RESEARCH PAPER

Multifaceted Study of Aqueous and Ethanolic Extract of Vetiveria Zizanioides against Hyperlipidemia

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ABSTRACT
Hyperlipidemia has been linked to cardiovascular disease. Statins and fibrates are the anti-hyperlipidemic medicines for the treatment of increased plasma cholesterol and triglycerides, may cause severe muscular and liver side effects respectively. The present study focuses on investigating aqueous and ethanolic extracts anti-hyperlipidemic activity of Vetiveria zizanioides (VZ) as an alternative drug source. In-vitro study, the roots were extracted with water and ethanol and subjected to phytochemical, GCMS analysis, Insilco analysis and homology modelling. In-vivo study, albino rats were treated with VZ, blood and organs were collected and used for biochemical and histological analysis.
GCMS analysis identified 22 compounds in aqueous and 19 compounds in ethanol extract. The compounds were screened based on physiochemical properties, solubility, lipophilicity and toxicity analysis. 20 compounds of VZ were subjected to ADMET analysis confirmed the drug likeliness and its pharmacological activities. Norethindrone predicted as highest binding energy with HMDH, LIPL and APOA5 proteins. The best docked ligands play a vital role in stabilizing a (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione- FABP4 complex with minimal RMSD fluctuation. Low (300mg/kg) and high dose (600mg/kg) of VZ (aqueous and ethanol extracts) treated albino rats showed profound decreased cholesterol, LDL-C, triglyceride and increased HDL-C. Treatment with these extracts reduced fat deposition as well degenerative changes in organs liver, kidneys and heart which was analysed by H&E staining. VZ could be a potential source of antihyperlipidemic agent owing to the confirmatory evidence of docking ligand of (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione- FABP4 complex.

Keywords: *Vetiveria zizanioides (VZ); Hyperlipidemia; Phytochemical Molecular Dynamics; Docking; Albino Wistar rats*
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INTRODUCTION

Hyperlipidemia, a heterogeneous disorder characterized by abnormal lipid elevation in the bloodstream, including cholesterol, triglycerides, phospholipids, cholesterol esters, and plasma lipoproteins [1]. It can be classified as familial or acquired, with primary genetic abnormalities or underlying disorders being the primary cause, respectively. Primary types involve increased levels of lipoproteins and decreased levels of high density lipid, while secondary types are associated with various underlying conditions. Prevention and treatment strategies focus on lifestyle modifications, dietary changes, and medication use.

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However, pharmacological interventions may have adverse side effects [2].

Hyperlipidemia is a prominent risk factor of cardiovascular diseases and is highly prevalent worldwide, with varying rates across different regions and it is influenced by a combination of lifestyle, environmental and genetic factors. According to World Health Organization (WHO) estimates, the prevalence of dyslipidemia is substantial, with Southeast Asia, America, Western Pacific, and Europe reporting rates of 30.3%, 47.7%, 36.7%, and 53.7%, respectively. In specific countries within the Asia-Pacific region, the prevalence ranges from 12.2% in China to 71.3% in the Philippines. In India, hyperlipidemia affects a significant proportion of the population, with 25-30% of urban and 15-20% of rural individuals being affected. Furthermore, specific lipid abnormalities are prevalent, including hypercholesterolemia (13.9%), low HDL cholesterol (72.3%), high LDL cholesterol (11.8%) and hypertriglyceridemia (29.5%). Regional studies within India have also reported high prevalence of high LDL cholesterol (15.8%) and hypercholesterolemia (18.3%) [3].

As an alternative, herbal remedies and medicinal plants have gained attention for their hypolipidemic properties. Ayurvedic herbs and home remedies, such as nuts, oatmeal, fish oil, and ginger, have shown cholesterol-lowering effects [4]. Medicinal plants like *Amaranthus spinosus*, *Moringa oleifera*, and *Withania somnifera* have demonstrated antihyperlipidemic activity with minimal side effects [5].

VZ, a Poaceae family member traditionally used in various applications with studies including pharmacological properties. Phytochemical screenings have identified numerous compounds with potential medical applications, including antioxidant, antimicrobial, and anti-inflammatory activities [6-7]. This study aims to conduct a comprehensive investigation into the antihyperlipidemic activity of *VZ* using a multi-faceted approach encompassing In-vitro, Insilico, and In-vivo analyses. We have reported the bioactive compounds present in *VZ* through phytochemical and GCMS analysis. The retrieved compounds were screened and evaluated using Molecular Docking and Molecular Simulation. Finally, antilipidemic activity of aqueous and ethanol extract of *VZ* in Albino wistar rats was analysed through biochemical and histopathological studies.

