.263	4.018×10^7	0.36	N/A
28	Ethyl palmitoleate [Ethyl ester of palmitoleic acid]	$C_{18}H_{34}O_2$ [PubChem CID 6436624]	282.256	283.262	15.48	−1.09	57.0703, 69.0702, 83.0857, 95.0857, 121.103, 135.116, 177.163, 240.662, 247.241, 265.252	**3.677×10^7**	0.33	N/A
29	5,7-dihydroxy-2-(4-hydroxyphenyl)-6,8-bis (3,4,5-trihydroxyoxan-2-yl)-4H-chromen -4-one [Anthraquinone glycoside of ruberythric acid]	$C_{25}H_{26}O_{13}$ [PubChem CID 92101]	534.137	535.144	5.59	−0.28	121.028, 295.059, 307.059, 321.075, 351.086, 379.086, 409.092, 481.112, 499.122	3.323×10^7	0.30	N/A
30	NP-018730	$C_{21}H_{20}O_{10}$ [PubChem CID 5281377]	432.106	433.112	5.67	0.12	84.9101, 121.028, 283.060, 284.068, 295.059, 313.070, 323.091, 415.101, 433.112	2.897×10^7	0.26	N/A
31	Tridemorph [Morpholine]	$C_{19}H_{39}NO$ [PubChem CID 32518]	297.302	298.309	15.80	−2.72	57.070, 102.091, 116.107, 130.122, 199.656, 199.656, 257.062, 298.123, 298.310	2.823×10^7	0.26	N/A

32	Prolyl leucine [Amino acid]	$C_{11}H_{20}N_2O_3$ [PubChem CID 6420119]	228.147	229.154	1.16	−0.76	70.0655, 78.6304, 114.055, 142.086, 170.080, 229.154, 229.031	2.720×10^7	0.25	N/A
33	trans-3-Indoleacrylic acid	$C_{11}H_9NO_2$ [PubChem CID 5375048]	187.063	188.070	2.16	−0.75	85.0283, 91.0544, 115.054, 117.069, 118.065, 144.080, 146.059, 188.070	2.643×10^7	0.24	N/A
34	10-methoxy-4H-benzo[4,5] cyclohepta[b] thiophen-4-one	$C_{14}H_{10}O_2S$ [PubChem CID 2825162]	242.040	243.047	15.13	−1.52	93.0696, 105.069, 131.085, 133.101, 145.101, 159.116, 187.147, 243.047, 243.210	2.536×10^7	0.23	N/A
35	Guanine [Purine nucleoside base]	$C_5H_5N_5O$ [PubChem CID 135398634]	151.049	152.056	1.05	−1.31	108.081, 109.050, 110.035, 128.045, 135.030, 153.040, 152.056	2.192×10^7	0.20	N/A
36	3-Acetylmorphine [Alkaloid]	$C_{19}H_{21}NO_4$ [PubChem CID 5462504]	327.146	328.152	4.93	−2.17	58.0656, 137.022, 191.084, 207.079, 237.090, 265.085, 282.088, 283.097, 297.111, 328.153	2.012×10^7	0.18	N/A
37	Ergosta-3,5-diene Synonym: 24-methylcholesta-3,5-diene [Sterol]	$C_{28}H_{46}$ [PubChem CID 157040]	382.359	383.367	18.22	−1.94	81.0702, 95.0856, 109.101, 147.116, 149.132, 215.178, 243.212, 333.607, 383.368	2.077×10^7	0.18	N/A
38	1-Naphthol [Phenol]	$C_{10}H_8O$ [PubChem CID 7005]	144.057	145.064	12.53	0.58	62.9294, 69.0338, 91.0545, 99.0442, 115.054, 117.070, 130.041, 145.064	1.982×10^7	0.18	N/A
39	(2E)-3-(4-Hydroxyphenyl)-N-[2-(4-hydroxyphenyl) ethyl] acrylamide	$C_{17}H_{17}NO_3$ [PubChem CID 5372945]	283.121	284.128	7.30	−0.35	91.0543, 119.049, 121.064, 147.043, 164.071, 243.048, 284.127, 284.295	1.921×10^7	0.17	N/A

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Table 1 (Continued).

