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ORIGINAL RESEARCH

# Anti-lipidemic and anti-diabetic properties of *Gymnema sylvestre* saponins: an in-silico approach

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## Abstract

Diabetes mellitus and dyslipidemia make a significant contribution to mortality and morbidity. The *Gymnema Sylvestre's* saponins have a variety of pharmacological effects, including the possibility of lowering diabetes and cholesterol levels. In the present study, molecular docking and molecular dynamic simulations were used in silico in order to understand the protein league stability and molecular interactions by aiming at anti-diabetic and anti-lipidemic proteins. As well we performed the drug likeliness and its toxicity of 13 *G. sylvestre* saponins, against anti-diabetic target proteins Aldose reductase, α- amylase, α- glycosidase and antilipidemic target proteins HMG-CoA reductase, Fatty acid synthase, Pancreatic Lipase target proteins. *Gymnemasin B* and *Gymnema saponin– IV* were shown the high energy between the target protein. As well these compounds shown good ADMET properties with standard oral antidiabetic compound Linagliptin. Molecular dynamics simulations further supported their strong binding interactions with the target proteins over time using 100 ns MD simulations. These findings suggest that these saponins hold promise as potential active molecules to making them possible candidates for the development of novel therapies for diabetes mellitus.

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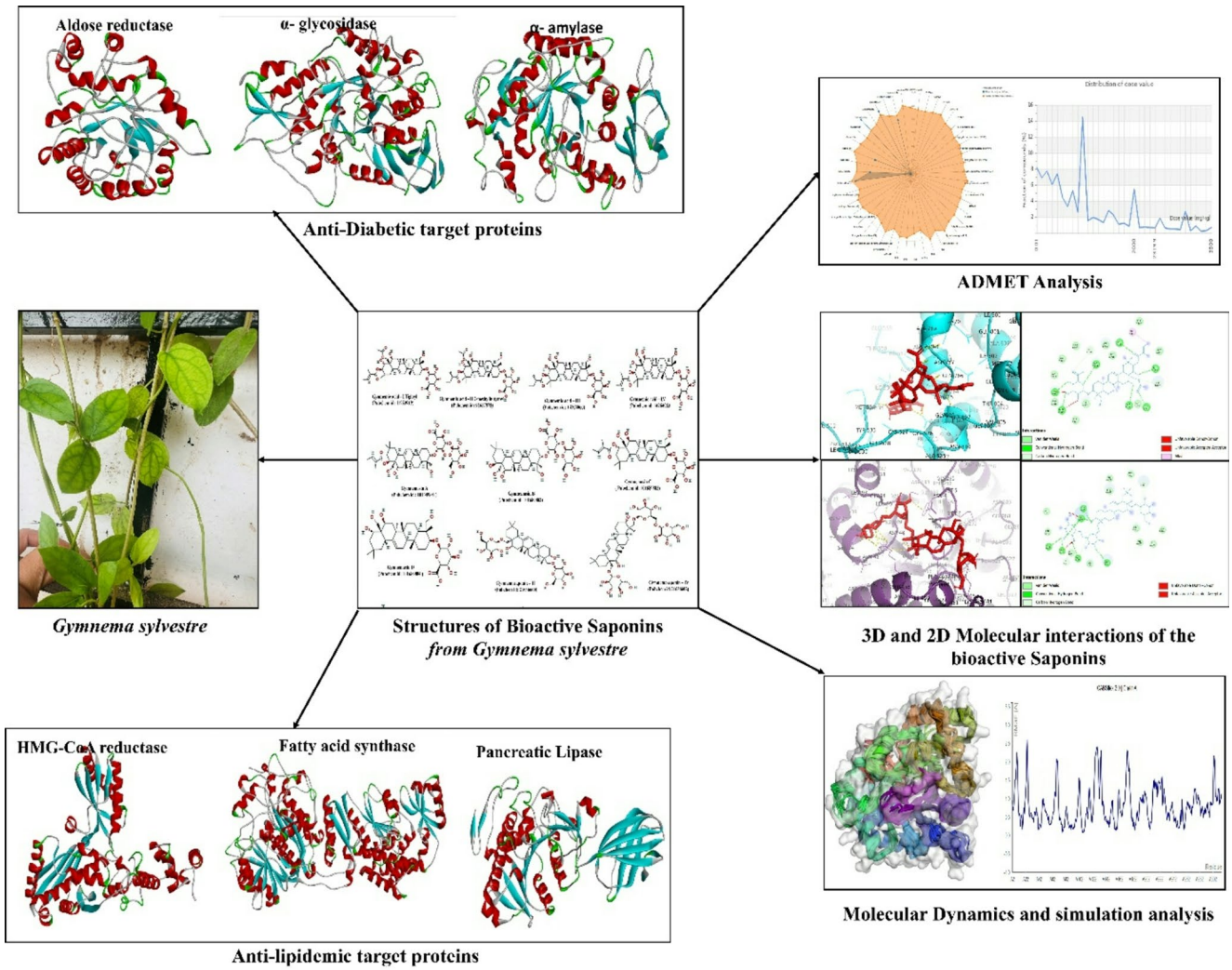
**Graphical abstract**




**Keywords** *Gymnema sylvestre* · Saponins · Anti-lipidemic · Anti-diabetic activities · Gymnema saponin

## Introduction

Diabetes mellitus and Dyslipidemia are pivotal factors that greatly impact cardiovascular morbidity and mortality among diabetic patients. Diabetes mellitus represents a significant worldwide health concern and is regarded as a prominent cause of mortality on a global scale, with the increased prevalence of the disease linked to unhealthy food habits (Parasuraman et al. 2019; Gunny et al. 2024). Diabetes mellitus also known as diabetic dyslipidemia, is a metabolic illness characterized by elevated blood glucose levels brought on by an absolute or relative shortage of insulin, which causes hyperglycemia, considering its inability to metabolize fat, protein, and carbohydrates. The condition exhibits a pattern of high triglycerides and low-density lipoprotein, which leads to long-term organ damage, dysfunction, and sometimes organ failure (Tran et al. 2020; Chandra et al. 2024; Ojo et al. 2022). Poor glycemic control is a marker of both Type 1 and Type 2 diabetes mellitus, which is characterized by elevated serum triglyceride, VLDL, and intermediate-density lipoprotein cholesterol levels and decreased levels of high-density lipoprotein cholesterol. Diabetes frequently results in insulin resistance, which can raise the release of very low-density lipoproteins. Thus, the interaction between lipid metabolism and carbohydrates affects blood lipid levels (Elekofehinti et al. 2013). Oxidative stress, Hyperlipidemia, and Hyperglycemia are the crucial attributes of diabetes mellitus that represent a major risk factor, leading to the development of symptoms of diabetes mellitus (Hammeso et al. 2019).

Many medicinal plants contain anti-hyperglycemic and anti-hyperlipidemic compounds that are becoming more and more popular compared to synthetic medications since they have less or no harmful side effects. They are easily available and quickly absorbed by the body (Alam et al. 2022; Mahwish et al. 2023). The drawbacks of the present diabetic therapies, such as oral medication and insulin therapy have adverse side effects and also are expensive (McGill et al. 2024). As a result, novel and efficient diabetic treatments are required. Gymnemagenin has shown significant effects on lipid metabolism. It enhances the breakdown of triglycerides, a process known as lipolysis. This is important because it helps the body use fat for energy more effectively. In addition to this, Gymnemagenin increases the activity of a key gene involved in fat cell formation, or adipogenesis. By doing so, it plays a role in managing body weight and fat distribution (DasNandy et al. 2022).

*G. sylvestre*, a woody plant belonging to the Asclepiadaceae family, is also referred to as sugar destroyer or gurmar. It is a conventional herb used in Ayurvedic medicine since ages to treat variety of diseases such as, blood pressure, tachycardia or arrhythmias, hypolipidemia, weight loss, constipation in the gastrointestinal tract, fluid retention, and liver disease. Additionally, it can be used to reduce blood sugar, triglycerides, and serum cholesterol. Also, it is potentially used as an anti-inflammatory and anti-cancer agent (Thakur et al. 2012).

*G. sylvestre* contains various bioactive phytochemicals such as Gymnema - saponins, gymnemic acids, and polypeptide gurmarin. These bioactive compounds from *G. sylvestre* have therapeutic benefits like lowering sweet cravings, regulating blood glucose, and promoting regeneration of pancreatic cells., thus, making it an alluring candidate for both pharmaceutical research and natural diabetes treatment (Muddapur et al. 2024). Saponins have been shown to exhibit several pharmacological characteristics, including the capacity to cause hypoglycemia and to lower plasma triglyceride levels, both of which are antidiabetic effects. This property of saponins helps prevent high blood sugar levels after meals, which is essential for the treatment of type I and type II diabetes. Furthermore, these saponins have a strong chance of having an anti-diabetic impact when consumed as drugs (El Barky et al. 2017; Alhujaily et al. 2022).