MATERIALS AND METHODS

Ethics

Our study approved by SRM Medical College Institutional Animal Ethical Committee and Ethical clearance as per CPCSEA guidelines was obtained from Institutional Review Board and the ethical approval number: 18123/835/PO/Re, dated 31-07-2018.

In-Vitro Analysis:

Phytochemical Analysis

The plant extracts were prepared by dissolving the powdered sample in two different solvents aqueous and ethanol and extracted using soxhlet equipment [8]. The qualitative phytochemical analysis of plant extracts (aqueous and ethanol) was performed to analyse the availability of bioactive compounds as per standard methods [9-10].

GCMS Analysis

Gas Chromatography and Mass Spectrometry (GC/MS) were used for determine active components and characterise the chemical composition of plant extract. The GC/MS analysis of *VZ* extracts was carried out using a Shimadzu QP-2010 plus GC/MS with a thermal desorption system TD 20, with Rtxa 5MS (30mx0.25mm) column and GCMS solution software [11].

Insilico Analysis:

Compound Library

The 2D structure ligands identified by GCMS analysis of *VZ* was retrieved from PubChem redundancy structural database (https://pubchem.ncbi.nlm.nih.gov/). The three-dimensional structure of the chemical was constructed using the Marvin sketch, and the energy consumption was minimised by using Avogadro. The most reliable three-dimensional conformer of the compound was identified and saved as a PDB file for future use.

Physiochemical Property Prediction

The physiochemical properties of the selected ligands were investigated using Swiss ADME. They consist of the total polar surface area, H-bond acceptors, rotatable bonds, number of heavy atoms, polar surface area, and mass and formula of the molecule. Lipinski's Rule of Five was used for drug probability, screening, and pre-filtering of discovered ligands. The drug's lipophilicity (Log P) value and HLB value (Hydrophilic-Lipophilic Balance number) measure the compound's solubility using the Marvin sketch program.

ADMET Analysis

The pharmacokinetics of a therapeutic molecule are comprised of ADMET analysis of Absorption, Distribution, Metabolism, Excretion, and Toxicity. In this work, the Swiss ADME and servers were used to predict drug likeness and toxicity was analysed by CLC -pred and Protox web tool [12].

HOMOLOGY MODELLING:

Homology Modelling and Evaluation

Swiss model was used to model the proteins' three-dimensional structure [13]. The cumulative quality and conformation of the backbone torsion angles phi [Φ] and psi [ψ) were assessed using Ramachandran plot analysis [14].

Molecular Docking
The computer application AutoDock Vina 1.1.2 performed molecular docking experiments and predict the binding energy of selected compound against therapeutic protein targets for dyslipidaemia [15]. The 3D structures of the protein-ligand interaction were then visualised using the programme BIOVIA Discovery studio 2020.

Molecular Simulation
The Desmond module via Maestro of the Schrödinger suite 2020-3 was utilised for molecular dynamics (MD) simulation on a Linux computer. A 200-ns MD Simulation research was conducted to examine the docked complex stability with the ligand [16].

IN-VIVO ANALYSIS:

Animal Grouping Induction
Albino wistar rats with body weight 150-200gms (n=6) used in this study were fed standard chow or laboratory chow enriched with high fat diet for 8 weeks. High Fat Diet (HFD) with 19:3 tallow: groundnut oil from NIN institute, Hyderabad. Animals grouped as I - VII orally fed with Standard Chow Diet (SCD), High Fat Diet (HFD), HFD with 1mg/kg BW Simvastatin, HFD with 300mg/kg BW Low Dose Aqueous extract of *VZ* (LdAe), HFD with 600mg/kg BW High Dose Aqueous extract of *VZ* (HdAe), HFD with 300mg/kg BW Low Dose Ethanolic extract of *VZ* (LdEe), HFD with 600mg/kg BW High Dose Ethanolic extract of *VZ* (HdEe) respectively for eight weeks**.** Body weight of rats measured at the end of weeks. Blood samples were collected 1st, 4th and 8th week for biochemical analysis. Two animals from each group was dissected at 8th week, tissue samples liver, kidney and heart were stored in formalin for histological analysis.

Biochemical Analysis
Enzymatic colorimetric techniques were used to measure plasma lipid parameters (total cholesterol, HDL, LDL and triglyceride using commercial kits. Blood samples were processes centrifugation at 4000rpm for 20min and serum separated used for lipid analysis. Serum total cholesterol, HDL-C, LDL-C, triglyceride were analysed by CHOD-PAP [17], GPO-PAP [18], by Patel, et al. [19] respectively.

Histopathology
Tissue sections were stained by Hematoxylin and Eosin (H&E) automatic stainer. Tissue sections was prepared using microtome and mounted on glass slide. Standard protocol of H&E staining was carried out and images was observed using microscopy. Microscopical assessment of structural and cellular alterations was photomicrographed using 40x magnification at Leica BM5000 microscope with DFC 300 FX camera in RGB mode [20].

