



# Deciphering the the molecular mechanism of aloe-emodin in managing type II diabetes mellitus using network pharmacology, molecular docking, and molecular dynamics simulation approaches

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## Abstract

Aloe-emodin (AE) has drawn interest due to its potential activity against type II diabetes mellitus (T2DM). However, the mechanisms underlying its antidiabetic activity are not well explored. Using network pharmacology, molecular docking and molecular dynamics simulation studies, we investigated its molecular mechanisms in the management of T2DM. Potential target genes of AE were predicted using the Swiss Target Prediction (<http://www.swisstargetprediction.ch/>) database. The GeneCards, OMIM and DisGeNET databases were used to compile a comprehensive list of genes associated with T2DM. A compound-disease-target network was constructed, and protein–protein interaction networks were analysed to identify hub genes. Finally, molecular docking and interaction analysis between AE and the identified proteins were performed using AutoDock tools. Investigation of AE targets and genes associated with T2DM identified 32 overlapping genes. Gene ontology studies revealed that AE may exert its anti-diabetic effects by modulating glucose metabolism and enhancing cellular response to glucose. Furthermore, KEGG pathway analysis suggested that AE influences these processes by targeting pathways related to apoptosis, insulin resistance, and T2DM signaling. The core target proteins identified were TNF, ALB, TP53, PPARG, BCL2, CASP3, and EGFR. AE interaction with each of these proteins exhibited a binding energy of  $>-5$  kcal/mol, with TNF showing the lowest binding energy ( $-7.75$  kcal/mol). Molecular dynamics simulation further validated the molecular docking results with TNF and EGFR exhibiting a strong affinity for AE and forming stable interactions. AE exerts its antidiabetic activity through multiple mechanisms, with the most significant being the amelioration of pancreatic  $\beta$ -cell apoptosis by binding to and inhibiting the actions of TNF $\alpha$ . Further cellular and molecular studies are needed to validate these findings.

**Keywords** Aloe emodin · Type II diabetes mellitus · Network pharmacology · Molecular docking

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## Introduction

Diabetes mellitus type II (T2DM) is a common metabolic disorder marked by decreased insulin sensitivity in tissues and a reduction in insulin production by pancreatic  $\beta$ -cells (Taylor 2012). The International Diabetes Federation (IDF) estimates that 783 million people globally will suffer from T2DM by 2045, an increase from 536.6 million people in 2021. Ninety percent (90%) of all diabetes cases worldwide are of T2DM. This high prevalence of T2DM is attributed to urbanization, reduced physical activity, high prevalence of obesity among other factors (Galicía-García et al. 2020;

Yan et al. 2022). Several pharmacological agents are used in the management of T2DM including biguanides, sulfonylureas, and thiazolidinediones. These drugs work by increasing insulin secretion from the pancreas and boosting insulin sensitivity in the muscle, liver, and fat cells, reversing insulin resistance and decreasing excess glucose release by the liver (DeFronzo and Abdul-Ghani 2011; Inzucchi et al. 2015; Steinberg and Carlson 2019). Despite several breakthroughs in the pharmacotherapy of T2DM, few drugs target the improvement of insulin receptor sensitivity and relative beta cell function, which is the principal cause of T2DM. To improve the effectiveness of T2DM treatment, current research is focusing on novel molecules that lower insulin resistance, retain and protect pancreatic beta cells and minimize subsequent tissue damages (Lyu et al. 2017).

The use of herbal remedies in the management of T2DM has become popular worldwide due to their accessibility and affordability (Usai et al. 2022). In addition, these plants also provide additional properties like wound healing, antioxidant capacity and antibacterial properties which are crucial in the management of T2DM complications (Pang et al. 2019). Some clinical trials have demonstrated more translational potential that herbal remedies have strong hypoglycemic potential at both the cellular and molecular level (Omale et al. 2023; Willcox et al. 2021).

Aloe-emodin, a natural anthraquinone derivative found in *Aloe vera*, *Rubia cordifolia*, *Rheum palmatum*, *Polygonum multiflorum*, and various *Cassia* species (Chiang et al. 2012; Sihanat et al. 2018) has been widely studied for its pharmacological properties, including anti-inflammatory (Li et al. 2022; Park et al. 2009), anticancer (Chen et al. 2014; Şeker et al. 2022), hepatoprotective (Arosio et al. 2000), antimicrobial (Huang and Yan 2023; Zhu et al. 2023) and wound healing agent (Furkan et al. 2017). AE has been reported to enhance glucose metabolism by upregulating glycolytic enzymes such as hexokinase, glucose-6-phosphatase (G6P), and fructose-1,6-bisphosphatase (F16BP) (Anand et al. 2010). Additionally, AE has been shown to increase liver glycogen synthase levels in streptozotocin-induced diabetic rat (Anand et al. 2016b), reduce lipid peroxidation, and improve antioxidant status in diabetic models, (Anand et al. 2016a). Notably, AE also enhances insulin signaling by promoting phosphorylation of insulin downstream regulators in skeletal muscle tissues at a dosage of 30 mg/kg (Gadewar et al. 2023). Its potential to mitigate diabetes-related complications, including neuropathy (Dong et al. 2020) and retinopathy. (Wu et al. 2016) highlights its therapeutic promise for addressing  $\beta$ -cell dysfunction and insulin resistance in T2DM (Kong et al. 2021).

Despite these promising findings, the precise molecular mechanisms underlying AE's antidiabetic effects remain poorly understood (Dong et al. 2020). Computational

approaches, including network pharmacology, molecular docking, molecular dynamics (MD) simulations, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis, have emerged as valuable tools for elucidating drug-target interactions and predicting the pharmacokinetic properties of bioactive compounds (Chandrasekar et al. 2020). Molecular docking studies predict the binding affinity and interaction sites of drug candidates with key disease-related proteins by simulating molecular interactions at atomic levels (Edache et al. 2024a, b). These docking simulations provide insights into hydrogen bonding, hydrophobic interactions, and van der Waals forces that contribute to ligand-receptor stability (Edache et al. 2023). To further validate the docking results, molecular dynamics (MD) simulations analyze the stability and conformational dynamics of drug-protein complexes over time (Shafiq et al. 2024). MD simulations use Newtonian mechanics to model molecular movement, ensuring a realistic representation of biomolecular interactions under physiological conditions (Van Der Spoel et al. 2005). Additionally, ADMET profiling assesses the drug's pharmacokinetic viability, predicting the absorption, distribution, metabolism, excretion, and potential toxicity. These predictions are essential for determining the drug-likeness and safety profiles of drug candidates before advancing to experimental validation. By integrating these computational methods, we can systematically investigate the therapeutic potential of promising compounds while streamlining the drug discovery process (Edache et al. 2023).

In this study, we employed these computational techniques to elucidate the molecular targets and mechanisms underlying AE's antidiabetic activity. Specifically, we aimed to evaluate the binding affinity and stability of AE- T2DM target protein interactions using molecular docking and MD simulations, and assessing the pharmacokinetic properties of AE to determine its drug-likeness and therapeutic potential. These findings will provide a comprehensive understanding of AE's mechanistic role in T2DM management and contribute to the development of novel plant-based antidiabetic therapeutics.

## Materials and methods

### Data mining from web repositories for compound identification

Literature repositories such as Google scholar (<https://scholar.google.com/>), PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), PubChem (<https://pubchem.ncbi.nlm.nih.gov/>), Springer (<https://link.springer.com>) accessed from 6 to 15th January 2024, and Science Direct (<https://www.sciencedirect.com>

) from 20 to 24th January 2024 were used for a scholarly literature search to identify the bioactive compounds from *Aloe vera*. The following keywords were used to conduct the survey; *Aloe vera* or *Aloe barbadensis* or Aloe compounds or Aloe constituents or phyto-constituents or active compounds in Aloe) and (antidiabetic or hypoglycemic or anti-hyperglycemic or blood sugar lowering or glucose lowering). Only full-text articles in peer-reviewed journals were considered. *In-vivo*, *in-silico* and in vitro studies on the anti-diabetic effect of the bioactive compounds were considered. Only compounds with ethnopharmacology evidence of their antidiabetic activity were selected. The bioavailability and safety profile of the selected compounds were also considered. Compounds with poor absorption or high toxicity were eliminated. The most outstanding and reported anti-diabetic compound in *Aloe vera* was identified as AE with 11/29 mentions in the articles reviewed and was prioritized for further in silico studies.

