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Peperomia pellucida Herbal Tea: An Initial Assessment of Cardiovascular and Metabolic Parameters, with *in Silico* Insights

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ABSTRACT

Medicinal plant-derived herbal teas are gaining recognition for their health-promoting properties. This preliminary study aimed to investigate the potential of *Peperomia pellucida* herbal tea to modulate cardiovascular and metabolic risk factors. The effects of twice-daily consumption of the tea for one week on systolic blood pressure, fasting blood sugar, uric acid, and cholesterol levels in three female patients (ages 37-61) with pre-existing elevated levels were measured. In addition, in silico methods, including molecular docking against the insulin receptor tyrosine kinase (1IR3) and ADMET (absorption, distribution, metabolism, excretion, and toxicity) analysis were used to assess the antidiabetic potential of twenty *P. pellucida* metabolites. The clinical observations showed reductions in systolic blood pressure (20-50 mmHg), fasting blood sugar (21-51 mg/dL), cholesterol (18-52 mg/dL), and uric acid (0.1-1.5 mg/dL). Molecular docking revealed strong binding affinities (average -8.9 kcal/mol) of most metabolites to 1IR3. Based on ADMET profiles, four compounds including brachystamide B (**1**), isoschaftoside (**5**), loliodide (**8**), and luteolin (**9**) showed comparable or superior predicted drug-like properties compared to known antidiabetic drugs like metformin. Isovitexin (**8**) displayed the most promising combination of binding affinity and ADMET characteristics. Interestingly, isovitexin, along with vitexin, has been reported to play an important role in targeting pathophysiological and metabolic pathways of diabetes mellitus. While suggestive of potential antidiabetic, antihypertensive, anticholesterolemic, and uric acid-lowering effects of *P. pellucida*, these findings must be considered preliminary due to the study's methodological limitations, including a small sample size, warranting more rigorous investigation to validate these results.

Keywords: Anti-Diabetic, Herbal Tea, *In-Silico*, Isovitexin, *Peperomia pellucida*.

Introduction

Type 2 diabetes mellitus (T2DM) represents a pressing health issue, comprising 90% of all diabetes cases worldwide. This condition is clinically defined by persistent hyperglycemia[1,2] and its incidence is projected to nearly triple by 2035, creating a substantial burden on international healthcare systems and economies.[3,4] Although metformin has long been the first-line treatment, concerns regarding its side effects such as lactic acidosis and potential contaminants indicate the need for new and safer antidiabetic agents.[5,6] Traditional medicinal plants offer a promising avenue for discovering novel antidiabetic compounds. *Peperomia pellucida*, a plant in the Piperaceae family, has demonstrated antidiabetic potential in *in vitro*, *in silico*, and *in vivo* studies.[7] Extracts of *P. pellucida* have been shown to reduce blood glucose levels in animal models,[8,9] and a novel chromone compound isolated from the plant has been shown to exhibit strong inhibitory activity against enzymes involved in diabetic processes.[9,10] Furthermore, *P. pellucida* herbal tea prepared under various processing methods has been investigated.[11]

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However, the effects of *P. pellucida* herbal tea on key cardiovascular and metabolic risk factors, such as systolic blood pressure, fasting blood sugar, uric acid, and cholesterol levels, remain largely unexplored, and molecular docking studies targeting the insulin receptor (1IR3) are limited. This observation and the growing interest in herbal teas,[12] suggest the need for rigorous investigation of their potential health benefits and safety. In addition to traditional experimental approaches, computational methods are increasingly being used as valuable tools in drug discovery, particularly for complex diseases like T2DM.[13–16] *In silico* techniques, such as molecular docking and ADMET prediction, can rapidly screen large libraries of compounds, identify promising candidates for further investigation, and provide insights into potential mechanisms of action.[13,14] These methods are highly efficient in terms of both cost and time. Consequently, they are invaluable tools for prioritizing laboratory work and accelerating the development of new therapeutic agents.[13,15] In the present study, an *in-silico* method was used to complement the preliminary clinical observations and provide a more comprehensive assessment of the potential of *P. pellucida* for managing diabetes. This preliminary study aimed to evaluate the impact of *P. pellucida* herbal tea on cardiovascular and metabolic risk factors in a small group of patients. The *in-silico* antidiabetic potential of *P. pellucida* metabolites was further investigated by assessing their binding affinity to the insulin receptor, and evaluating their predicted drug-likeness properties using ADMET analysis, and comparing them to established antidiabetic drugs. These findings may provide a foundation for developing new, effective, and safer treatments for diabetes and related metabolic diseases

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Materials and Methods

Preparation of herbal tea
The herbal tea was prepared by an aqueous infusion method. Specifically, 100 g of *Peperomia pellucida* whole plant (roots, stems, and leaves) was first subjected to rigorous washing. The cleansed plant material was infused in 150 mL of freshly boiled water for 10 minutes.

Study area
The study was conducted in Manganitu District, Sangihe Islands Regency, North Sulawesi, Indonesia, geographically positioned at approximately 1°45'05.0"N and 124°49'31.9"E.

Ethical approval
Ethical approval for this study was obtained from the Health Research Ethics Committee of Politeknik Kesehatan Manado (Approval No. KEPK.01/09/275/2023A). The research protocol ensured that all procedures involving human participants adhered to the ethical principles of informed consent, anonymity, confidentiality, non-maleficence, and justice.

Clinical study
The preliminary clinical trial on patients aimed to evaluate the effects of *P. pellucida* on diabetes mellitus, hypercholesterolemia, hypertension, and gouty arthritis. The participants were patients with elevated blood sugar, high blood pressure, high blood cholesterol, and high blood uric acid who met the following criteria; willingness to participate and a history of the mentioned conditions. *Peperomia pellucida* herbal tea infusion (150 mL) was provided to each participant for oral consumption twice daily for one week. Standardized assessment of biochemical markers and blood pressure was performed using the Multi-Monitoring System Autocheck 3-in-1 and the OMRON HEM-7156 digital tensiometer, as previously specified.
The research involved three important steps; (1) measurement of blood sugar, cholesterol, uric acid, and blood pressure of patients before they consumed *P. pellucida* herbal tea. Biochemical parameters, including capillary blood glucose, total cholesterol, and uric acid concentrations, were determined using a point-of-care Multi-Monitoring System (Autocheck 3-in-1; General Life Biotechnology Co., Ltd, Taiwan). For these assessments, the designated fingertip was first disinfected with an alcohol swab. A capillary blood sample was subsequently obtained via a sterile lancing device. The collected blood was immediately applied to the respective analyte-specific test strips. Quantitative results were typically generated within approximately 5 seconds for blood glucose, 26 seconds for total cholesterol, and 15 seconds for uric acid.
Arterial blood pressure was measured using a calibrated digital oscillometric tensiometer (OMRON, model HEM-7156; OMRON Healthcare Co., LTD, Japan). Participants were instructed to sit comfortably with their back supported, feet uncrossed and flat on the floor, and the measurement arm resting on a flat surface, ensuring the antecubital fossa was at heart level. An appropriately sized cuff was secured around the upper arm, with its inferior border positioned 1 - 2 cm superior to the antecubital fossa and the cuff tubing aligned over the presumed course of the brachial artery. Following activation of the device, automated cuff inflation and deflation occurred, and the resulting systolic and diastolic blood pressures were recorded from the digital display. (2) Only patients with levels of blood sugar >200 mg/dL, cholesterol >200 mg/dL, uric acid <4 mg/dL or >7 mg/dL, and systolic blood pressure >130 mmHg were involved as research subjects, and (3) Remeasurement of the parameters after the patients consumed *P. pellucida* herbal tea.

In silico studies
Target protein preparation
The docking of all ligands into the protein targets insulin receptor tyrosine kinase (PDB ID: 1IR3) was performed using PyRx (version 0.8). The 1.90 Å resolution crystal structure of the protein target, insulin, was obtained from the Protein Data Bank (PDB ID: 1RE3) (http://www.Rcsb.Org/pdb).

Ligand preparation
The 2D structures of all ligands were retrieved from the PubChem database. These structures were then processed in Chem3D Pro 12, where they were geometrically optimized using the MM2 force field and subsequently converted to the Mol2 file format in preparation for molecular docking.

Molecular docking
Molecular docking was performed using PyRx,[17] requiring ligand and receptor preparation. The isomeric SMILES (Simplified Molecular-Input Line Entry System) of all molecules were retrieved from PubChem webtool. The SMILES from each individual molecule was pasted on ChemDraw 12.0 and saved as CDX type file, uploaded to PyRx, minimized and converted to pdbqt file before docking.