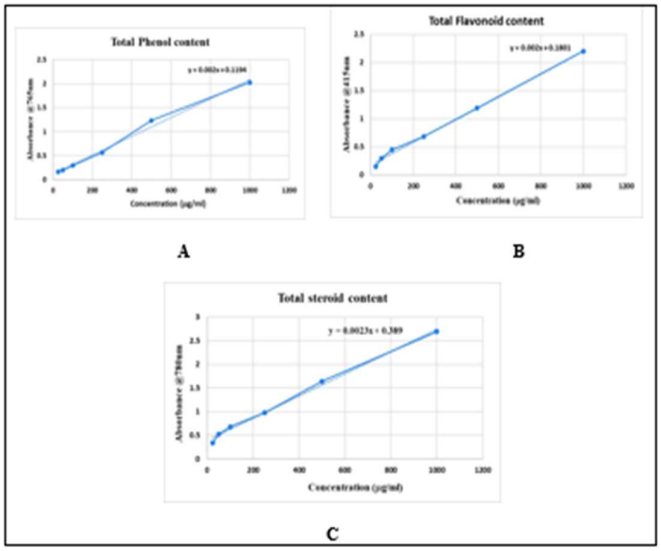
Statistical Analysis
Biochemical analysis was done and the average values was calculated and presented as graphs with standard error bars. ANOVA analysis was done using SPSS 22.0 statistical software and significance P values less than 0.05 was considered as statistical significance.

RESULTS

In-Vitro Analysis:

Phytochemical Analysis
The qualitative phytochemical analysis revealed presence of phytocompounds such as phenol, flavonoid, alkaloid, steroid, saponins, tannins, terpenoid. Figure 1a depicts the quantitative phytochemical analysis of phenol (1aA), flavonoid (1aB) and steroid (1aC) with standard such as gallic acid, quercitin and beta sitostertol. The concentration of bioactive compounds in aqueous extract was higher compared to ethanol extract of *VZ*.

GCMS Analysis
The GCMS analysis of aqueous extract revealed the presence of 22 active compounds (Figure 1bA) while 19 compounds (Figure 1bB) were identified in ethanol extract. The GCMS analysis of *VZ* aqueous extract reveals presence of bioactive compounds with diverse properties. The compound 1-hexylamine (5.520%) exhibits antimicrobial activity. Linalool oxide (cis-, furanoid) (2.855%) suggests anti-inflammatory and analgesic effects, while Sinulariolide (2.456%) shows antitumor and antiangiogenic property. Taylorione (2.291%) and 11-dehydrosinulariolide (1.866%) contribute to antioxidant and antimicrobial activities. Methyl gallate (0.896%) has antioxidant and anticancer effects. (1s,2s,3e,7s,8r,10e,12z)-7-acetoxy-8,11-epoxycembra3,10-diene (4.689%) has anti-inflammatory and antifungal properties, Eugenol (1.410%) has analgesic and antimicrobial effects, and Quercetin 3-O-glucuronide (0.348%) showed antioxidant and anti-inflammatory activities. Epsilon-muurolene (0.301%) exhibits antimicrobial and anti-inflammatory properties. Overall, these findings highlight the diverse bioactive potential of *VZ* aqueous extract, showcasing its relevance in various pharmaceutical and therapeutic applications.



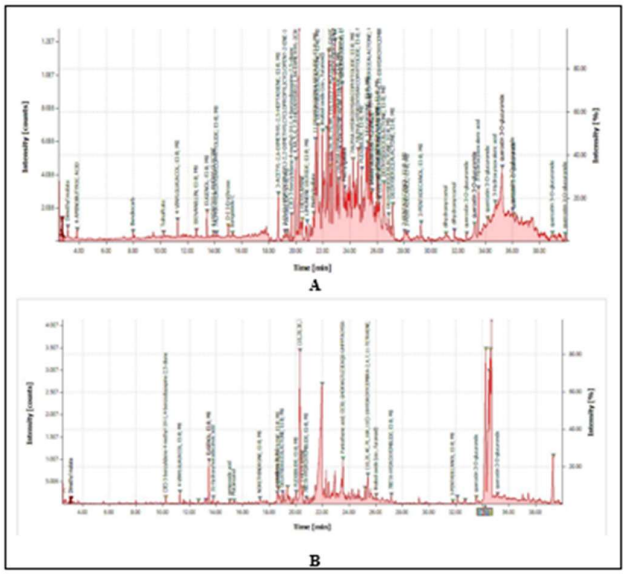


Figure 1a: Phytochemical Analysis A) Total phenol B) Total flavonoid C) Total steroid.