**Table 1** List of bioactive *G. sylvestre* saponins

| Constituents | Chemical Name | PubChem ID |
|---|---|---|
| Triterpene saponins | Gymnemic acid - I Tigloyl | 11,953,919 |
| | Gymnemic acid - II 2-methylbutyroyl | 91,617,872 |
| | Gymnemic acid - III | 14,264,066 |
| | Gymnemic acid - IV | 14,264,063 |
| Triterpenoid saponins | Gymnemasin A | 101,689,881 |
| | Gymnemasin B | 101,689,882 |
| | Gymnemasin C | 101,689,883 |
| | Gymnemasin D | 101,689,884 |
| Oleanane Saponins (Gymnemic acids and gymnemasaponins) | Gymnemasaponin - II | 21,636,600 |
| | Gymnemasaponin - IV | 21,636,602 |
| Dammarene Saponins | Gymnemoside A | 6,442,217 |
| | Gymnemoside B | 6,442,215 |
| | Gymnemoside C | 101,933,150 |

Despite many studies showings the therapeutic potential of *G. sylvestre*, there are no intensive studies focused on identifying its antilipidemic and antidiabetic properties and investigating the underlying mechanisms of natural bioactive *G. sylvestre* saponins. Hence, the present research work is planned to investigate the antidiabetic and antilipidemic activity of the *G. Sylvestre* saponins. Molecular docking and ADMET were performed against three antidiabetic target proteins (aldose reductase, amylase, glycosidase) and three antilipidemic target proteins (HMG-CoA reductase, fatty acid synthase, pancreatic lipase), which have been reported in the literature to play an important role in glucose metabolism to demonstrate their antidiabetic and antilipidemic properties to determine the effect.

## Materials and methods

*Accession of Anti-Diabetic and Anti-lipidemic target proteins*: The three-dimensional structure of antidiabetic target proteins (i) Aldose reductase (PDB ID- 1IEI) (Kinoshita et al. 2002), (ii) α- amylase (PDB ID- 1B2Y) (Nahoum et al. 2000), (iii) α- glycosidase (PDB ID-3WY1) (Shen et al. 2015) and anti-lipidemic target proteins (i) HMG-CoA reductase (PDB ID-1HW8) (Istvan and Deisenhofer 2001), (ii) Fatty acid synthase (PDB ID- 3TJM) (Zhang et al. 2011), (iii) Pancreatic Lipase (PDB ID-1N8S) (van Tilbeurgh et al. 1992) was downloaded from the RCSB protein database (Helen et al. 2000) (https://www.rcsb.org/).

*Preparation of the ligand*: The chemical structures of all the Bioactive *G. sylvestre* saponin ligands (Table 1) used in the study were identified and reported by Tiwari et al. 2014; Khan et al. 2019 (Tiwari et al. 2014; Khan et al. 2019) and the SDF format of ligand molecules were downloaded from PubChem database (Kim et al. 2025)(https://pubchem.ncbi.nlm.nih.gov/) to determine the possible molecular binding mechanism of the chosen ligands as potential inhibitors target proteins for anti-diabetic and anti-lipidemic activity.

*Molecular Docking*: Molecular docking simulations were performed to study the binding interactions between the Bioactive Saponins *of G. sylvestre* as Potential anti-lipidemic and anti-diabetic target proteins. Potential 13 natural saponin compounds were subjected to molecular docking analysis with target proteins under control with standard

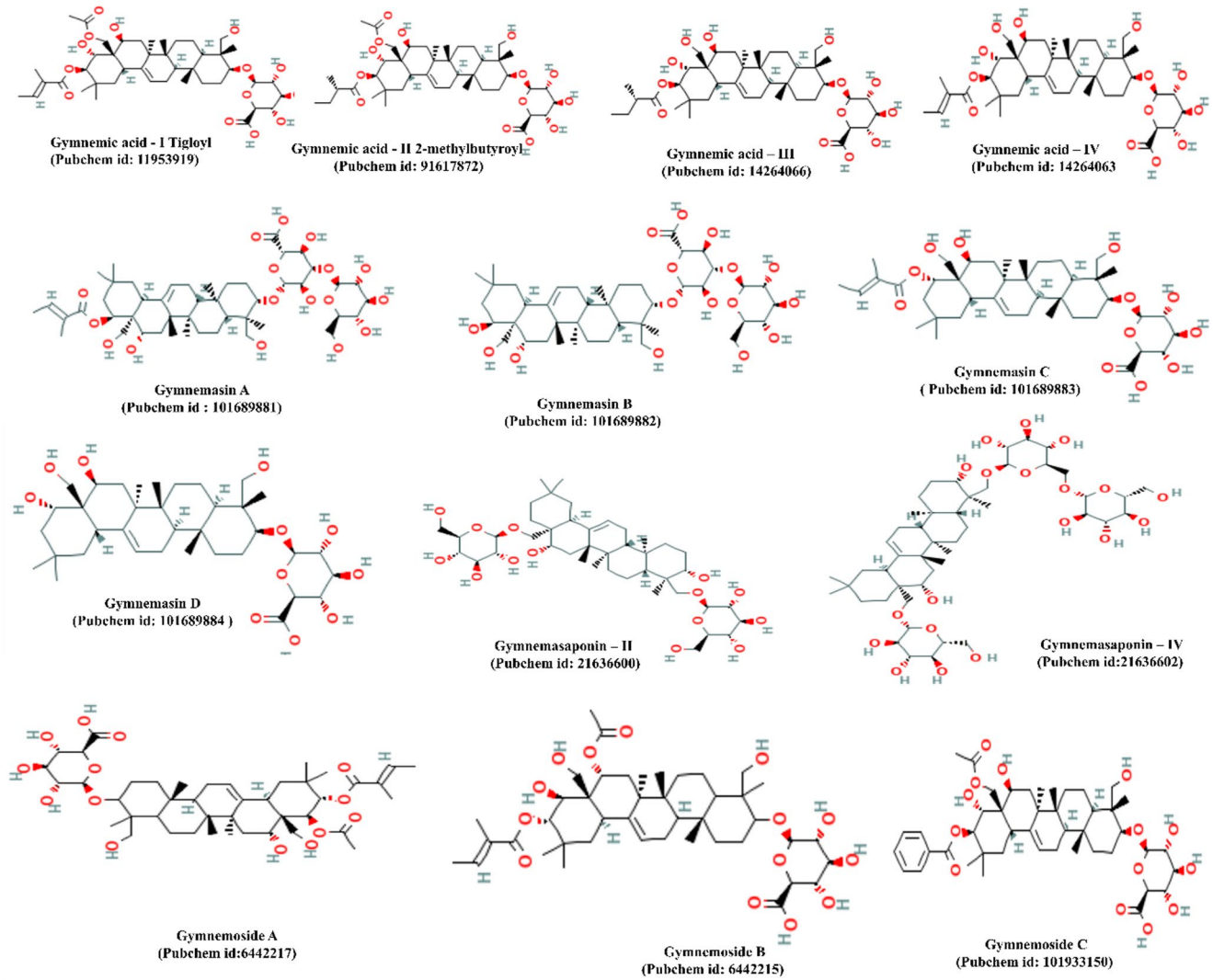



**Fig. 1** Structures of Bioactive Saponins *from G. sylvestre*

FDA-approved drug inhibitors using cavity detection-guided blind docking (CB-Dock) (Liu et al. 2022; Kuriata et al. 2018). The docked complex results were visualized using PyMol 3.1 Viewer software (Lilkova et al. 2015) and Accelyrs Discovery Studio Client (version 24.1) (Biovia 2019). Docking studies provided information about binding affinity and possible interactions that contribute to the inhibition and thus, act as a potential anti-lipidemic and anti-diabetic compound.

*Molecular dynamics simulation*: The compounds with the highest binding energies and hydrogen bond interactions with all protein targets were selected for molecular dynamics simulations. These simulations were performed using the GROMACS-2024.2 software, according to Vijh et al. in 2024. To define the interactions, all-atom force fields were carefully chosen from the CHARMM27 set. The topology, detailing the structure of both proteins and ligands, was created using the SwissParam server, as mentioned by Vegad et al. in 2023. For the simulation setup, the complex consisting of the protein-ligand interaction was resolved using the TIP3P water model. This model helps in accurately simulating the behavior of water molecules around the complex. The system was then neutralized by adding sodium ($Na^+$) and chloride ($Cl^-$) ions. This step was

**Table 2** The molecular interactions and binding energy (kcal/mol) of antidiabetic targets proteins (i) aldose reductase, (ii) α- amylase, (iii) α- glycosidase with *G. sylvestre* saponins