ADMET assessment
To evaluate their ADMET profiles, the isomeric SMILES for all ligands were obtained from PubChem and submitted to the pkCSM (http://structure.bioc.cam.ac.uk/pkcsm) and SwissADME (http://www.swissadme.ch/) web tools.

ADMET analysis
A quantitative ADMET scoring function was established based on 18 distinct endpoints. Within this framework, each endpoint was dichotomized, assigning a quality score (q) of 1 for predicted favorable ADMET properties and 0 for unfavorable ones. Specifically, predictions indicating unfavorable characteristics (e.g., Ames mutagenicity, AO activity, carcinogenicity [CARC], inhibition of specific CYP isoforms [CYP1A2, CYP2C9, CYP2D6, CYP2C19, CYP3A4], general CYP inhibition [CYPPRO], hERG channel blockade [indicated as hERG+], OCT2 inhibition, or P-gp inhibition) were assigned q = 0. Conversely, predictions indicating favorable characteristics (e.g., absence of hERG blockade [hERG–]) received q = 1. The aggregated ADMET score, derived from these binary classifications, was subsequently normalized to a 0 - 1 scale (0 indicating the least desirable profile, 1 the most desirable), benchmarked against the scores of oral drugs cataloged in Drug Bank.[18]

Results and Discussion

Review articles suggest that previous studies have investigated the antidiabetic potential of *P. pellucida* (Figure 1A) using *in vitro*, *in silico*, and *in vivo* approaches with various extracts, fractions, isolated compounds, and herbal tea preparations.[8,9] However, while some studies suggest a reduction in cholesterol levels with *P. pellucida*,[19–21] many remain limited to animal models, and robust, controlled human trials are scarce. Furthermore, while *in silico* studies have identified potential antidiabetic compounds derived from *P. pellucida* (T 1B), many focus on a limited number of compounds and lack comprehensive toxicity assessments.[20,22] Therefore, this study aimed to investigate the effect of *P. pellucida* herbal tea on blood glucose, cholesterol, uric acid, and blood pressure levels in patients, as well as to evaluate the *in silico* antidiabetic potential and predicted toxicity of several *P. pellucida* metabolites against key target proteins. This integrated approach provides new insights into the potential of *P. pellucida* for managing cardiovascular and metabolic disorders.

Preliminary clinical trial
One week of twice-daily *P. pellucida* herbal tea consumption was associated with changes in systolic blood pressure, cholesterol, and uric acid profiles in three female patients (Table 1, Figure 2). The average reduction in systolic blood pressure was 36.67 mmHg, with individual decreases ranging from 20 to 50 mmHg (Table 1, Figure 2A). Fasting blood sugar levels decreased, with an average reduction of 36.67 mg/dL (range: 21 - 51 mg/dL). Cholesterol levels also decreased, with an average reduction of 36 mg/dL (range: 18 - 52 mg/dL). Uric acid levels showed inconsistent changes: one participant experienced a reduction of 0.1 mg/dL, while the other two experienced increases of 0.8 mg/dL and 1.5 mg/dL, respectively.

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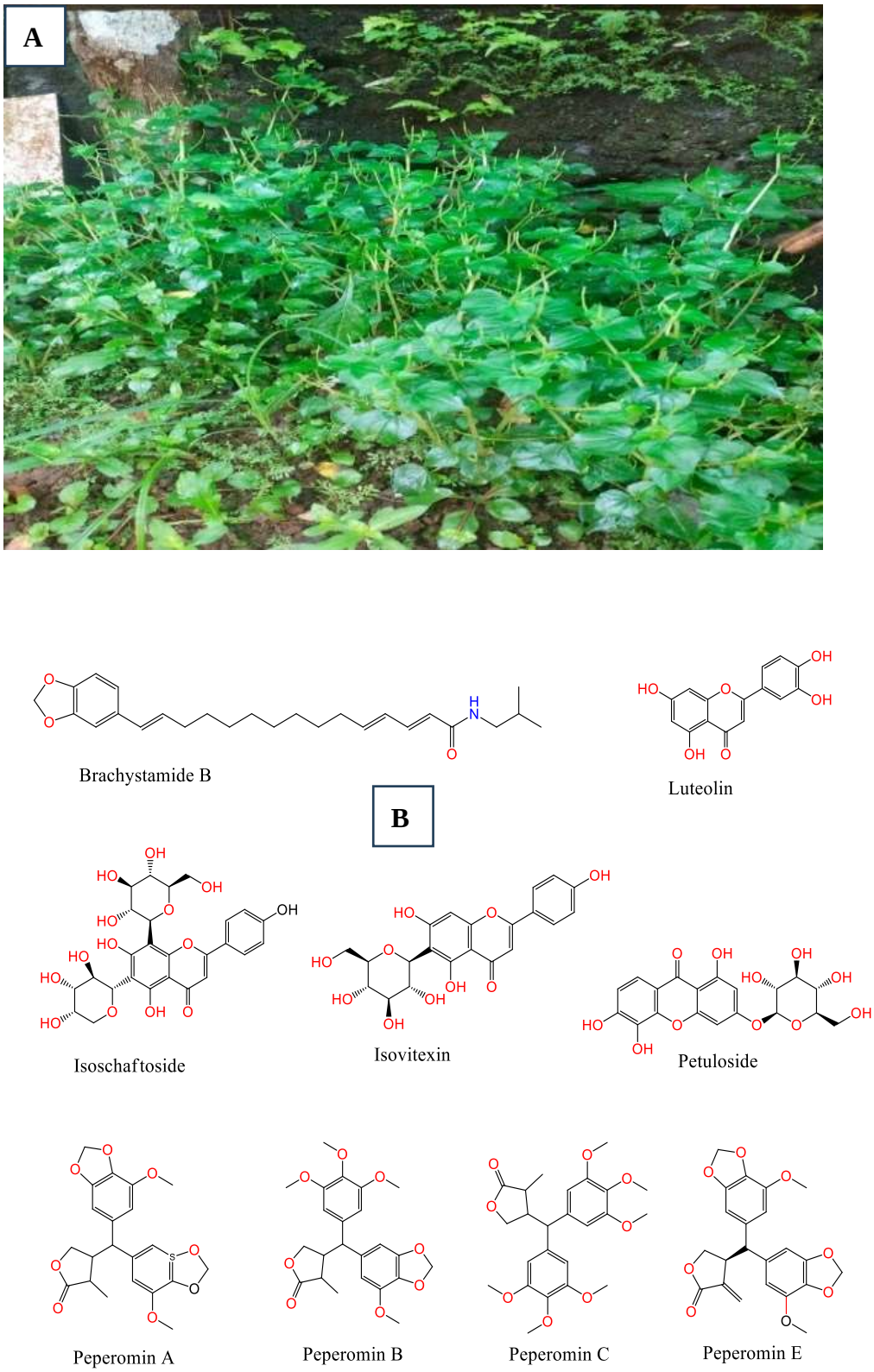

Figure 1: *Peperomia pellucida* plant (A) and chemical structures of some compounds isolated from *Peperomia pellucida* (B)

