



RESEARCH ARTICLE

Integrative computational, ethnomedicinal and system pharmacology approach to decipher the anti-diabetic potential of *Mangifera indica* L. phytochemicals

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Received: 31 July 2025; Accepted: 19 February 2026; Available online: Version 1.0: 13 July 2026

Cite this article: Chandra ST, Santosh KB, Amrita KP, Sagarika P. Integrative computational, ethnomedicinal and system pharmacology approach to decipher the anti-diabetic potential of *Mangifera indica* L. phytochemicals. Plant Science Today (Early Access). <https://doi.org/10.14719/pst.11000>

Abstract

The global increase in adult Type 2 diabetes mellitus (T2DM) cases is attributed to unhealthy diets, insufficient physical activity and increased work pressure, leading to elevated glucose levels. Human dipeptidyl peptidase 4 (DPP-4) regulates post-prandial insulin release, with increased bioavailability resulting from inhibition and increased Glucagon-Like Peptide-1 (GLP-1) levels. The NAD(H)/NAD ratio affects 11-beta-hydroxysteroid dehydrogenase 1 (HSD11B1), which converts cortisone to cortisol. It promotes glucose metabolism by increasing phosphoenolpyruvate carboxykinase (PEPCK) transcription. The present study aims to identify novel lead compounds from *Mangifera indica* L. for T2DM therapies that could inhibit key targets DPP-4 and HSD11B1, overcoming current medication limitations. 14 phytochemicals were screened from 63 and docked against the key targets DPP-4 and HSD11B1. To evaluate the reactivity and properties of the potential molecules, a quantum-mechanical simulation was performed using an arbitrary postulate of density functional theory (DFT). The phyto-compound kaempferol exhibited higher interaction with better binding affinity against T2DM targets DPP-4 and HSD11B1 out of 14 screened phyto-constituents, followed by other compounds. Kaempferol showed optimal binding energies of -7.6 and -9.0 kcal mol⁻¹ for DPP-4 and HSD11B1, respectively, compared with the standard drug metformin. Subsequently, kaempferol exhibited higher reactivity than the standard per quantum-chemical calculations. The molecular dynamics (MD) simulation studies of complexes with kaempferol demonstrated stable, consistent dynamics over a specific period. The results suggest that natural compounds from mango leaves may represent a promising approach for developing new therapies, potentially reducing reliance on conventional drug discovery procedures.

Keywords: docking; *in silico*; kaempferol; molecular dynamics; simulation; type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder characterized by persistent hyperglycaemia resulting from a combination of insulin resistance and impaired insulin secretion. It is a major global health concern, contributing to significant morbidity and mortality through both acute and long-term complications. Compared to the general population, patients with diabetes are more prone to several associated disorders, which frequently require prolonged hospitalization (1). In the long run, uncontrolled diabetes may adversely affect the eyes, kidneys, central nervous system, cardiovascular system and other organs. A healthy diet is essential for the body's metabolism and overall functioning (2). The current study focuses on managing T2DM by targeting its associated genes. Type 2 diabetes mellitus (T2DM) is a further prevalent condition linked to obesity and progressive ageing. High blood glucose levels associated with T2DM are driven by increased hepatic glucose production, reduced insulin secretion and insulin resistance in peripheral tissues, which closely match brain insulin resistance (3).

The genes Human Dipeptidyl peptidase 4 (DPP4) and 11-beta-hydroxysteroid dehydrogenase 1 (HSD11B1) have been revealed to play a pivotal contribution in the T2DM mechanism. The most significant regulators of postprandial insulin release, incretin hormones, are substrates of the DPP4. Increased bioavailability of these proteins is due to inhibition of DPP4, which lengthens the half-life of insulin. Most of the effects experienced after ingesting a DPP4 inhibitor are attributed to a spike in Glucagon-Like Peptide-1 (GLP-1) levels (4). The NAD(H)/NAD ratio influences the performance of the bifunctional enzyme HSD11B1. The cortisone (E) to cortisol (F) conversion is indicated by type 1 activity of the HSD11B1. By promoting the transcription of phosphoenolpyruvate carboxykinase (PEPCK), cortisol produced by HSD11B1 in hepatocytes can boost glucose metabolism. There is no association involving an upsurge in hepatic glucose production and insulin, glucagon, or free fatty acids (FFA). The metabolic syndrome, but not obesity, evolves in mutant mice that overexpress HSD11B1. This has given rise to the theory that T2DM is a localized variant of Cushing's syndrome (5). So, DPP4 and HSD11B1 consequently became essential targets for the therapeutic management of T2DM.