1b: GCMS Analysis of *Vetiveria zizanioides* A) Aqueous extract; B) Ethanol extract

Insilico Analysis

Compound Library Screening

The compounds identified by GCMS analysis of aqueous extract was further screened for physiochemical properties, solubility and toxicity parameters. Based on the data obtained from SwissADME, out of 22 compounds of aqueous extract, 3 compounds (Quercetin 3-O-glucuronide, Bungeiside C and Tolnaftate) were found to violate Lipinski rule of 5 and excluded from study. The screened compounds exhibited favourable physiochemical properties, solubility, and lipophilicity, suggesting their potential for efficient drug delivery and distribution. They complied Lipinski's Rule of Five, indicating good oral bioavailability at the score of 0.55. Among the 19 compounds, five compounds were found to be toxic (1-hexylamine, Deoxysericealactone, Sinulariolide, Taylorione and 11-dehydrosinulariolide) and thus excluded from the study. Overall, 14 compounds of aqueous extract were selected for ADMET analysis. Other compounds which were non-toxic to normal cell line could be a potential drug candidate.

Simultaneously same filters were applied to screen ethanol extract compounds. 8 compounds were found to be identical to aqueous extract and hence were neglected from further screening. Based on the data obtained from SwissADME, out of 11 compounds, 5 ligand molecules were found to violate Lipinski rule of 5. Majority of compounds of ethanol extract had positive log P value.

Six compounds were subjected to Cytotoxicity prediction. All the 6 compounds of ethanol extract were predicted to be non- toxic to normal cell line. Overall, 20 compounds integrating ethanol and aqueous extract were subjected to molecular docking against antilipidemic targets.

Homology Modelling

Swiss Model employs the QMEAN score, which demonstrates strong agreement between model and experimental structures of comparable size. A number of 0 to -4 suggests high quality models, while a score of less than that indicates bad quality models. Figure 4a explains the Qmean, Ramachandran flavoured % and Clash score of target protein. The Q mean value of all the selected target protein were within the optimum range. For validation of structure, Ramachandra plot was constructed (Figure 2A-L). The results revealed that all the modelled structures had more than 90% of residues in allowed region. Hence Ramachandra plot suggest the good quality of predicted model. Clash score assess overall severity of the structure's clashes. Clashes are steric overlaps of at least 0.4 A between non-bonded atom. The clash scores of target proteins were within optimum range. Higher scores of proteins indicate that the specific model is in a higher energy.

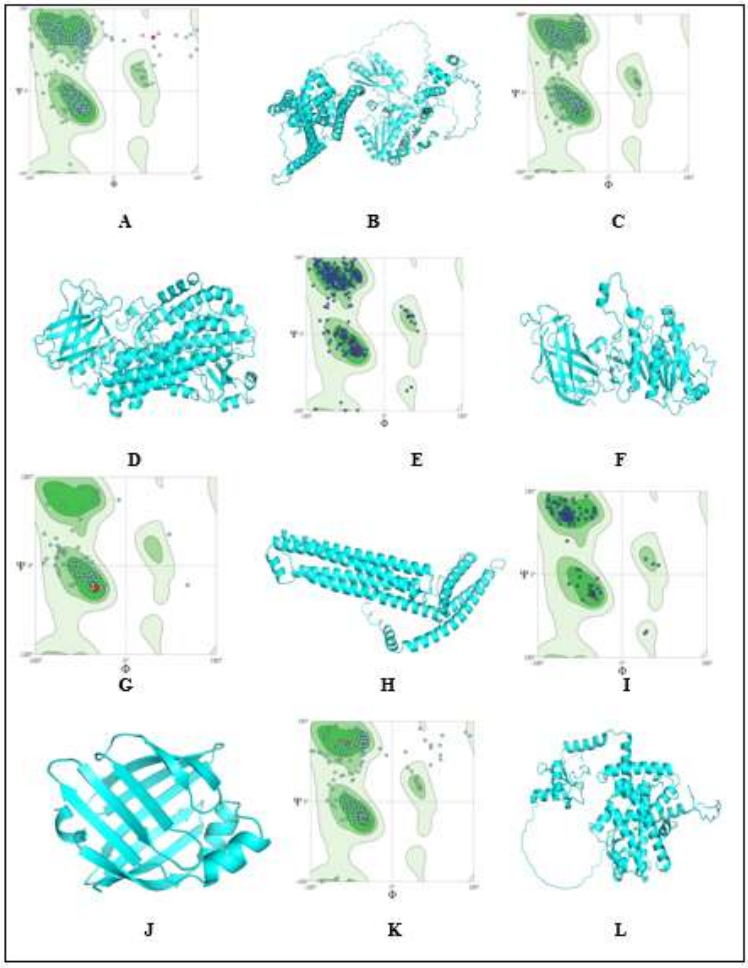


Figure 2: Ramachandran plot and 3D structure of protein 3-hydroxy-3-methylglutaryl-coenzyme A reductase (A and B); Polyunsaturated fatty acid 5-lipoxygenase (C and D); Lipoprotein lipase (E and F); Apo lipoprotein A-V (G and H); Fatty acid-binding protein, adipocyte (I and J); Peroxisome proliferator-activated receptor alpha (K and L)