No	Name of Compound [Class of Metabolite]	Molecular Formula	$[M+H]^+$ m/z		Retention Time (min)	Δ Mass (ppm)	Main Product IONS (MS/MS, m/z)	Area (Max)	Relative Abundance (%)	Antidiabetic-Related Biological Activity [Reference]
			Calculated Mass (Da)	Accurate Mass (Da)						
40	1-Linoleoyl glycerol [Fatty acid glycerol]	$C_{21}H_{38}O_4$ [PubChem CID 6436630]	354.276	355.283	11.54	−3.06	81.0701, 95.0856, 107.085, 109.101, 149.132, 245.226, 263.236, 281.247, 337.272	1.918×10^7	0.17	N/A
41	NP-001798	$C_{16}H_{17}NO_2$ [PubChem CID 1242]	255.126	256.133	8.27	−0.7	70.0651, 91.0544, 105.033, 117.069, 134.096, 238.121, 239.105, 256.133	1.827×10^7	0.17	N/A
42	4'-Methoxyacetophenone [Phenyl ketone]	$C_9H_{10}O_2$ [PubChem CID 8785]	150.068	151.075	11.13	−2.19	80.0622, 86.9929, 87.0042, 91.0544, 107.049, 108.057, 121.064, 151.075	1.624×10^7	0.15	N/A
43	Scopoletin acetate [Phenolic coumarin]	$C_{12}H_{10}O_5$ [PubChem CID 342221]	234.053	235.059	8.38	−1.22	119.085, 121.064, 143.033, 161.059, 177.018, 192.041, 204.077, 220.036	1.613×10^7	0.15	N/A
44	Glycitein [O-methylated isoflavone]	$C_{16}H_{12}O_5$ [PubChem CID 10639]	284.068	285.075	10.07	−2.6	92.2065, 93.0698, 167.033, 177.007, 240.232, 242.056, 270.051, 285.075	1.539×10^7	0.13	Antidiabetic [45]
45	4,4'-dimethoxy[1,1'-biphenyl]-2-carbonitrile	$C_{15}H_{13}NO_2$ [PubChem CID 5896]	239.094	240.101	4.21	−2.84	130.065, 134.059, 135.044, 162.054, 196.094, 225.077, 240.101	1.394×10^7	0.13	N/A
46	2-(2-thienyl)-4H-chromen-4-one	$C_{13}H_8O_2S$ [PubChem CID 29886]	228.024	229.031	0.85	−1.24	70.0654, 91.8626, 139.087, 142.085, 183.148, 229.031, 229.118, 229.153	1.151×10^7	0.10	N/A
47	Salsolinol [Quinoline]	$C_{10}H_{13}NO_2$ [PubChem CID 3442]	179.094	180.101	1.03	−1.15	68.9973, 85.0284, 98.0599, 111.007, 117.069, 145.064, 163.075	1.000×10^7	0.09	N/A

48	Oleoyl ethanolamide [Fatty acid ethanolamide]	$C_{20}H_{39}NO_2$ [PubChem CID 5283454]	325.297	326.304	14.10	−3.37	55.0545, 62.0605, 69.0700, 135.116, 171.013, 287.978, 309.278, 326.304, 326.376	9.341×10^6	0.08	N/A
49	4-methoxy-6-(prop-2-en-1-yl)-2H-1,3-benzodioxole [Myristicin, alkenylbenzene]	$C_{11}H_{12}O_3$ [PubChem CID 4276]	192.078	193.085	11.26	−1.42	79.0543, 86.9601, 105.069, 118.041, 133.064, 150.067, 162.067, 165.090, 193.085	8.694×10^6	0.08	N/A
50	Methyl N-benzoylphenylalaninate [Derivative of amino acid]	$C_{17}H_{17}NO_3$ [PubChem CID 5372945]	283.120	284.127	10.15	−1.75	81.0702, 95.0491, 105.033, 173.749, 224.106, 243.047, 252.101, 284.128	8.157×10^6	0.07	N/A