| Chemical Name | PubChem ID | i. Aldose reductase (PDB ID- 1IEI) | | | ii. α- amylase (PDB ID- 1B2Y) | | | iii. α- glycosidase (PDB ID-3WY1) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Number of hydrogen bonds | Interactive amino acids | Binding energy kcal/mol | Number of hydrogen bonds | Interactive amino acids | Binding energy kcal/mol | Number of hydrogen bonds | Interactive amino acids | Binding energy kcal/mol |
| Gymnemic acid - I Tigloyl | 11,953,919 | 3 | ASP 216; PRO A218; Gly A:49 | -8.4 | 5 | ASN 352; GLY 304; GLY 306; ASP 300; ARG 195 | -9.2 | 2 | ASN 301; ALA 229 | -8.1 |
| Gymnemic acid - II 2-methylbutyroyl | 91,617,872 | 2 | TRP 20; GLY 25 | -7 | 3 | GLY306; GLU233; ASP197 | -7.9 | 4 | ASP 379; ARG 429; GLU 231; ALA232 | -7.9 |
| Gymnemic acid - III | 14,264,066 | 3 | TYR 177; LEU 72; GLU 70 | -7.4 | 4 | ASP 300; GLY 233; GLY 238; GLY 239 | -8.8 | 4 | GLU 377; ALA 229; GLU 231; VAL 380; ASP 379 | -7.2 |
| Gymnemic acid - IV | 14,264,063 | 4 | TYR 177; LEU 72; GLU 70; ARG 3 | -6.4 | 2 | GLY 240; THR 163 | -8.4 | 4 | GLU 231; ASP 379; GLU 377; ARG 429 | -7.4 |
| Gymnemasin A | 101,689,881 | 5 | ASP 277; GLU 71; ARG 3; SER 2 | -7.6 | 4 | ASP 300; THR 163; LEU | -8.2 | 1 | ARG 429 | -8.2 |
| Gymnemasin B | 101,689,882 | 5 | ARG 296; TRY 291; ARG 232; SER 290 | -6.8 | 4 | PRO 332; GLY 334; SER 3; ARG 92 | -9.4 | 5 | ASN 301; ALA 229; LEU 300; GLY 399; GLU 377 | -8.7 |
| Gymnemasin C | 101,689,883 | 5 | TRP 111; HIS 110; CYS 298; TYR 48; SER 22 | -9.8 | 4 | ARG 389; TRP 382; CYS 378; ASP 381 | -7.8 | 3 | LEU 300; ASP 333; TYR 389 | -8.4 |
| Gymnemasin D | 101,689,884 | 4 | LEU 5; ASN 7; TRY 177; LYS 176 | -7.3 | 2 | ASP 300; ASN 53 | -8.6 | 2 | ALA 229; ALA 378 | -8.6 |
| Gymnemasaponin - II | 21,636,600 | 3 | TRP 20; TRP 111; ASP 216 | -8.4 | 3 | ASP356; HIS305;ASN352 | -8.3 | 5 | ARG 437; ALA 349; TYR 530; HIS 515; THR 448 | -8.4 |
| Gymnemasaponin - IV | 21,636,602 | 3 | GLU 71; LEU 72; ARG 3 | -7.6 | 5 | SER 289; SER 3; THR 6; ARG 92; SER 226 | -8.9 | 5 | ASP 48; ASN 4; ARG 457; ALA 43; GLY 94 | -8.9 |
| Gymnemoside A | 6,442,217 | 2 | ALA 270; ARG 40 | -6.8 | 3 | SER 226; THR 6; THR 2 | -8.2 | 4 | LYS 398; VAL 380; GLY 402; ASN 301 | -7.2 |
| Gymnemoside B | 6,442,215 | 4 | CYS 298; TYR 48; HIS 110 | -6.9 | 4 | ARG 398; GLY 334; ARG 252; GLN 404 | -8.2 | 4 | THR 445; ARG 437; GLN 531; THR 517 | -8.5 |
| Gymnemoside C | 101,933,150 | 2 | LYS 307; ASN 171 | -5.9 | 4 | GLY 403; ARG 421; SER 289; SER 226 | -9.1 | 3 | GLU 432; ARG 437; GLN 531 | -7.9 |
| Linagliptin | 1E+07 | 4 | THR 304; SER 305; HIS 312 | -7.4 | 3 | LEU 162; GLY 306; HIS 305 | 9.1 | 2 | GLY 766; GLY 765; ILE 762 | -8.3 |

**Table 3** The molecular interactions and binding energy (kcal/mol) of anti-lipidemic target proteins (i) HMG-CoA reductase, (ii) fatty acid synthase, (iii) pancreatic lipase (PDB ID-1N8S) with *G. sylvestre* saponins

| Saponins Chemical Name | PubChem ID | i. HMG-CoA reductase (PDB ID-1HW8) | | | ii. Fatty acid synthase (PDB ID- 3TJM) | | | iii. Pancreatic Lipase (PDB ID-1N8S) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Number of hydrogen bonds | Interactive amino acids | Binding energy kcal/mol | Number of hydrogen bonds | Interactive amino acids | Binding energy kcal/mol | Number of hydrogen bonds | Interactive amino acids | Binding energy kcal/mol |
| Gymnemic acid - I Tigloyl | 11,953,919 | 5 | GLN 814; GLY 808; GLN 766; LYS 691 | -9.1 | 5 | ALA 418; SER 445; GLN 446; ASP 447; | -8.6 | 5 | PRO 277; ASP 394; LYS 363; ASN 362; | -7.1 |
| Gymnemic acid - II 2-methylbutyroyl | 91,617,872 | 2 | CYS 526; MET 534 | -7.6 | 2 | VAL 770; ARG 773 | -7.8 | 5 | ASN 35; LYS 32; SER 57; GLU 51 | -7.3 |
| Gymnemic acid - III | 14,264,066 | 2 | ARG 515; TYR 533 | -8 | 4 | ASP 547; LYS 787; GLU 543; ARG 773 | -7.7 | 1 | TYR 288 | -6.9 |
| Gymnemic acid - IV | 14,264,063 | 2 | SER 705; GLY 700 | -6.8 | 5 | LYS 787; GLU 543; ASN 644; THR 650 | -8.8 | 3 | ARG 111; PHE 258; ASP 79 | -7.4 |
| Gymnemasin A | 101,689,881 | 5 | ILE 536; MET 534; TYR 517; ALA 763; GLN 814 | -8.5 | 3 | PRO 818; LYS 236; GLN 409; | -8.3 | 5 | GLU 233; ASP 328; TYR 326; TYR 288 | -7.6 |
| Gymnemasin B | 101,689,882 | 5 | ILE 536; LYS 691; GLN 766; ILE 762; GLN 814 | -8.8 | 3 | THR 677; GLN 502; ASP 547 | -8.6 | 4 | ILE 78; TRP 252; ILE 251 | -8.6 |
| Gymnemasin C | 101,689,883 | 5 | ILE 536; TYR 517; ASP 767; VAL 805; GLY 806 | -8.9 | 5 | GLY 678; GLN 502; THR 648; ASN 644 | -8.9 | 1 | PHE 258 | -7.7 |
| Gymnemasin D | 101,689,884 | 4 | GLN 766; GLN 814; TYR 533 | -8.3 | 1 | GLN 502 | -8.2 | 5 | CYS 304; GLN 306; ARG 313; ASP 394 | -7.5 |
| Gymnemasaponin - II | 21,636,600 | 3 | CYS 527; TYR 479; ASN 529 | -7.6 | 5 | SER 552; GLN 502; ASP 547; THR 650; ASN 644 | -9.3 | 2 | ARG 313; ASN 425 | -8.2 |
| Gymnemasaponin - IV | 21,636,602 | 4 | ALA 525; ASN 658; GLY 765; ILE 536 | -9.3 | 5 | SER 552; GLN 502; ASP 547; LYS 787; ARG 773 | -9.1 | 5 | GLU 127; ASN 35; SER 58; ASP 55; GLU 51 | -8.5 |
| Gymnemoside A | 6,442,217 | 5 | GLY 532; ILE 531; GLN 814 | -8.1 | 4 | MET 570; ASP 809; GLY 807; ALA 462 | -7.6 | 2 | ASP 391; TYR 340 | -7.5 |
| Gymnemoside B | 6,442,215 | 3 | GLN 814; ILE 536; GLY 532 | -7.6 | 2 | GLN 502; ARG 773 | -8.3 | 4 | TYR 340; ASN 425; CYS 304; ARG 313 | -7.6 |
| Gymnemoside C | 101,933,150 | 5 | TYR 517; GLN 814; ASN 529 | -7.9 | 4 | ASN 644; THR 650; ASP 547; GLN 502 | -8.5 | 2 | GLU 233; ASN 229 | -7.9 |
| Linagliptin | 10,096,344 | 2 | GLN 766; GLY 765; ILE 762 | -8.1 | 1 | LYS 787 | -8 | 1 | ARG 256 | -8.6 |

crucial in ensuring that there were no unwanted charges in the system. After this, the complex was equilibrated under controlled conditions. The equilibration was conducted in a canonical ensemble, which keeps the number of particles (N), the system volume (V), and the temperature (T) constant. This approach ensures that the simulation reflects realistic physical conditions, setting the stage for further analysis of the molecular dynamics.

The final molecular dynamics (MD) simulation of protein-ligand complexes lasted for 100 nanoseconds. This simulation was conducted in the NPT ensemble, which maintains a constant number of particles, pressure, and temperature. The temperature was set at 300 K, and the pressure was kept at 1 bar. After completing the simulation, the trajectory files were extracted for further analysis. The trajectory extracted files were used to calculate the Root Mean Square Deviation (RMSD), Root Mean Square Fluctuations (RMSF) for protein and ligand, Radius of gyration (RoG) of ligand in the complex to understand the proper dynamic changes of the protein–ligand complex at molecular level (Macalalad and Gonzales 2022; Patil et al. 2021).

## ADMET analysis

The ADMET (absorption, distribution, metabolism, elimination, and toxicity) properties of the high binding *G. sylvestre* saponin compounds against antilipidemic and antidiabetic targets compared with Linagliptin (10096344), an FDA-approved oral antidiabetic drug were screened to predict the important pharmacokinetic properties. The high-binding energy saponin compounds were retrieved from the PubChem server (https://pubchem.ncbi.nlm.nih.gov/) in

