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Unraveling the anti-dyslipidemic activity of *Pandanus* amaryllifollus leaf extract in diabetic rat model: A combined *in-vivo* and molecular docking approach

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Abstract: The plant *Pandanus amaryllifolius* Roxb (pandan), has been shown to have antidyslipidemic activity. This study showed the activity of various alkaloids and flavonoids from pandanus leaf that worked as antidyslipidemic. The *in-vivo* testing was done by taking the blood samples of normal and diabetic male albino rat and assessed the lipid profile. The molecular docking testing was done by the interactions of the alkaloids and flavonoids with the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, Peroxisome Proliferator Activator Receptor (PPAR) alpha and the Niemann Pick C1 Like 1 receptor (NPC1L1) at receptor 1HW9, 6LX4 and 7DFZ respectively. Analyses were carried out by studying the binding affinity of the different alkaloids (pandanamine, pandamarilactonine A and pandamarilactonine B) and flavonoids (catechin, epicatechin, epigallocatechin, kaemferol, myricetin, quercetin) present in pandan leaves. Cholestrol HDL ratio, triglycerides, VLDL decreased and HDL increased. The binding energy of alkaloids pandamarilactonine B at 6LX4 was -9.3 kcal/mol, at 7DFZ were -8.9 and at 1HW9 receptor binding energy of pandamarilactonine A was more negative as compared to standard drug simvastatin showed higher level of interaction between the above mentioned alkaloid, flavonoids and receptors. The studied concluded that pandanus alkaloids and flavonoids have marked good antidyslipidemic activity.

Keywords: *Pandanus amaryllifolius*, alkaloids, flavonoids, *in-vivo* testing, antidyslipidemic, molecular docking.

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INTRODUCTION

Dyslipidemia, characterized by abnormal levels of lipids in the blood, is a major risk factor for ischemic heart disease, resulting in over 4 million annual deaths (Moini *et al*., 2020). It can lead to the development of atherosclerosis, endothelial dysfunction and increased vascular resistance (Fuster *et al*., 2021). However, conventional synthetic treatments are limited by side effects, including muscular, metabolic and neurological issues. (Thompson *et al*., 2016). Herbal medicine offers a viable alternative for disease prevention and treatment (Shaito *et al*., 2020). *Pandanus amaryllifolius* Roxb (pandan), native to Africa and tropical Pacific regions is valued for its aroma and natural coloring. It is commonly known as pandan leaves, has been traditionally used in Southeast Asian medicine to treat various ailments including dyslipidemia. Recent studies have validated the antidyslipidemic properties of *Pandanus amaryllifolius*, highlighting its potential as a natural remedy for managing lipid pro files. Research indicates pandan extracts may effectively manage dyslipidemia (Azhar *et al*., 2022).

A study conducted by Lim *et al*. in 2020 investigated the effects of the ethanolic extract of *Pandanus amaryllifolius* on lipid profiles in rats with high-fat diet-induced hyperlipidemia. The findings revealed that the extract substantially decreased total cholesterol, triglycerides and LDL cholesterol levels, while concurrently increasing HDL cholesterol levels. According to the researchers, the extract's ability to inhibit enzymes involved in lipid metabolism may be responsible for its antidyslipidemic effects.

Kumar *et al*, 2019 showed the antidyslipidemic effects of aqueous extract of *Pandanus amaryllifolius* in streptozotocin-induced diabetic rats. Thoi *et al*, demonstrated that the pandanus extracts reduced cholesterol and triglyceride levels in mice induced by Triton WR-1339 (Salim *et al*., 2004). In addition, water extracts of pandan improved metabolic syndrome, including triglyceride and LDL levels, in rat models (Cheng *et al*., 2017). Studies by Takayama *et al* have showed that the Pandan-derived alkaloids, such as pandamarilactonine A and B, exhibit significant antidyslipidemic activity. (Srivastava *et al*, 2012, Stankovic *et al*., 2011). These alkaloids originate from

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pandanamine, with recently discovered pandanusines showing potential antidyslipidemic actions. (Takayama *et al*, 2000).

This study explored the role of *Pandanus amaryllifolius* (pandan) alkaloids and flavonoids in lipid metabolism, demonstrating its antidyslipidemic properties through in vivo and molecular docking methods. Despite pandan's traditional use, previous research had not investigated combine *in-vivo* with interactions between its bioactive compounds, key enzymes and receptors involved in lipid metabolism. This study addressed this knowledge gap by examining the potential interactions between pandan's alkaloids, flavonoids, targeted enzymes and receptors. The investigation revealed that pandan's alkaloids and flavonoids may interact with crucial enzymes and receptors, including 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase, Peroxisome poliferator activator receptor (PPAR) alpha and the Niemann Pick C1 Like 1 receptor (NPC1L1) at 1HW9, 6LX4 and 7DFZ respectively. These interactions may contribute to pandan's antidyslipidemic effects. Notably, these enzymes and receptors play a vital role in lipid homeostasis and are targeted by conventional antidyslipidemic medications.

MATERIALS AND METHODS

In-vivo study

Preparation of extract

The leaves of *Pandanus amryllifolius* were collected from a local nursery of Karachi and identification by Karachi University Herbarium and Botanic garden, No. 97673. The leaves were washed and chopped into small pieces. collected, washed and chopped into small pieces (± 1 cm). A 100g leaves were then mixed with 500ml of ethanol (1:5 ratio) and stored in a dark container at room temperature (25°C ± 2°C) for 15 days. The mixture was filtered using Whatman No. 1 filter paper (pore size: 11 µm). The ethanol was then separated from the pandan leaf extract using a rotatory evaporator at a temperature of 40°C ± 5°C and a reduced pressure of 175 mbar. The evaporation process took approximately 2-3 hours, resulting in a paste-like extract (Siti *et al*, 2023).

In this study, male Wistar rats (200-250 g) were used. Diabetes was induced using 1-ml syringe and 25-G needles and injecting the streptozotocin solution at 40 mg/kg intraperitoneally in the experimental group of animals for 2 minutes. The animals having fasting blood glucose level higher than 180mg/dl, pandanus extract and standard drug was administered orally in the morning for three months. Animals were housed singly on a 12:12 hour light dark cycle in temperature (16–22°C) and humidity (30-70%). Cage racks were cleaned once per week and cage pans were cleaned thrice weekly. In the whole study, laboratory rat diet and filtered tap water has been given.

Animals were divided into four groups and each group has 10 animals (n=40)

Group 1: Normal control group (Normal saline)

Group 2: Diabetic control group (Streptozotocin, 55 mg/kg)

Group 3: Diabetic treated group (*Pandanus amaryllifolius* extract 200mg/kg)

Group 4: Diabetic treated group (Standard drug, simvastatin, 20mg/kg)

During the study, drugs and pandanus extract were administered orally with mentioned standard doses (Kumar *et al*., 2020) for 3 months on daily basis. After the end of 3 months, cardiac puncture has done to collect blood samples from the rats for various biochemical analyses.

For biochemical analysis of lipid profile (total cholesterol, triglycerides, LDL and HDL), blood samples of normal and diabetic male rat were collected and taken for analysis by centrifugation for 20min. centrifugation was done at 4°C and stored at -20°C.

Inclusion criteria

- Male rats weighing between 200-250 grams that developed diabetes following STZ injection (50 mg/kg, i.p.) and had fasting blood glucose levels of 180 mg/dL or higher were selected.
- Healthy rats without any visible signs of illness or injury were also included.