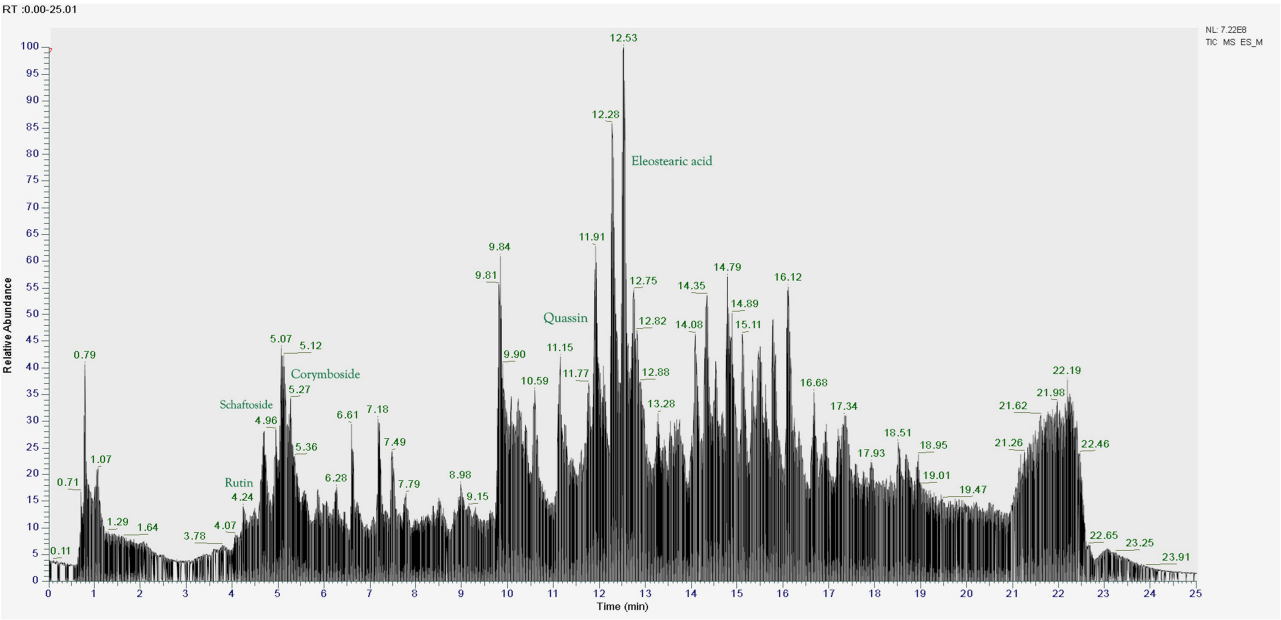

Figure 4 UHPLC chromatogram of EEPP 1 mg in 1 mL in 96% HPLC-grade methanol, at 40°C, flow rate of 0.3 mL/min, injection volume of 3 µL.

indicating the hypoglycemic effects of EEPP. Intriguingly, sitagliptin (a hypoglycemic control drug) had no effect at this time point. At T60, glucose levels ranged from the lowest at 86.4 ± 17.9 mg/dL (in the normal control group) to the highest at 513.6 ± 115.0 mg/dL (in the negative control group). At this time point, there was a significant difference between the groups ($p = 0.012$ in Table 3), and a significant difference between the normal control, positive control, EEPP 125 mg/kg body weight, and EEPP 500 mg/kg body weight groups compared to the negative control ($p < 0.05$ in Table 4), indicating the hypoglycemic effects of EEPP and sitagliptin. At T90, glucose levels ranged from the lowest at 89.6 ± 9.9 mg/dL (in the normal control group) to the highest at 391.6 ± 128.9 mg/dL (in the negative control group). At this time point, there was a significant difference between the groups ($p = 0.044$ in Table 3), and a significant difference between the normal control and positive control groups compared to the negative control ($p < 0.05$ in Table 4). EEPP intervention reduced blood glucose levels in the rats, but the difference was not statistically significant ($p > 0.05$). At T120, glucose levels ranged from the lowest at 102.8 ± 26.3 mg/dL (in the normal control group) to the highest at 341.2 ± 135.8 mg/dL (in the negative control group). At this time point, there was no significant difference between the groups

Table 2 Hypoglycemic Effects of EEPP on the Acute Glucose Load in Normoglycemic Sprague-Dawley Rats (Using Sitagliptin as the Control Drug)

Group	Glucose (mg/dL) ± SD					% Decrease (T_{30}-T_{120}/T_{30} x 100)
	T_0	T_{30}	T_{60}	T_{90}	T_{120}	
Normal Control	81.8 ± 8.7	85.8 ± 9.9	86.4 ± 17.9	89.6 ± 9.9	102.8 ± 26.3	−19.8
Negative Control	332.0 ± 61.9	482.8 ±133.3	513.6 ± 115.0	391.6 ± 128.9	341.2 ± 135.8	29.3
Positive Control (Sitagliptin 2.5 mg/rat)	148.4 ± 77.6	288.2 ±118.0	246.0 ± 115.2	202.2 ± 85.0	137.4 ± 60.7	52.3
EEPP 125 mg/kg body weight	159.4 ± 139.3	267.4 ± 198.2	286.2 ± 187.0	221.0 ±155.6	175.4 ± 177.9	34.4
EEPP 250 mg/kg body weight	146.6 ± 58.6	329.4 ± 220.0	313.0 ± 225.3	265.0 ± 198.8	213.4 ± 165.3	35.2
EEPP 500 mg/kg body weight	83.0 ± 27.4	270.0 ± 170.3	265.8 ± 197.8	228.0 ±133.0	176.4 ± 137.4	34.7

Notes: T0 (the time point at 5 min after sitagliptin or EEPP intervention together with glucose load, representing the baseline of each group); T30 (30 min after glucose load); T60 (60 min after glucose load); T120 (120 min after glucose load). Data are presented as an average (n = 5) ± SD.