ADME Prediction

ADMET properties was predicted using SWISS ADME and Protox. ADMET parameters plays pivotal role in drug discovery. 40% of drug fail in the market is due to these properties. Among the compounds, 3-acetyl-2,6-dimethyl-2,5-heptadiene and Limonene dioxide demonstrate the highest absorption values of 100, Linalool oxide (cis-, furanoid) also exhibits a high absorption value of 96.408, suggesting efficient absorption through the human intestinal wall. On the other hand, Pantothenic acid displays a lower absorption value of 36.538, indicating relatively poor absorption. The permeability values revealed Limonene dioxide (57.607) and Eugenol (46.887) exhibited higher permeability values, suggesting efficient transport across the intestinal epithelium and indicating favorable absorption potential. Conversely, D-(-)-erythrose

(0.5801) and Pantothenic acid (0.2177) displayed lower permeability values, indicating limited absorption potential. 3-acetyl-2,6-dimethyl-2,5-heptadiene, 7alpha-hydroxysarcophytolide, (1s,2s,3e,7s,8r,10e,12z)-7-acetoxy-8,11-epoxycembra-3,10-diene, Norethindrone, and Flexibilide exhibited significant P-gp inhibition. These findings have implications for drug interactions and bioavailability, emphasizing the importance of considering P-gp modulation in drug development and clinical practice. Compounds such as Eugenol, Norethindrone, and 16-Hydroxyhexadecanoic acid exhibit high plasma protein binding, suggesting a strong affinity for plasma proteins. D-(-)-erythrose, (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione, Eugenol, and 4-vinylguaiacol demonstrate weak or negligible activity as CYP substrates or inhibitors. These findings provide valuable insights into the metabolic characteristics and potential drug interactions of these compounds, contributing to a better understanding of their pharmacokinetic profiles. Based on the data provided, the compounds exhibit varying half-life periods ranging from 0.223 to 0.942 hours. Similarly, the clearance rates vary predicting drug efficacy and safety.om 1.326 to 18.935 ml/min/kg. These values reflect the efficiency of drug elimination and safety.

Molecular Docking

The molecular docking results of selected ligands against potential target molecules is given in Figure 3A-F. Low binding energy score molecules represents high binding affinity. Among the 20 ligand molecules, Norethindrone and (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione showed high binding affinity towards target protein. The interaction of the 2 compounds and its amino acid interaction are represented in figures 5a–5f. The highest docking score of Norethindrone was predicted to be -8.7, -8.6 and -8 Kcal/mol for HMDH, LIPL and APOA5 proteins respectively. In particular, inhibiting HMDH could slow the progression of atherosclerosis and lower the risk of CHD by decreasing cholesterol biosynthesis, particularly via lowering low-density lipoprotein cholesterol. While the highest binding energy of (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione was -8.1, -8.6 and -7.3 for LOX5, FABP4 and PPARA respectively.

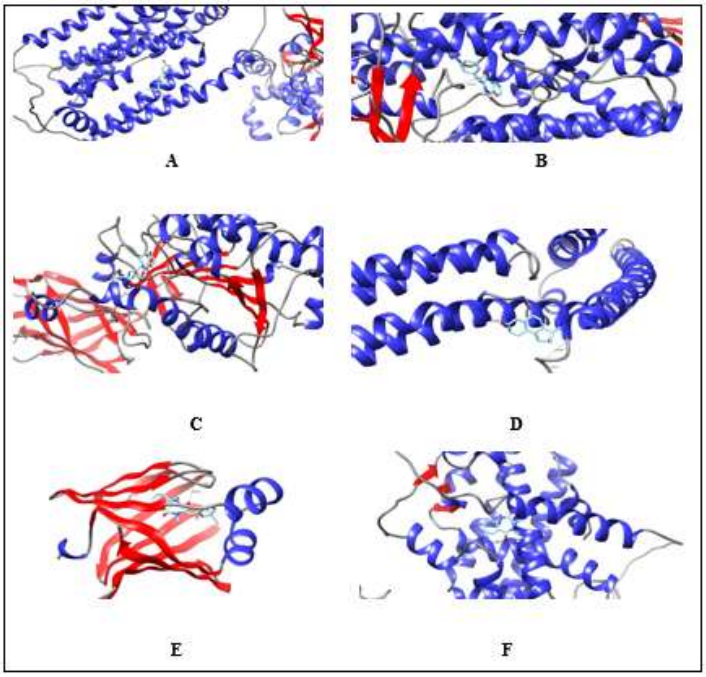


Figure 3: Molecular Docking And Stimulation A) Interaction of Norethindrone with HMDH; B) Interaction of (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione with LOX5; C) Interaction of Norethindrone with LIPL; D) Interaction of Norethindrone with APOA5; E) Interaction of (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione with FABP4; F) Interaction of (3E)-3-benzylidene-4-methyl-1H-1, 4-benzodiazepine-2,5-dione with PPARA