**Table 4** ADMET pharmacokinetics evaluation of Anti-Diabetic and Anti-lipidemic *G. sylvestre* saponins:

| Model Name | Gymnemasin B | Gymnemasaponin - IV | Linagliptin | Units |
|---|---|---|---|---|
| *Absorption* | | | | |
| Water solubility | -2.807 | -2.753 | -2.955 | log mol/L |
| Caco-2 permeability | -0.801 | -0.974 | 0.356 | log Papp in 10–6 cm/s |
| Intestinal absorption (human) | 0 | 0 | 83.98 | % Absorbed |
| Skin Permeability | -2.735 | -2.735 | -2.736 | log Kp |
| P-glycoprotein substrate | Yes | Yes | No | Yes/No |
| P-glycoprotein I inhibitor | No | Yes | Yes | Yes/No |
| P-glycoprotein II inhibitor | No | No | No | Yes/No |
| *Distribution* | | | | |
| VDss (human) | -0.58 | -0.596 | 0.26 | log L/kg |
| Fraction unbound (human) | 0.525 | 0.404 | 0.236 | Fu |
| BBB permeability | -1.993 | -1.966 | -1.509 | log BB |
| CNS permeability | -4.966 | -5.451 | -2.958 | log PS |
| *Metabolism* | | | | |
| CYP2D6 substrate | No | No | No | Yes/No |
| CYP3A4 substrate | No | No | Yes | Yes/No |
| CYP1A2 inhibitor | No | No | No | Yes/No |
| CYP2C19 inhibitor | No | No | No | Yes/No |
| CYP2C9 inhibitor | No | No | Yes | Yes/No |
| CYP2D6 inhibitor | No | No | No | Yes/No |
| CYP3A4 inhibitor | No | No | Yes | Yes/No |
| *Excretion* | | | | |
| Total Clearance | 0.185 | 0.263 | 0.385 | log ml/min/kg |
| Renal OCT2 substrate | No | No | No | Yes/No |
| *Toxicity* | | | | |
| AMES toxicity | No | No | Yes | Yes/No |
| Max. tolerated dose (human) | -1.12 | -1.028 | 0.7 | log mg/kg/day |
| hERG I inhibitor | No | No | No | Yes/No |
| hERG II inhibitor | No | Yes | Yes | Yes/No |
| Oral Rat Acute Toxicity ($LD_{50}$) | 2.609 | 2.753 | 2.62 | mol/kg |
| Oral Rat Chronic Toxicity (LOAEL) | 3.607 | 4.18 | 1.144 | log mg/kg_bw/day |
| Hepatotoxicity | No | No | Yes | Yes/No |
| Skin Sensitisation | No | No | No | Yes/No |
| T.Pyriformis toxicity | 0.285 | 0.285 | 0.285 | log ug/L |
| Minnow toxicity | 7.893 | 9.704 | 0.76 | log mM |

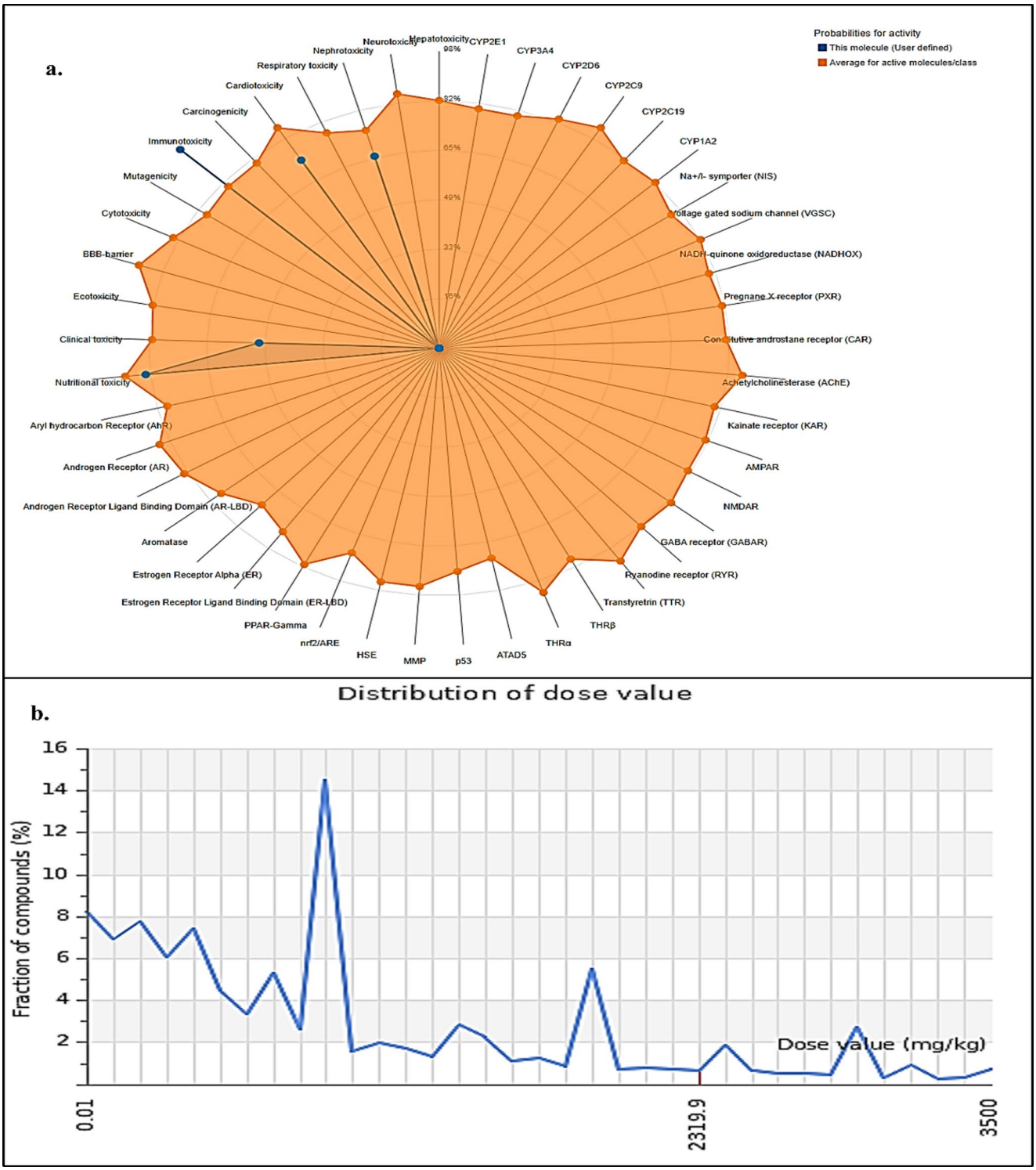



**Fig. 2** The toxicity radar chart is intended to quickly illustrate the confidence of positive toxicity results of higher biding energy Anti-Diabetic and Anti-lipidemic Gymnema saponin IV

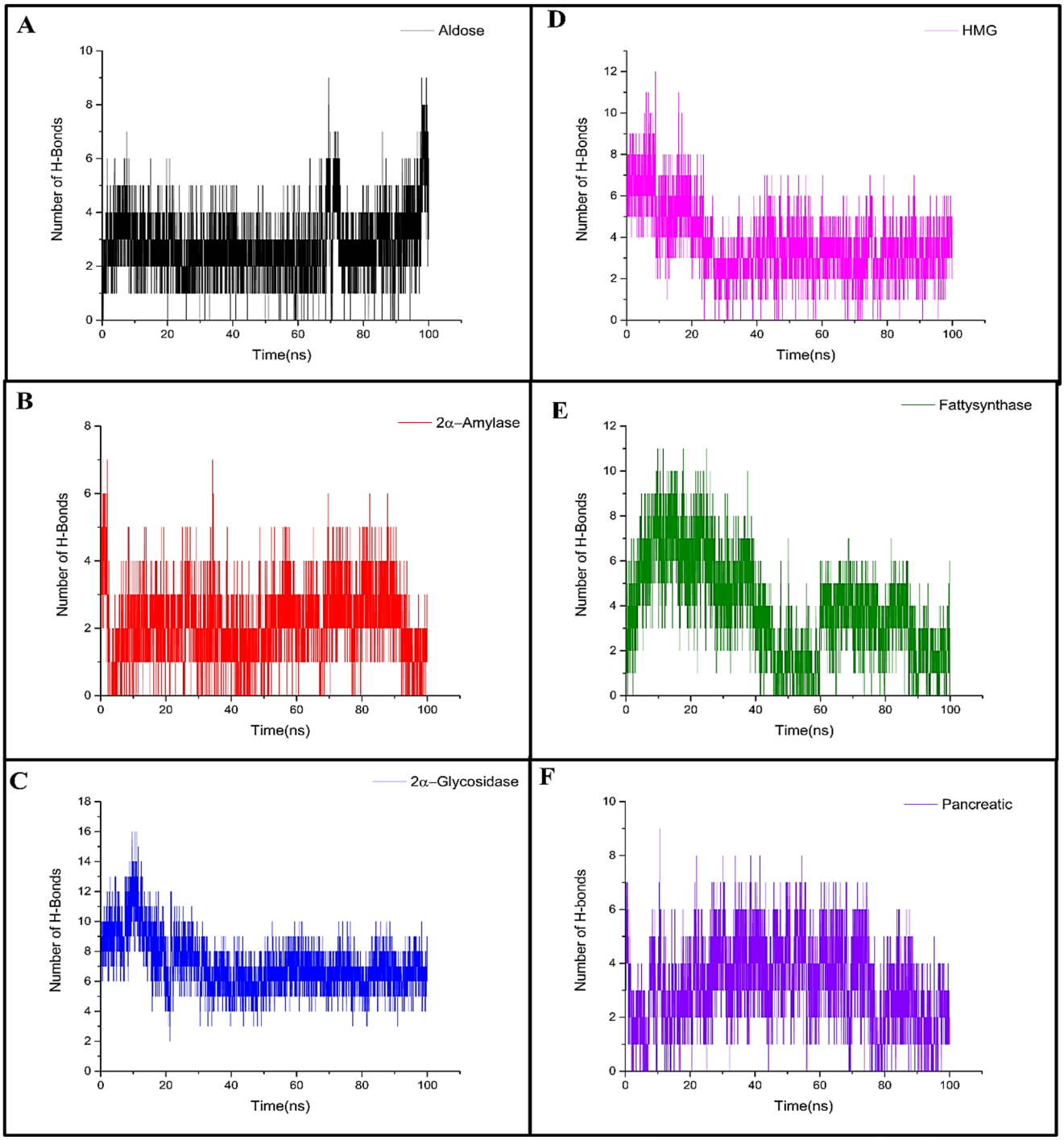



**Fig. 3** Number of H-Bonds Plot at 100 ns with **A** Aldose reductase, **B** α- amylase, **C** α- glycosidase, **D** HMG-CoA reductase, **E** Fatty acid synthase, **F** Pancreatic Lipase with Gymnema saponin IV

the simplified molecular-input line-entry system (SMILES) format and used for in-silico predictions in the web server. While the toxicological endpoints (Mutagenicity, Carcinogenicity, Immunotoxicity, Hepatotoxicity) and the level of toxicity ($LD_{50}$, mg/Kg) were studied by using ProTox 3.0 ( https://comptox.charite.de/protox3/). These predictions pro vided valuable insights into the drug-like properties of the compounds aiding in the selection of candidates for further evaluation (Burranboina et al. 2022) (Pratama et al. 2023).