Table 3 ANOVA Statistical Analysis of the Effects of EEPP on the Acute Glucose Load in Normoglycemic Sprague-Dawley Rats (Using Sitagliptin as the Control Drug)

		Sum of Squares	df	Mean Square	F	Significance (*p*)
T0	Between Groups	209649.067	5	41,929.813	7.504	0.000*
	Within Groups	134102.400	24	5587.600		
	Total	343751.467	29			
T30	Between Groups	406455.067	5	81,291.013	3.284	0.021*
	Within Groups	594084.800	24	24,753.533		
	Total	1000539.867	29			
T60	Between Groups	471874.167	5	94,374.833	3.731	0.012*
	Within Groups	607044.000	24	25,293.500		
	Total	1078918.167	29			
T90	Between Groups	239295.500	5	47,859.100	2.724	0.044*
	Within Groups	421711.200	24	17,571.300		
	Total	661006.700	29			
T120	Between Groups	170852.300	5	34,170.460	2.035	0.110
	Within Groups	402934.400	24	16,788.933		
	Total	573786.700	29			

Notes: * indicates a significant difference between groups ($p < 0.05$).
T0 (the time point at 5 min after sitagliptin or EEPP intervention together with glucose load, representing the baseline of each group); T30 (30 min after glucose load); T60 (60 min after glucose load); T120 (120 min after glucose load).

Table 4 Multiple Comparisons (LSD) Statistical Analysis of the Effects of EEPP on the Acute Glucose Load in Normoglycemic Sprague-Dawley Rats Using Sitagliptin as the Control Drug (Compared to the Negative Control)

Dependent Variable	(I) Rat Group	(J) Rat Group	Mean Difference (I-J)	Standard Error	Significance (*p*)	95% Confidence Interval	
						Lower Bound	Upper Bound
T0	Negative Control	Normal Control	250.20	47.276	0.000*	152.63	347.77
		Positive Control	183.60	47.276	0.001*	86.03	281.17
		EEPP 125 mg/kg body weight	172.60	47.276	0.001*	75.03	270.17
		EEPP 250 mg/kg body weight	185.40	47.276	0.001*	87.83	282.97
		EEPP 500 mg/kg body weight	249.00	47.276	0.000*	151.43	346.57

(*Continued*)

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Table 4 (Continued).

Dependent Variable	(I) Rat Group	(J) Rat Group	Mean Difference (I-J)	Standard Error	Significance (*p*)	95% Confidence Interval	
						Lower Bound	Upper Bound
T30	Negative Control	Normal Control	397.00	99.506	0.001*	191.63	602.37
		Positive Control	194.60	99.506	0.062	−10.77	399.97
		EEPP 125 mg/kg body weight	215.40	99.506	0.041*	10.03	420.77
		EEPP 250 mg/kg body weight	153.40	99.506	0.136	−51.97	358.77
		EEPP 500 mg/kg body weight	212.80	99.506	0.043*	7.43	418.17
T60	Negative Control	Normal Control	427.20	100.585	0.000*	219.60	634.80
		Positive Control	267.60	100.585	0.014*	60.00	475.20
		EEPP 125 mg/kg body weight	227.40	100.585	0.033*	19.80	435.00
		EEPP 250 mg/kg body weight	200.60	100.585	0.058	−7.00	408.20
		EEPP 500 mg/kg body weight	247.80	100.585	0.021*	40.20	455.40
T90	Negative Control	Normal Control	302.00	83.836	0.001*	128.97	475.03
		Positive Control	189.40	83.836	0.033*	16.37	362.43
		EEPP 125 mg/kg body weight	170.60	83.836	0.053	−2.43	343.63
		EEPP 250 mg/kg body weight	126.60	83.836	0.144	−46.43	299.63
		EEPP 500 mg/kg body weight	163.60	83.836	0.063	−9.43	336.63
T120	Negative Control	Normal Control	238.40	81.949	0.008*	69.27	407.53
		Positive Control	203.80	81.949	0.020*	34.67	372.93
		EEPP 125 mg/kg body weight	165.80	81.949	0.054	−3.33	334.93
		EEPP 250 mg/kg body weight	127.80	81.949	0.132	−41.33	296.93
		EEPP 500 mg/kg body weight	164.80	81.949	0.056	−4.33	333.93

Notes: T0 * indicates a significant difference between groups ($p < 0.05$).
(the time point at 5 min after sitagliptin or EEPP intervention together with glucose load, representing the baseline of each group); T30 (30 min after glucose load); T60 (60 min after glucose load); T120 (120 min after glucose load).

($p = 0.110$ in Table 3), but there was a significant difference between the normal control and the positive control groups compared to the negative control ($p < 0.05$ in Table 4). EEPP intervention reduced blood glucose levels in rats, but the difference was not statistically significant ($p > 0.05$). The blood glucose decrease (T30-T120/T30 x 100) is 29.3% for rats in the negative control group, 52.3% for rats treated with sitagliptin, and 34.4–35.2% for rats treated with EEPP. This study did not have human endpoints and was not repeated every week.