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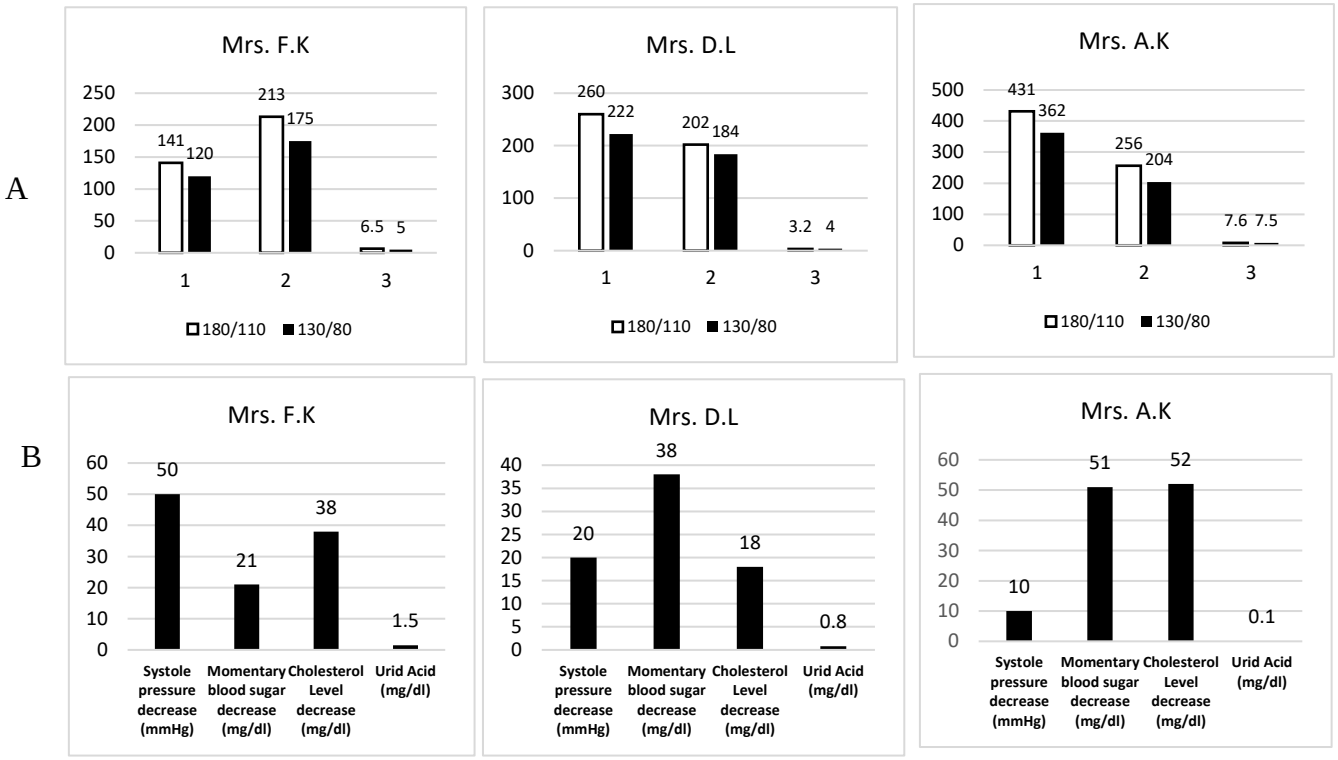

Figure 2: Effect of *Peperomia pellucida* tea on systolic blood pressure of three patients before (A) and after drinking the tea (B)

These results suggest a potential association between *Peperomia pellucida* tea consumption and changes in key health parameters.

The observed effects on systolic blood pressure, cholesterol, and uric acid are consistent with the traditional use of *P. pellucida*, *Cosmos caudatus*, and other plants claimed as a medicinal tea for managing diabetes and other metabolic disorders, as reported in ethnobotanical surveys.[23,24] However, much of the existing research has focused on characterizing the plant's phytochemical profile, particularly its flavonoid content, or on optimizing drying processes to preserve its nutritional value.[24,25] While ethnobotanical claims regarding *P. pellucida* are prevalent, well-documented clinical procedures are lacking. Therefore, as a pilot project and to exercise caution given the limited prior human data, this study employed a small sample size and a short treatment duration. This allowed for an initial *in vivo* assessment of the potential effects of *P. pellucida* herbal tea on blood pressure, blood glucose, cholesterol, and uric acid in humans. Although the small sample size and lack of a control group preclude definitive conclusions, the observed changes warrant further investigation in larger, randomized, placebo-controlled trials with longer durations to confirm these preliminary findings, elucidate the mechanisms of action, and rigorously assess the potential benefits and risks of *P. pellucida* tea.

Molecular docking

The preliminary clinical trial result encouraged the further evaluation of the antidiabetic potential of metabolites from *P. pellucida* against the antidiabetic molecular target: insulin receptor tyrosine kinase (PDB ID: 1IR3). The docking results revealed that several compounds derived from *P. pellucida* bind to the active sites of 1IR3 shown by three different arrows inside the red sphere based on receptor cavity analyzed on Discovery Studio Visualizer. Three active sites for 1IR3 consist of active site 1 or AC1 indicated by blue arrow with amino acid residues Asn:1137 and Asp:1150, active site 2 or AC2 shown in black arrow with amino acid residue Asp1150 as well as active site 3 or AC3 shown in red arrow with amino acid residues Asn1137, Asp1150, Arg1136, Ser1006, Lys1030, Gly1005, Met1076, ValA1010, Ala1028, Leu1002, Met1079, Gly1003, and Asp1083 (Figure 3A). Despite being a target for kinase inhibitor, these active sites are consistent with the active site for the insulin receptor tyrosine kinase (PDB ID: 1IR3) reported by Breen and Soellner.[26]

Molecular docking showed that most of the metabolites reported from *P. pellucida* bind to active site 3 (AC3) to a greater extent than to active sites 1 (AC1) and 2 (AC2) of 1IR3. The binders to AC3 include isoschaftoside (**5**), isovitexin (7), loliodide (8), luteolin (**9**), patuloside (**10**), peperomin A (**11**), peperomin B (12), peperomin C (**13**), sitagliptin (**23**), and vildagliptin (**24**). However, ligands such as peperomin D (14) and peperomin E (**15**) appear to bind to AC2 in a manner similar to metformin (**20**), while the antidiabetic drugs linagliptin (**21**) and saxagliptin (**22**) interacted with a binding site outside the defined active sites (Figure 3B). These results indicate that known antidiabetic drugs bind to different sites on the insulin receptor, including active sites 1 and 3, and possibly to an allosteric binding site, particularly in the case of linagliptin (**21**) and saxagliptin (**22**).

Binding affinity

With the exception of peperomin D and E, all other *P. pellucida* metabolites examined in this study bound to an active site of the target receptor. The docking analysis also revealed that the majority of *P. pellucida* metabolites exhibit robust binding affinity toward the insulin receptor. Of the twenty *P. pellucida* metabolites tested, more than half (11 compounds) showed robust binding affinities, including caryatin (**3**), isoschaftoside (**5**), isoswertisin (**6**), isovitexin (**7**), luteolin (**9**), patuloside (**10**), peperomin A (**11**), peperomin B (**12**), peperomin D (**14**), peperomin E (**15**), and seamin (**18**), with binding affinities of -8.10, -9.10, -8.70, -8.90, -8.60, -9.40, -8.60, -8.00, -8.80, -8.40, and -8.70 kcal/mol, respectively. In contrast, other metabolites, including brachystamide B (**1**), bexagliflozin (**2**), guineesine (**4**), loliodide (**8**), peperomin C (**13**), pelucidin A (**17**), as well as the antidiabetic drugs; metformin (**20**), saxagliptin (**22**), and vildagliptin (**24**) showed weaker binding affinities (<-8.0 kcal/mol). The -8.0 kcal/mol affinity was the cutoff used for defining robust binding affinity in this study. Although, the binding affinities for all the metabolites were lower than that of the insulin inhibitor caethochromin (-9.80 kcal/mol), they all surpassed that of metformin (-4.70 kcal/mol), and most ligands with binding affinities >-8.0 kcal/mol were stronger binders than saxagliptin (-6.70 kcal/mol) and vildagliptin (-7.40 kcal/mol). These findings indicate that many *P. pellucida* metabolites exhibit strong binding affinity toward the insulin receptor, primarily by binding to the active site, particularly active site 3 of the receptor (Table 2, Figure 3A/3B).

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Table 1: Blood pressure, sugar, cholesterol, and uric acid levels of patients before and after drinking *Peperomia pellucida* herbal tea

Name of Patient	Gender	Age (years)	Condition before drinking *P. pellucida*	Condition after drinking *P. pellucida*	Analysis of clinical trial result
Mrs. D. L	Woman	50	BP. 140/80 mmHg	BP. 120/80 mmHg	Systolic pressure decreased by 20 mmHg, resulting in normal blood pressure
Mrs. D. L	Woman	50	FBS. 260 mg/dL	FBS. 222 mg/dL	Fasting blood sugar decreased by 38 mg/dL.
Mrs. D. L	Woman	50	Cholesterol. 202 mg/dL	Cholesterol 184 mg/dL	Cholesterol level decreased by 18 mg/dL resulting in normal blood cholesterol levels.
Mrs. D. L	Woman	50	Uric Acid 3.2 mg/dL	Urid Acid. 4.0 mg/dL	Uric acid level improved normal/increased by 0.8 mg/dL
Mrs. F. K	Woman	37	BP. 180/110 mmHg	BP. 130/80 mmHg	Systolic pressure decreased by 50 mmHg, resulting in normal blood pressure.
Mrs. F. K	Woman	37	MBS. 141 mg/dL	MBS. 120 mg/dL	Momentary Blood Sugar level decreased by 21 mg/dL
Mrs. F. K	Woman	37	Cholesterol. 213 mg/dL	Cholesterol. 175 mg/dL	Cholesterol level decreased by 38 mg/dL.
Mrs. F. K	Woman	37	Uric Acid 6.5 mg/dL	Uric Acid 5.0 mg/dL	Uric Acid level decreased by 1.5 mg/dL
Mrs. A. K	Woman	61	BP. 150/70 mmHg	BP. 110/60 mmHg	Systolic pressure decreased by 40 mmHg towards normal, diastolic decreased by 10 mmHg
Mrs. A. K	Woman	61	MBS. 431 mg/dL	MBS. 362 mg/dL	Momentary Blood Sugar level decreased by 51 mg/dL
Mrs. A. K	Woman	61	Cholesterol 256 mg/dL	Cholesterol 204 mg/dL	Cholesterol level decreased by 52 mg/dL
Mrs. A. K	Woman	61	Uric Acid 7.6 mg/dL	Uric Acid 7.5 mg/dL	Uric Acid level decreased by 0.1 mg/dL.