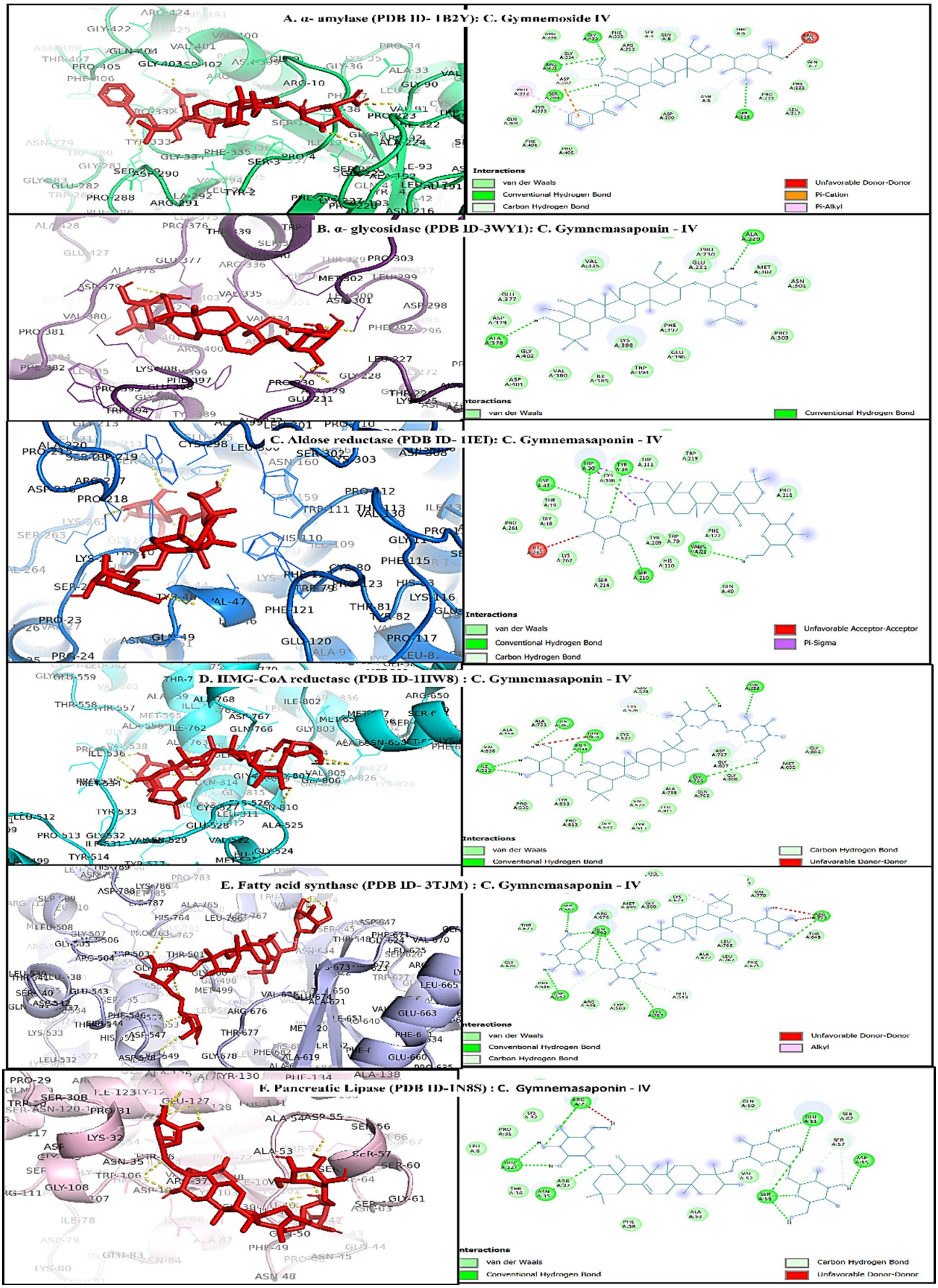

A. α- amylase (PDB ID- 1B2Y): C. Gymnemoside IV
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Unfavorable Donor-Donor
Pi-Cation
Pi-Alkyl
B. α- glycosidase (PDB ID-3WY1): C. Gymnemasaponin - IV
Interactions
van der Waals
Conventional Hydrogen Bond
C. Aldose reductase (PDB ID- 1IEI): C. Gymnemasaponin - IV
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Unfavorable Acceptor-Acceptor
Pi-Sigma
D. HMG-CoA reductase (PDB ID-1HW8) : C. Gymnemasaponin - IV
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Unfavorable Donor-Donor
E. Fatty acid synthase (PDB ID- 3TJM) : C. Gymnemasaponin - IV
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Unfavorable Donor-Donor
Alkyl
F. Pancreatic Lipase (PDB ID-1N8S) : C. Gymnemasaponin - IV
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Unfavorable Donor-Donor

**Fig. 4** 3D and 2D Molecular interactions of the bioactive Saponins (Gymnemasaponin– IV) with target proteins **A** α- amylase, **B** α- glycosidase, **C** Aldose reductase, **D** HMG-CoA reductase, **E** Fatty acid synthase, **F** Pancreatic Lipase

## Results and discussion

*G. sylvestre* is a natural herb that helps to protect against diabetes, high cholesterol, liver damage, and poor kidney function. The bioactive compounds found in *G. sylvestre* mainly, Gymnema-saponins, Gymnemic acids, and polypeptide gurmarin are known for their potential therapeutic effects. Furthermore, *G. sylvestre's* capacity to lower sweet cravings, regulate blood glucose and pancreatic cells regeneration make it an interesting choice for treating diabetes in pharmaceutical research. Hence, more studies are required to identify the anti-diabetic and anti-hyper lipidemic active components in the plant extract (Mandal et al. 2024; Muddapur et al. 2024).

Saponin has been extensively studied for its potential antidiabetic activity. Research indicates that saponin compounds found in various marine animals and plants have hypo glycemic effects by regulating blood glucose levels and preventing diabetic complications through their antioxidant properties (Choudhary et al. 2021). These compounds have known to rejuvenate insulin, amend insulin signalling, release insulin from beta cell islets, inhibit disaccharides, activate glycogen synthesis, inhibit gluconeogenesis, inhibit α-glucosidase activity, inhibit expression of mRNA of glycogen phosphorylase and glucose 6-phosphatase, and increase the expression of Glut4 Additionally, saponins have been found to possess antidiabetic activity by stimulating insulin secretion, insulin stimulation, and acting as α-glucosidase inhibitors. Further, research is needed to fully understand the pharmacological role of saponins in the treatment of diabetes (Ashafa and Nafiu 2018; Singh et al. 2014; Xu et al. 2018).

The present research work revealed anti-diabetic and anti-lipidemic activity of Molecular interactions 13 bioactive saponins compounds from *G. sylvestre* by targeting therapeutic target proteins Fig. 1. Triterpene saponins from the oleanane and dammarane classes were found in *G. sylvestre* leaves. Saponin inhibits the enzymes that convert disaccharides into monosaccharides, hence lowering the rise in blood glucose levels. This impact is noteworthy for the management of individuals with Type I and Type II diabetes and aids in preventing elevated blood sugar levels after meals (Amiraragab et al. 2017). The selected 13 bioactive saponin compounds from *G. sylvestre* showed in Fig. 1 were evaluated for their anti-diabetic target protein proteins, (i) Aldose reductase, (ii) α- amylase, (iii) α- glycosidase and Anti-lipidemic anti-lipidemic target proteins (i) HMG-CoA reductase, (ii) Fatty acid synthase, (iii) Pancreatic Lipase.

### Anti-diabetic activity of saponin compounds on target proteins (i) Aldose reductase, (ii) α- amylase, (iii) α- glycosidase

The in-silico approach was carried out for the molecular docking and interaction analysis was done using a protein-ligand docking program "CB-Dock2" by a curvature-based cavity detection technique and the binding locations of target proteins were detected. Former mentioned in-silico approach and the binding poses of query ligands using AutoDock Vina energy values, CB-Dock are known for their accuracy and effective docking process. The molecular interaction results showed anti-diabetic activity saponin compounds with target proteins- (i) Aldose reductase, (ii) α- amylase, (iii) α- glycosidase.

i. Aldose reductase

Aldose reductase (AR) is a key target in the conception of treatments for health issues brought on by hyperglycemia (Shahab et al. 2023). The saponins' potential to inhibit aldose reductase (AKR1B1) is one of their newly discovered properties alongside their antioxidant and antidiabetic properties. Numerous hydrophilic and hydrophobic aldehydes can be reduced in a NADPH-dependent manner by this enzyme (EC 1.1.1.21). In-vitro models of diabetic peripheral neuropathy and in-vivo diabetic rats have both shown that a triterpenoid oleanane saponin inhibits aldose reductase, interfering with the polyol pathway (Balestri et al. 2019).