For the acarbose set: At T0, glucose levels ranged from the lowest at 90.6 ± 7.4 mg/dL (in the EEPP 125 mg/kg body weight group) to the highest at 117.2 ± 25.4 mg/dL (in the negative control group). At this time point, there was a significant difference between the groups ($p = 0.014$ in Table 6), and a significant difference between the positive control, EEPP 125 mg/kg body weight, and 250 mg/kg body weight groups compared with the negative control ($p < 0.05$ in Table 7). At T30, glucose levels ranged from the lowest at 97.60 ± 15.2 mg/dL (in the EEPP 250 mg/kg body weight group) to the highest at 158.2 ± 22.7 mg/dL (in the negative control group). At this time point, there was a significant difference between the groups ($p < 0.001$ in Table 6), and a significant difference between all groups compared to the negative control ($p < 0.05$ in Table 7), indicating the hypoglycemic effects of EEPP. At T60, glucose levels ranged from the lowest at 88.4 ± 19.5 mg/dL (in the EEPP 125 mg/kg body weight group) to the highest at 109.2 ± 19.9 mg/dL (in the negative control group). At this time point, there was no significant difference between the groups ($p = 0.421$ in Table 6), and no significant difference between the groups compared to the negative control ($p > 0.05$ in Table 7). At T90, glucose levels ranged from the lowest at 86.4 ± 8.6 mg/dL (in the EEPP 125 mg/kg body weight group) to the highest at 101.8 ± 6.7 mg/dL (in the normal control group). At this time point, there was no significant difference between the groups ($p > 0.05$), and no significant difference between the groups compared to the negative control ($p > 0.05$ in Table 7). EEPP intervention reduced blood glucose levels in the rats, but the difference was not statistically significant ($p > 0.05$). At T120, glucose levels ranged from the lowest at 80.4 ± 9.8 mg/dL (in the positive control group) to the highest at 90.0 ± 24.9 mg/dL (in the EEPP 500 mg/kg body weight group). At this time point, there was no significant difference between the groups ($p > 0.05$), and no significant difference between the groups compared to the negative control ($p > 0.05$ in Table 7). EEPP intervention reduced blood glucose levels in rats, but the difference was not statistically significant ($p > 0.05$). Rats treated with EEPP have shown a maintenance in blood glucose levels, although the blood glucose decrease is only 14.7–35.8%. This study did not have human endpoints and was not repeated every week.

Table 5 Hypoglycemic Effects of EEPP on the Acute Glucose Load in Normoglycemic Sprague-Dawley Rats (Using Acarbose as the Control Drug)

Group	Glucose (mg/dL) ± SD					% Decrease (T_{30}-T_{120}/T_{30} x 100)
	T_0	T_{30}	T_{60}	T_{90}	T_{120}	
Normal Control	99.4 ± 1.5	117.6 ± 8.9*	98.6 ± 10.7	101.8 ± 6.7	89.6 ± 6.7	23.8
Negative Control	117.2 ± 25.4	158.2 ± 22.7	109.2 ± 19.9	97.2 ± 15.4	88.6 ± 11.2	43.9
Positive Control (Acarbose 2.5 mg/rat)	91.6 ± 23.9*	117.6 ± 17.7*	98.6 ± 13.8	90.4 ± 7.7	80.4 ± 9.8	31.6
EEPP 125 mg/kg body weight	90.6 ± 7.4*	126.2 ± 10.9*	88.4 ± 19.5	86.4 ± 8.6	81.0 ± 4.2	35.8
EEPP 250 mg/kg body weight	90.8 ± 16.4*	97.60 ± 15.2*	99.8 ± 6.9	91.2 ± 7.3	83.0 ± 4.2	14.7
EEPP 500 mg/kg body weight	99.2 ± 18.7	109.4 ± 21.5*	88.6 ± 25.4	94.6 ± 21.0	90.0 ± 24.9	17.7

Notes: T0 (the time point at 5 min after acarbose or EEPP intervention together with glucose load, representing the baseline of each group); T30 (30 min after glucose load); T60 (60 min after glucose load); T120 (120 min after glucose load); and T240 (240 min after glucose load). Data are presented as an average (n = 5) ± SD. Data were analyzed using a paired *t*-test compared to the T0 of each group; * indicates a significant difference between groups ($p < 0.05$).