Exclusion criteria

- Female rats, male rats with weight less than 200g and more than 250g.
- Rats with pre-existing medical conditions such as kidney disease, liver disease, or cardiovascular disease were excluded.
- Rats that did not develop diabetes after STZ injection and had fasting blood glucose levels below 180 mg/dL were also excluded.

Molecular docking

MGL Tools (version 1.5.7) for performing docking, AutoDock Vina for creating PDBQT files (Trott O *et al*., 2010), Discovery Studio Visualizer (DSV) (Studio, 2020), PyMol Molecular Visualization Tool (Salentin set *et al*., 2015) used for result analysis.

Preparation of ligands

All compounds of alkaloids and flavonoids were draw and converted into three-dimensional molecules by Chem 3D Ultra. The energies of all studied compounds were minimized by using MMFF94X force- field with a minimum RMS gradient of 0.10. the iteration value was set as 1000 and save it into PDB format. PDBQT files were generated by using AutoDock Tools (version 1.5.7) for performing molecular docking study.

Selection and preparation of protein

The receptor proteins were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein data bank with respective PDB ID of 1HW9 (ES Istvan *et al*., 2001), 6LX4 (Shotaro *et al*., 2020), 7DFZ (Miaoqing *et al*., 2021) and resolution of 2.33 Å ,2.13 Å, 3.58 Å, for HMG-CoA reductase, PPAR alpha and NPC1L1 (Martohap *et al*.,2023) respectively.

The bound ligand, water molecules and extra chains were removed by BioVia Discovery Studio Visualizer (DSV). Furthermore, the energy of protein was minimized by SPDBV and polar hydrogens and Kollman united atom charges were introduced in PDB file by using AutoDock Tools. Finally, AutoDock Tools (version 1.5.7) was used to convert the PDB file of protein into PDBQT for the analysis of docking study.

Docking calculations

The molecular docking experiments were conducted using AutoDock Vina version 1.1.2. A grid box was created within the active site residues of receptors. The grid box was generated on the active site of protein 6LX4 with the size of 44 x 40 x 40 at x, y, z and center value was 1.950, -5.577, 15.399 Å. Meanwhile, for 1HW9 grid box was fixed with dimension of 40 x 50 x 50 at x, y, z and center value = 2.79,-9.013,-8.889 Å. The 7DFZ had grid box size of 60 x 55 x 65 at x, y, z and center value = 170.727, 174.895, 183.850 Å.

Analysis of docking results

The protein-ligand interaction has been analyzed by PyMol and discovery studio visualizer (DSV) for the interaction with amino acids, hydrogen bond hydrophobic bond.

Limitations of molecular docking

Molecular docking techniques is use to study the binding ability of small molecules with the target protein but there are several potential limitations to be considered while interpretation the results of molecular docking. The selected proteins must be completed in their structure. The resolutions of selected proteins were not more than 4 Å. The protein structures having resolution more than 4 Å were not selected. In our case the resolution of all protein between 2.13 to 3.58 Å. The structure of selected proteins was completed and missing residues were added by ADT before docking study. The incomplete structures were not considered for this study.

The active site of proteins was evaluated by the study of interaction pattern of co-crystal ligand for each protein. The binding pockets of all proteins were carefully generated with the center of residues present at the active site of protein and grid box dimensions were accurately calculated before starting docking study. The best pose of interacting ligand was selected on the bases of binding affinity. The ligand which was not bond with the residues of actives pocket of protein was rejected. The interaction between ligand and protein were carefully calculated in terms of hydrogen bonding, electrostatic, hydrophobic binding and van der Waal attraction.

Ethical approval

The project was approved by the ASRB (Advance study and research board) of University of Karachi (ASRB/No./06788/PHARM) dated 17 October 2022.

STATISTICAL ANALYSIS

All statistical analyses were conducted using the SPSS 20.0 software (IBM SPSS, USA) with a two-sided p-value of less than 0.05 considered statistically significant. Continuous variables that followed a normal distribution and exhibited homogeneity of variance were expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was employed to compare the means of continuous variables among different groups. In the event of a significant ANOVA result, a post hoc analysis was conducted to determine which specific groups differed from one another. The post hoc analysis, Tukey's test was used to identify which groups had significantly different means and highlighting specific differences between groups.

RESULTS

The study investigated the effects of *Pandanus amaryllifolius* (pandan) administration on cholesterol, triglyceride, VLDL, LDL and HDL levels in diabetic and non-diabetic rats.

Effect on cholesterol and triglyceride

The control non-diabetic rats had cholesterol and triglyceride levels of 44 ± 0.57 mg/dl and 96.6 ± 1.00 mg/dl, respectively. In contrast, the control diabetic rats had higher levels of 45.36 ± 1.52 mg/dl and 121.6 ± 1.5 mg/dl, respectively. Administration of the standard drug reduced these levels to 52.6 ± 1.0 mg/dl and 101.3 ± 1.51 mg/dl, respectively. Notably, pandan administration further reduced cholesterol and triglyceride levels to 51.6 ± 1.0 mg/dl and 101.6 ± 1.0 mg/dl, respectively, with significant p-values of 0.001 and 0.006, respectively, compared to the control diabetic group.

Effect on VLDL and LDL

The control non-diabetic group had VLDL and LDL levels of 21.0 ± 1.08 mg/dl and 18.3 ± 1.02 mg/dl. In contrast, the control diabetic group had higher levels of 28.6 ± 1.08 mg/dl and 22.6 ± 1.02 mg/dl while administration of the standard drug reduced these levels to 21.3 ± 1.52 mg/dl and 21.6 ± 1.52 mg/dl, respectively. Pandan administration further reduced VLDL and LDL levels to 20.0 ± 1.0 mg/dl and 21.0 ± 1.08 mg/dl, with a significant p-value of 0.001 compared to the control diabetic group.

Effect on HDL

The control non-diabetic group had an HDL level of 5.6 ± 0.57 mg/dl, while the control diabetic group had a lower level of 4.6 ± 1.57 mg/dl. Administration of the standard drug restored HDL levels to 5.6 ± 0.57 mg/dl. Notably, pandan administration increased HDL levels to 6.3 ± 0.51 mg/dl.

The above result showed that pandan administration significantly reduced cholesterol, triglyceride, VLDL and LDL levels, while increasing HDL levels in diabetic rats (fig. 1). These findings suggest that pandan have potential therapeutic benefits in managing dyslipidemia.

Molecular docking

A molecular docking analysis was performed to investigate the potential interactions between a set of alkaloids (pandanamine, pandanusine B, pandamarilactonine A, pandamarilactonine B) and flavonoids (catechin, epicatechin, epigallocatechin, kaemferol, myricetin and quercetin) with HMG-CoA reductase, PPAR-alpha and NPC1L1.

Validation of docking study

The co-crystal ligands of selected proteins were separated and re-docked with AutoDock-Vina to validated the docking protocol. It was observed that re-docked co-crystal ligand was bind with the same interaction pattern as original ligand when super embossed. The RMSD values of redocked cocrystal ligand were calculated using command line on PyMol and the RMSD value of SIM (cocrystal of 1HW9), F5A (cocrystal of 6LX4) and H56 (cocrystal of 7DFZ) were 2.057 Å, 1.03 Å and 1.250 Å respectively. The RMSD values of all studies cocrystal ligand were less than and equal to 2 which were inacceptable range (fig. 2a-c).