Table 2: Docking results of metabolites from *Peperomia pellucida* (1 - 19), metformin (20) and FDA approved drugs (21 - 24)

Ligands	Binding Affinity 1IR3 (Kcal/mol)	Important Amino Acid Interaction
Brachystamide B (**1**)	-5.90	Gln1111, Gln1111, Glu1115, Ser1270, Ser1270, Thr1145, Val1274
Bexagliflozin (**2**)	-7.50	Ala1028, Asp1132, Asp1150, Gly1048, Glu1043, Glu1043, Glu1043, Leu1002, Leu1170, Met1139, Ser1006, , Ser1006, Ser1006,
Caryatin (**3**)	-8.10	Ala1028, Asp1150, Glu1047, Gly1047, Gly1003, Leu1002, Leu1002, Lys1030, Met1139, Met1139, Val1010, Val1010
Guineesine (**4**)	-6.50	Ala1028, Asp1083, Asp1083, Leu1002, Met1079, Met1139, Phe1007 , Ser1006, Val1010,
Isoschaftoside (**5**)	-9.10	Ala1028, Asp1105, Gln1004,Gln104,Glu1043,Leu1002,Met1139,Ser1006,Ser1086, Val1010,Val1010
Isoswertisin (**6**)	-8.70	Ala1028, Asp1150, Asp1083, Leu1002, Lys1030, Met1076, Met1079, Met1139, Met1139, Val1010, Val1010
Isovitexin (**7**)	-8.90	Ala1028, Asn1137, Gln1004, Lys1030, Leu1002, Met1139, Ser1006, Val1010, Val1010
Loliodide (**8**)	-5.70	Arg1039, Lys1030, Glu1043, Leu1170, Leu1170, Met1153
Luteolin (**9**)	-8.60	Ala1028, Asn1137, Leu1002, Lys1030, Met1139, Met1079, Met1139, Met1076, Val1010, Val1010,
Patuloside (**10**)	-9.40	Ala1028, Arg1136, Asp1150,Asp1083, Lys1030, Met1139, Met1079, Ser1086, Val1010
Peperomin A (**11**)	-8.60	Asp1150, Asp1083, Asp1150, Arg1136, Gly1005, Lys1030, Met1079, Met1139, Val1010,
Peperomin B (**12**)	-8.00	Ala1028, Arg1136, Asp1150, Asp1083, Asp1150, Gly1005, Lys1030, Leu1002, Met1079, Met1139, Met1076, Met107, Met1139, Val1010/
Peperomin C (**13**)	-7.10	Ala1028, Asp1083, Asp1083, Gly1003, Leu1002, Leu1002, Lys1030, Lys1030, Met1139, Met1139, Met1076, Met1079, Met1139, Met1076, Met1139, Ser1086.
Peperomin D (**14**)	-8.80	Gln1111, His1268, His1268, Try1087
Peperomin E (**15**)	-8.40	Gly11076, Gly1111, Gln1111, Gly1108, His1268, Phe1144, Ser1270, Thr1145
Pepercide (**16**)	-6.80	Lys1030, Arg1039, Glu1043, Met1153, Leu1170, Leu1170

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Pelucidin A (**17**)	-6.90	Asp1150, Ala1028, Arg1139, Glu1077, Ser1006, Ser1006, Met1079, Val1010, , Phe10 Val1010
Seamin (**18**)	-8.70	Asn1137, Asp1150, Gly1005, Lys103, Met1139, Ser1006, Val1010,
Caethochromin (**19**)	-9.80	Arg1136, Arg1136, Arg1136, Gly1004, Gly103, Gly1005, Met11139, Met1139, Val1010, Val1010
Metfromin (**20**)	-4.70	Asp1143, Glu1115, Thr1145, Glu1115, Asp1143, Glu1108
Linagliptin (**21**)	-8.40	Asp1129, Asp1232, Asp1229, Gln1230, Leu1213, Leu1231, Phe1221, Trp1200, Trp1200
Saxagliptin (**22**)	-6.70	Tyr1210, Glu1207, Ser1204, Trp1200, Trp1200
Sitagliptin (**23**)	-8.40	Ala1028, Asp1083, Asp1150, Asp1150, Asp1150, Gly1082, Gly1043, Gly1047, Gly1077, Leu1002, Lys1030, Lys1030, Met1079, Met1079, Val1010, Met1139, Phe1007, Ser1006.
Vildagliptin (**24**)	-7.40	Asp1143, Asp1143, Gln1111, Glu1108, Glu1115, His1057, Val1274