Molecular Simulation

The best docked ligand and target proteins were subjected to MD simulation. Molecular simulation plays vital role in analysing the stability and performance of ligand- protein complex. Run traectories of 200 ns were analysed for Norethindrone and HMDH Complex and 3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione and FABP4 Complex. A protein's root-mean-square deviation (RMSD) is a measure of variation from initial structure accountability for the stability of protein structure's during simulation. The fluctuation in RMSD was within acceptable limit of 2 Å, suggesting stable (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione and FABP4 complex while Norethindrone and HMDH

shows major deviations which shows unstability of complex (Figure 4A-D). Hydrogen and hydrophobic interactions play a vital role in stabilizing a complex. The hydrogen bonds i.e., Arg107, Ala76, Gln96, Arg79 and hydrophobic interactions i.e.,Ile105, Ile52, Val26, Met21 were involved in stabilizing the compounds. While the major hydrogen and hydrophobic interactions of Norethindrone and HMDH complex was Tyr311, Ala329, Ile73 and Ile76, Tyr77, Phe80, Tyr311, Leu312, Leu332, Tyr336 respectively.

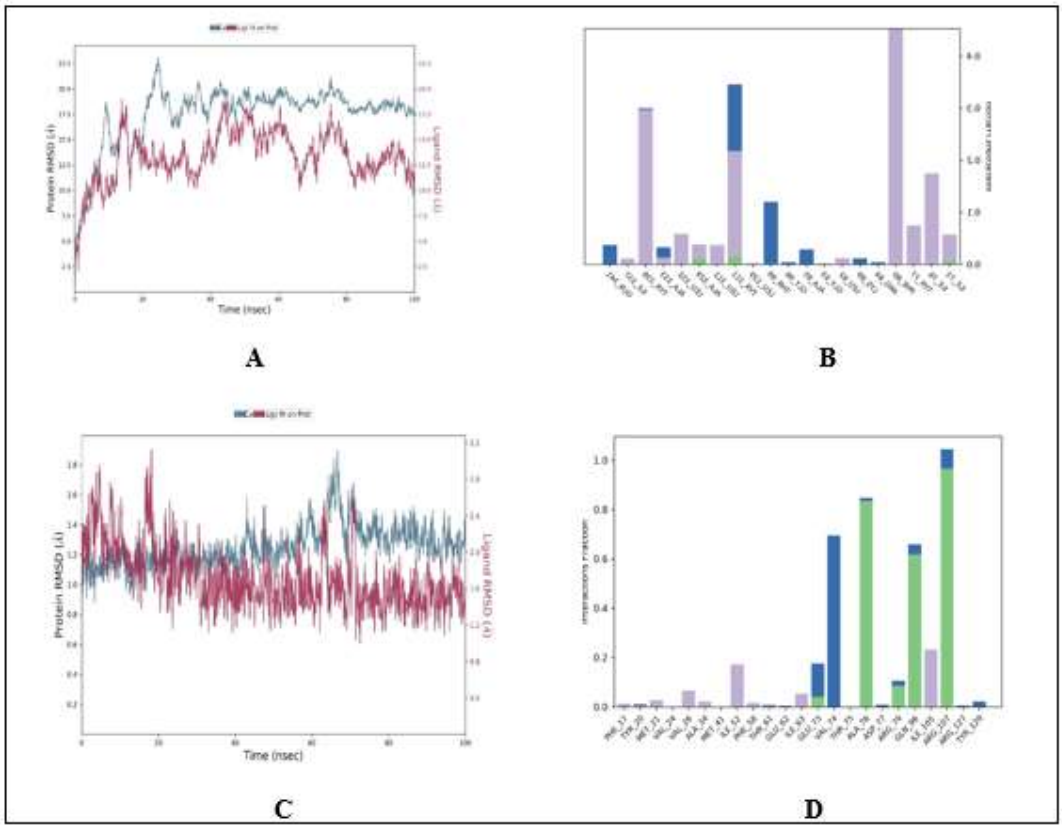


Figure 4: Molecular Dynamic Simulation A) Norethindrone_HMDH Complex (G1 - Protein-ligand RMSD; B) - Percentage Protein-ligand contact); C) (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione_FABP4 Complex (H1 - Protein-ligand RMSD); D) - Percentage Protein-ligand contact

In-Vivo Analysis

Body Weight

Animals in control group maintained standard body weight throughout the study whereas there was gradual increase body weight in HFD and HFD with simvastatin treated animals. Body weight of *VZ* ethanolic or aqueous extracts treated animals were decreased (Figure 5a).