### Drug-likeness prediction, pharmacokinetics and toxicity screening of aloe-emodin

The AE drug-likeness features, pharmacokinetics and toxicity parameters were evaluated by uploading its canonical smile obtained from PubChem onto the SwissADME web tool (<http://www.swissadme.ch/>) on 13th February 2024. A virtual screening run was made using following default parameters; physicochemical properties (Molecular weight (MW), Number of hydrogen bond donors and acceptors, Topological polar surface area (TPSA), Lipophilicity, Water Solubility), Pharmacokinetics (Gastrointestinal absorption and blood–brain barrier penetration, Substrate or inhibitor of P-glycoprotein (P-gp), Interaction with major cytochrome P450 iso-enzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), skin permeation, Drug-Likeness (Lipinski's rule-of-five, Ghose, Veber, Egan, Muegge, bioavailability score), Medicinal Chemistry parameters (PAINS alerts, Brenk alerts and lead likeness).

### Prediction of target genes of aloe-emodin

The possible human target genes of AE were identified using the Comparative Toxicogenomics Database (CTD) (<https://ctdbase.org/>), SuperPred (<https://prediction.charite.de/>), TargetNet databases (<http://targetnet.scbdd.com/>) and SWISS Target Predict (<http://www.swisstargetprediction.ch/>) all accessed on 15th February 2024. To obtain the target genes, the search excluded genes from organisms other than *Homo sapiens* to ensure relevance to human biology. The duplicated genes were eliminated using Microsoft Excel to arrive at the final target gene list.

### Prediction of target genes in diabetes mellitus

The potential human target genes associated with diabetes mellitus were harvested from online databases including GeneCards (<http://www.genecards.org/>), accessed on 18th February 2024, DisGeNET (<https://www.disgenet.org/>), and the Online Mendelian Inheritance in Man (OMIM; <https://www.omim.org/>), accessed on 18th February 2024. The key word “Non-Insulin dependent diabetes mellitus” was used to execute the search and duplicated genes were removed to arrive at a complete list of human diabetes associated genes.

### Compound-disease-target (C-D) network

AE target genes associated with diabetes mellitus were derived by comparing both the obtained compound target genes and the disease genes using the JVenn (<https://jvenn.toulouse.inrae.fr/app/index.html>) accessed on 28th February 2024. In order to identify the overlapping genes between the aloe emodin gene targets and T2DM gene targets the Venn diagram was constructed. Cytoscape Software version 3.9.1 was then used to develop the Compound-Disease network by integrating the shared target genes of both AE and diabetes mellitus.

### Protein–protein interaction (PPI) Network construction and analysis

The STRING database Version 11.5 (<https://string-db.org/>) accessed on 29th February 2024 was used to construct the PPI network of AE and diabetes mellitus genes, limiting the analysis to human proteins. High confidence interactions (confidence score > 0.6) (Hosur et al. 2012) should be used to select nodes for network visualization, this facilitates the creation of reliable PPI network ensuring that the interactions are highly reliable, biologically relevant, and derived from high-quality data (Bozhilova et al. 2019). In this study, we used a confidence score of at least 10.00 to select nodes for network visualization, justifying this choice to further enhance the reliability and relevance of the interactions depicted in the network. Network visualization and analysis was conducted using Cytoscape software and the genes of significance identified using the CytoHubba plugin basing on three parameters; maximal clique centrality (MCC), maximum neighborhood component (MNC), and degree. The top 10 significant genes were identified basing on their scores. The data were imported to JVenn (<https://jvenn.toulouse.inrae.fr/app/index.html>) accessed on 28th February 2024 and an intersect constructed to identify probable hub genes in the network.

## Gene ontology and Kyoto encyclopedia of genes and genomes (KEGG) enrichment studies

To further understand the different biological mechanisms underlying the potential antidiabetic activity of aloe-emodin, the gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis on the Compound Target Disease network were performed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID), version 2021 (<https://david.ncifcrf.gov/home.jsp>) accessed on 28th February 2024)). The top genes were presented as bar graphs for GO analysis and as bubble plots for KEGG analysis. Statistical significance was tested at  $p$  value  $< 0.05$  (Shamsol Azman et al. 2023).

## Molecular docking

The AutoDock tools software version 1.5.7 (<http://autodock.scripps.edu/>) was used to analyse the interactions between the AE and the identified hub genes. The three-dimensional structures of the target proteins; TNF, ALB, TP53, PPARG, BCL2, CASP3 and EGFR, were obtained from the RCSB Protein Data Bank (<https://www.rcsb.org/>, accessed on 29th February 2024) as PDB formats. These were then prepared for binding by adding polar hydrogens, eliminating water molecules, removing residual chains and ligands, adding Kollman charges, assigning atoms as AD4 type and then saving them as .pdbqt extension. Converting files to the PDBQT format is crucial for preparing coordinate files for use in AutoDock tools because this format includes polar hydrogen atoms, atomic partial charges, and specific atom types required by the AutoDock force field to accurately represent physiological hydrogen bonding and realistic protein geometry. It also provides information on torsional degrees of freedom, which is essential for modeling ligand flexibility, and allows for the inclusion of flexible side-chain coordinates in proteins. The PDBQT format ensures that all necessary details for accurate molecular docking simulations are represented so that proper calculation of electrostatic interactions can be performed, making it compatible with Auto Dock Tools for seamless preparation and reliable docking results (Morris et al. 1996). The AE 3D structure was retrieved from PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>), accessed on 29th February 2024. This was then imported into the AutoDock software and prepared as a ligand by detecting the root and the number of its rotatable bonds and saving it as .pdbqt format. The strength of interactions between the Ligand and the target proteins was then predicted by AutoDock software using binding energy as a predictor, thereafter the molecular interactions were then visualized using Discovery Studio Visualizer 2021 and presented as figures.

## Molecular dynamics simulation

Molecular docking and network pharmacology offered valuable insights into the interaction pathways and potential binding modes of AE. However, these methods did not account for time-dependent stability and full receptor flexibility. To validate the docking results and network pharmacology findings, we performed classical molecular dynamics (MD) simulations of the top-scoring complex, as described in our recent work (Shayo et al. 2024). To investigate the plausible mode of action and the ligand's ability to explore the binding pocket in a bulk solution, we conducted a 100 ns self-assembly process using Gromacs v20. The protein and ligand topologies were derived using the OPLS-AA force field (Dodda et al. 2017; Jorgensen & Schyman 2012). Initially, both protein and ligand were soaked in a simulation box filled with TIP4P water (González and Abascal 2011) and neutralized with  $\text{Na}^+$  at a physiological concentration of 0.15 M. The system was energy minimized before being heated in an NVT (constant number of particles, volume, and temperature) ensemble with positional restraints for 200 ps, maintaining a temperature of 310 K using the V-rescale thermostat (Bussi et al. 2007). Subsequently, the system was equilibrated in an NPT (constant pressure and temperature) ensemble for 500 ps, with positional restraints and pressure maintained using the Parrinello-Rahman barostat (Parrinello and Rahman 1981). To assess ligand self-recognition, we conducted a production run without positional restraints in an NPT ensemble for 100 ns, with temperature and pressure held at 310 K and 1 bar, respectively, using the V-rescale thermostat and Parrinello-Rahman barostat (Bussi et al. 2007; Parrinello and Rahman 1981). Throughout the simulation, the equations of motion were integrated with a time step of 2 fs, and periodic boundary conditions (PBC) were applied in all directions. The LINCS algorithm (Hess et al. 1997) constrained covalent bonds, while the Particle Mesh Ewald (PME) method (Darden et al. 1993) handled long-range electrostatic interactions with a cut-off distance of 11 Å. The free energy surface ( $F$ ) was calculated using the formula  $F = -k_B T \ln(P)$ , where  $k_B$  is the Boltzmann constant,  $T$  is the temperature, and  $P$  is the probability distribution along the selected reaction coordinate. Visualization and plotting of the MD simulation data were performed using VMD (Humphrey et al. 1996), Python, and Gnuplot (Williams et al. 1986).