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Table 6 ANOVA Statistical Analysis of the Effects of EEPP on the Acute Glucose Load in Normoglycemic Sprague-Dawley Rats (Using Acarbose as the Control Drug)

		Sum of Squares	df	Mean Square	F	Significance (*p*)
T0	Between Groups	5730.800	5	1146.160	3.639	0.014*
	Within Groups	7560.000	24	315.000		
	Total	13290.800	29			
T30	Between Groups	10580.300	5	2116.060	7.373	< 0.001*
	Within Groups	6888.400	24	287.017		
	Total	17468.700	29			
T60	Between Groups	1530.400	5	306.080	1.033	0.421
	Within Groups	7110.400	24	296.267		
	Total	8640.800	29			
T90	Between Groups	745.200	5	149.040	0.984	0.448
	Within Groups	3636.000	24	151.500		
	Total	4381.200	29			
T120	Between Groups	495.767	5	99.153	0.644	0.669
	Within Groups	3697.600	24	154.067		
	Total	4193.367	29			

Notes: * indicates a significant difference between groups ($p < 0.05$).
T0 (the time point at 5 min after acarbose or EEPP intervention together with glucose load, representing the baseline of each group); T30 (30 min after glucose load); T60 (60 min after glucose load); T120 (120 min after glucose load).

Table 7 Multiple Comparisons (LSD) Statistical Analysis of the Effects of EEPP on the Acute Glucose Load in Normoglycemic Sprague-Dawley Rats Using Acarbose as the Control Drug (Compared to the Negative Control)

Dependent Variable	(I) Rat Group	(J) Rat Group	Mean Difference (I-J)	Standard Error	Significance (*p*)	95% Confidence Interval	
						Lower Bound	Upper Bound
T0	Negative Control	Normal Control	17.80	11.225	0.126	−5.37	40.97
		Positive Control	25.60	11.225	0.032*	2.43	48.77
		EEPP 125 mg/kg body weight	26.60	11.225	0.026*	3.43	49.77
		EEPP 250 mg/kg body weight	46.40	11.225	< 0.001*	23.23	69.57
		EEPP 500 mg/kg body weight	18.00	11.225	0.122	−5.17	41.17

(*Continued*)

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Table 7 (Continued).

Dependent Variable	(I) Rat Group	(J) Rat Group	Mean Difference (I-J)	Standard Error	Significance (*p*)	95% Confidence Interval	
						Lower Bound	Upper Bound
T30	Negative Control	Normal Control	40.60	10.715	< 0.001*	18.49	62.71
		Positive Control	40.60	10.715	< 0.001*	18.49	62.71
		EEPP 125 mg/kg body weight	32.00	10.715	0.006*	9.89	54.11
		EEPP 250 mg/kg body weight	60.60	10.715	< 0.001*	38.49	82.71
		EEPP 500 mg/kg body weight	48.80	10.715	< 0.001*	26.69	70.91
T60	Negative Control	Normal Control	10.60	10.886	0.340	−11.87	33.07
		Positive Control	10.60	10.886	0.340	−11.87	33.07
		EEPP 125 mg/kg body weight	20.80	10.886	0.068	−1.67	43.27
		EEPP 250 mg/kg body weight	9.40	10.886	0.396	−13.07	31.87
		EEPP 500 mg/kg body weight	20.60	10.886	0.071	−1.87	43.07
T90	Negative Control	Normal Control	−4.60	7.785	0.560	−20.67	11.47
		Positive Control	6.80	7.785	0.391	−9.27	22.87
		EEPP 125 mg/kg body weight	10.80	7.785	0.178	−5.27	26.87
		EEPP 250 mg/kg BW	6.00	7.785	0.448	−10.07	22.07
		EEPP 500 mg/kg BW	2.60	7.785	0.741	−13.47	18.67
T120	Negative Control	Normal Control	−1.00	7.850	0.900	−17.20	15.20
		Positive Control	8.20	7.850	0.307	−8.00	24.40
		EEPP 125 mg/kg body weight	7.60	7.850	0.343	−8.60	23.80
		EEPP 250 mg/kg body weight	5.60	7.850	0.483	−10.60	21.80
		EEPP 500 mg/kg body weight	−1.40	7.850	0.860	−17.60	14.80

Notes: * indicates a significant difference between groups ($p < 0.05$).
T0 (the time point at 5 min after acarbose or EEPP intervention together with glucose load, representing the baseline of each group); T30 (30 min after glucose load); T60 (60 min after glucose load); T120 (120 min after glucose load).