In the current investigation, the leaves of *Mangifera indica* L. (mango) tree are targeted as a source of natural compounds with anti-diabetic properties. The mango is the most recognized tropical Asian fruit, an expansive, evergreen tree belonging to the Anacardiaceae family. India is acknowledged as the nation that yields the most mangoes. Various plant parts, including the bark, leaves, roots, fruits and flowers, have been used as dentifrices, disinfectants, astringents, diaphoretics, stomachics, vermifuges, tonics, laxatives and diuretic agents to treat piles, dysentery, anemia, asthma, bronchitis, cough, hypertension and insomnia (6). The physiological effects of mango leaf extracts (MLs) have been reported for their anticancer, antidiabetic, antioxidant, antimicrobial, antiobesity, lipid-lowering, hepatoprotective and antidiarrheal properties, which are currently under investigation. The antidiabetic, antioxidant and anti-inflammatory properties of five mango samples have been reported in the published literature. Furthermore, it has been demonstrated that the ultimate 2,2-diphenyl-1-picrylhydrazyl (DPPH) (74.23 %) and Superoxide (66.04 %) activity was detected in all mango samples, with gallic acid being the predominant phenolic acid and quercetin being the most abundant flavonoid (7).

Molecular docking, pharmacokinetic profiling, network pharmacology analysis, antioxidant, anti-inflammatory and anti-diabetic traits and phytochemical characterisation of the primary phytoconstituents of raw and in various ways dried *M. indica* (Himsagar cultivar): *in vitro* and *in silico* investigations (8).

Traditional medicine has employed mango leaf extracts to treat syphilis, diabetes, bronchitis, diarrhea, asthma, renal problems, scabies, breathing problems and infections in the urinary tract (9, 10). Benzophenones, phenolic acids, flavonoids, carotenoids, quercetin, isoquercetin, ascorbic acid and tocopherols are the subsequent most potent biological substances found in mango leaves, following mangiferin. The primary molecule responsible for the biological activity is mangiferin. In light of their numerous phytochemical, biological and pharmacological properties, including antibacterial, antioxidant, antidiabetic, anticancer and immunomodulatory activities, mango leaves have great potential for additional value. Monoterpenes, sesquiterpenes, tiny quantities of non-terpenoid and oxygenated hydrocarbons and trace amounts of other analogs are all embedded in mango leaf oil. The essential oil comprises an assortment of antimicrobial compounds, including camphor, α -gurjunene, trans-caryophyllene, α -humulene and α -selinene and exhibits bacteriostatic properties. Mango leaves produce benzophenone compounds with considerable immunosuppressive and α -glucosidase-inhibiting effects (11).

Based on its medicinal properties, the mango leaf/leaf extract was considered to contain phytoconstituents with anti-diabetic properties. Subsequently, an *in-silico* approach was used to identify and explore potential phytoconstituents from the leaves of *M. indica* L. (mango) with anti-diabetic properties by evaluating the key therapeutic targets DPP4 and HSD11B1 in T2DM. To date, very few studies have been conducted on these key targets. The uncontrolled mechanism of action of DPP4 directly impacts glucose homeostasis and insulin secretion. On the other hand, altered HSD11B1 activity is directly linked to increased obesity and opposes insulin's action by promoting glucose production. The altered activity of these key targets must be brought under control to manage T2DM using natural molecules from mango leaves.

A series of *in silico* approaches, including pharmacokinetic property analysis of constituents, molecular docking between selected phytoconstituents and T2DM proteins, network analysis, quantum chemical simulations and molecular dynamics (MD) simulations, were implemented to evaluate phyto molecules with better efficacy. This investigation could provide a fundamental basis for further *in vitro* and *in vivo* studies to assess their effectiveness as novel drugs and their targets for T2DM therapeutics. Additionally, this will make it quicker for pharmaceutical companies to develop more effective medicines for T2DM.