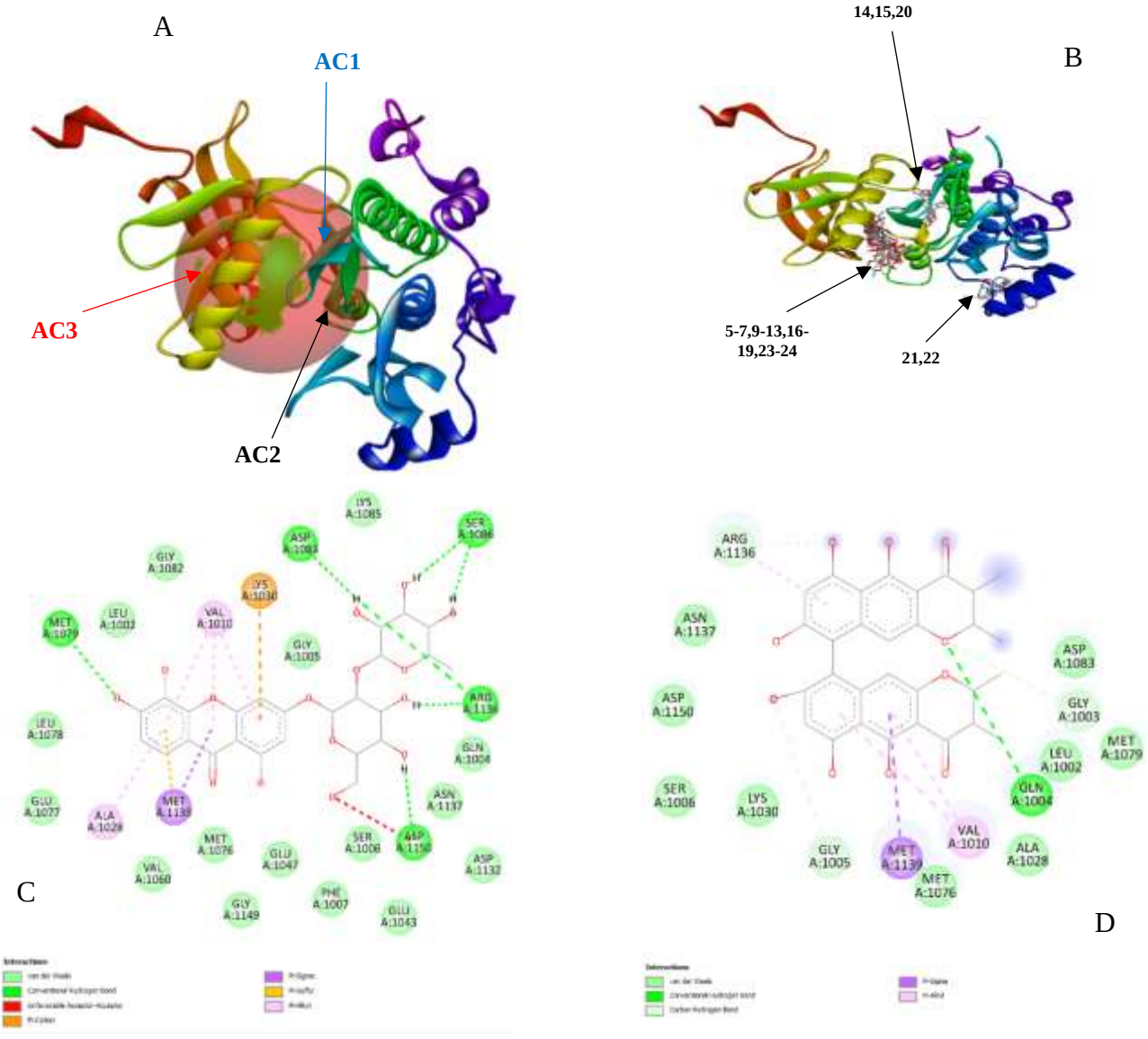

Figure 3: (A) Receptor cavities indicating the binding site of 1RE3 (red sphere). (B) Binding of *P. pellucida*-derived molecules. (C) Amino acid residues of 1IR3 interacting with petuloside via van der Waals, hydrogen, Pi-cation, Pi-sulfur, Pi-sigma, and Pi-alkyl bonds. (D) Amino acid residues of 1IR3 interacting with cathechomrin via van der Waals, hydrogen, carbon-hydrogen, Pi-sigma, and Pi-alkyl bonds. Data obtained through Discovery Studio Visualizer.

As previously mentioned, the amino acid residues that interacted with the active site of 1IR3 include Asn1137, Asp1150, Arg1136, Ser1006, Lys1030, Gly1005, Met1076, Val1010, Ala1028, Leu1002, Met1079, Gly1003, and Asp1083. Docking results indicated that strong binders exhibited the most frequent interactions with residues Ala1028, Asp1150, Asp1083, Lys1030, Val1010, Leu1002, Met1079, and

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Ser1006 within these active sites. These results suggest that the frequent interactions between strong binders such as isoschaftoside (**5**), isoswertisin (**6**), isovitexin (**7**), luteolin (**9**), patuloside (**10**), and peperomin D (**14**), and these key active site residues, contribute to the strong binding affinities observed (-9.80 to -8.60 kcal/mol). Therefore, compounds **5**, **6**, **7**, **9**, **10**, and **14** are potential inhibitors or modulators of the 1IR3 receptor, which is recognized as an emerging antidiabetic drug target.[27]

To further evaluate the antidiabetic potential of the metabolites from *P. pellucida* , the toxicity of the strong binders (binding affinity > -8.0 kcal/mol) was assessed using ADMET scores, as reported by Guan *et al*.[18] Subsequently, the ADMET profiles of these metabolites were compared with those of metformin,[28] a last-resort drug for antidiabetic treatment, and with recently approved antidiabetic drugs from the sitagliptin family, including linagliptin (**21**), saxagliptin (**22**), sitagliptin (**23**), and vildagliptin (**24**).[29] Consequently, based on the molecular docking results, the pharmacological and ADMET data for carvatin (**3**), isoschaftoside (**5**), isoswertisin (**6**), isovitexin (**7**), luteolin (**9**), patuloside (**10**), peperomin A (**11**), peperomin B (**12**), peperomin C (**13**), peperomin D (**14**), peperomin E (**15**), and seamin (**18**), as well as the aforementioned antidiabetic drugs were obtained using SwissAdme (http://www.swissadme.ch/), pkCSM (https://biosig.lab.uq.edu.au/pkcsm/), and AdmetSAR (http://lmmd.ecust.edu.cn/admetsar2/) (Tables 2 and 3).

The Lipinski rule of five (LRo5)[30] was initially evaluated, for all the *P. pellucida* metabolites and the results were compared with those of the commercial antidiabetic drugs. A compound's potential to be an effective oral drug was assessed based on its drug-like properties. Molecules were considered promising candidates if they complied with key physicochemical thresholds, including a molecular weight below 500 Da, a LogP value of 5 or less, fewer than five hydrogen bond donors, fewer than ten hydrogen bond acceptors, and a molar refractivity in the 40-130 range.[18] As shown in Table 2, all the antidiabetic drugs and the majority of the *P. pellucida* metabolites satisfied the LRo5. The exceptions are isoschaftoside (**5**) and patuloside (**10**), which violate three of the LRo5 criteria: molecular weight > 500 Dalton, HBD > 5, and HBA >10 (Table 3).

Table 3: The physicochemical properties of the metabolites from *Peperomia pellucida* and antidiabetic drugs

No	Ligands	Molecular Docking and Properties						
		Molecular Weight (MW) (g/mol)	HBD	HBA	nortb	LogP	TPSA (Å)	Violations of LRo5
1	Brachystamide B (**1**)	306.31	1	5	6	0.98	80.86	0
2	Bexagliflozin (**2**)	464.94	4	7	9	2.41	108.61	0
3	Caryatin (**3**)	330.29	3	7	3	1.88	109.36	0
4	Guineesine (**4**)	383.52	1	3	13	5.58	47.56	0
5	Isoschaftoside (**5**)	564.49	10	14	4	-1.64	250.97	3
6	Isoswertisin (**6**)	446.40	6	10	4	0.36	170.05	1
7	Isovitexin (**7**)	446.40	6	10	4	0.36	170.05	1
8	Loliodide (**8**)	196.24	0	3	0	1.55	46.53	0
9	Luteolin (**9**)	286.24	4	6	1	1.73	111.13	0
10	Patuloside (**10**)	568.48	9	15	5	-1.34	249.20	3
11	Peperomin A (**11**)	414.41	0	8	5	3.27	81.68	0
12	Peperomin B (**12**)	430.45	0	8	7	3.38	81.68	0
13	Peperomin C (**13**)	446.49	0	8	9	3.51	81.68	0
14	Peperomin D (**14**)	354.35	0	6	3	3.30	63.22	0
15	Peperomin E (**15**)	412.39	0	8	5	3.02	172.387	0
16	Pepercide (**16**)	355.47	1	3	11	5.02	47.56	0
17	Pelucidin A (**17**)	388.45	0	6	8	3.86	55.38	0
18	Seamin (**18**)	354.35	0	6	2	2.79	55.38	0
19	Caethochromin (**19**)	546.52	6	10	1	3.94	173.98	2
20	Linagliptin (**21**)	472.53	1	10	4	1.14	201.58	0
21	Saxagliptin (**22**)	315.14	2	4	3	1.24	90.35	0
22	Sitagliptin (**23**)	407.31	1	10	6	2.51	77.04	0

However, despite its usefulness in expediting drug discovery, particularly for orally active drugs, the Lipinski rule of five (Ro5) should not be the sole determinant, as many effective drugs do not meet all its criteria.[31] Therefore, this analysis was supplemented with a scoring function developed through machine learning, which is frequently applied in ADMET assessments. Based on the methodology described in a previously reported paper on ADMET SAR development with a slight modification,[18] the ADMET-score was calculated using 18 ADMET-related properties. These properties were categorized as either beneficial (q = 1) or harmful (q = 0), with weights assigned to each endpoint. Harmful properties included various toxicological endpoints, such as Ames test results and specific enzyme inhibition. The final ADMET-score was normalized between 0 and 1, with 1 representing the best possible score and 0 the worst.[18]

In this analysis, ADMET data were first compiled for the 18 properties or endpoints (Table 4). These properties were then converted into a binary system, categorizing them as either beneficial (q = 1) or harmful (q = 0), as shown in Table 5. Finally, the ADMET-score was calculated by multiplying the binary values by the established weights in the reported article[18] and divided the total values with the 18 endpoints, yielding the final values presented in Table 6.

The ADMET analysis for metabolites from *Peperomia pellucida* indicated that some compounds had less favorable ADMET profiles than caethochromin, an antidiabetic inhibitor, as well as antidiabetic drugs such as linagliptin and sitagliptin. Specifically, six compounds, namely; bexagliflozin, guineesine, luteolin, peperomin E, seamin, and pipercide had lower ADMET scores than caethochromin (Table 6). These lower scores were primarily attributable to issues with metabolism and absorption. Many of these compounds acted as inhibitors or substrates for glycoprotein and cytochrome P450 enzymes (CYP1A2, CYP2C19, CYP2C9, CYP3A4) and exhibited low Caco-2 permeability (Table 3), suggesting poor bioavailability in human intestinal mucosa.[32] This could prevent cellular uptake by P-glycoprotein,[33] and lead to deactivation, activation, or toxicity due to interactions with cytochrome enzymes.[34]

The ADMET profiles of other metabolites from *Peperomia pellucida* showed similar patterns, despite their more favorable ADMET scores compared to caethochromin and antidiabetic drugs such as linagliptin and sitagliptin. Metabolites such as isoschaftoside, isoswertisin, peperomins A-E, and pellucidin A had ADMET scores greater than 0.25.