All the explored compounds showed strong molecular interaction and binding scores with i) Aldose reductase compared to the clinical oral antidiabetic drug Linagliptin. The tested saponin showed a binding energy ranging from Gymnemic acid - II 2-methylbutyroyl (-5.9 kcal/mol) to - Gymnemasin C (9.8 kcal/mol). The compounds are Gymnemasin C interactive amino acids were TRP 111; HIS 110; CYS 298; TYR 48; SER 22 and Binding energy −9.8 kcal/mol, Gymnemasaponin - II interactive amino acids were TRP 20; TRP 111; ASP 216, and binding energy −8.4 kcal/mol. The best 3D and 2D ligand-binding poses molecular interactions of the bioactive saponins against aldose reductase with the amino acid residues involved in the interaction are shown in supplementary Fig. 1 and the number of hydrogen bonds, interactive amino acids, and binding energy kcal/mol are represented in Table 2.

ii. α- amylase

The pancreas and salivary glands both generate amylase, an enzyme that aids in the digestion of carbohydrates. Through regulation of starch degradation, pancreatic α-amylase

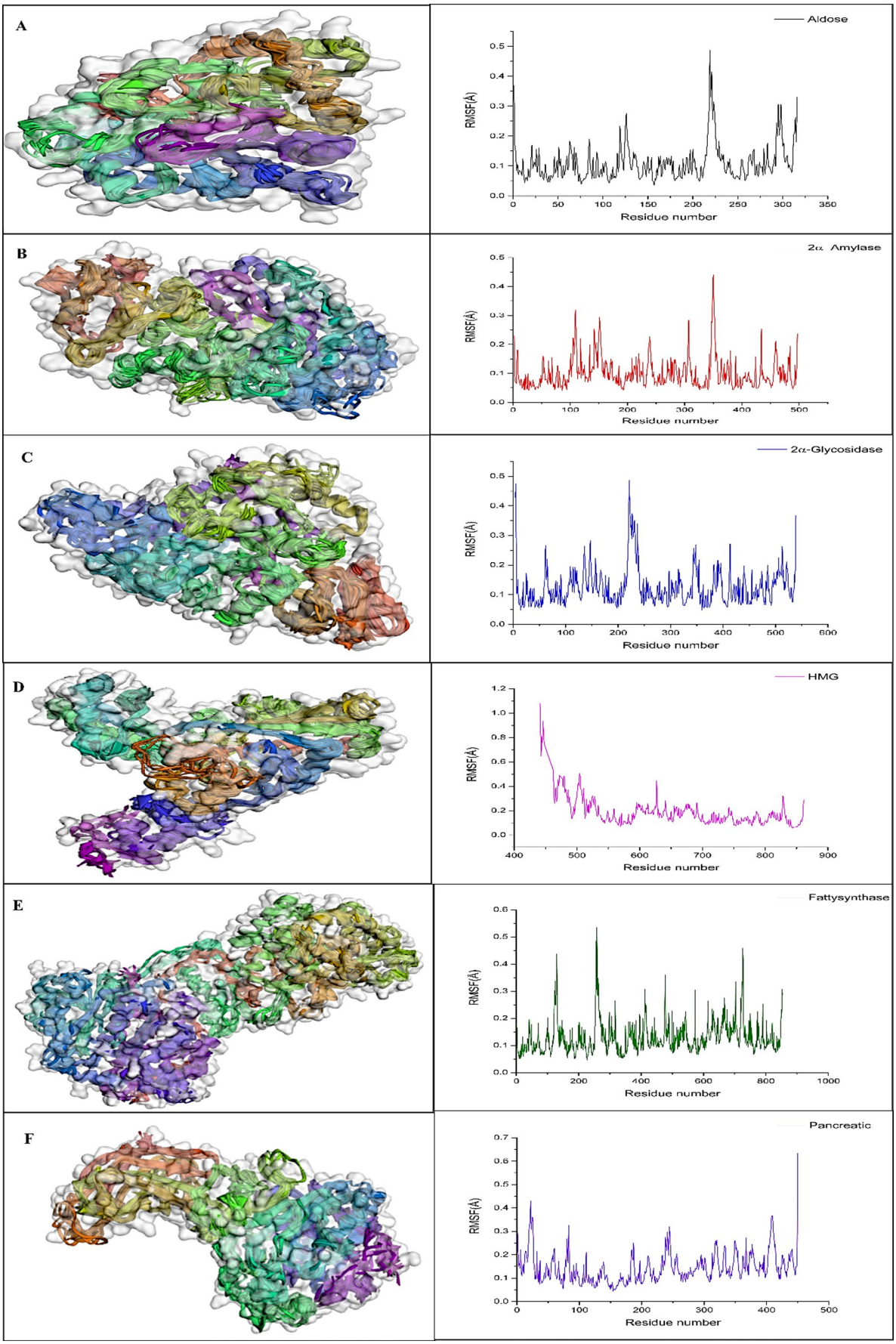

A
Aldose
RMSF(Å)
Residue number
B
2α Amylase
RMSF(Å)
Residue number
C
2α-Glycosidase
RMSF(Å)
Residue number
D
HMG
RMSF(Å)
Residue number
E
Fattysynthase
RMSF(Å)
Residue number
F
Pancreatic
RMSF(Å)
Residue number

**Fig. 5** RMSF Fluctuation Plot **A** Aldose reductase, **B** α- amylase, **C** α- glycosidase, **D** HMG-CoA reductase, **E** Fatty acid synthase, **F** Pancreatic Lipase with Gymnema saponin IV

inhibitors provide a useful method for reducing postprandial hyperglycemia levels (Bhavi et al. 2024). α-amylase inhibitory activities of The two major saponins, Araloside A and Stipuleanoside R2 from *Panax bipinnatifidus* (Ngoc et al. 2023).

All the identified compounds showed strong binding scores with ii. α- amylase compared to the clinical oral antidiabetic drug Linagliptin. The tested saponin showed a binding energy ranging from Gymnemic acid - II 2-methylbutyroyl (-5.9 kcal/mol) to - Gymnemasin C (9.8 kcal/mol). The compounds in Gymnemic acid - I Tigloyl showed interactive amino acids TRP 111; HIS 110; CYS 298; TYR 48; SER 22 with binding energy −9.2 kcal/mol, Gymnemasin B showed interactive amino acids PRO 332; GLY 334; SER 3; ARG 92 with Binding energy −9.4 kcal/mol and Gymnemoside C showed interactive amino acids LYS 307; ASN 171; GLY 403; ARG 421; SER 289; SER 226 with Binding energy −9.1 kcal/mol. The best 3D and 2D ligand-binding poses molecular interactions of the bioactive saponins against α- amylase with the amino acid residues involved in the interaction are shown in supplementary Fig. 2 and the Number of hydrogen bonds, Interactive amino acids with Binding energy kcal/mol is represented in Table 2.

iii. α- glycosidase

The small intestine contains α-glucosidase (EC 3.2.1.20) which catalyzes the release of glucose from complex sugars. In individuals with diabetes mellitus, the release of glucose has been associated with the development of postprandial hyperglycemia (Fatmawati et al. 2023). The tested saponin showed a binding energy ranging from Gymnemasin C (-7.8 kcal/mol) to Gymnemasaponin - IV (-8.9 kcal/mol). The compounds are Gymnemasin B showed interactive amino acids ASN 301; ALA 229; LEU 300; GLY 399; GLU 377 with Binding energy −8.7 kcal/mol, Gymnemasin D showed interactive amino acids ALA 229; ALA 378 with binding energy −8.6 kcal/mol and Gymnemasaponin - IV showed interactive amino acids ASP 48; ASN 4; ARG 457; ALA 43; GLY 94 with Binding energy −8.9 kcal/mol supplementary Fig. 3.

## Anti-lipidemic activity saponin compounds by targets proteins (i) HMG-CoA reductase, (ii) Fatty acid synthase, (iii) Pancreatic Lipase

A metabolic condition known as type II diabetes is characterized by elevated blood sugar and blood pressure as well as insulin resistance over time. While various changes in the fat metabolism and inadequate insulin function cause hypercholesterolemia, insufficient insulin production or inappropriate insulin action causes hyperglycemia. The main risk factor for coronary artery disease in this current population is believed to be the considerable increase in blood lipid levels observed in patients with diabetes mellitus (Ezeja et al. 2015; Deepak et al. 2020).

The molecular interaction study results showed anti-lipidemic activity of saponin compounds against target proteins (i) HMG-CoA reductase, (ii) Fatty acid synthase, (iii) Pancreatic Lipase was downloaded from the PDB.

i. HMG-CoA reductase

The primary enzyme in the mevalonate pathway, which generates cholesterol is 3-hydroxy-3-methyl-glutaryl-coenzyme-A (HMG-CoA) reductase. By inhibiting HMG-CoA reductase eventually lowers the production of cholesterol in the liver (Baskaran et al. 2015; Ibrahim et al. 2020). Since HMG-CoA reductase inhibitors lower cholesterol production (Tanaka et al. 2007) they are used to treat hypercholesterolemia in addition to diet and exercise. The enzyme functions by raising the level of high-density lipoprotein cholesterol while lowering the levels of low-density lipoprotein cholesterol, total cholesterol, and triglycerides (Lins et al. 2022; Almalki et al. 2024).