Materials and Methods

Sequence, structure and functional analysis

The sequence, structural and functional and publication assessments information on the target genes of T2DM (DPP4 and HSD11B1) was obtained from the UniProtKB database (12). The altered expression of DPP4 and HSD11B1 affects glucose metabolism and contributes to insulin resistance in patients with T2DM. These specific reasons led to the prioritization of these two genes. The experimentally verified 3-dimensional structures (3D) of these selected proteins were obtained from the Protein Data Bank (PDB) (13). For the corresponding 3D protein structures of DPP4 and HSD11B1, the selected genes in T2DM, the PDB IDs chosen are 4A5S (1.62 Å) and 1XU9 (1.55 Å), respectively, with chain A of each structure selected for analysis.

Disease association of DPP4 and HSD11B1 within the human body

Employing the standard protocol for genome analysis, the selected two genes, DPP4 and HSD11B1, are analysed to detect associated linked diseases (14). The expressiveness of DPP4 and HSD11B1 is also studied computationally to detect overexpression in the human body (15). Here, the blood proximity assay for comparing a male and a female has also been studied. Computational analysis of cancer progression and cell line changes during overexpression of the selected genes has also been conducted.

Retrieval of phytoconstituents

By peering up information from multiple published literature, sixty-three phytoconstituents (Table 1) of *M. indica* L. (mango) were retrieved from its leaf source during this survey (16, 17). The PubChem database provided structural details for the retrieved phytochemical components (18).

Lipinski rule of five and toxicity profiling of phytocompounds

Lipinski's rule of five stipulates that an orally active medicine needs to abide by the parameters of molecular weight (MW) (≤ 500 D), $\log P$ (≤ 5), hydrogen bond donor (HBD) (≤ 5), hydrogen bond acceptors (HBA) (≤ 10) and molar refractivity (MR) (40–130), is the most integral specifications for opting for a medication (19). If any of its rules are violated, a molecule/compound cannot be considered a drug. To estimate Lipinski's rule of five, the TargetNet web server (http://targetnet.scbdd.com/calcnnet/calc_rule_text/#) (20) was executed. The phyto-molecules were classified utilising Lipinski's rule of five and qualifying compounds were further investigated for their toxicity using Toxicity Checker (<https://mucle.com/apps/toxicity-checker/>) (21), Protox-II (https://tox-new.charite.de/protox_II/) (22). The tool parameters were all reverted to their original standard configurations.

Table 1. Phytochemical list of *M. indica* L. (mango) retrieved from the leaf source

Plant name	Phyto-chemical constituents
<i>M. indica</i> L.	Alpha-cadinene, Acarbose, Alpha-eudesmol, Alpha-guaiene, Alpha-gurjunene, Alpha-pinene, Alpha-terpineol, Amentoflavone, Alpha-elemene, Alpha-damascenone, Alpha-humulene, Apigenin, Beta-caryophyllene, Beta-selinene, Borneol, Caffeic acid, Caryophyllene oxide, Cis-3-hexenyl benzoate, Catechin, Delta-3-carene, Ellagic acid, Eicosyl oleate, Foliamangiferoside B, Elemol, Gallic acid, Germacrene A, Globulol, Guajavarin, Guaiol, Hypericin, Hyperin, Hyperoside, Isomangiferin, Isovitexin, Isoswertisin, Isoquercetin, Kaempferol, Kainic acid, Kaempferol-3-O-rutinoside, Lupeol, Linoleic acid, Maclurin, Mangiferin, Mangiferonic acid, Nerolidol, Norathyriol, Oleic acid, Palustrol, Protocatechuic acid, Pentagalloylglucose, Palmitic acid, Phytol, Stigmasterol, Squalene, Theogallin, Taxifolin, Trans-caryophyllene, Quercetin, Quercetin 3-O-rhamnoside, Rhamnetin, Vitexin, Viridiflorol

Prediction of the binding site

The binding proximity of specific ethnic proteins deemed targets for T2DM (DPP4 and HSD11B1) was assessed using the CASTpFold and GheCom web servers (23, 24). It was determined that most outcomes identified active amino acid residues that portrayed the binding region of phyto-constituents.

Molecular docking of screened phytoconstituents against selected target proteins of T2DM

To more accurately juxtapose the two targets of T2DM (DPP4 and HSD11B1), the AutoDock 4.2 tool was used to determine the grid box value and the AutoDock vina tool was used for molecular docking to identify the best phytocompounds against the target proteins (25, 26). The corresponding standard drug, Metformin (Biguanide class), was used for comparative analysis with the natural compounds (27).