Niemann pick C1 like 1 receptor (NPC1L1) (PDB: 7DFZ)

Flavonoids

Catechin forms hydrogen bonding with TYR-1102 (2.20Å) and hydrophobic interactions with specific residues in PDB 3EBO, namely VAL-1166, ALA-876, LEU-621, PHE-1101, VAL-380, ILE-625, LEU-382, ALA-768. These interactions have a binding energy of -8.0 kcal/mol. Epicatechin forms hydrophobic interactions with TYR-1062, PRO-899, PHE-404, PHE-405, ARG-406, VAL-896, TYR-886, GLN-409, hydrogen bonding with specific sites, namely GLU-618 (1.76Å), LEU-1056 (3.05Å), PHE-894 (3.25Å) and have a binding energy -8.1 kcal/mol. The epigallocatechin, forms hydrophobic interactions with PHE-1101, THR-1098, TYR-1062, PRO-1055, VAL-896, PHE-894, GLN-409, TYR-886, MET-616, THR-407, PHE-405 and hydrogen bonding with specific sites, namely LEU-1056 (3.04), GLU-618 (2.36Å) have a binding energy of -7.6 kcal/mol (fig. 3). Kaemferol forms hydrophobic interactions with LEU-871, VAL-701, PHE-1239, PHE-772, VAL-769, ILE-698, SER-695, LEU-382, VAL-380, ILE-625 , myricetin forms hydrogen bonding with specific sites GLN 873 (2.29Å), ASP-378 (2.95Å), PRO-379 (2.18Å) and hydrophobic interactions with LEU-871, TRP-383, PHE-1101, TYR-1102, LEU-621, LEU-1236, VAL-697.quercetin form hydrogen bonding with ALA-626 (2.68Å), SER-695 (2.46Å), ALA-768 (2.49Å) and and hydrophobic interactions with VAL-380, ASP-378, THR-377, LEU-1234, PHE-1239, VAL-701, PHE-772, VAL-769.These interactions result in a binding energy of -7.8,-8.0,-8.2 kcal/mol as mentioned in table 1.

Alkaloids

Pandamarilactonine-A, B and Pandanamine form hydrogen bond with with VAL-769 (3.23Å), ILE-698 (3.50Å) and hydrophobic interactions with VAL-1166, ALA-768, TRP-383, LEU-871, GLN-873, GLN-873, ILE-698, VAL-1166, PHE-1239, VAL-701, ALA-768, ILE-625, VAL-380, ALA-876, VAL-701, PHE1239 a binding energy of -8.6,-8.9 -8.0 kcal/mol.

Standard drug

Simvastatin form hydrophobic interaction with LEU-370, GLU-374, MET-684, LEU-699, VAL-680, GLN-700, PHE-636 with a binding energy of -7.0 kcal/mol.

Peroxisome Proliferator Activator Receptor (PPAR) alpha (PDB: 6LX4)

Flavonoids

Catechin forms hydrogen bonding with ALA-454 (2.55Å) and hydrophobic interactions with PHE-273,PHE-351, ALA-455, LYS-448, GLN-277, TYR-464, LEU-460,TYR-314, SER-280 specific residues in PDB 3A4A (fig. 4). These interactions have a binding energy of -8.3 kcal/mol .Epicatechin forms hydrophobic interactions withMET-330, LEU-321, SER-323, LYS-222, ASN-221, TYR-214, PHE-218, ASN-219, GLU-282, TYR-334, ALA-333, VAL-332, two hydrogen bonding with specific sites, namely LEU-331 (2.54 Å), MET-220 (2.62Å) and have abinding energy -8.3 kcal/mol. The epigallocatechin, forms hydrogen bonding with SER-280 (2.03 Å), CYS-276(2.65Å) and hydrophobic interactions PHE-273, PHE-351, ILE-447, LEU-456, TYR-464, GLN-277, LEU-460,TYR-314, PHE-318, ILE-317, LEU-321, MET-330 and have a binding energy of -8.0 kcal/mol. Kaemferol formshydrogen bonding with LEU-331 (2.67Å), THR-283 (2.54Å), hydrophobic interactions with ASN-219, MET-220,GLY-335, TYR-334, VAL-332, ALA-333, THR-279, MET-330, TYR-314, PHE-318, SER-280 and have a bindingenergy -8.6 kcal/mol. Myricetin forms hydrophobic interactions with LEU-321, MET-330, THR-279, SER-280,TYR-314, LEU-460, GLN-277, TYR-464, LEU-456, PHE-351, PHE-273, ILE-354, PHE-318, LYS-358 and have abinding energy -8.5 kcal/mol as mentioned in table 2.

Table 1: The binding energy, residues involve in hydrogen bonding and Van der Waal forces with Alkaloids and flavonoids at (NPC1L1).

Complex	Binding energy (Kcal/mol)	Residues involve in hydrophlic and hydrophobic bonding with ligand (bond length in Å)	Residues involve in Van der Waal attractions
Catechin	-8.0	HYDROGEN BOND: TYR-1102 (2.20) PI-SIGMA: LEU-1234 (3.99), PI-ALKYL: TRP-383 (3.92, 4.16), LEU-871 (5.50), PI-PI T-SHAPED: TRP-383 (4.52, 3.70), ACCEPTOR-ACCEPTOR: GLN-873 (2.87)	VAL-1166, ALA-876, LEU-621, PHE-1101, VAL-380, ILE-625, LEU-382, ALA-768
Epicatechin	-8.1	HYDROGEN BOND: GLU-618 (1.76), LEU-1056 (3.05), PHE-894 (3.25) PI-SIGMA: ILE-1097 (3.62), THR-407 (3.65) ALKYL: ALA-898 (3.97), PI-ALKYL: LEU-890 (5.00), ALA-898 (4.26) AMIDE-PI STACKED: GLY-897 (3.95)	TYR-1062, PRO-899, PHE-404, PHE-405, ARG-406, VAL-896, TYR-886, GLN-409
epigallocatechin	-7.6	HYDROGEN BOND: LEU-1056 (3.04), GLU-618 (2.36) AMIDE-PI STACKED: GLY-897 (4.01), PI-ALKYL: LEU-890 (4.92), ALA-898 (4.32, 4.00), PI-SIGMA: ILE-1097 (3.46), DONOR-DONOR: LEU-1056 (2.37)	PHE-1101, THR-1098, TYR-1062, PRO-1055, VAL-896, PHE-894, GLN-409, TYR-886, MET-616, THR-407, PHE-405, PHE-404, ARG-406
Kaemferol	-7.8	PI-SIGMA: VAL-1166 (3.79), PI-ALKYL: LEU-1234 (5.42), VAL-697 (5.34), ALA-768 (5.42) PI-PI STACKED: TRP-383 (4.26, 4.18, 5.62, 4.64)	LEU-871, VAL-701, PHE-1239, PHE-772, VAL-769, ILE-698, SER-695, LEU-382, VAL-380, ILE-625
Myricetin	-8.0	HYDROGEN BOND: GLN 873 (2.29), ASP-378 (2.95), PRO-379 (2.18) PI-SIGMA: ALA-876, VAL-380, ILE-625 (3.47, 3.83), LEU-382 (3.93), ACCEPTOR-ACCEPTOR: GLN-873 (2.72)	LEU-871, TRP-383, PHE-1101, TYR-1102, LEU-621, LEU-1236, VAL-697
Quercetin	-8.2	HYDROGEN BOND: ALA-626 (2.68), SER-695 (2.46), ALA-768 (2.49) PI-SIGMA: LEU-382 (3.26), PI-ALKYL: LEU-382 (5.02), ILE-625 (5.43), ILE-698 (5.26), VAL-1166 (5.33) PI-PI STACKED: TRP-383 (5.62),	VAL-380, ASP-378, THR-377, LEU-1234, PHE-1239, VAL-701, PHE-772, VAL-769
Pandamarilactonine-A	-8.6	HYDROGEN BOND: VAL-769 (3.23) ALKYL: LEU-621 (5.18), ALA-876 (4.35), ILE-625 (4.29), LEU-382 (4.83), VAL-380 (4.47), LEU-1234 (5.41), VAL-701 (4.75), VAL-697(4.18), ILE-698 (4.24) PI-ALKYL: PHE-772 (4.38)	VAL-1166, ALA-768, TRP-383, LEU-871, GLN-873, PRO-379, PHE-1239
Pandamarilactonine-B	-8.9	PI-SIGMA: TRP-383 (3.90), PI-ALKYL: TRP-383 (4.61, 3.82), PHE-772 (4.45), PHE-1101 (3.69) ALKYL: VAL-769 (4.10), LEU-1234 (5.17), LEU-382 (4.98), VAL-697 (4.78), VAL-380 (4.88)	GLN-873, ILE-698, VAL-1166, PHE-1239, VAL-701, ALA-768
Pandanamine	-8.0	HYDROGEN BOND: ILE-698 (3.50) ALKYL: LEU-382 (4.94), ALA-768 (4.83), VAL-697 (3.87), VAL-769 (4.06), LEU-1234 (4.25), LEU-871 (5.01), VAL-1166 (4.01, 5.26), PI-ALKYL: PHE-772 (4.51), TRP-383 (3.89, 4.68, 4.28)	ILE-625, VAL-380, ALA-876, VAL-701, PHE1239
Simvastatin	-7.0	PI-SIGMA: PHE-704 (3.65), PI-ALKYL: PHE-704 (5.46), ALKYL: TYR-640 (5.25) PRO-703 (3.55), MET-681 (4.19), LEU-677 (4.31), LEU-633 (4.64, 5.42, 3.97, 3.78), ALA-637 (5.18)	LEU-370, GLU-374, MET-684, LEU-699, VAL-680, GLN-700, PHE-636
Cocrystal ligand (H56)	-8.35	HYDROGEN BOND: LEU-875 (2.51) PI-ALKYL: ILE-698 (4.85), ALA-768 (5.26), LEU-1234 (4.02), ALA-876 (4.15, 4.88) AMIDE-PI STACKED: VAL-697 (4.84) PI-SIGMA: LEU-871 (2.45)	PHE-1238, GLN-1233, VAL-1166, VAL-769, PHE-772, PHE-1239, VAL-701, LEU-382, TRP-383, GLN-873, LEU-621, ILE-625, VAL-380