**Table 1** Drug-likeness prediction, pharmacokinetics and toxicity screening of Aloe-emodin

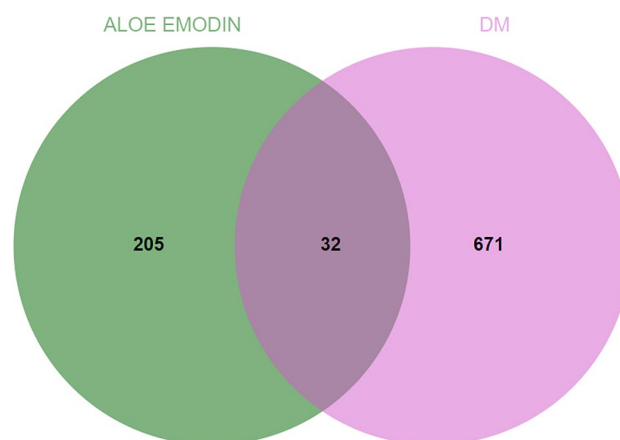
| Parameter                                           | Result |
|-----------------------------------------------------|--------|
| <b>Pk parameters</b>                                |        |
| Molecule Weight (MW) (Da)                           | 270.24 |
| #Heavy atoms                                        | 20     |
| GI absorption                                       | High   |
| BBB permeant                                        | No     |
| Pgp Substrate                                       | No     |
| CYP1A2 Inhibitor                                    | Yes    |
| CYP2C19 Inhibitor                                   | No     |
| CYP2C9 Inhibitor                                    | No     |
| CYP2D6                                              | No     |
| CYP3A4 Inhibitor                                    | Yes    |
| Bioavailability Score (probability value)           | 0.55   |
| PAINS Alerts (number of alerts)                     | 2      |
| Brenk Alerts (number of alerts)                     | 1      |
| Lead likeness Violation (Number of violations)      | 0      |
| Synthetic Accessibility (Range 1–20)                | 2.54   |
| <b>Organ toxicity parameters</b>                    |        |
| H-HT hepatotoxicity to humans (probability value)   | 0.047  |
| DILI (Drug-induced liver injury (probability value) | 0.955  |
| Rat oral acute toxicity (probability value)         | 0.124  |
| Skin Sensitivity (probability value)                | 0.801  |
| Carcinogenicity (probability value)                 | 0.855  |
| Eye corrosion (probability value)                   | 0.004  |
| Eye irritation (probability value)                  | 0.954  |
| Respiratory (probability value)                     | 0.06   |
| LD50 (mg/kg)                                        | 0      |
| Oral skin sensitization (probability value)         | 8      |
| <b>Genotoxicity parameters</b>                      |        |
| Ames (mutagenic potential) (probability value)      | 0.873  |

For the classification endpoints, the prediction probability values are transformed into six symbols: 0–0.1(–), 0.1–0.3(–), 0.3–0.5(–), 0.5–0.7(+), 0.7–0.9(++), and 0.9–1.0(+++) (reference: <https://admetmesh.cbdd.com/service/evaluation/cal>)

## Results

### Pharmacokinetics and toxicity profile of aloe-emodin

The results of the pharmacokinetic and toxicity profile (organ toxicity, Genotoxicity and environmental toxicity) of AE are shown in Table 1 below. The ranges of the pharmacokinetic parameters like GI absorption, and PAINS alerts were obtained from (Xiong et al. 2021). From the results, aloe-emodin has a molecular weight of 270.24 Daltons, a high gastrointestinal absorption, an aquatic toxicity of 2, a mutagenic potential of 0.873 and did not violate any criterion in the Lipinski rule of five with LD<sub>50</sub> of 0.



**Fig. 1** Venn diagram showing the potential targets between aloe emodin and T2DM targets. There were a total of 32 overlapping genes and these are represented in the intersection (Darker purple intersection)

### Identification of targets

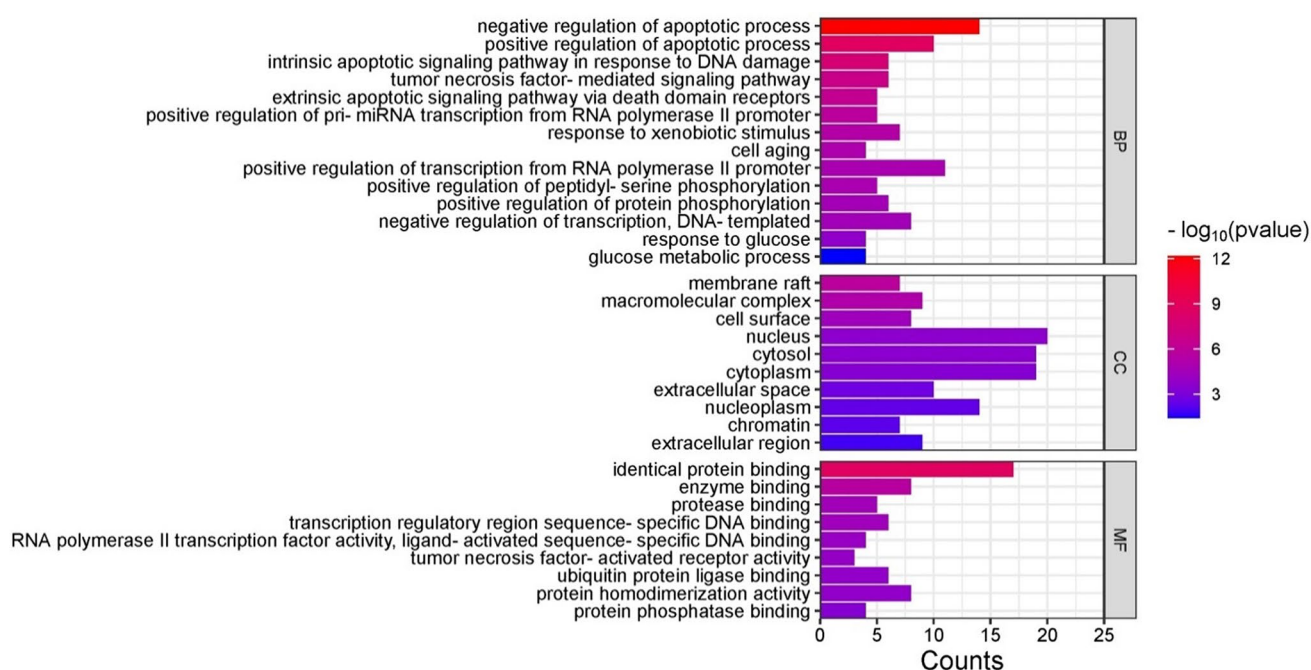
A total of 237 AE target genes and 703 T2DM associated genes were identified and a total of 32 genes were identified as the intersection (Fig. 1).

### Gene ontology (GO) enrichment analysis

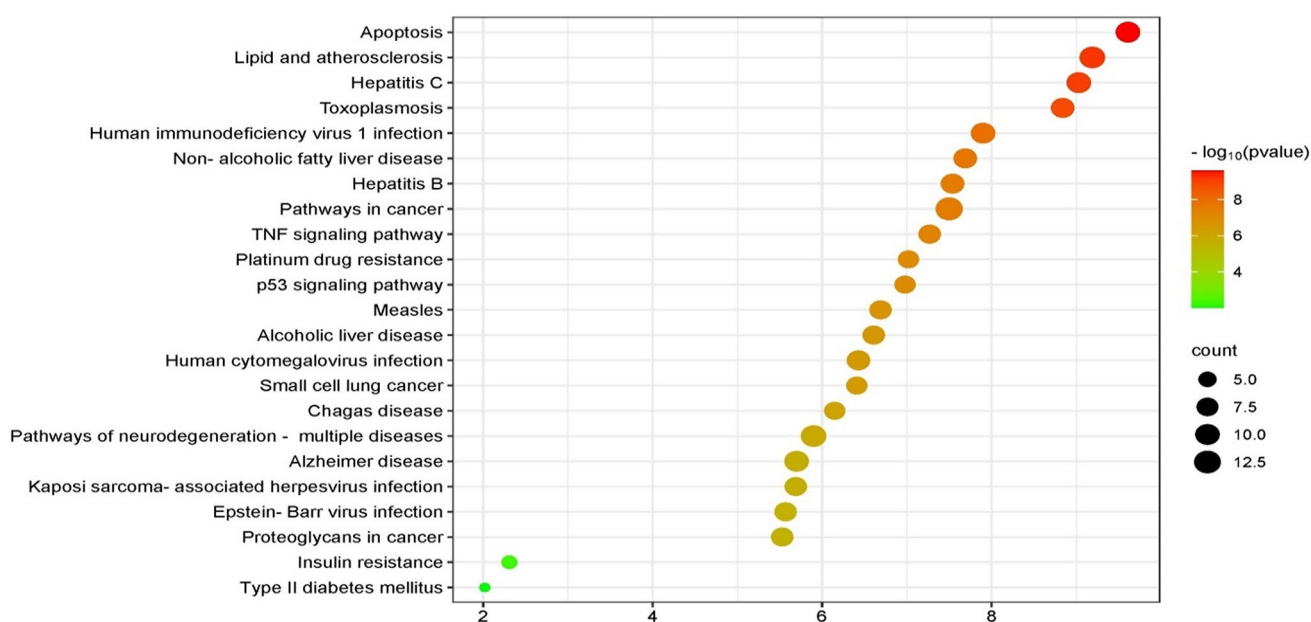
The analysis showed that the top biological processes associated with the aloe emodin targets were related to negative and positive regulation of apoptotic process and positive regulation of transcription from RNA polymerase II promoter. The cellular component analysis showed that the targets were primarily involved in the nucleus, cytoplasm, and cytosol. In terms of molecular function, the most significant enrichment terms included identical protein binding, enzyme binding and protein phosphatase binding (Fig. 2).