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Table 4: The ADMET analysis of metabolites from *Peperomia pellucida*

Ligand	Ames toxicity	herG I Inhibitor	herG II Inhibitor	Carcino genicity	Oral Rat Acute Toxicity (LD50)	Organic Cation Transporter	GI Absorption	CYP Inhibitory promiscuity	CacO-2 Permeability	P-Glycoprotein Substrate	P-Glycoprotein Inhibitor	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP3A4 Inhibitor	CYP2D6 Inhibitor	CYP2D6 Substrate	CYP2C9 Substrate	CYP3A4 Substrate
Brachystamide B	No	No	No	No	0.630	No	81.150	0.6840 (H)	0.789	No	No	No	No	No	No	No	No	No	Yes
Bexagliflozin	No	No	Yes	No	0.560	No	56.350	0.5000 (H)	0.550	Yes	Yes	No	No	No	No	No	No	No	No
Guineesine	No	No	No	No	0.500	No	87.950	0.5779 (H)	1.190	Yes	No	Yes	Yes	No	No	No	No	No	No
Caryatin	No	No	Yes	No	0.527	No	92.360	0.6721 (H)	1.382	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Guineesine	No	No	Yes	No	0.647	No	45.385	0.7632 (H)	-1.18	Yes	No	Yes	Yes	No	No	No	No	No	Yes
Isoschaftoside	No	No	Yes	No	0.406	No	66.660	0.5599 (H)	-0.46	Yes	No	No	No	No	No	No	No	No	No
Isoswertisin	No	No	Yes	No	0.659	No	66.660	0.5828 (H)	-0.46	Yes	No	No	No	No	No	No	No	No	No
Isovitexin	No	No	No	No	0.650	No	95.690	0.7806 (L)	1.240	No	No	No	No	No	No	No	No	No	No
Loliolide	No	No	No	No	0.560	No	81.130	0.9870 (L)	0.090	Yes	No	No	No	No	No	No	No	No	Yes
Luteolin	Yes	No	No	No	0.735	No	21.330	0.5822 (H)	-0.47	Yes	No	Yes	No	No	Yes	No	No	No	No
Patuloside	Yes	No	No	No	0.620	No	100.00	0.8472 (L)	1.203	No	Yes	No	No	No	No	No	No	No	No
Paperomin A	No	No	Yes	No	0.472	No	99.531	0.8363 (H)	1.502	No	Yes	No	Yes	Yes	Yes	No	No	No	Yes
Paperomin B	No	No	Yes	No	0.470	No	99.995	0.8363 (H)	1.554	No	Yes	No	Yes	Yes	Yes	No	No	No	Yes
Paperomin C	No	No	No	No	0.560	No	99.633	0.8670 (H)	1.275	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Paperomin D	No	No	No	No	0.640	No	100,00	0.7943 (H)	1.392	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Paperomin E	No	No	Yes	No	0.457	No	93.050	0.9625 (H)	1.394	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Pepercide	No	No	No	No	0.640	No	76.000	0.7632 (H)	1.000	No	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
Pellucidin A	Yes	No	No	No	0.655	No	97.443	0.7237 (H)	1.137	No	Yes	Yes	Yes	No	No	No	No	No	Yes
Seamin	No	No	Yes	No	0.755	No	99.698	0.8340 (L)	1.484	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Chaetochromin	No	No	Yes	No	0.630	No	92.176	0.5140 (L)	-0.151	Yes	Yes	Yes	No	Yes	No	No	No	No	No
Metformin	Yes	No	No	No	0.730	No	91.560	0.9862 (L)	0.896	No	No	No	No	No	No	No	No	No	No
Linagliptin	No	No	Yes	No	0.610	No	83.900	0.8562 (L)	0.665	Yes	No	No	No	No	No	No	No	No	Yes
Saxagliptin	No	No	No	No	0.497	No	55.560	0.9003 (L)	0.987	No	No	No	No	No	No	No	No	No	Yes
Sitagliptin	No	No	No	No	0.602	Yes	87.420	0.8336 (H)	1.250	Yes	No	No	Yes	Yes	Yes	No	No	No	Yes
Vildagliptin	No	No	No	No	0.590	No	74.000	0.5061 (H)	0.591	No	No	No	No	No	No	No	No	No	Yes

Table 5: Binary system analysis for metabolites from *Peperomia pellucida*

Ligand	Ames toxicity	herG I Inhibitor	herG II Inhibitor	Carcino genicity	Oral Rat Acute Toxicity (LD50)	Organic Cation Transporter	GI Absorption	CYP Inhibitory promiscuity	CacO-2 Permeability	P-Glycoprotein Substrate	P-Glycoprotein Inhibitor	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP3A4 Inhibitor	CYP2D6 Inhibitor	CYP2D6 Substrate	CYP2C9 Substrate	CYP3A4 Substrate
Brachystamide B	1	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	0

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Bexagliflozin	1	1	0	1	0	1	0	0	1	0	0	1	1	1	1	1	1	1	1
Guineesine	1	1	1	1	0	1	1	0	1	0	1	0	0	1	1	1	1	1	1
Caryatin	1	1	0	1	0	1	1	0	1	0	0	0	0	1	1	1	1	1	1
Guineesine	1	1	0	1	0	1	0	0	0	0	1	0	0	1	1	0	1	1	0
Isoschaftoside	1	1	0	1	0	1	0	0	0	0	1	1	1	1	1	1	1	1	1
Isoswertisin	1	1	0	1	0	1	0	0	0	0	1	1	1	1	1	1	1	1	1
Isovitexin	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Loliolide	1	1	1	1	0	1	1	1	0	0	1	1	1	1	1	1	1	1	0
Luteolin	0	1	1	1	0	1	0	0	0	0	1	0	1	1	0	1	1	1	1
Patuloside	0	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1
Paperomin A	1	1	0	1	0	1	1	0	1	1	0	1	0	0	0	1	1	1	0
Paperomin B	1	1	0	1	0	1	1	0	1	1	0	1	0	0	0	1	1	1	0
Paperomin C	1	1	1	1	0	1	1	0	1	1	0	0	0	0	0	1	1	1	0
Paperomin D	1	1	1	1	0	1	1	0	1	1	0	0	0	0	0	1	1	1	1
Paperomin E	1	1	0	1	0	1	1	0	1	0	0	0	0	0	0	0	1	1	0
Pepercide	1	1	1	1	0	1	1	0	1	1	0	0	0	0	1	0	1	1	0
Pellucidin A	0	1	1	1	0	1	1	0	1	1	0	0	0	1	1	1	1	1	0
Seamin	1	1	0	1	0	1	1	1	1	1	0	0	0	0	0	0	1	1	1
Chaetochromin	1	1	0	1	0	1	1	1	0	0	0	0	1	0	1	1	1	1	1
Metformin	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Linagliptin	1	1	0	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0
Saxagliptin	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	0
Sitagliptin	1	1	1	1	0	0	1	0	1	0	1	1	0	0	0	1	1	1	0
Vildagliptin	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	0
	No =1 Yes =0	No =1 Yes =0	No =1 Yes =0	No =1 Yes =0	>1=1 <1=0	No =1 Yes =0	>70=1 <70=0	high = 0 low = 1	>0.5=1 <0.5=0	No =1 Yes =0	No =1 Yes =0	No =1 Yes =0	No =1 Yes =0	No =1 Yes =0	No =1 Yes =0	No =1 Yes =0	No =1 Yes =0	No =1 Yes =0	No =1 Yes =0

Table 6: ADMET score of 18 endpoints analysis of the metabolites from *Peperomia pellucida* and antidiabetic drugs