Table 2: The binding energy, residues involve in hydrogen bonding and Van der Waal forces with Alkaloids and flavonoids at (PPAR) alpha.

Complex	Binding energy (Kcal/mol)	Residues involve in hydrophlic and hydrophobic bonding with ligand (bond length in Å)	Residues involve in Van der Waal attractions
Catechin	-8.3	HYDROGEN BOND: ALA-454 (2.55) PI-CATION: HIS-440 (3.95), HIS- PI-SIGMA: ILE-447 (3.76), LEU-456 (3.79), ALKYL: VAL-444 (5.09), ILE-354 (5.36 ALKYL), PI-ALKYL: VAL-444 (5.40), ALA-454 (4.82) PI-PI T-SHAPED: 440 (4.96)	PHE-273, PHE-351, ALA-455, LYS-448, GLN-277, TYR-464, LEU-460 TYR-314, SER-280
Epicatechin	-8.3	HYDROGEN BOND: LEU-331 (2.54), MET-220 (2.62) PI-SIGMA: THR-279 (3.61), ALKYL: VAL-324 (4.30), PI-ALKYL: MET-320 (4.51), MET-220 (5.30)	MET-330, LEU-321, SER-323, LYS-222, ASN-221, TYR-214, PHE-218, ASN-219, GLU-282, TYR-334, ALA-333, VAL-332
epigallocatechin	-8.0	HYDROGEN BOND: SER-280 (2.03), CYS-276 (2.65) PI-ALKYL: HIS-440 (4.57), MET-355 (5.17), ILE-354 (5.46), VAL-444 (5.08)	PHE-273, PHE-351, ILE-447, LEU-456, TYR-464, GLN-277, LEU-460, TYR-314, PHE-318, ILE-317, LEU-321, MET-330
Kaemferol	-8.6	HYDROGEN BOND: LEU-331 (2.67), THR-283 (2.54) PI-ALKYL: VAL-324 (4.24), CYS-276 (5.21), LEU-321 (4.74) PI-SIGMA: LEU-321 (3.96)	ASN-219, MET-220, GLY-335, TYR-334, VAL-332, ALA-333, THR-279, MET-330, TYR-314, PHE-318, SER-280, MET-355, ILE-317
Myricetin	-8.5	PI-CATION: HIS-440 (4.00) PI-ALKYL: MET-355 (5.45), CYS-276 (4.76), VAL-444 (5.17, 5.31), ILE-447 (5.08) PI-PI T-SHAPED: HIS-440 (4.96), SULFUR-X: MET-355 (3.06)	LEU-321, MET-330, THR-279, SER-280, TYR-314, LEU-460, GLN-277, TYR-464, LEU-456, PHE-351, PHE-273, ILE-354, PHE-318, LYS-358
Quercetin	-8.3	HYDROGEN BOND: TYR-464 (2.46) PI-CATION: HIS-440 (3.93), PI-ALKYL: MET-355 (5.40), CYS-276 (4.80), VAL-444 (5.13, 5.34), ILE-354 (5.41), ILE-447 (5.11), PI-PI-PI T-SHAPED: HIS-440 (4.88)	LYS-358, PHE-318, ILE-317, LEU-321, MET-330, SER-280, TYR-314, THR-279, LEU-460, GLN-277, LEU-456, PHE-351, PHE-273
Pandamarilactonine-A	-9.2	HYDROGEN BOND: SER-280 (2.55), HIS-440 (2.38) ALKYL: VAL-324 (4.94), LEU-321 (4.06, 5.29), ILE-354 (4.10), PI-ALKYL: PHE-218 (5.16), MET-355 (5.04), PHE-273 (5.12), HIS-440 (4.79)	TYR-464, TYR-314, PHE-318, ILE-317, MET-330, THR-279, VAL-332, LEU-331, THR-283, MET-220, ASN-219, GLU-286, TYR-214, MET-320, CYS-276
Pandamarilactonine-B	-9.3	ALKYL: ILE-447 (5.30), VAL-444 (4.95), LYS-448 (4.02), LEU-456 (3.82), ILE-354 (4.34), LEU-321 (4.75), MET-355 (4.66) PI-ALKYL: PHE-273 (4.78),PHE-318 (4.69)	ALA-455, ALA-454, TYR-464, GLN-277, LEU-460, TYR-314, LYS-358, CYS-276, SER-280, THR-279
Pandanamine	-7.7	HYDROGEN BOND: TYR-314 (1.88), CYS-276 (2.55), SER-280 (2.66), ASN-219 (2.29), THR-283 (2.83) PI-ALKYL: HIS-440 (5.30), VAL-444 (5.07), MET-220 (4.12), LEU-321 (4.95), VAL-324 (4.15), ILE-317 (5.29), MET-355 (5.06)	TYR-464, LEU-460, GLN-277, ILE-354, PHE-273, PHE-318, GLU-282, TYR-334, THR-279
Simvastatin	-6.6	HYDROGEN BOND: ASN-236 (ASN-236) ALKYL: LEU-254 (4.91), ALA-333 ()4.37, 4.35), ALA-250 (3.81, 3.76), PI-ALKYL: PHE-239 (4.73)	THR-253, ASN-336, VAL-332, GLY-337, ILE-241, PRO-238, PRO-237
Cocrystal ligand (F5A)	-7.41	HYDROGEN BOND: TRY-314 (2.05) HIS-440 (2.53), SER-280 (3.07), GLN-277 (274) ALKYL: LYS-448 (3.36), LEU-456 (4.13) PI-ALKYL: ILE-447 (4.72), ALA-454 (4.78), VAL-444 (5.01), ILE-354 (5.31), LEU-456 (4.27)	LEU-460, CYS-276, PHE-318, PHE-273, PHE-351, ALA-455 TYR-464