All the saponin compounds showed a strong binding score with i. HMG-CoA reductase. The tested saponins showed a binding energy ranging from Gymnemic acid - IV (-6.8 kcal/mol) to Gymnemasaponin - IV (-9.3 kcal/mol). The compound Gymnemic acid - I Tigloyl showed interactive amino acids GLN 814; GLY 808; GLN 766; LYS 691; ALA 768 and binding energy −9.1 kcal/mol, Gymnemasin C showed interactive amino acids ILE 536; TYR 517; ASP 767; VAL 805; GLY 806 and binding energy −8.9 kcal/mol, Gymnemasaponin - IV showed interactive amino acids ALA 525; ASN 658; GLY 765; ILE 536 and binding energy −9.3 kcal/mol. The best 3D and 2D ligand-binding poses molecular interactions of the bioactive saponins interacting against Aldose reductase along with the amino acid residues are shown in supplementary Fig. 4 and the number of hydrogen bonds, interactive amino acids and binding energy kcal/mol represented in Table 3.

ii. Fatty acid synthase

Diabetes affects fatty acid synthase(FAS), an important *de novo* lipogenesis enzyme, which changes lipid metabolism. Recently, it was shown that individuals with cancer and hyperinsulinemia have circulating FAS in their blood. Synergistic glucolipotoxicity is the term used to describe the potentially harmful consequences of simultaneous exposure

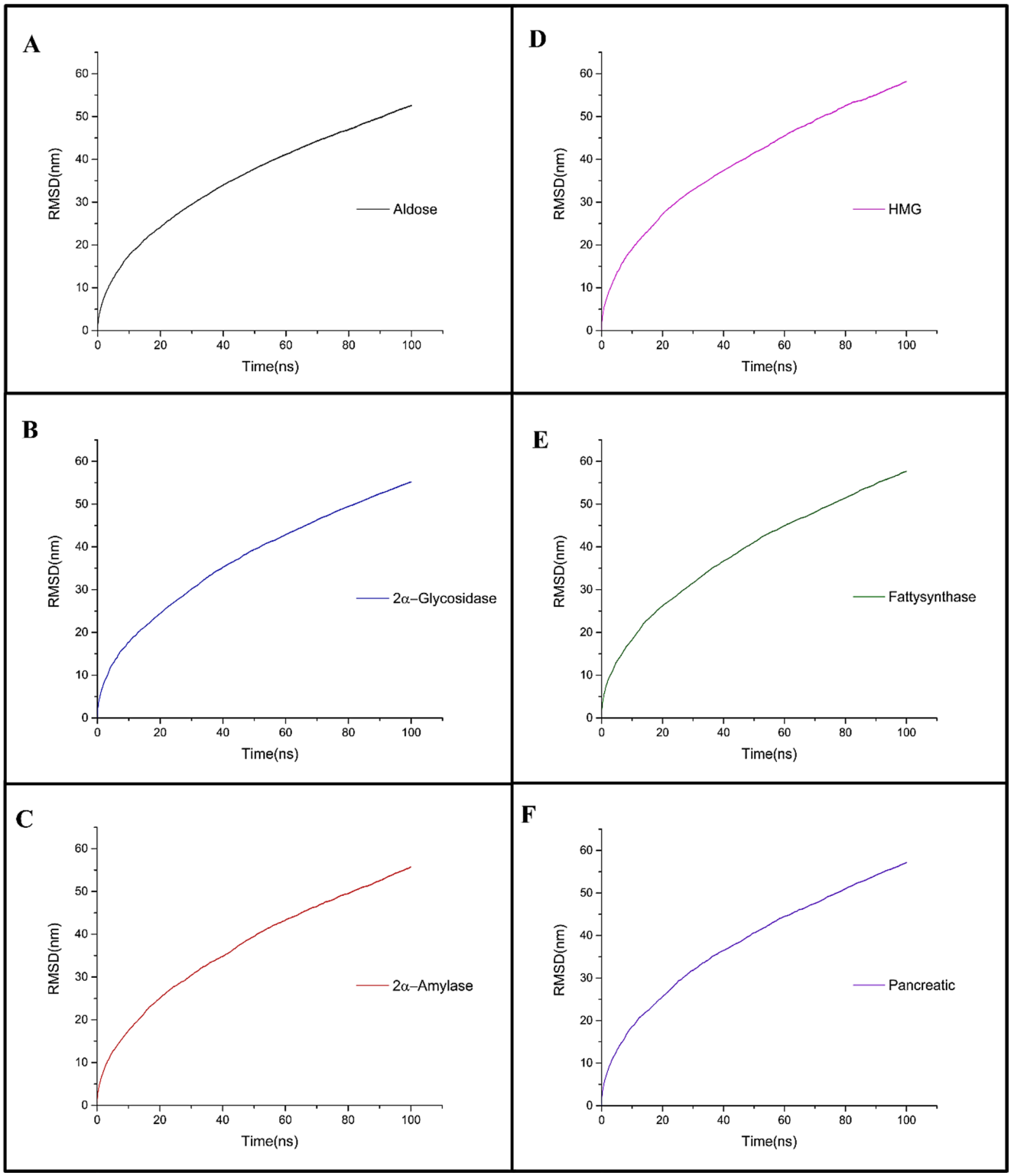



**Fig. 6** RMSD Fluctuation Plot **A** Aldose reductase, **B** α- amylase, **C** α- glycosidase, **D** HMG-CoA reductase, **E** Fatty acid synthase, **F** Pancreatic Lipase with Gymnema saponin IV

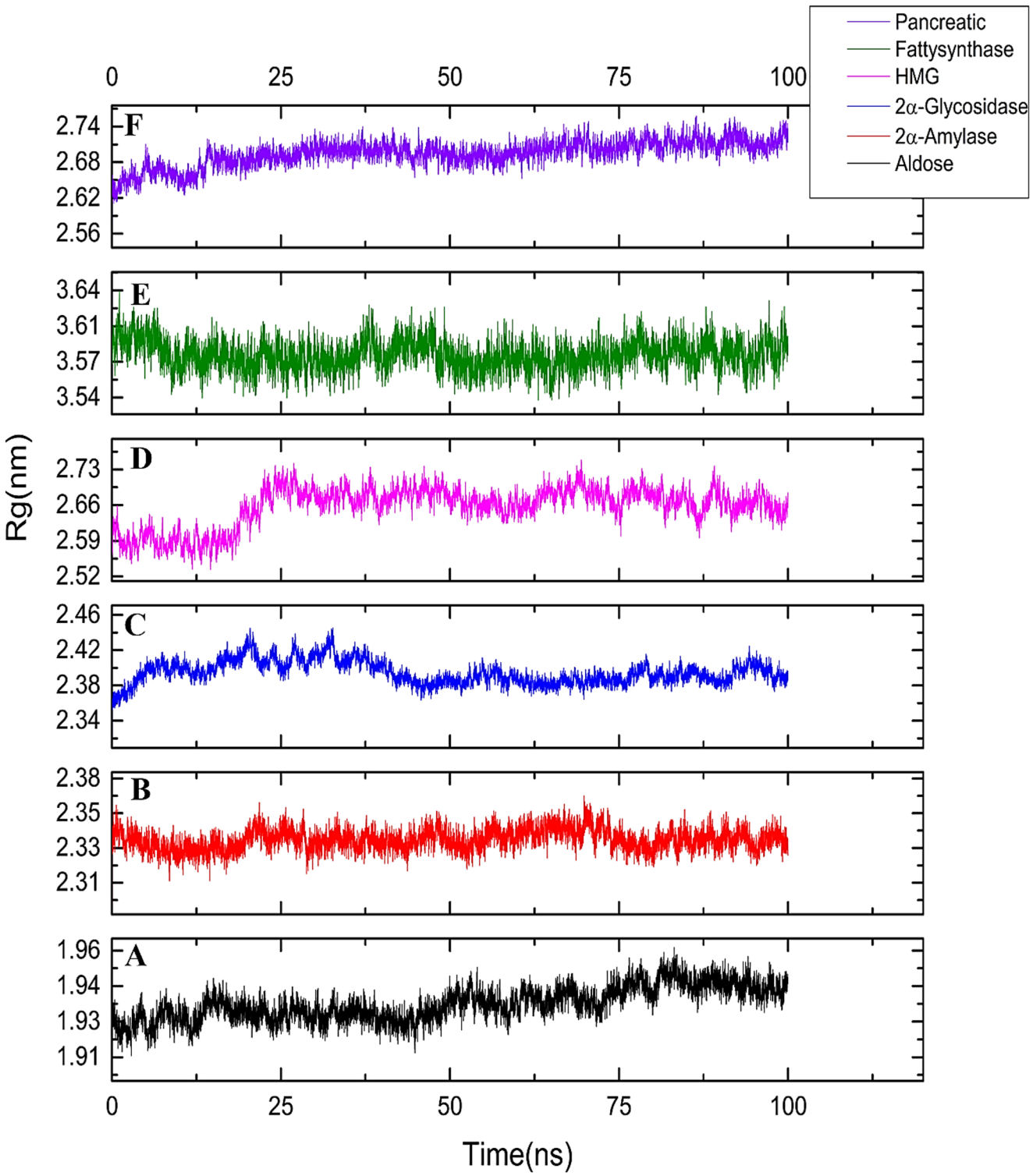



**Fig. 7** Radius of gyration (RoG) Plot **A** Aldose reductase, **B** α- amylase, **C** α- glycosidase, **D** HMG-CoA reductase, **E** Fatty acid synthase, **F** Pancreatic Lipase with Gymnema saponin IV

to increased glucose levels and chronic elevation in free fatty acid levels on glucose control (De Silva et al. 2019; Nicholas et al. 2024). The consequences of these therapies must be carefully assessed at the organismic and cellular levels that confirm fatty acid metabolic enzymes as promising targets for medication therapy (Worthmann et al. 2024).