Biochemical Analysis

The cholesterol, triglycerides, HDL-C, LDL-C was estimated in rat model. The significant reduction of serum cholesterol levels at 8th week in both the ethanolic and aqueous extract treated rats indicates that *VZ* have a greater impact in reducing the cholesterol level in hyperlipidemic condition Figure 5b. Figure 5c serum triglyceride levels decreased in all-time points in both ethanolic and aqueous extract of *VZ* treated rats compared to HFD and HFD+SIM treated rats. Figure 5d confirms that HDL-C levels were slightly decreased in HFD treated animals, showed positive effect in *VZ* extracts treated animals compared to control. *VZ* treated animals showed low LDL-C levels compared to HFD and HFD+SIM treated rats (Figure 5e). Overall result evident that high dose (600mg/kg) *VZ* extracts (ethanolic and aqueous) shown lipid reduction.

ANOVA Analysis

Statistical ANNOVA analysis of parameters have shown it is highly significant in HDL P<0.000, LDL levels P<0.010, total cholesterol P<0.002 and triglyceride P<0.034 between groups and within groups (supplementary table 7).

Histopathology

The study examined the effects of different dietary interventions on animal tissues by H&E staining (Figure 5f). Animals fed with HFD exhibited adverse changes, including fat deposition, inflammation, and degeneration in liver, heart and kidneys. However, the administration of

HFD+simvastatin mitigated some of these effects, reducing fat deposition and degenerative changes in the kidney, heart and liver. Furthermore, the use of low-dose ethanolic extract of *VZ* showed mild improvements, including reduced fat deposition and focal hypertrophic muscle fibers in the heart, as well as decreased congestion, fatty changes, and lymphohistiocytic infiltrate in the liver. Similarly, low-dose aqueous extract of *VZ* demonstrated mild benefits, such as attenuated fat deposition, reduced fatty changes, and interstitial lymphohistiocytic infiltrate in the liver. High-dose ethanolic extract of *VZ* exhibited minimal detrimental effects on the heart, liver, and kidneys, with only subtle fatty changes observed. High-dose aqueous extract showed mild fatty changes in the heart, minimal changes in the liver, and inconclusive effects on the kidneys.