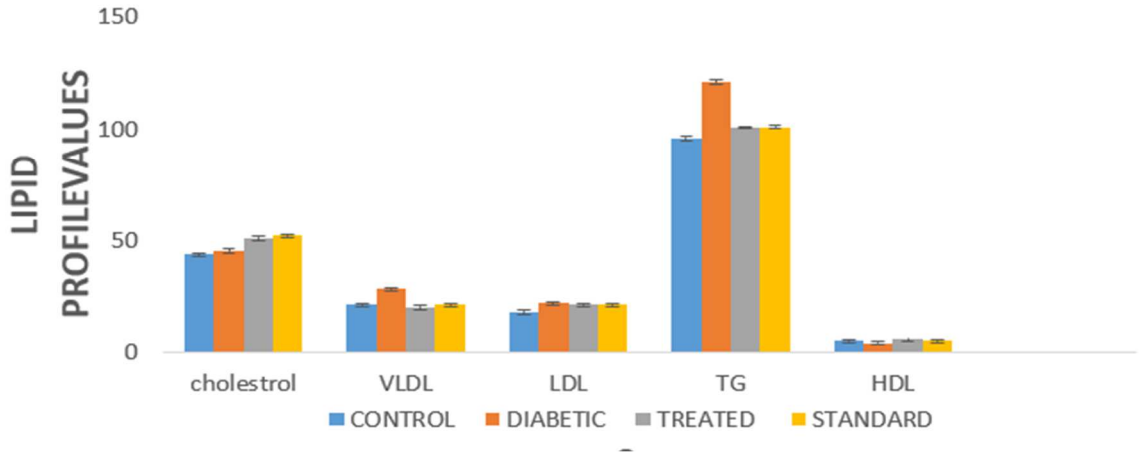
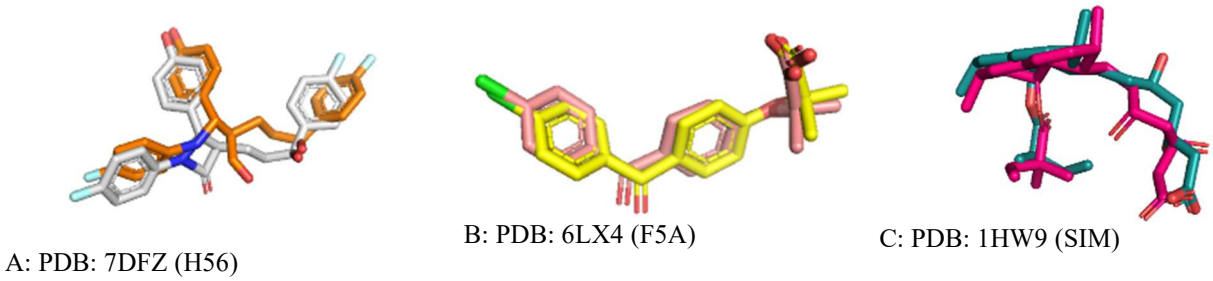


Fig. 1: Graph showed the effect of *Pandanus amaryllifolius* and standard drug on lipid profile



A: PDB: 7DFZ (H56)

B: PDB: 6LX4 (F5A)

C: PDB: 1HW9 (SIM)

Fig. 2: The root mean square deviation (RMSD) was calculated between the original co-crystal ligand (A: brown, B: light pink, C: dark pink) and redocked poses (A: grey, B: yellow, C: cyan) for validation of molecular docking results.

Quercetin

Pandamarilactonine-B

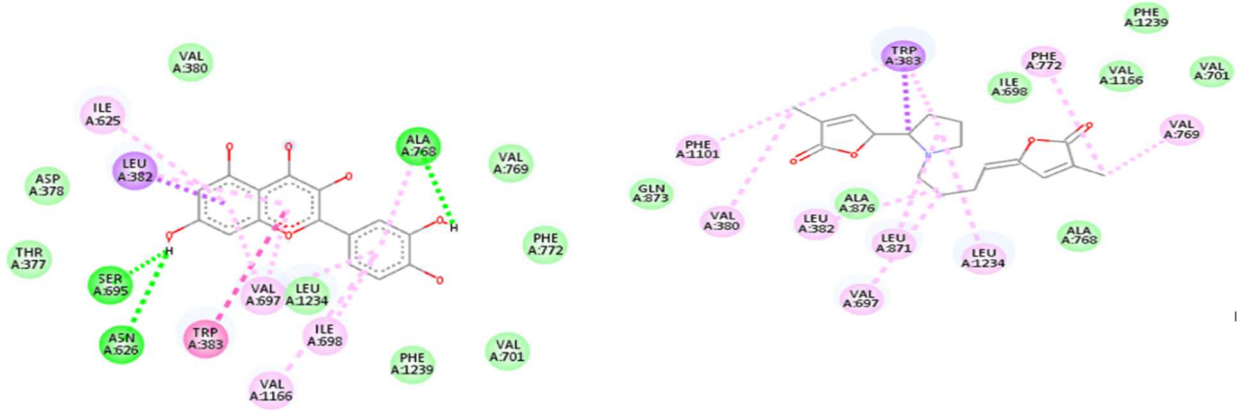


Fig. 3: Binding energy, residues involve in hydrogen bonding and Van der Waal forces with Alkaloids and flavonoids at (NPC1L1).

Alkaloids. Pandamarilactonine-A form hydrogen bond with SER-280 (2.55Å), HIS-440 (2.38Å) hydrophobic interaction with TYR-464, TYR-314, PHE-318, ILE-317, MET-330, THR-279, VAL-332, LEU-331, THR-283, MET-220, ASN-219, GLU-286, TYR-214, MET-320, with a binding energy of -9.2 kcal/mol. Pandamarilactonine-B forms hydrophobic interaction with ALA-455, ALA-454, TYR-464, GLN-277, LEU-460, TYR-314, LYS-358, CYS-276, SER-280, THR-279 with a binding energy of -9.3 kcal/mol. Pandanamine form hydrophobic interaction with TYR-464, LEU-460, GLN-277, ILE-354, PHE-273, PHE-318, GLU-282, TYR-334, and hydrogen bonding with TYR-314 (1.88Å), CYS-276 (2.55Å), SER-280 (2.66Å), ASN-219 (2.29Å), THR-283 (2.83Å) and a bindingenergy of -7.7 kcal/mol.

Standard drug

Simvastatin form hydrophobic interaction with THR-253, ASN-336, VAL-332, GLY-337, ILE-241, PRO-238, PRO-237 hydrogen bond with TRY-314 (2.05Å) and binding energy of -6.6 kcal/mol.