The compound Gymnemasin C showed interactive amino acids GLY 678; GLN 502; THR 648; ASN 644 and binding

energy −8.9 kcal/mol, Gymnemasaponin - II showed interactive amino acids SER 552; GLN 502; ASP 547; THR 650; ASN 644 and binding energy −9.3 kcal/mol, Gymnemasaponin - IV showed interactive amino acids SER 552; GLN 502; ASP 547; LYS 787; ARG 773 and binding energy −9.1 kcal/mol. The best 3D and 2D ligand-binding poses molecular interactions of the bioactive saponins against Aldose reductase with the amino acid residues involved in the interaction, are shown in supplementary Fig. 5 and the number of hydrogen bonds, interactive amino acids, and binding energy kcal/mol represented in Table 3.

iii. Pancreatic lipase

Pancreatic lipase is a vital enzyme in the human digestive system that breaks down dietary fat. Blocking the gastrointestinal tract's capacity to absorb fat is one potential obesity treatment strategy. Pancreatic lipase is a crucial enzyme in the hydrolysis of triglycerides. Pancreatic lipase inhibitors are medications that block the function of the enzyme in the small intestine mostly it works by reducing the absorption of fat. The most studied approach to identify potential anti-obesity medications is by suppressing pancreatic lipase activity (Pinto et al. 2024; Djamil et al. 2024). The tested saponins against iii) Pancreatic Lipase showed binding energy ranging from Gymnemic acid - I Tigloyl (-7.1 kcal/mol) to Gymnemasin B (-8.6 kcal/mol). The compound Gymnemasin B showed interactive amino acids ILE 78; TRP 252; ILE 251 and binding energy −8.6 kcal/mol, Gymnemasaponin– II showed interactive amino acids ARG 313; ASN 425 and binding energy −8.2 kcal/mol, Gymnemasaponin - IV showed interactive amino acids GLU 127; ASN 35; SER 58; ASP 55; GLU 51 and binding energy −8.5 kcal/mol. The best 3D and 2D ligand-binding poses molecular interactions of the bioactive saponins against Aldose reductase with the amino acid residues involved in the interaction are shown in supplementary Fig. 6 and the number of hydrogen bonds, interactive amino acids and binding energy kcal/mol represented in Table 3.

## ADMET analysis

The Pharmaco-kinetic properties of *G. sylvestre* saponin compounds against antilipidemic and antidiabetic targets compared with Linagliptin (10096344) an FDA Approved oral antidiabetic drug were screened to predict the important ADME effects. Proteins known as "toxicity targets" have been linked to harmful medication responses and other side effects. Here, we used a set of protein-ligand based pharmacophores to predict potential binding to toxicity targets. The web servers used were ProTox 3.0 (https://comptox.charite.de/protox3/), and pkCSM (https://biosig.unimelb.edu.au/pkcsm) which are small molecule toxicity prediction tools. Among ADME-T's attributes- Absorption characteristics include water solubility, Caco-2 permeability, skin permeability, human intestinal absorption, substrate for P-glycoprotein, inhibitors for P-glycoprotein I and II; Distribution: (human VDss, human fraction unbound, permeability of the BBB, permeability of the CNS), Metabolism: (Inhibitors of CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 substrate, CYP2D6 inhibitor, CYP3A4 inhibitor), excretion: Total elimination, Renal OCT2 substrate. The toxicity testing such as, Ames toxicity, maximum tolerated dosage in humans, hERG I and hERG II inhibitors, oral rat acute and chronic toxicity ($LD_{50}$ and LOAEL), hepatotoxicity, skin sensitization, toxicity from *T. pyriformis*, and minnow toxicity. In-silico ADMET properties of the most potent saponin compounds Gymnemasin B and Gymnema saponin– IV with standard oral antidiabetic compound Linagliptin were calculated using pkCSM as an online software and the obtained results are listed in Table 4.

Prediction of oral acute toxicity and binding to 16 toxicity targets anti-diabetic and Anti-lipidemic *G. sylvestre* saponins. The $LD_{50}$ value is usually given in mg/kg body weight for toxic doses. Median lethal dose or $LD_{50}$ refers to the dose at which 50% of the test subjects are deceased. The standard lethal doses are often given as $LD_{50}$ values in mg/kg body weight and predicted $LD_{50}$ values which highly interact with *G. sylvestre* saponin are Gymnemic acid - I Tigloyl ($LD_{50}$: 2000 mg/kg), Gymnemasin B ($LD_{50}$: 4500 mg/kg), Gymnemasaponin - II ($LD_{50}$: 8000 mg/kg), Gymnemasaponin– IV ($LD_{50}$: 8000 mg/kg) with standard drug Linagliptin Predicted ($LD_{50}$: 684 mg/kg). The intent of the toxicity radar map is to rapidly demonstrate the degree of trust in the favorable toxicity results of the greater biding energy anti-lipidemic and anti-diabetic *G. sylvestre* saponins displayed in supplementary Fig. 7 and Fig. 2.

Research has shown that dietary saponins possess multidirectional anti-diabetic capabilities by regulating various signalling pathways (Zhou and Xu 2023). Crude saponin extracts from plants like *Leptodenia hastata* and *Adansonia digitata* have demonstrated anti-diabetic properties, making them promising candidates for future antidiabetic agents (Abubakar and Garba 2021). Studies on *Momordica charantia* suggest that saponins play a crucial role in the hypoglycemic effects observed, potentially stimulating insulin secretion and normalizing glucose metabolism (Keller et al. 2021). Saponin fractions from *Moringa oleifera* had shown notable antioxidant and antidiabetic activities (Hussain and Ikram 2020). Overall, saponins with their diverse structural characteristics have the potential to reduce hyperglycemia and inhibit diabetic complications, making them a promising avenue for developing alternative antidiabetic medications (Choudhary et al. 2021).

*Molecular dynamics and simulation analysis*: Analysis of the stability of the protein–ligand complex has been carried out using MD simulations, and to explain MD findings the RMSD, RMSF, Intramolecular hydrogen bonding and Rg have been used. curves show the complex's conformational response throughout time.

Binding affinity results for saponin ligand Gymnema saponin IV of the *G. sylvestre* against antidiabetic antilipidemic target proteins. The hydrogen bonds α- amylase 4 amino acid and interacted with ASN5, SER226, GLY403, GLN8, ARG421, ASP402, SER289, α- glycosidase hydrogen bonds are 2 and interactive amino acids are ALA229, ALA378, Aldose reductase hydrogen bonds 5 and the interactive amino acids are ASP43, TRP20.TYR 48, ASP43, SER210, HMG-CoA reductase interacted with 7 hydrogen bonds with residues are ALA 525, ASN658, ILE762, MET534,ILE536,GLY765, Fatty acid synthase 6 hydrogen bonds with interactve amino acids are SER 552, GLN502, ASP547, LYS787, ARG773, GlU543, Pancreatic Lipase 6 hydrogen bonds with interactive amino acids ARG7, GLU51, GLU127, ARG37, SER58 the detailed interactive hydrogen bonds and aminoacids showed in Figs. 3 and 4.

**T**he root mean squared fluctuation plot (Fig. 5) of gymnema saponin IV complex between anti-diabetic target proteins (Aldose reductase, α- amylase, α- glycosidase) and anti-lipidemic target proteins (HMG-CoA reductase, Fatty acid synthase, Pancreatic Lipase) showed high interaction. The variation in amino acids remains within the range of 1–3Å, as seen in the Fig. 5 which is considered to be stable.

Root Mean Square Deviation (RMSD): Root Mean Square Deviation (RMSD) values were calculated to measure how much the molecular complex changed during the simulation period. The Complex-RMSD reflects the movements of both the ligand and the protein backbone. This provides a comprehensive view of how the entire system behaves over time. In contrast, the ligand-RMSD focuses solely on the ligand. It captures its fluctuations while it resides within the binding pocket of the protein. Analyzing both RMSD types helps to understand the stability of the complex throughout the simulation. The arrangement of the natural protein shows that the root mean square deviation (RMSD) between two different compounds lies in a range that is considered acceptable (Fig. 6). This range spans from 1.0 Å to 3.5 Å. RMSD is a common way to measure how similar two structures are. A value within this range suggests that the compounds share a similar structure and spatial arrangement.

### Radius of gyration (RoG)

Gyration radius (Rg) plays a significant role in understanding the structural characteristics of macromolecules during simulations. This calculation helps scientists observe changes in the compactness of the structure over time. Fluctuations in Rg can indicate how tightly or loosely the components of a molecule are packed together. When the Rg value is high, it suggests that the chemical elements associated with the protein are not closely bound. This can mean that the structure is loose or less stable. Conversely, a low Rg value reflects good compactness, indicating that the components are held closely together within the protein structure. This compactness often suggests a more stable configuration, which can be important for the protein's function. Radius of gyration (RoG) Plot shows the Aldose reductase Rg values are −1.92 to 1.94, α- amylase 2.33 to 2.35, α- glycosidase 2.35 to 2.42, HMG-CoA reductase 2.51 to 2.73, Fatty acid synthase 3.57 to 3.62, and Pancreatic Lipase 2.62 to 2.68 (Fig. 7).

## Conclusion

The current study elucidates the possible roles of *G. sylvestre* saponins as a ligand binding with diabetic and lipidemic target proteins involved in Dyslipidemia and diabetes mellitus, a metabolic disorder. The ADMET and toxicity studies predicted potential ligands and its oral acute toxicity and binding to 16 toxicity targets. These compounds did not show non-carcinogenice effects. In addition, the possible interactions with the target protein molecules are confirmed by the in-silico approach and form a scientific basis to promote further pharmacological studies in animal models. Our study highlights the importance of *G. sylvestre* saponins as potential therapeutics for dyslipidemia and diabetes. The implications of this research may lead to significant treatment for individuals suffering from type I and type II diabetes.

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**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Conflict of interest** The authors declare no competing interests.

**Human and animal rights** This research article dose not contains any studies with animal or human subjects performed by the authors.

**Informed consent** Authors stated that there is no informed consent in the article.

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