### The Kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis of AE in T2DM

The analysis showed that the several targets of AE against T2DM were enriched in a number of signaling pathways such as the apoptotic process, lipid atherosclerosis, pathways in cancer, TNF signaling pathways and insulin resistance pathway. Importantly, the analysis also revealed that AE may play a role in Insulin resistance and T2DM pathways (Fig. 3). The molecular pathway that the intersecting genes are most likely to be involved in is indicated by the colored circles where by the more intense red color represents a lower *p* value and a greater significance while the size of the circle represents the number of genes regulating the pathway. The potential targets and mechanism of aloe emodin against Diabetes mellitus Type II are shown in Fig. 9.



**Fig. 2** Bar graphs showing Gene ontology (GO) enrichment analysis. The bar chart represents the most significantly enriched GO terms ( $-\log_{10}(p \text{ value})$ ) in biological processes, cellular components, and molecular function, comprising the top terms related to the target genes in T2DM



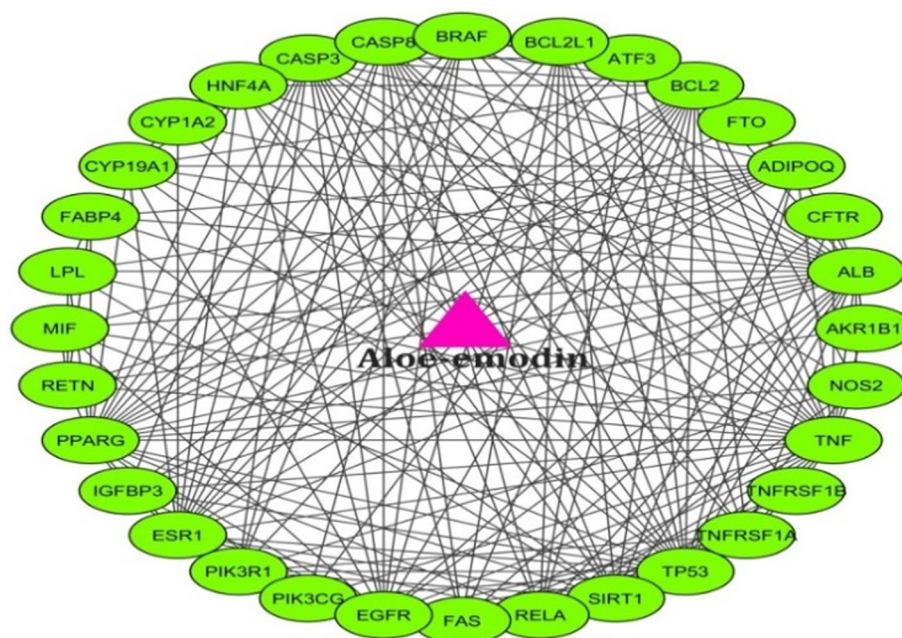
**Fig. 3** KEGG enrichment analysis of the Target genes. The bubble plots represent the top 23 enriched KEGG pathways of AE against T2DM

### Compound-target network constructions

The compound target network consists of 32 compound target nodes, 1 active compound node of aloe-emodin, and 203 edges. In the network, green circles represent T2DM target proteins, while purple triangles denote aloe-emodin. The network reveals that aloe emodin targets all T2DM proteins with an average node degree of 12.7, and a clustering

coefficient of 0.787. This clearly demonstrates the multi-targeted nature of aloe-emodin against T2DM. Consequently, we not only observed the relationship between aloe emodin and T2DM but also discovered potential pharmacological effects of aloe emodin from this network (Fig. 4).

**Fig. 4** The compound-target network of aloe-emodin against T2DM generated by Cytoscape Software. The green nodes represent the interacting target genes of T2DM and the purple triangle represent aloe-emodin node



### Protein–protein interaction (PPI) network

The average local clustering coefficient was 0.787 with a total number of edges of 203. The number of edges was 207 as compared to the expected number of edges of 89. The protein–protein interaction enrichment  $p$  value was  $<1.0 \times 10^{-16}$ . The network revealed that the proteins have more interactions among themselves than what would be expected for a random set of proteins of the same size and degree distribution drawn from the genome. This kind of enrichment indicates that the proteins are at least partially biologically connected, as a group indicating they all play a role in the pathophysiology of T2DM. The color gradients were used to highlight the degree value of the network nodes. The darker colors represent higher values and considered the most significance gens and these were highlighted dark red whereas the lighter colors represent lower values and are depicted light yellow (Figs. 5 and 6).

### Details of the protein targets in the PDB database

Table 2 presents details of the protein targets identified in the Protein Data Bank (PDB), along with their respective PDB IDs, resolution, and R-values obtained through X-ray diffraction methods. The target proteins include Tumor Necrosis Factor (TNF), Albumin (ALB), Tumor Protein p53 (TP53), Peroxisome Proliferator-Activated Receptor Gamma (PPARG), B-cell Lymphoma 2 (BCL2), Caspase-3 (CASP3), Epidermal Growth Factor Receptor (EGFR). The resolution values range from 1.80 to 2.80 Å.

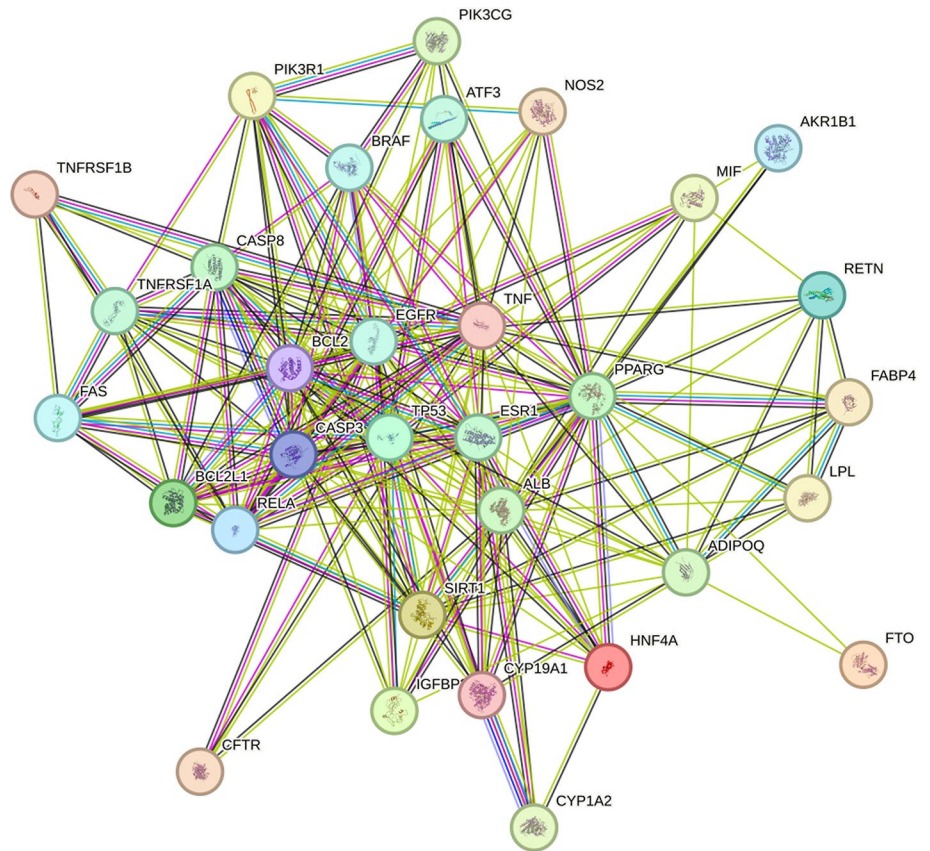
### Grid docking parameters in molecular docking

Table 3 presents the grid docking parameters used in molecular docking simulations for the various target proteins. The grid spacing represented in Angstrom units and is between 0.442 and 0.881. The X, Y, and Z center coordinates are also shown in the Tables 3 and 4 (Fig. 7).