Discussion

In this study, we report the nutritional and phytochemical composition of the whole plant of *P. pellucida* cultivated in Bogor, West Java, Indonesia, abbreviated to EEPP. EEPP contained ash of 29.39 ± 0.21%, carbohydrates of 39.44 ±

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0.59%, proteins of 14.40 ± 0.22%, fat of 2.36 ± 0.03%, water of 14.38 ± 0.12%, and a total energy of 236.82 ± 1.15 kcal per 100 g extract, and negligible levels of vitamin C (1.17 mg/100 g) and quercetin (0.01 mg/100 g). In agreement with our findings, a high ash content of 31.22 ± 2.06%, high carbohydrates of 46.58 ± 2.74%, proteins of 10.63 ± 0.07%, and fat of 3.24 ± 0.28% were reported by Ooi et al (2012) in the whole plant of *P. pellucida* collected from Guar Chempedak, Kedah, Malaysia.[9] High ash (20.01%) and carbohydrate (38.97%) contents were also found in the whole plant of *P. pellucida* harvested from Ibadan, Nigeria. Minerals such as calcium, magnesium, potassium, sodium, manganese, and iron were quantified.[10] In the leaves of the plant collected from Imo, South-Eastern Nigeria, low protein, low carbohydrate, and total ash, and vitamins such as vitamin A (2.33 ± 0.15 mg/100 g), B1 (0.21 ± 0.03 mg/100 g), B2 (0.34 ± 0.01 mg/100 g), B5, and C (8.74 ± 0.12 mg/100 g) were found.[11]

Our study confirms that EEPP contains a total phenol of 15.62 mg GAE/100 g dry extract, total flavonoids of 8.00 mg QE/100 g dry extract, and total sterols of 2461.5 mg β-sitosterol equivalent (BSE)/100 g dry extract. In addition, 50 phytochemicals were identified in EEPP using a UHPLC-HRMS/MS analysis, such as corymboside at a relative abundance of 8.06% with an [M+H] m/z of 565.154 Da, quassin at a relative abundance of 6.41% with an [M+H] m/z of 389.194 Da, 1-stearoylglycerol at a relative abundance of 6.21%, α-eleostearic acid at a relative abundance of 5.04%, schaftoside at a relative abundance of 4.96%, rutin at a relative abundance of 1.78%, vidarabine (1.30%), ergosta-3,5-diene sterol (0.18%), and many others. In agreement with our findings, a UHPLC-MS/MS of *P. pellucida* collected at Pará, Brazil, identified the presence of 16 compounds, such as, in alphabetical order: brachystamide B, dehydroretrofractamide C, di-tert -butyl-4-hydroxymethylphenol, guineensine, liolide, luteolin-6-C-glucoside-8-C-arabinoside, methoxy-methyl-tetrahydrofuro [2,3-h]chromen-4-one-*N*-methylcorydaldine, pellucidin A, pellucidin B, pipercallosidine, retrofractamide B (synonym: pipercide), schaftoside, trihydroxybutyrophenone, velutin, vidarabine (synonym: araadenosine).[12] Another study delineated that the plant collected at Can Tho City, Vietnam, contained high total phenols and total flavonoids.[13] It was described that 32 compounds, among which were apiol (22.64%), phytol (7.47%), stigmasterol (4.60%), campesterol (3.19%), α-sitosterol (2.92%), and vitamin E (0.76%), have been isolated from the *P. pellucida* plant harvested in Tamil Nadu, India.[14] (S)-2-methyl-2- (4-methylpent-3-enyl)-6-(propan-2-ylidene)-3,4,6,7- tetrahydropyrano[4,3-g]chromen-9 (2H)-one was successfully isolated from the leaves of *P. pellucida* collected in West Java, Indonesia.[15] Nonpolar compounds such as stigmasterol and beta-sitosterol-D-glucopyranoside were isolated from the aerial part of *P. pellucida* collected at Banten, Indonesia.[16] Moreover, 6-allyl-5-methoxy-1,3-benzodioxol-4-ol, pachypostaudin B, pellucidin A, dillapiole, and apiol were isolated from wild plants of *P. pellucida* collected at Cagak and Ciater Region, West Java, Indonesia.[17] Secolignans and tetrahydrofuran lignans were also identified in the whole plant of *P. pellucida* harvested at Shanghai, China.[46] Corymboside in colored wheat (*Triticum aestivum* L.) at an [M+H] m/z of 565.155 Da has shown a contribution to the plant's high antioxidant and anti-inflammatory properties.[37] Another phytochemical, quassin, was found in *Quassia amara* extract and showed antidiabetic properties.[38]

In our study, EEPP demonstrated hypoglycemic effects by reducing blood glucose levels by 14.7–35.8% in male normoglycemic Sprague-Dawley rats subjected to an acute glucose load. Sitagliptin, a known oral hypoglycemic drug used as a positive control, showed a reduction of 52.3%, while acarbose showed a decrease of 31.6%.