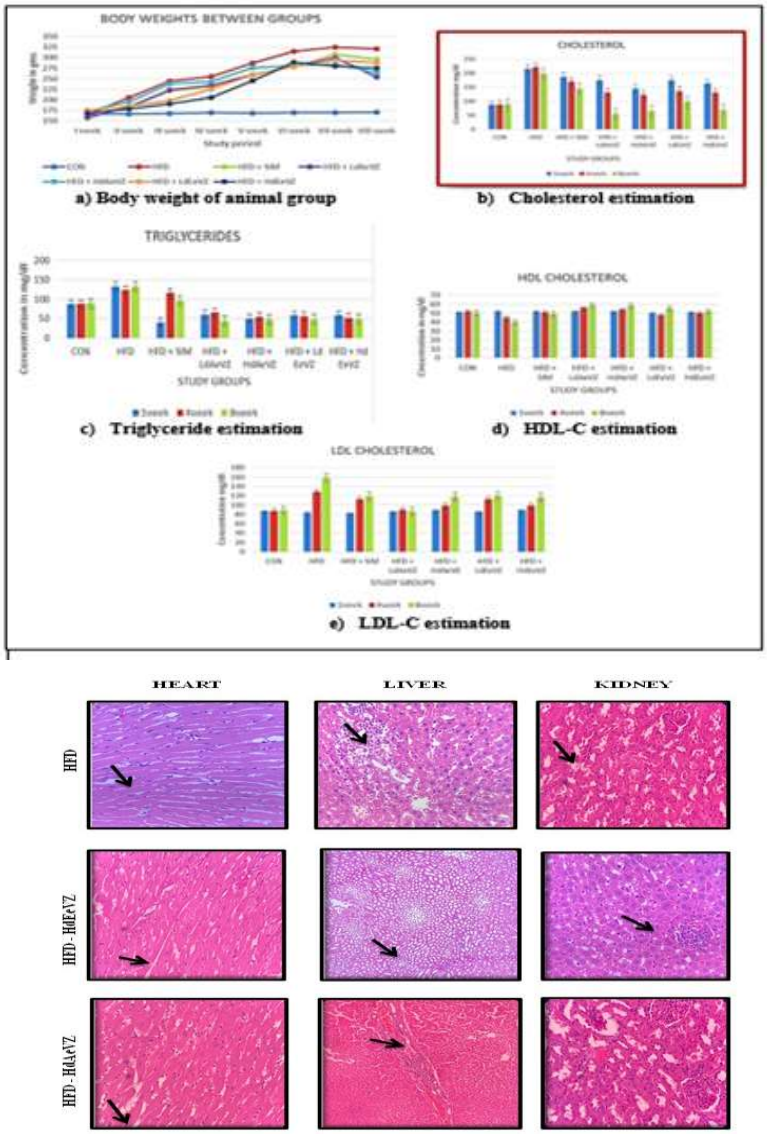


Figure 5: In-vivo Analysis– a) Body weight of Animal Group b) Cholestrol Estimation c) Triglyceride Estimation d) HDL – C Estimation e) LDL – C Estimation f) Histopathology analysis

DISCUSSION

Plant-based diets contain a variety of bioactive phytochemicals that can lower LDL levels via numerous biological pathways associated with hyperlipidemia [21]. The qualitative phytochemical analysis of ethanol and aqueous extract were in accordance with previous studies showing hypolipidemic activity [22-23]. Furthermore, polyphenols, saponins and phytosterols have hypocholesterolemic effects in humans and animals, leading to the phenomena of decreased atherosclerosis occurrence [24]. Flavonoids can manage lipid metabolism imbalances by blocking peroxidation and production while encouraging redistribution and metabolism, resulting in lipid reduction [25].

The GCMS analysis of aqueous extract shown 22 active compounds while 19 compounds in ethanol extract. Overall, 20 compounds integrating ethanol and aqueous extract were done molecular docking for against antilipidemic targets.

Among the 20 ligand molecules, Norethindrone and (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione showed high binding affinity towards target protein HMDH, LIPL, APOA5, LOX5, FABP4 and PPARA. Molecular simulation have vital role in analysing the stability and performance of ligand- protein complex. Run traectories of 200 ns were analysed for Norethindrone and HMDH Complex and 3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione and FABP4 Complex. Serum FABP4 levels are associated with body fat percentage, as well as risk factors metabolic as dyslipidaemia, obesity and heart failure biomarkers as known as N-terminal pro Brain-Natriuretic Peptide (NT-pro BNP) [26]. From the previous studies regarding hyperlipidemia, having HMDH and FABP4 as potential target receptors could be a solution for dyslipidemia.

A high-lipid diet can result in a variety of hyperlipidemic patterns. In rats, chronic feeding of a diet high in simple carbs and saturated fats produces metabolic syndrome symptoms. Metabolism of lipid abnormalities highly linked to obesity, heart illnesses and its comorbidity conditions [27]. Thus, hyperlipidemia regulation with *VZ* extract analysed in the current study.

Animal models of atherosclerosis, hyperlipidaemia widely used for studying potential therapeutic targets and provided safety information for human trials [28]. Our observed shown *VZ* treated rats decreases serum lipid parameters resulting hypolipidemic effect. Antihyperlipidemic action related studies will be estimated by lowering levels of serum lipid parameters like LDL-C, TC and TGs [29].

Animal treated with *VZ* root methanolic extract significantly decreased TG and TC levels, also prevented histological alterations i.e., fatty degeneration, periportal fibrosis, indicating extracts regulated the ethanol induced hyperlipidemia via hepatoprotective action [30]. The result obtained from the current study also confirms the role of *VZ* in lipid regulation with reservoir of bioactive compounds.

CONCLUSION

The finding of present study suggested that aqueous and ethanol extracts have enormous amount of phytocompounds that contribute to wide array of bioactivity. A total of 20 compounds in combination were screened based on Lipinski rule of five and toxicity analysis. Among the 20 ligand molecules, Norethindrone and (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione showed high binding affinity towards target protein. The fluctuation in RMSD was within acceptable limit of 2 Å, suggesting stable (3E)-3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-dione and FABP4 complex. In-vivo studies shown body weight of animals in *VZ* treated ethanolic or aqueous extracts reduced significantly. *VZ* have great positive anti-hyperlipidaemic effect by reducing LDL, cholesterol, triglycerides and increased HDL levels. *VZ* High-dose (aqueous and ethanolic extract) showed histological alterations such as fatty changes in heart, minimal changes in liver and inconclusive effects on the kidneys. This study markedly provided certain novel findings for hyperlipidemia treatment regime. Our study has limitations to provide the mechanistic evaluation as role of targets predicted effect of *VZ* on hyperlipedemia which can be carried out in our future research work.

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Conflicts of interest:
There is no conflict of interest between authors in this study.

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