Ligand	Ames toxicity	herG I Inhibitor	herG II Inhibitor	Carcinogenicity	Oral Rat Acute Toxicity (LD50)	Organic Cation Transporter	GI Absorption	CYP Inhibitory promiscuity	CacO-2 Permeability	P-Glycoprotein Subsrate	P-Glycoprotein Inhibitor	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP3A4 Inhibitor	CYP2D6 Inhibitor	CYP2D6 Substrate	CYP2C9 Substrate	CYP3A4 Substrate	ADMET SCORE
Brachystamide B	0.6021	0.4059	0.4059	0.6021	0	0.2564	0.754	0	0.3074	0.364	0.3735	0.2379	0.2685	0.2966	0	0.2829	0.2296	0.2633	0	0.297
Bexagliflozin	0.6021	0.4059	0	0.6021	0	0.2564	0	0	0.3074	0	0	0.2379	0.2685	0.2966	0.3421	0.2829	0.2296	0.2633	0.2691	0.230

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Guineesine	0.6021	0.4059	0.4059	0.6021	0	0.2564	0.754	0	0.3074	0	0.3735	0	0	0.2966	0.3421	0.2829	0.2296	0.2633	0.2691	0.284
Caryatin	0.6021	0.4059	0	0.6021	0	0.2564	0.754	0	0.3074	0	0	0	0	0.2966	0.3421	0.2829	0.2296	0.2633	0.2691	0.243
Guineesine	0.6021	0.4059	0	0.6021	0	0.2564	0	0	0	0	0.3735	0	0	0.2966	0.3421	0	0.2296	0.2633	0	0.177
Isoschaftoside	0.6021	0.4059	0	0.6021	0	0.2564	0	0	0	0	0.3735	0.2379	0.2685	0.2966	0.3421	0.2829	0.2296	0.2633	0.2691	0.233
Isoswertisin	0.6021	0.4059	0	0.6021	0	0.2564	0	0	0	0	0.3735	0.2379	0.2685	0.2966	0.3421	0.2829	0.2296	0.2633	0.2691	0.233
Isovitexin	0.6021	0.4059	0.4059	0.6021	0	0.2564	0.754	0.4808	0.3074	0.364	0.3735	0.2379	0.2685	0.2966	0.3421	0.2829	0.2296	0.2633	0.2691	0.355
Loliolide	0.6021	0.4059	0.4059	0.6021	0	0.2564	0.754	0.4808	0	0	0.3735	0.2379	0.2685	0.2966	0.3421	0.2829	0.2296	0.2633	0	0.305
Luteolin	0	0.4059	0.4059	0.6021	0	0.2564	0	0	0	0	0.3735	0	0.2685	0.2966	0	0.2829	0.2296	0.2633	0.2691	0.192
Patuloside	0	0.4059	0.4059	0.6021	0	0.2564	0.754	0.4808	0.3074	0.364	0	0.2379	0.2685	0.2966	0.3421	0.2829	0.2296	0.2633	0.2691	0.304
Paperomin A	0.6021	0.4059	0	0.6021	0	0.2564	0.754	0	0.3074	0.364	0	0.2379	0	0	0	0.2829	0.2296	0.2633	0	0.227
Paperomin B	0.6021	0.4059	0	0.6021	0	0.2564	0.754	0	0.3074	0.364	0	0.2379	0	0	0	0.2829	0.2296	0.2633	0	0.277
Paperomin C	0.6021	0.4059	0.4059	0.6021	0	0.2564	0.754	0	0.3074	0.364	0	0	0	0	0.3421	0.2829	0.2296	0.2633	0	0.253
Paperomin D	0.6021	0.4059	0.4059	0.6021	0	0.2564	0.754	0	0.3074	0.364	0	0	0	0	0	0.2829	0.2296	0.2633	0.2691	0.250
Paperomin E	0.6021	0.4059	0	0.6021	0	0.2564	0.754	0	0.3074	0	0	0	0	0	0	0	0.2296	0.2633	0	0.180
Pepercide	0.6021	0.4059	0.4059	0.6021	0	0.2564	0.754	0	0.3074	0.364	0	0	0	0	0.3421	0	0.2296	0.2633	0	0.239
Pellucidin A	0	0.4059	0.4059	0.6021	0	0.2564	0.754	0	0.3074	0.364	0	0	0	0.2966	0.3421	0.2829	0.2296	0.2633	0	0.237
Seamin	0.6021	0.4059	0	0.6021	0	0.2564	0.754	0.4808	0.3074	0.364	0	0	0	0	0	0	0.2296	0.2633	0.2691	0.239
Chaetochromin	0.6021	0.4059	0	0.6021	0	0.2564	0.754	0.4808	0	0	0	0	0.2685	0	0.3421	0.2829	0.2296	0.2633	0.2691	0.250
Metformin	0	0.4059	0.4059	0.6021	0	0.2564	0.754	0.4808	0.3074	0.364	0.3735	0.2379	0.2685	0.2966	0.3421	0.2829	0.2296	0.2633	0.2691	0.323
Linagliptin	0.6021	0.4059	0	0.6021	0	0.2564	0.754	0.4808	0.3074	0	0.3735	0.2379	0.2685	0.2966	0.3421	0.2829	0.2296	0.2633	0	0.300
Saxagliptin	0.6021	0.4059	0.4059	0.6021	0	0.2564	0	0.4808	0.3074	0.364	0.3735	0.2379	0.2685	0.2966	0.3421	0.2829	0.2296	0.2633	0	0.301
Sitagliptin	0.6021	0.4059	0.4059	0.6021	0	0	0.754	0	0.3074	0	0.3735	0.2379	0	0	0	0.2829	0.2296	0.2633	0	0.235
Vildagliptin	0.6021	0.4059	0.4059	0.6021	0	0.2564	0.754	0	0.3074	0.364	0.3735	0.2379	0.2685	0.2966	0.3421	0.2829	0.2296	0.2633	0	0.315

Among these, only isoschaftoside and isoswertisin faced absorption issues, characterized by low intestinal absorption, low Caco-2 permeability, and acting as substrates for P-glycoprotein (Table 3), suggesting low bioavailability in the gastric lamina and human intestinal mucosa, and susceptibility to P-glycoprotein enzymatic effects.[33–35] The remaining metabolites exhibited both absorption and metabolism issues, similar to the six metabolites with lower ADMET scores mentioned earlier. Interestingly, four *P. pellucida* metabolites, including guineesine (**4**), isovitexin (**7**), loliolide (**8**), and patuloside (**10**) demonstrated ADMET scores surpassing those of well-known antidiabetic drugs such as metformin (**20**), linagliptin (**21**), saxagliptin (**22**), sitagliptin (**23**), and vildagliptin (**24**) (Table 3), suggesting their promising potential as antidiabetic agents. However, brachystamide (**1**) and loliolide (**8**) exhibitedure weak binding affinity against 1IR3, low Caco-2 permeability, and acted as both substrates and inhibitors of CPY3A4, a major cytochrome P450 isoform responsible for drug metabolism ~~(Figure 4)~~.[36] Guineesine (**4**) and patuloside (**10**) did not meet the Lipinski rule of five: guineesine faced metabolism and adsorption issues, while patuloside had low Caco-2 permeability and mutagenicity concerns. In contrast, isovitexin (**7**) exhibited strong binding affinity, met the Lipinski rule of five, and displayed the most favorable ADMET profile. This suggests that while compounds **1**, **5**, and **9** require further optimization before they can become antidiabetic drug candidates, compound **7** appears to be the most promising candidate discovered in this study. Indeed, isovitexin and vitexin have been reported to show multitarget effect in controlling diabetes mellitus and its complications.[14]

Closer analysis of the last-resort antidiabetic drug metformin and the FDA-approved antidiabetic drugs linagliptin (**21**), saxagliptin (**22**), sitagliptin (**23**), and vildagliptin (**24**) also suggests that these drugs are not entirely free from ADMET-related issues. For example, metformin, despite its renowned safety profile, exhibits mutagenic properties and bioavailability issues due to its low Caco-2 permeability. Similarly, while all the DPP-4 inhibitors (**21-24**) recently approved as antidiabetic drugs are recognized for their glucose-lowering effects and favorable safety profiles, they also present metabolism and adsorption issues. Importantly, these drugs are substrates of CYP3A4, a major cytochrome P450 isoform responsible for the metabolism of 30% of currently available drugs.[36,37] This corroborates recent reports on the toxicity issues of metformin,[5,6] and other antidiabetic drugs such as linagliptin, sitagliptin, and saxagliptin,[38–40] highlighting the importance of discovering new antidiabetic drugs to address these ADMET-related concerns.