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (PDB: 1HW9)

Flavonoids

Catechin forms hydrogen bonding with ILE-746 (2.64Å, 2.01Å), ASN-776 (2.67Å) hydrophobic interactions with specific residues in PRO-693, VAL-772, GLY-747, GLY-748, ASN-750, CYS-777, SER-775. ALA-753, HIS-752, SER-745 .These interactions have a binding energy of -7.0 kcal/mol. Epicatechin forms hydrophobic interactions with SER-745, ALA-743, LYS-735, ASN-736, ALA-753, SER-775, ALA-754, GLY-748 and hydrogen bonding with specific sites, namely ASN-750 (2.10Å), SER-740 (2.18), GLY-739 (3.64 Å) and have a binding energy -6.9 kcal/mol (fig. 5). The epigallocatechin forms hydrogen bonding with VAL-772 (2.22Å), ILE-746 (2.18Å), ALA-751 (2.44Å), GLY-748 (3.54Å) and hydrophobic bonding with specific sites GLY-773, PRO-693, ASN-776, GLY-747, ASN-750, HIS-752, ASN-771, SER-745, SER-775.Kaemferol forms hydrophobic interactions with specific residues in ALA-743, SER-745, GLY-748, VAL-772, ASN-771, ALA-754, ASN-750, ASN-736, ALA-751 and hydrogen bonding with SER-740 (2.30Å), SER-775 (3.61 Å) myricetin forms hydrophobic interactions with ALA-743, SER-740, SER-745, GLY-747, ASN-776, PRO-693, GLY-773, SER-775 and hydrogen bonding with ALA-751 (2.56Å), ASN-750 (3.26Å), VAL-772 (2.43Å), ILE-746 (2.47Å), GLY-748 (3.41Å). quercetin form hydrogen interaction with ASN-776 (2.64Å), SER-740 (2.35Å), SER-745 (2.25Å), SER-775 (3.52Å, 3.59Å) and hydrophobic interaction with LYS-735, ALA-751, ASN-750, GLY-747, ASN-771, VAL-772, ALA-754, GLY-748, ILE-746. These interactions result in a binding energy of -7.2, -7.5, -7.2 kcal/mol, as indicated in table 3.

Alkaloids

Pandamarilactonine-A form hydrophobic interaction with GLY-739, ASN-736, GLY-748, ASN-750, SER-740, SER-745, ASN-734, GLU-730 with a binding energy of -7.0kcal/mol. Pandamarilactonine-B form hydrophobic interaction with GLY-808, GLN-766, ASP-767, THR-809, GLY-803, GLY-806, VAL-805, ASN-658, ALA-654, hydrogen bond with GLY-656 (2.16), GLY-765 (3.55) with a binding energy of -6.7 kcal/mol. Pandanamine form hydrophobic interaction with VAL-772, ASN-776, GLY-747, ALA-743, SER-745, SER-740,hydrogen bond with ASN-750 (2.30), SER-775 (3.51), GLY-748 (3.67Å) and a binding energy of -5.3kcal/mol.

Standard drug

Simvastatin form hydrophobic interaction with ASN-771, GLY-747, ASN-776, PRO-693, ILE-746, ALA-751, SER-745, ASN-750, HIS-752 and hydrogen bond with GLY-748 (2.46Å, 3.53Å), SER-775 (3.62 Å) with a binding energy of -6.8kcal/mol.

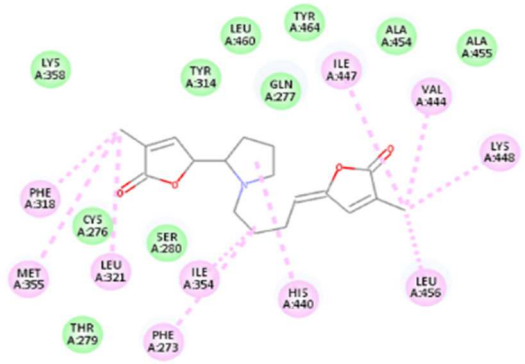
DISCUSSION

Dyslipidemia is associated with obesity and coronary heart disease. Taking fatty food is one of the leading causes which increased fat accumulation, resulting in metabolic syndromes such as dyslipidemia (Sikaris, 2014). These lipids include cholesterol, triglycerides, VLDL, LDL and HDL. Increased levels of LDL are related to the development of atherosclerosis (Smith *et al*, 2004). Research suggested that pandan possesses potential therapeutic properties for dyslipidemia management (Martohap *et al*., 2023). To investigate this, an animal model induced by a high-fat diet was employed, as it is a well-established model for studying human metabolic disorders (Buettner *et al*., 2007). The pandan species, *Pandanus amaryllifolius* contains a diverse range of bioactive compounds including flavonoids, alkaloids, benzenoids and steroids. Key alkaloids present in this species include pandanamine, pandamarilactonine-A and pandamarilactonine-B. Additionally, the phenolic and flavonoid profiles of pandan feature catechin, epicatechin, quercetin, myrecetin and kaemferol exert antidyslipidemic effect (Nguyen *et al*., 2023).

Pandan leaves exhibited anti-dyslipidemic effects due to their flavonoid compounds which reduced oxidative stress as atherosclerosis is one of the leading causes which increased fat accumulation, resulting in metabolic syndromes, such as dyslipidemia (Sikaris, 2004).

The anti-dyslipidemic effects of pandanus extract was due to their flavonoid compounds which reduced oxidative stress, inflammation and improve lipid profiles (Talirevic *et al*., 2012), alkaloids which decreased cholesterol and triglyceride levels and used in the treatment of dyslipidemia (Martohap *et al*., 2024). According to the findings of the study administration of pandan leaf ethanol extract for 8 weeks significantly reduced total

Pandamarilactonine-B



Kaemferol

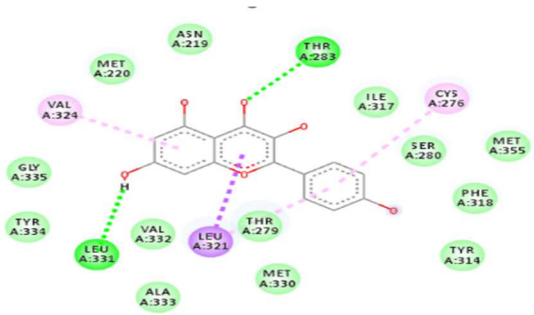
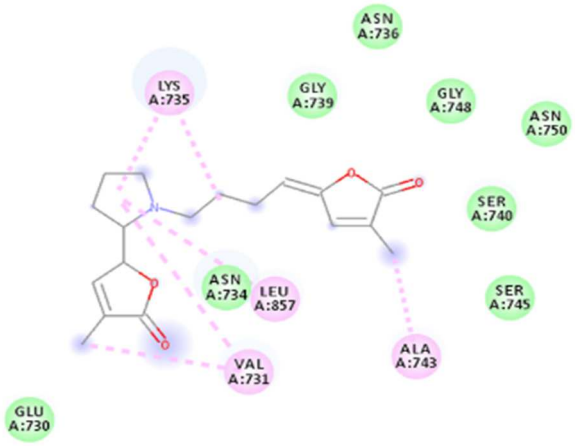


Fig. 4: Binding energy, residues involve in hydrogen bonding and Van der Waal forces with alkaloids and flavonoids at at (PPAR) alpha receptors

Pandamarilactonine-A



Myrecetin

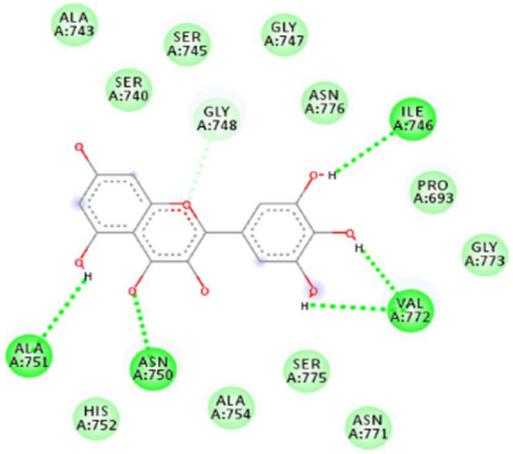


Fig. 5: Binding energy, residues involve in hydrogen bonding and Van der Waal forces with alkaloids and flavonoids at at HMG coA reductase

cholesterol, LDL and triglycerides. This study employed molecular docking to investigate the pose of selected alkaloids and flavonoids present in pandan leaves ligand at the binding site of protein.