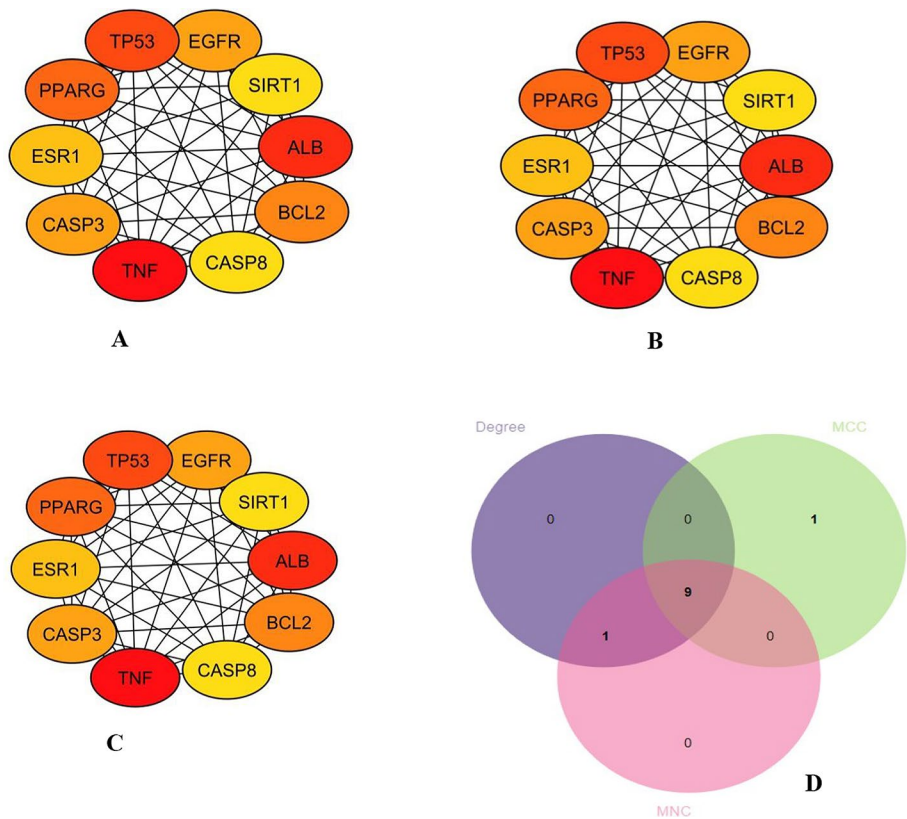
### Molecular dynamics simulation

Ligand recognition of protein active sites is a key factor in assessing ligand efficacy. To investigate this, we computed the ability of a free ligand in solution to recognize the binding pocket by measuring the distance between the protein and the ligand. To decipher the binding process of AE to the targets, we considered the best docked target TNF and the least-docked target EGFR. Initially, in all cases, the ligand was distant from the proteins, but over time, it approached the protein surface and eventually bound to the active site residues, as observed in docking calculations (Fig. 8A). The log–log plot of distances indicates that AE bound to TNF in two sites, the one that was observed in docking calculation but with low concentration as evidenced by the free energy surface (Fig. 8C), then moved to recognize another binding site with high affinity with other residues (Fig. 8A). This suggests that AE may exhibit an on–off binding or have an allosteric effect in treating diabetics through inhibition of TNF. On the other hand (Fig. 8B), AE self-assembled into EGFR and bound stable with few fluctuations observed although not in the exact site as observed in docking calculations. This observation highlights the value of molecular dynamics simulations in complementing docking results,

**Fig. 5** Protein–protein interaction networks are constructed using the STRING database. The degree value of nodes was visually represented in the network diagram using color gradients, with darker colors indicating higher values



**Fig. 6** The top ten hub gene networks of AE against T2DM by incorporating three algorithms—**A** maximal clique centrality (MCC), **B** maximum neighborhood component (MNC), **C** degree of nodes, and **D** The Venn diagram illustrates nine hub genes



**Table 2** Details of the protein targets in the PDB database

| Target name | PDB ID | Method            | Resolution (Å) | R-value free | R-value work | R-value observed |
|-------------|--------|-------------------|----------------|--------------|--------------|------------------|
| TNF         | 1A8M   | X-RAY DIFFRACTION | 2.3            | 0.240        | 0.218        | 0.218            |
| ALB         | 1AO6   | X-RAY DIFFRACTION | 2.50           | 0.282        | 0.218        | 0.218            |
| TP53        | 1XNI   | X-RAY DIFFRACTION | 2.80           | 0.269        | 0.247        | 0.267            |
| PPARG       | 4R06   | X-RAY DIFFRACTION | 2.22           | 0.240        | 0.186        | 0.189            |
| BCL2        | 4IEH   | X-RAY DIFFRACTION | 2.10           | 0.218        | 0.179        | 0.181            |
| CASP3       | 1RE1   | X-RAY DIFFRACTION | 2.50           | 0.261        | 0.194        | 0.255            |
| EGFR        | 1M14   | X-RAY DIFFRACTION | 2.60           | 0.286        | 0.238        | 0.240            |

**Table 3** Grid docking parameters in molecular docking

| Targets | Spacing (angstrom) | X-center | Y-center | Z-center |
|---------|--------------------|----------|----------|----------|
| TNF     | 0.442              | 20.083   | 49.892   | 39.738   |
| ALB     | 0.664              | 28.423   | 8.392    | 23.263   |
| TP53    | 0.469              | -14.248  | 17.837   | -27.224  |
| PPARG   | 0.519              | 28.119   | 10.07    | 27.091   |
| BCL2    | 0.547              | -18.5    | 5.722    | 3.722    |
| CASP3   | 0.525              | -16.612  | 19.376   | 23.283   |
| EGFR    | 0.881              | 23.592   | 9.727    | 58.829   |

**Table 4** Binding energy between AE and prioritized T2DM target proteins

| Targets | Residues                           | Binding energy (kcal/mol) |
|---------|------------------------------------|---------------------------|
| TNF     | GLU-104, GLN-102, CYS-101, SER-99  | -7.75                     |
| ALB     | ASN-312                            | -6.75                     |
| PPARG   | GLU-343, ILE-342, ILE-282, HIS-266 | -7.27                     |
| BCL2    | VAL-92                             | -5.56                     |
| CASP3   | GLU-396, TYR-334, GLY-321          | -5.93                     |
| EGFR    | GLU-907                            | -5.07                     |
| TP53    | ASP-1536, LEU-1540, TRY-1600       | -6.96                     |

which are often limited by global flexibility and the exclusion of explicit water molecules.

The 1D free energy surface as a function of distance (Fig. 8C and D) reveals that AE has the smallest binding distance to residue Glu42 in TNF. However, in EGFR protein, AE showed the smallest binding distance to Trp707, followed by residues Leu680 and Leu679. The proximity between AE with Glu42 and Trp707 indicates the strongest interactions, which is crucial for modulating antidiabetic activity in both proteins. This interaction aligns with the principles of Structure–Activity Relationship (SAR), where residues with closer binding interactions typically correlate with higher biological activity. The strong binding to Glu42 and Trp707 suggests that modifications to AE that enhance interactions with this residue could improve its efficacy. This trend is further validated by internal residue fluctuations induced by AE upon binding (Fig. 8E and F). In solution, the distance between residues and the ligand shows minimal fluctuations. However, upon binding, fluctuations increase, highlighting the dynamic nature of the binding interaction. The slight decrease in the distance, for example,