The findings from the present study have significant implications for the discovery of new antidiabetic drug candidates, addressing the urgent need for effective and safe treatments. First, the preliminary short tests on human subjects for one week provided valuable insights into the antidiabetic potential of herbal tea prepared from *P. pellucida*, as well as its significant effects on reducing systolic blood pressure, cholesterol, and uric acid levels. This aligns with the new era of antidiabetic drugs characterized by cardiovascular safety.[41] Ilias *et al*.[41] reported that patients treated with various types of antidiabetic drugs (SGLT2 inhibitors, GLP-1 agonists, and TZDs) showed a slight reduction in systolic blood pressure but not diastolic, which was also observed in this study, confirming the potential of herbal tea prepared from *P. pellucida* as a promising antidiabetic drug candidate. However, the ADMET profiles of many compounds derived from *P. pellucida* suggest that further detailed molecular identification and toxicity analysis through improved *in vitro*, *in silico*, and *in vivo* analyses should be the focus of future studies, as has been a major concern for many herbal teas.[42,43]

The results of the molecular docking studies revealed that the majority of the metabolites from *Peperomia pellucida* appear to bind to the binding sites of the insulin receptor, particularly at site AC3, which is distinct from the binding sites of metformin and saxagliptin but similar to those of linagliptin (**21**) and saxagliptin (**22**) (Figure 3A/3B). This aligns with ongoing efforts to discover new antidiabetic drug candidates, as highlighted by Lawrence and Niu (1998),[44] and Breen and Soellner (2015).[26] One reason for this interest is the increased focus on developing small molecule inhibitors targeting enzymatic receptors, including the insulin receptor, specifically at the protein substrate binding site.[26] The substrate binding site strategy offers improved selectivity, making the discovery of small molecules capable of inhibiting substrate phosphorylation, including insulin receptor inhibitors, highly desirable. This approach addresses the current dire need for new antidiabetic drugs.[45]

The data also demonstrate a general trend where a higher number of active site interactions correlates with stronger binding affinities between ligands and the 1IR3 target (Figure 4). Despite a few exceptions for isoschaftoside and peperomin D, ligands exhibiting a greater multiplicity of interactions within the active site, such as isoswertisin (-8.7 Kcal/mol, 7 interactions), patuloside (-9.4 Kcal/mol, 7 interactions), and sitagliptin (-8.4 Kcal/mol, 8 interactions), consistently show more favorable (higher) binding affinity values. This suggests that the formation of multiple, simultaneous contacts within the active site is a primary determinant of binding strength, likely due to increased avidity and a reduction in the entropic penalty associated with binding, a principle supported by studies on protein-protein binding where the importance of binding site residues and the multiplicity of interactions significantly influence affinity.[46] Conversely, ligands with fewer active site interactions, like brachystamide B (-5.9 Kcal/mol, 2 interactions) or Loliolide (-5.7 Kcal/mol, 4 interactions), typically exhibit weaker binding affinities, further supporting the hypothesis that the extent of active site engagement is critical for potent ligand-receptor association. Moreover, the toxicity analysis revealed that a few metabolites from *P. pellucida* also showed favorable ADMET profiles comparable to or better than both insulin inhibitors and antidiabetic drugs. Except for isovitexin (**7**), many metabolites had issues mainly with metabolism, adsorption, and, to a certain extent, mutagenicity and physicochemical properties (i.e., failing to meet the LRo5). Nevertheless, similar features were also observed for metformin, sitagliptin, and linagliptin, which opens opportunities for further optimization of the potential metabolites of *P. pellucida* before they can become good candidates for antidiabetic agents especially isovitexin, which was recently reported to be involved in pathophysiological and metabolic pathway of diabetes mellitus.[14]

It is also worth noting that while ADMET profiling provides crucial preliminary insights, it does not encompass all aspects of efficacy or clinical utility. Therefore, although isovitexin shows potential, comprehensive clinical trials and further pharmacological studies are necessary to fully ascertain its therapeutic value. Similarly, the ongoing need for new antidiabetic drugs indicates the importance of optimizing other metabolites of *P. pellucida*, especially those with strong binding affinity and favorable safety profiles. Despite the promising results, especially for isovitexin, the toxicity studies were conducted computationally, necessitating further *in vivo* studies on both animals and humans. Additionally, the current study's limited sample size and experimental time may not fully capture the antidiabetic potential of compounds derived from *P. pellucida*. Furthermore, the toxicity of isovitexin should be further investigated *in vivo* to ensure its safety, thus addressing potential toxicity. Nevertheless, this study highlights the potential of *Peperomia pellucida*, especially its metabolite isovitexin, as a novel antidiabetic agent, providing a foundation for the development of new, effective treatments for this debilitating disease.

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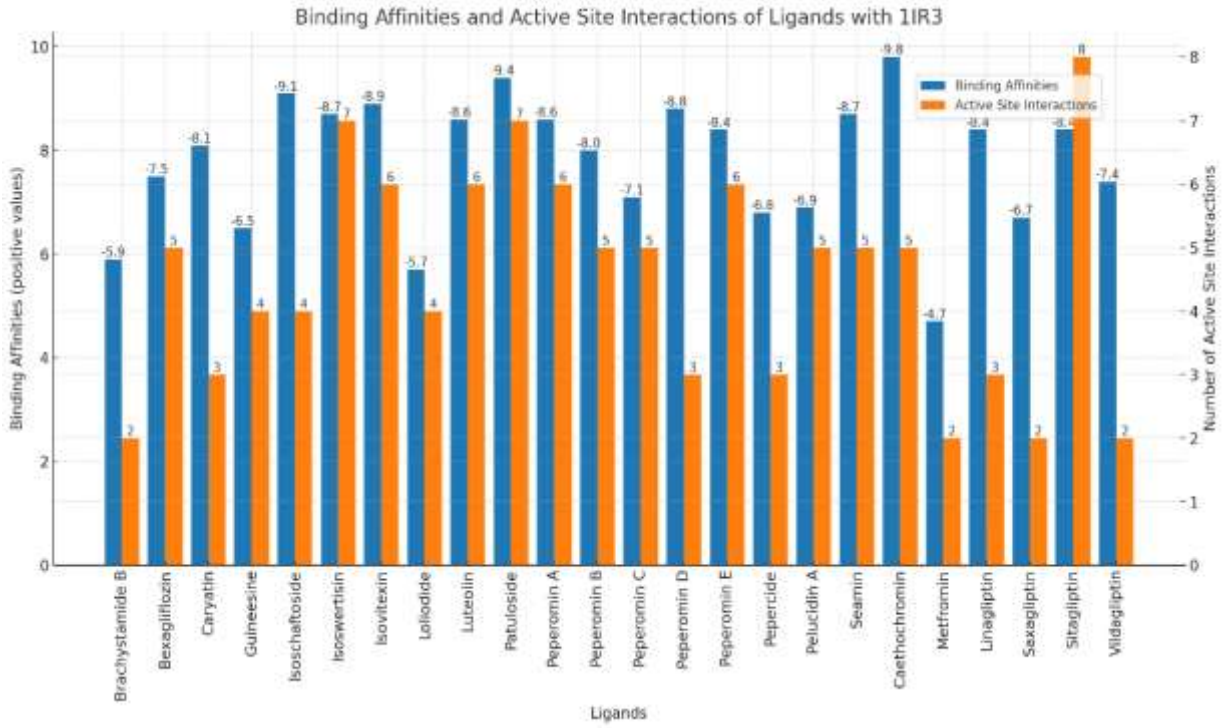

Figure 4: Binding affinity and active site interactions of metabolites from *Peperomia pellucida* along with antidiabetic drugs showing binding affinity (blue bar) and number of active site interactions (orange).

Conclusion

In this pilot study, *Peperomia pellucida* herbal tea consumption was associated with changes in systolic blood pressure and cholesterol levels in a small group of female patients aged 37 to 61. *In silico* molecular docking studies identified several *P. pellucida* metabolites with strong binding affinities for the insulin receptor (1IR3). However, ADMET analysis suggested that only a subset of these metabolites, particularly isovitexin, possessed favorable predicted drug-like properties. In addition to its high binding affinity, isovitexin showed more favourable ADMET profiles compared to all antidiabetic drugs such as metformin, linagliptin, sitagliptin and saxagliptin. These findings, coupled with recent reports highlighting the potential role of isovitexin in modulating key pathophysiological and metabolic pathways in diabetes, suggest that *P. pellucida*, particularly its metabolite isovitexin, as a promising candidate for further investigation. This highlights how molecular docking accelerate drug discovery, which will be useful when undertaking *in vivo* studies to determine its efficacy, safety, and mechanisms of action.

Conflict of interest

The authors declare no conflicts of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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