Few animal studies have reported the antidiabetic properties of *P. pellucida*. In one study reported by Hamzah et al (2012), *P. pellucida* collected from Ibadan, Nigeria, showed glucose-lowering effects in alloxan monohydrate-induced diabetic albino rats. In their study, diabetic rats treated with *P. pellucida* for 28 days showed significantly reduced glucose, total cholesterol, triglycerides, and LDL-cholesterol ($p < 0.05$) compared to untreated diabetic rats.[47] Another article described that the ethanol extract of *P. pellucida* leaves exhibited hypoglycemic and anti-inflammatory properties in streptozotocin-induced diabetic rats, as evidenced by reduced blood glucose and IL-1β levels, and improved pancreatic histology.[48] The whole plant of *P. pellucida* collected from the riverside in Khulna, Bangladesh, at a dose of 300 mg/kg body weight, showed hypoglycemic effects by reducing 62.64% of blood glucose levels at 120 minutes after an acute glucose load.[49]

Phytochemicals, including primary and secondary metabolites, have been shown to maintain blood glucose levels. Carbohydrates, which are primary plant metabolites, have been reported to have hypoglycemic effects. A study reported that glucomannan polysaccharide, a high molecular weight fraction of *Aloe vera*, when supplemented three times daily for 12 weeks to patients with T2DM (who were nonadherent to their oral hypoglycemic medication), resulted in

a significant hypoglycemic effect.[50] Similarly, another study reported that *A. vera* supplementation at a dose of 300 mg twice per day for four weeks significantly reduced fasting blood glucose and HbA1c in patients with pre-diabetic symptoms.[51] Epidemiological studies have evidenced an inverse association between the risk of myocardial infarction and the consumption of tea or the intake level of some particular flavonoids.[52] In a review article by Arts and Hollman (2005) on twelve cohort studies on flavonoid intake and the risk of coronary artery disease (CAD), and five cohort studies on the risk of stroke, revealed that seven of the studies confirmed the protective effects of flavonoids against CAD, with a 65% reduction of mortality risk.[53] Another study documented the supplementation of polyphenols at a dose of 683.3 ± 5.8 mg/day in people with DM using validated databases of the polyphenol content of food.[54] A cross-sectional population-based survey, which was conducted in Viçosa, Brazil, by recruiting 620 elderly people, suggested a beneficial average total polyphenol intake of 1198.6 mg/day for the elderly.[55]

Plant secondary metabolites, such as flavonoids, polyphenols, glycosides, and sterols, have been shown to exhibit their hypoglycemic effects. The mechanisms by which these phytochemicals exert their effects are by stimulating insulin secretion, enhancing pancreatic β-cells regeneration, increasing lipid and glucose metabolism, antioxidant, and other glucose-related mechanisms.[56] Phytosterols have been proven for their properties in inhibiting insulin resistance through several mechanisms, such as promoting fatty acid β-oxidation, inhibiting gluconeogenesis, promoting glycogen synthesis, and GLUT4 translocation by activating PI3K/Akt signaling pathway.[57,58] Plant alkaloids, such as berberine, catharanthine, vindoline, jambosine, and many more, were also described to possess antidiabetic properties.[59]

Limitations of the Study

This study has limitations, including a small sample size of animals, a single animal gender, a short time window for blood glucose monitoring, the absence of dose–response curves, and a lack of mechanistic biomarker analysis (eg, insulin or oxidative stress markers).

Conclusion

In conclusion, the whole plant of *P. pellucida* collected from Bogor, West Java, Indonesia, contains total ash of 29.39 ± 0.21%, carbohydrates of 39.44 ± 0.59%, proteins of 14.40 ± 0.22%, fat of 2.36 ± 0.03%, a total energy of 236.82 ± 1.15 kcal per 100 g extract, a negligible level of vitamin C and quercetin, a TPC of 15.62 mg GAE/100 g dry extract, a TFC of 8.00 mg QE/100 g dry extract, and total sterols of 2461.5 mg BSE/100 g dry extract. Metabolite profile assessed using UHPLC-HRMS/MS identified the presence of 50 metabolites, among which were flavonoids, flavonoid glycosides, alkaloids, sterols, fatty acid esters, chromenes, coumarins, and other metabolites. The whole plant of *P. pellucida* may have the potential to be developed into a nutraceutical supplement, particularly in maintaining blood glucose levels, because it demonstrates hypoglycemic effects by reducing blood glucose levels by 14.7–35.8% in male normoglycemic Sprague-Dawley rats subjected to an acute glucose load, although this reduction is not significant. However, the hypoglycemic mechanisms, molecular pathways, translational potential for nutraceutical development, the necessity for chronic in vivo, network pharmacology, and molecular docking-molecular dynamics validation are yet to be unraveled.

Data Sharing Statement

The data that support the findings of this study are disclosed within the manuscript.

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Disclosure

The authors declare no potential conflicts of interest regarding the research, authorship, or publication of this paper.

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