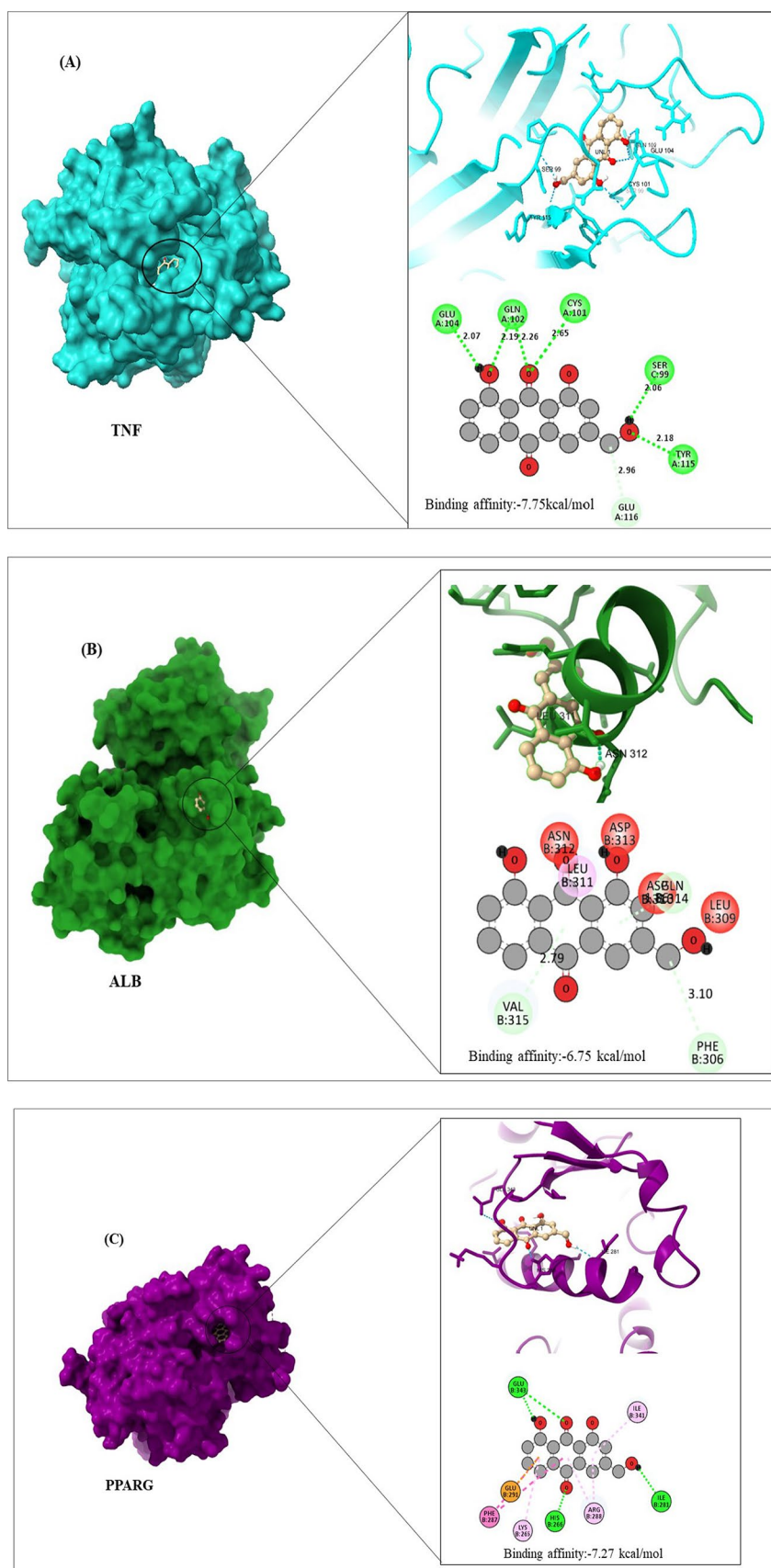
between residues Leu679 and Leu680 in EGFR is attributed to AE binding closer to Trp707, which induces a conformational shift bringing these residues nearer to Leu679. This finding underscores the importance of specific residue interactions in determining the ligand's activity, supporting SAR principles that link binding affinity and biological activity. Molecular dynamics simulation further supports that even though the docking calculations for TNF with AE showed strong affinity, both simulations show that AE has good activity towards the two proteins, despite that, EGFR ranked the least in docking calculation (Fig. 9).

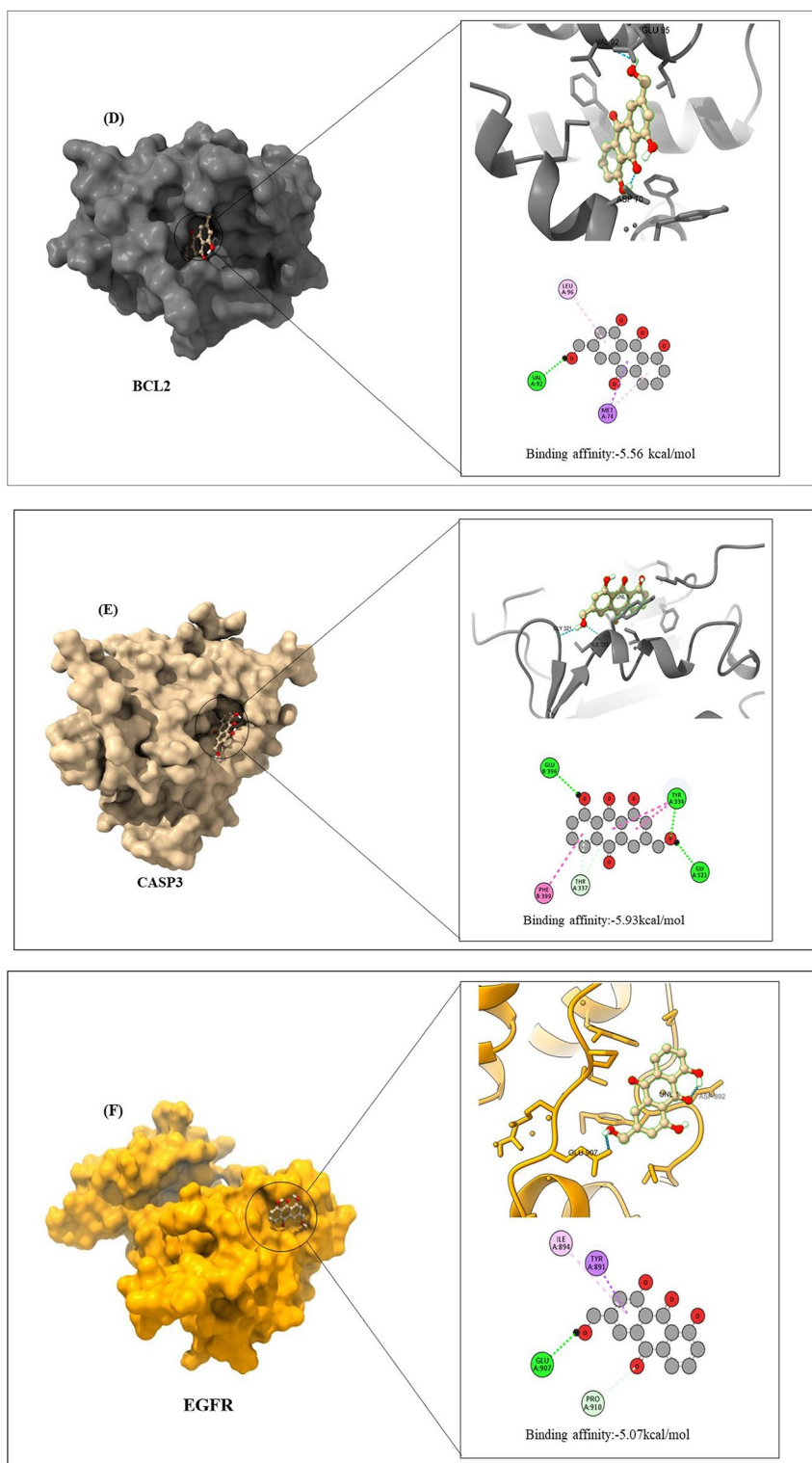
## Discussion

Scientific research has robustly linked the anti-diabetic properties of *Aloe vera* to specific phytochemical components, such as AE (Firdiana et al. 2023). This study endeavors to enhance our comprehension of the potential therapeutic mechanisms and molecular interactions of AE in the management of T2DM through in silico approaches, employing network pharmacology, molecular docking, and molecular dynamic studies.

AE exhibited good drug-likeness properties with a molecular weight of 270.24 Da permitting its oral absorption with low ability to cross the blood–brain barrier, hence, giving it a moderate bioavailability with minimal neurotoxicity, further Yun et al. (2010) reported that the bioavailability of vitamin B12 and vitamin C was enhanced on ingestion with AE-containing plants. The inhibitory effect of AE on some liver enzymes including CYP1A2 and CYP3A4 indicates its potential drug–drug interaction at metabolism. CYP3A4 enzyme is implicated in the metabolism of more than 50% of all prescribed medications and its activity (Rahmioglu et al. 2011). This implies that there is a need to adjust doses of other drugs in patients taking AE containing plants like *Aloe vera* to avoid the potential interactions. CYP1A2 enzyme activity was found to be increased in T2DM patients who are habitual caffeine users which is a potent CYP1A2 inducer (Urry et al. 2016). This study shows AE as CYP1A2 inhibitor which could be utilized to reduce the effects of CYP1A2 in T2DM patients who are habitual caffeine users. The significant hepatotoxicity observed implies the potential of

**Fig. 7** Molecular docking images of aloe-emodin and the hub target proteins. **A** aloe-emodin-TNF, **B** aloe-emodin-ALB, **C** aloe-emodin-PPARG, **D** aloe-emodin-BCL2, **E** aloe-emodin-CASP3, **F** aloe-emodin-EFGR, **G** aloe-emodin-TP53



**Fig. 7** (continued)

AE to cause damage to the human liver (Nunes et al. 2022; Stournaras and Tziomalos 2015). Therefore, herbal remedies containing AE need to be used cautiously with continuous monitoring of liver function.