The molecular docking results revealed that specific amino acids interacted with the examined alkaloids and flavonoids, which may also play a crucial role in binding standard ligands (simvastatin) to target macromolecules HMG-CoA reductase (1HW9), PPAR alpha (6LX4) and NPC1L1 (7DFZ).The result suggested that pandan leaf's alkaloids and flavonoids may inhibit HMG-CoA reductase (reducing cholesterol synthesis), activate PPAR alpha (enhancing fatty acid oxidation and lipid metabolism) and interact with NPC1L1 (influencing cholesterol absorption). HMG-CoA reductase plays a crucial role in cholesterol production and statins effectively lower blood cholesterol by inhibiting this enzyme (Istvan, 2002; Chen *et al*., 2023; Lumbanraja, 2001). Our results revealed that pandamarilactonine-A (-7.0 kcal/mol) from alkaloids and myrecitin (-7.5 kcal/mol) from flavonoids showed more negative binding energy than simvastatin (-6.8 kcal/mol) and co-crystal ligand, SIM, (-4.8 Kcal/mol) which indicate that pandamarilactonine-A and myrecitin has strong binding affinity and similar interaction patterns with HMG-CoA reductase suggested its potential character as a natural inhibitor, comparable to simvastatin. With PPAR alpha (Fruchart *et al*., 2019), our findings indicate that pandamarilactonine B (-9.3 kcal/mol) and kaemferol (-8.5 kcal/mol) from flavonoids exhibits a stronger binding affinity to PPAR alpha than the reference ligand simvastatin (-6.6 kcal/mol) and co-crystal ligand (-7.4 kcal/mol), as evidenced by its more negative binding energy .In the NPC1L1 protein (Huang *et al*., 2020), pandamarilactonine-B (-8.9 kcal/mol) from alkaloids and quercetin (-8.2 kcal/mol) from flavonoids showed more negative binding energy than simvastatin (-7.0 kcal/mol) and native (-8.3 kcal/mol) indicated that the higher level of interaction between the alkaloid, flavonoids and NPC1L1 protein as compared to standard drug.

These findings suggest that pandan's bioactive compounds may inhibit HMG-CoA reductase influenced cholesterol absorption from flavonoids showed more negative binding energy than simvastatin (-6.8 kcal/mol) which

Table 3: showed the binding energy, residues involve in hydrogen bonding and Van der Waal forces with Alkaloids and flavonoids at HMG CoA reductase.

Complex	Binding energy (Kcal/mol)	Residues involve in hydrophlic and hydrophobic bonding with ligand (bond length in Å)	Residues involve in Van der Waal attractions
Catechin	-7.0	HYDROGEN BOND: ILE-746 (2.64, 2.01), ASN-776 (2.67) ALKYL: ALA-754 (4.60) PI-ALKYL: ALA-754 (4.04)	PRO-693, VAL-772, GLY-747, GLY-748, ASN-750, CYS-777, SER-775. ALA-753, HIS-752, SER-745
Epicatechin	-6.9	HYDROGEN BOND: ASN-750 (2.10), SER-740 (2.18), GLY-739 (3.64)	SER-745, ALA-743, LYS-735, ASN-736, ALA-753, SER-775, ALA-754 GLY-748
epigallocatechin	-7.0	HYDROGEN BOND: VAL-772 (2.22), ILE-746 (2.18), ALA-751 (2.44), GLY-748 (3.54) ACCEPRTOR-ACCEPTOR: VAL-772 (2.70), DONOR-DONOR: SER-748 (1.48)	GLY-773, PRO-693, ASN-776, GLY-747, ASN-750, HIS-752, ASN-771, SER-745, SER-775, ALA-743, GLY-739
kaemferol	-7.2	HYDROGEN BOND: SER-740 (2.30), SER-775 (3.61)	ALA-743, SER-745, GLY-748, VAL-772, ASN-771, ALA-754, ASN-750, ASN-736, ALA-751, LYS-735
myricetin	-7.5	HYDROGEN BOND: ALA-751 (2.56), ASN-750 (3.26), VAL-772 (2.43), ILE-746 (2.47), GLY-748 (3.41)	ALA-743, SER-740, SER-745, GLY-747, ASN-776, PRO-693, GLY-773, SER-775, ASN-771, ALA-754, HIS-752
quercetin	-7.2	HYDROGEN BOND: ASN-776 (2.64), SER-740 (2.35), SER-745 (2.25), SER-775 (3.52, 3.59)	LYS-735, ALA-751, ASN-750, GLY-747, ASN-771, VAL-772, ALA-754, GLY-748, ILE-746, ALA-743
Pandamarilactonine-A	-7.0	ALKYL: LYS-735 (3.80, 4.67), LEU-857 (4.97), VAL-731 (5.18, 4.49), ALA-743 (3.63)	GLY-739, ASN-736, GLY-748, ASN-750, SER-740, SER-745, ASN-734, GLU-730
Pandamarilactonine-B	-6.7	HYDROGEN BOND: GLY-656 (2.16), GLY-765 (3.55) ALKYL: MET-811 (5.11), MET-655 (4.48)	GLY-808, GLN-766, ASP-767, THR-809, GLY-803, GLY-806, VAL-805, ASN-658, ALA-654, MET-657, CYS-526, GLY-807
Pandanamine	-5.3	HYDROGEN BOND: ASN-750 (2.30), SER-775 (3.51), GLY-748 (3.67) ALKYL: ALA-754 (1.19)	VAL-772, ASN-776, GLY-747, ALA-743, SER-745, SER-740
simvastatin	-6.8	HYDROGEN BOND: GLY-748 (2.46, 3.53), SER-775 (3.62) ALKYL: VAL-772 (3.73, 5.33), ALA-754 (4.24, 5.40, 4.13, 3.77) DONOR-DONOR: SER-740 (2.07)	ASN-771, GLY-747, ASN-776, PRO-693, ILE-746, ALA-751, SER-745, ASN-750, HIS-752
Cocrystal ligand (SIM)	-5.1 (-4.78)	HYDROGEN BOND: LYS-735 (2.45), ALA-751 (3.04) PI-ALKYL: HIS-752 (5.04) ALKYL: LEU-853 (4.13), ALA-856 (5.18), CYS-561 (4.58)	LEU-857, ASN-755, GLU-559, LEU-562, SER-565

indicate that pandamarilactonine-A and myrecitin has strong binding affinity and similar interaction patterns with HMG-CoA reductase suggested its potential character as a natural inhibitor, comparable to simvastatin. These findings suggest that pandan's bioactive compounds may inhibit HMG-CoA reductase, activate PPAR alpha and interact with NPC1L1, ultimately leading to reduced cholesterol synthesis, enhanced fatty acid oxidation and lipid metabolism and influenced cholesterol absorption. The correlation between the *in vivo* and molecular docking results provides insights into the potential antidyslipidemic mechanisms of pandan leaf's bioactive compounds, supporting further investigation into their therapeutic potential.

CONCLUSION

In conclusion, the study demonstrates the potential of pandan as a natural remedy for managing dyslipidemia,

with its bioactive compounds exhibiting strong binding affinity to target macromolecules and reducing cholesterol, triglyceride and LDL levels in an animal model. Further research is necessary to confirm the efficacy and safety of pandan leaf extracts in humans. The above mentioned alkaloid and flavonoids may offer a novel avenue for cholesterol reduction in the body.

Conflict of interest

There is no conflict of interest.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author's contribution

All authors contributed equally in the manuscript

CONCLUSION

This study investigated the potential therapeutic properties of *Pandanus amaryllifolius* (pandan) in managing dyslipidemia. The key findings of this study include the administration of pandan leaf significantly reduced lipid profile. Molecular docking analysis revealed that amino acids present at the active site interacted with the alkaloids and flavonoids which are present in the leaf of pandas and it was concluded that alkaloid specially pandamarilactonine -A and B play a crucial role in managing antidyslipidemia. These findings suggest that pandan leaf alkaloids may offer a novel, natural approach for the management of dyslipidemia, potentially providing an effective adjunct or alternative to existing treatments. The exploration of these natural compounds may lead to the development of effective and sustainable therapies for these prevalent diseases in future.

REFERENCES

Azhar ANH, Amran NA, Yusup S and Mohd Yusoff MH (2022). Ultrasonic extraction of 2-Acetyl-1-Pyrroline (2AP) from *Pandanus amaryllifolius* Roxb. using ethanol as solvent. *Molecules*, **27**(15): 4906.

Buettner R, Scholmerich J and Bollheimer LC (2007). High-fat diets: Modeling the metabolic disorders of human obesity in rodents. *Int. J. of Obesity*, **15**(4): 798-808.

Chen D, Oezguen N, Urvil P, Ferguson C, Dann SM and Savidge TC (2016). Regulation of protein-ligand binding affinity by hydrogen bond pairing. *Sci. Adv*., **2**(3): 1501240.

ES Istvan and J Deisenhofer (2006). Structural mechanism for statin inhibition of HMG-CoA reductase. *Sci.,* **292**(5519): 1160-4.

Fruchart JC, Santos RD, Aguilar-Salinas C, Aikawa M, Al Rasadi K, Amarenco P, Ceska R, Corsini A, Després JP, Duriez P, Eckel RH, Ezhov MV, Farnier M (2019).The selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα) paradigm: Conceptual framework and therapeutic potential: A consensus statement from the International Atherosclerosis Society (IAS) and the Residual Risk Reduction Initiative (R3i) Foundation. *Car Diab.*, **18**(1): 71.

Huang CS, Yu X, Fordstrom P, Choi K, Chung BC and Roh SH (2020). Cryo-EM structures of NPC1L1 reveal mechanisms of cholesterol transport and ezetimibe inhibition. *Sci Adv.*, **6**(25): eabb1989.

Istvan ES (2002). Structural mechanism for statin inhibition of 3-hydroxy 3-methylglutaryl coenzyme A reductase. *Am. Heart J.*, **144**(6): 27-32

Jacobson MS (1998) Heart healthy diets for all children: No longer controversial*. J. Pediatr.*, **133**: 1-2.

Kamata S, Oyama T, Saito K, Honda A, Yamamoto Y and Suda K (2020). PPARα Ligand-binding domain structures with endogenous fatty acids and fibrates. *I. Sci.,* **23**(11): 101727.

Lim J and Lee (2020). Antidyslipidemic effects of ethanolic extract of Pandanus amaryllifolius in high-fat diet-induced hyperlipidemic rats. *J. Ethnopharm.*, **247**: 112341.

Martohap Parotua Lumbanraja, Kusnandar Anggadiredja, Hubbi Nashrullah Muhammad and Neng Fisheri Kurniati (2023). Alkaloids from *Pandanus amaryllifolius* roxb leaf as promising candidates for antidyslipidemic Agents: An in silico study. *Pharmacogn. J.*, **15**(1): 106-111

Miaoqing Hu, Fan Yang, Yawen Huang, Xin You, Desheng Liu, Shan Sun and Sen-Fang Sui (2021).Structural insights into the mechanism of human NPC1L1-mediated cholesterol uptake. *Sci. Adv.*, **7**(29): 3188

Moini J, Miller C, Ahangari R and Samsam M (2020). .Global health complications of obesity. *Int J of Obesity.,* 9780-12- 819751-6.

Nguyen Duong Ngoc Thoi1, Tran Manh Hung, Huynh Ngoc Trinh (2019). Hypolipidemic effect of ethanolic extract from *Pandanus amaryllifolius* leaves on triton WR-1339-induced hyperlipidemia in mice; *Int. J Pharm. Res.,* 2277-3312

Perunov N and England JL (2014). Quantitative theory of hydrophobic effect as a driving force of protein structure. *Prot. Sci*., **23**(4): 387 99.

Lilkova E, Petkov P, Ilieva N and Litov L (2015). The PyMOL molecular graphics system, Version 2.0 Schrodinger, LLC.

Ramiırez D and Caballero J (2018). Is it reliable to take the molecular docking top scoring position as the best solution without considering available structural data. *Molecules*., **23**(5): 1038.

Salentin S, Schreiber S, Haupt VJ, Adasme MF and Schroede M (2015). PLIP: Fully automated protein-

ligand interaction profiler. *Nucl. Acids Res*., **43**(W1): W443-W447.

Shaito A, Thuan DTB, Phu HT, Nguyen THD, Hasan H and Halabi S (2020). Herbal medicine for cardiovascular diseases: Efficacy, mechanisms and safety. *Front Pharm.*, **11**: 422.

Sikaris KA (2004). The clinical biochemistry of obesity. *Clin. Bio. Rev*., **25**(3): 165-81.

Siti Malihatus Sa'adah, Fensy Rania Putri, Afina Anjani Ibtisam, Robiatush Sholichah Arrohmah and Fitriyah (2023). *J. Nat. Scien. & Math. Res.,* **9**(2): 135-140

Smith SC, Jackson R, Pearson TA, Fuster V and Yusuf S (2004) Principles for national and regional guidelines on cardiovascular disease prevention: A scientific statement from the World Heart and Stroke. *Forum, Cir.,* **109**: 3112-21.

Srivastava N, Chauhan AS and Sharma B (2012). Isolation and characterization of some phytochemicals from Indian traditional plants. *Bio. Res. Int.,* **2012**: 549850

Stankovic MS, Niciforovic N, Topuzovic M and Solujic S (2011). Total phenolic content, flavonoid concentrations and antioxidant activity, of the whole plant and plant parts extracts from *Teucrium montanum* L. var. montanum, f. supinum (L.) Reichenb. *Bio & Bio Equip.,* **25**(1): 2222-7.

Takayama H, Ichikawa T, Kuwajima T, Kitajima M, Seki H and Aimi N (2000). Structure characterization, biomimetic total synthesis and optical purity of two new pyrrolidine alkaloids, Pandamarilactonine-A and -B, isolated from *Pandanus amaryllifolius* Roxb. *J. Am. Chem. Soc.*, **122**(36): 8635-8639.

Talirevic E and Jelena S (2004). Quercetin in the treatment of dyslipidemia. *Med. Arh.*, **66**(2): 87-88.

Thompson PD, Panza G, Zaleski A and Taylor B (2016). Statin-associated side effects. *J. Am. Coll. Cardiol.*, **67**(20): 2395-410.