The GO analysis of the intersecting genes revealed that AE may exert its anti-diabetic effects by modulating the glucose metabolic process and enhancing cellular response to glucose. AE glycosides have demonstrated the ability

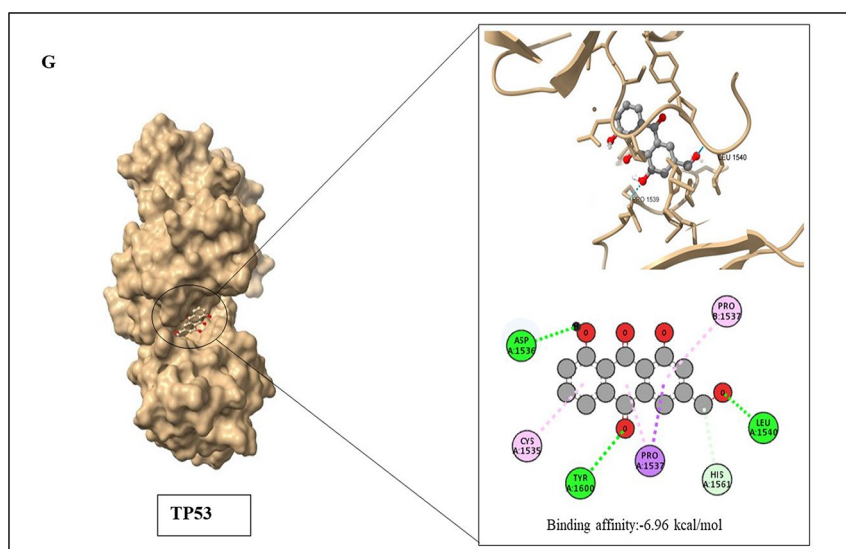
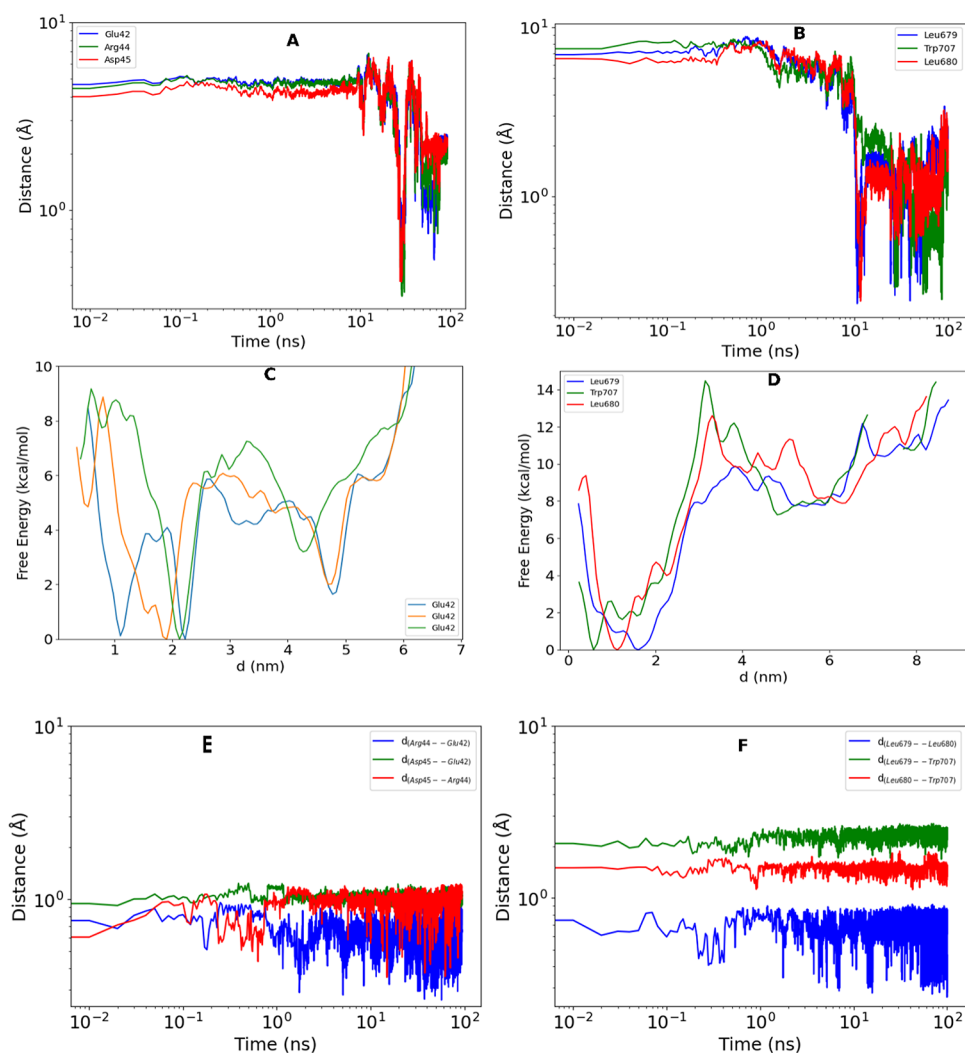
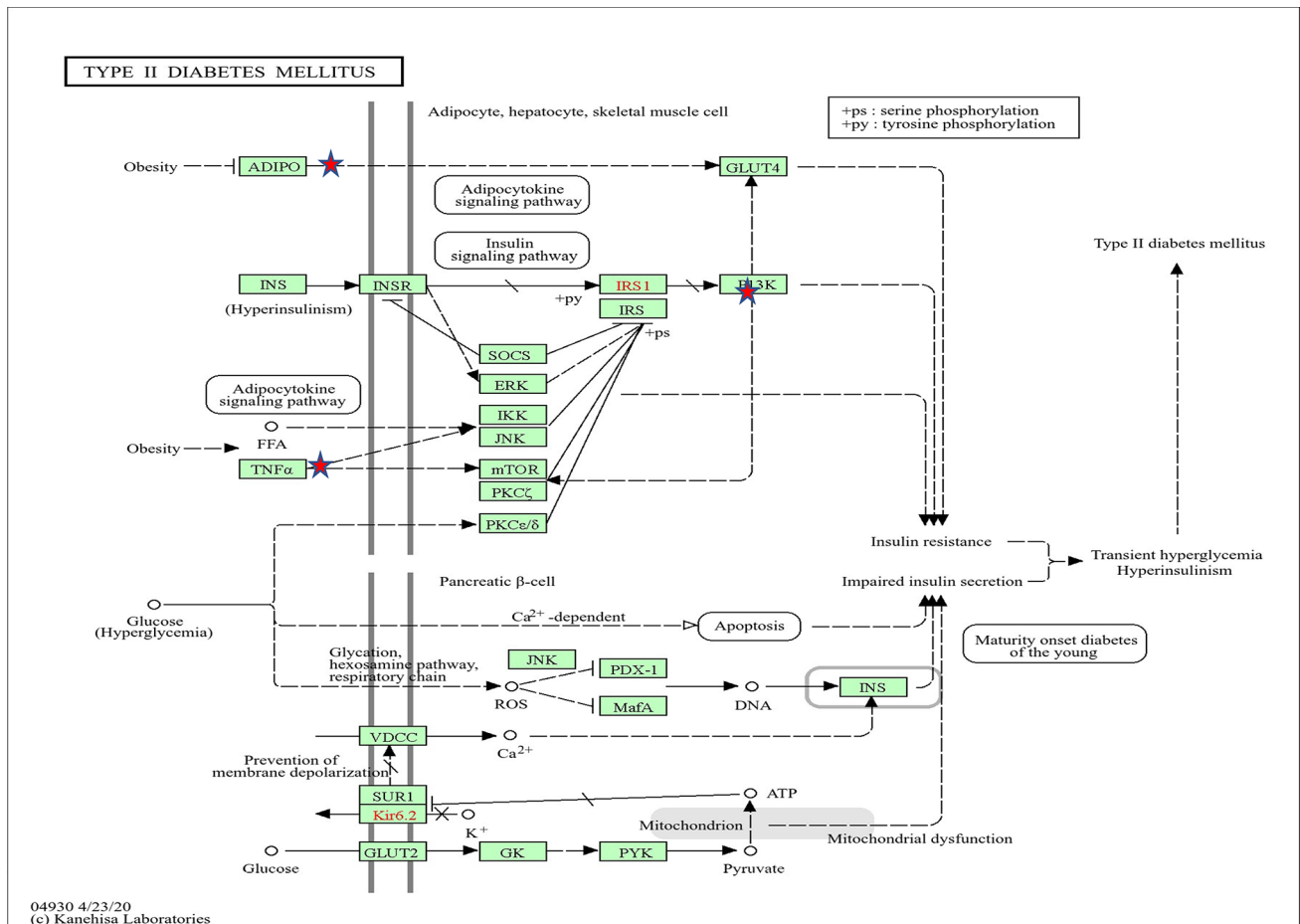


Fig. 7 (continued)

**Fig. 8** log–log plot of AE self-assembly into TNF (**A**) and EGFR (**B**) protein showing the changes in distance as the function of time. 1D free energy surface of AE binding to TNF (**C**) and EGFR (**D**) shows that AE self-assembles in TNF at two binding pockets while in EGFR AE only binds to one pocket. Internal fluctuations of TNF (**E**) and EGFR (**F**) induced by aloe emodin upon self-assembly process measured by the distance between residues within the proteins





**Fig. 9** Potential targets and mechanism of aloe emodin against Diabetes mellitus Type II. Red stars represent targeted genes involved in Type II Diabetes Mellitus pathway

to improve glucose transportation by modulating both the proximal and distal makers of glucose absorption and conversion into glycogen (Anand et al. 2010). Through immunoblot analysis, it was observed that AE glycosides exhibit an insulin-like glucose transport mechanism, as evidenced by its activation of key markers within the insulin signaling pathway, including insulin receptor beta (IR $\beta$ ), insulin receptor substrate 1 (IRS1), 85 phosphatidylinositol 3' kinase (PI3K), and Protein kinase B (PKB) (Anand et al. 2016b). The etiology of T2DM is multifactorial, including obesity-associated insulin resistance, defective insulin secretion, and loss of  $\beta$ -cell mass through  $\beta$ -cell apoptosis (Kaur et al. 2020). Multiple signaling pathways contribute to the progression of the disease and drug effects by influencing various genetic targets (Cao et al. 2023). The KEGG enrichment pathway analysis revealed the involvement of several signaling pathways in the pathophysiology of T2DM. The key pathways included; apoptosis, insulin resistance and T2DM signaling pathway. The apoptotic pathway plays a significant role in the pathophysiology of T2DM (Tomita 2016). Overwhelming evidence suggests the modulation of

T2DM through pancreatic  $\beta$ -cell apoptosis, a pathological feature often accelerated by glucose toxicity due to insulin resistance and visceral obesity (Eizirik et al. 2020; Hu & Wang 2021; Šrámek et al. 2021).

The protein–protein network analysis revealed seven hub genes that are potential targets for AE in the treatment of T2DM. These genes include *TNF $\alpha$* , *ALB*, *TP53*, *PPARG*, *BCL2*, *CASP3*, and *EGFR*. Scientific evidence suggests the involvement of all the proteins coded by the above genes (TNF $\alpha$ , ALB, TP53, PPARG, BCL2, CASP3, and EGFR in the pathogenesis of T2DM. For example, TNF- $\alpha$  elevation is associated with insulin resistance induction in adipocytes and peripheral tissues by impairing insulin signaling (Akash et al. 2018). Activation of TP53 has been demonstrated to worsen diabetic phenotypes. This protein is induced and activated in various cell types in both animals and humans with diabetes. In numerous instances, pharmacological inhibition of p53 has resulted in an improvement in diabetic phenotypes (Kung & Murphy 2016). The PPAR $\gamma$  has been linked to several key physiological processes such as glucose metabolism, lipid metabolism and adipose differentiation

and its synthetic analogues i.e. thiazolidinediones, are currently used in the management of T2DM (Yang et al. 2009). The Bcl-2 protein family not only regulates the mitochondrial pathway of  $\beta$ -cell apoptosis induced by pro-inflammatory cytokines or lipotoxicity but also controls glucose metabolism and  $\beta$ -cell function (Gurzov and Eizirik 2011). Inhibition of EGFR activation has been shown to increase the levels of the adipokine adiponectin in circulation, which possesses insulin-sensitizing, anti-inflammatory, and kidney-protective properties (Li et al. 2018).

All the prioritized proteins exhibited strong binding energy ( $\geq -5$  kcal/mol) with AE; TNF $\alpha$  and PPAR $\gamma$  showed the highest binding energies. TNF $\alpha$  is a crucial protein in the apoptotic pathway of pancreatic  $\beta$ -cells linked to the development of T2DM (Akash et al. 2018). PPAR $\gamma$  is the drug target for thiazolidinediones or “glitazones (Giglio et al. 2022)”. These agents bind strongly to PPAR $\gamma$  in adipocytes, promoting adipogenesis and enhancing fatty acid uptake in peripheral fat while reducing circulating fatty acid concentrations and lipid availability in the liver and muscles, consequently, improving the patient's insulin sensitivity (Won 2021). Molecular dynamics simulations further support docking and network pharmacology findings, where, AE in the presence of bulk water and global protein flexibility was able to recognize the proteins' active site and bind stably.

In silico approaches have facilitated the discovery and design of novel compounds with potential antidiabetic activity. Over 30 novel compounds with potential efficacy against type 1 diabetes mellitus (T1DM) have been identified through computational screening. Among these, Compound 17 exhibited the highest binding affinity ( $-9.2$  kcal/mol) with key residues, including Glu50, Ser271, Arg266, Pro270, and Tyr66. Molecular dynamics (MD) simulations confirmed the stability of the protein–ligand complex, with root-mean-square deviation (RMSD) values stabilizing around 2.0 Å (Edache 2021). Furthermore, a designed compound, D385, demonstrated strong binding interactions with its target proteins, exhibiting comparable binding properties to standard antidiabetic drugs (Edache et al. 2024a, b).

Similarly, phytochemicals related to aloe-emodin have also demonstrated promising therapeutic activities against type 2 diabetes mellitus (T2DM). For instance, cassuquinone A, an anthraquinone derivative, exhibited potent  $\alpha$ -glucosidase inhibitory activity, with an IC<sub>50</sub> of 11.72  $\mu$ M—significantly more potent than acarbose (IC<sub>50</sub>=190.60  $\mu$ M). Molecular docking studies revealed stable interactions with key residues, including Arg315, Phe314, Glu411, Val232, and Ser240. Additionally, molecular dynamics simulations demonstrated that cassuquinone A stabilizes  $\alpha$ -glucosidase by reducing enzyme flexibility, particularly within the active site, thereby hindering substrate access and product release (Le et al. 2025).

Consistent with these findings, (Arvindekar et al. 2015) reported that five isolated 1,8-dihydroxyanthraquinones exhibited antihyperglycemic activity, with aloe-emodin showing the most significant reduction in blood glucose levels during an oral glucose tolerance test. Meanwhile, emodin exhibited potent intestinal  $\alpha$ -glucosidase inhibition ( $93 \pm 2.16\%$ ), with an IC<sub>50</sub> significantly lower than that of acarbose.

Collectively, these findings align with our results, reinforcing the potential of natural products as alternative therapeutic agents for diabetes mellitus and its associated complications. The diverse pharmacological properties of these bioactive compounds highlight the crucial role of plant-derived molecules in the ongoing search for effective and safe antidiabetic therapies. Furthermore, these findings underscore the significance of computer-aided drug discovery (CADD) approaches in accelerating the drug discovery process and enhancing the identification of promising therapeutic candidates.

The major limitation of our study is that it relies on insilico approaches (network pharmacology, molecular docking, and molecular dynamics simulations), which are predictive tools. However, the biological effects of aloe-emodin on Type II diabetes (T2DM) must be validated through in vitro (cell-based assays) and in vivo (animal model) studies. Additionally, further experimental validation through well-designed clinical trials are essential to confirm its pharmacological efficacy and safety profile.

## Conclusion

In computational models, AE exhibits strong binding affinities for TNF $\alpha$  and PPAR $\gamma$  along with other key genes involved in the pathophysiology of DM. TNF $\alpha$  plays a crucial role in the mitigation of pancreatic  $\beta$ -cell apoptosis while PPAR $\gamma$  enhances cellular insulin sensitivity respectively. These mechanisms highlight the promising therapeutic potential of AE against T2DM. However, *In-vitro* and *in-vivo* studies are necessary to validate these findings and facilitate their translation into drug development programs against T2DM.

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literature search, investigation, data curation, analysis and manuscript drafting. All authors read, agreed and approved the final version of the manuscript.

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**Data availability** All the data is available in this article.

## Declarations

**Conflict of interest** The authors declare that there is no conflict of interest regarding the publication of this paper.

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