DFT analysis

A quantum computational simulation was executed using a presumptive assumption from density functional theory (DFT) to estimate the reactivity and effectiveness of the attainable compounds applied in this investigation. Density functional theory Becke 3-parameter, Becke, 3-parameter, Lee-Yang-Parr () correlation function was used to figure out the expressiveness and efficiency of the function (28). On the ligand compounds with superior docking scores and treatments that are readily available (standard) commercially for the corresponding targeted disorders, the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies were determined employing DFT investigation. The ORCA Program, version 4.0, was deployed to estimate the power (29, 30).

Molecular dynamic simulation

Molecular dynamics is a method for investigating and predicting atomic and molecular motions within a hierarchy of macromolecular structure-to-function relationships using complex algorithms (31). By providing atoms and molecules with a fixed time window for interaction, the dynamic "evolution" of the entire structure is exemplified (32). The Desmond program (Schrödinger Release 2022-4: Maestro, Schrödinger, LLC, New York, NY, 2022) was used to perform MD simulations on the Apo (only protein) forms of DPP4 and HSD11B1 in T2DM. In Holo states, the DPP4 complexed with 2 ligands is Holo1 and Holo2. In Holo, the states of the HSD11B1 complexed with 2 ligands are Holo3 and Holo4. After a 100 nanosecond (ns) MD simulation, the ligand-protein complexes that achieved the optimal score were assessed within the MD paradigm, which comprised minimization, heating, equilibration and production (33). Topology was automatically generated by using the OPLS4 force field to minimize protein-ligand interactions and atomic coordinates in an energy-based manner (34). The SPC solvent model was used to immerse the compound in an asymmetric box of $15 \times 15 \times 10$ Å. Adding 0.15 M NaCl abolished

the physiological pH. The water box was configured using the particle mesh ewald (PME) boundary conditions, ensuring no solute atoms are found below 10 Å of the frontier. Employing the NPT combination, the entire structure was simulated for 100 ns at 300 K. The proteins' structural perturbations and dynamic behaviour were probed using plots of root mean square deviation (RMSD) and root mean square fluctuation (RMSF). RMSD measures the difference in a protein's backbone between its initial and final positions, indicating the flexible regions of a protein or complex (35). The simulated reciprocation graph illustrates the ligand binding pattern at the protein binding site most likely to occur (36).

Principal component analysis

The statistical approach known as principal component analysis (PCA) facilitates the distinction between collective and local dynamics by partitioning large emotional datasets into smaller principal component subsets (37). The indispensable dynamics approach was used to perform PCA. The essential_dynamics.py ramification in Schrodinger Maestro v 2022.4 was implemented to accomplish coordinated motions in the protein's Apo and Holo states.

Results

Disease linked with DPP4 and HSD11B1

Using computational analysis and predefined protocols, the selected proteins DPP4 and HSD11B1 are analysed. It was found that these two proteins are associated with diseases such as autoimmune diseases, cancer, cardiovascular diseases, infectious diseases, metabolic diseases, Psychiatric diseases and pediatric diseases (Fig. 1).

Using the Blood proximity extension assay, the concentrations of DPP4 and HSD11B1 proteins were estimated and analysed. It was found that the concentrations of DPP4 and HSD11B1 are significantly higher in females than in males (Fig. 2). These two proteins were analysed computationally for their probable expression in cancer progression. It was obtained that DPP4 can be an expected candidate for causing cancer, like thyroid cancer, prostate cancer, liver cancer, Renal cancer, Endometrial cancer, head and neck cancer, stomach cancer, lung cancer, pancreatic cancer and colorectal cancer. HSD11B1 protein can cause cancer, such as liver cancer, thyroid cancer, ovarian cancer, melanoma, colorectal cancer and skin cancer (Fig. 3).

To establish preliminary evidence, a comparison was made between cancer cells with and without DPP4 and HSD11B1 overexpression. For DPP4, Prostate cells were chosen and for HSD11B1 protein, liver cells were chosen. When the selected proteins are overexpressed, a clear distinction is observed. These changes at the cellular level reflect the variation and damage caused by protein deformability (Fig. 4).



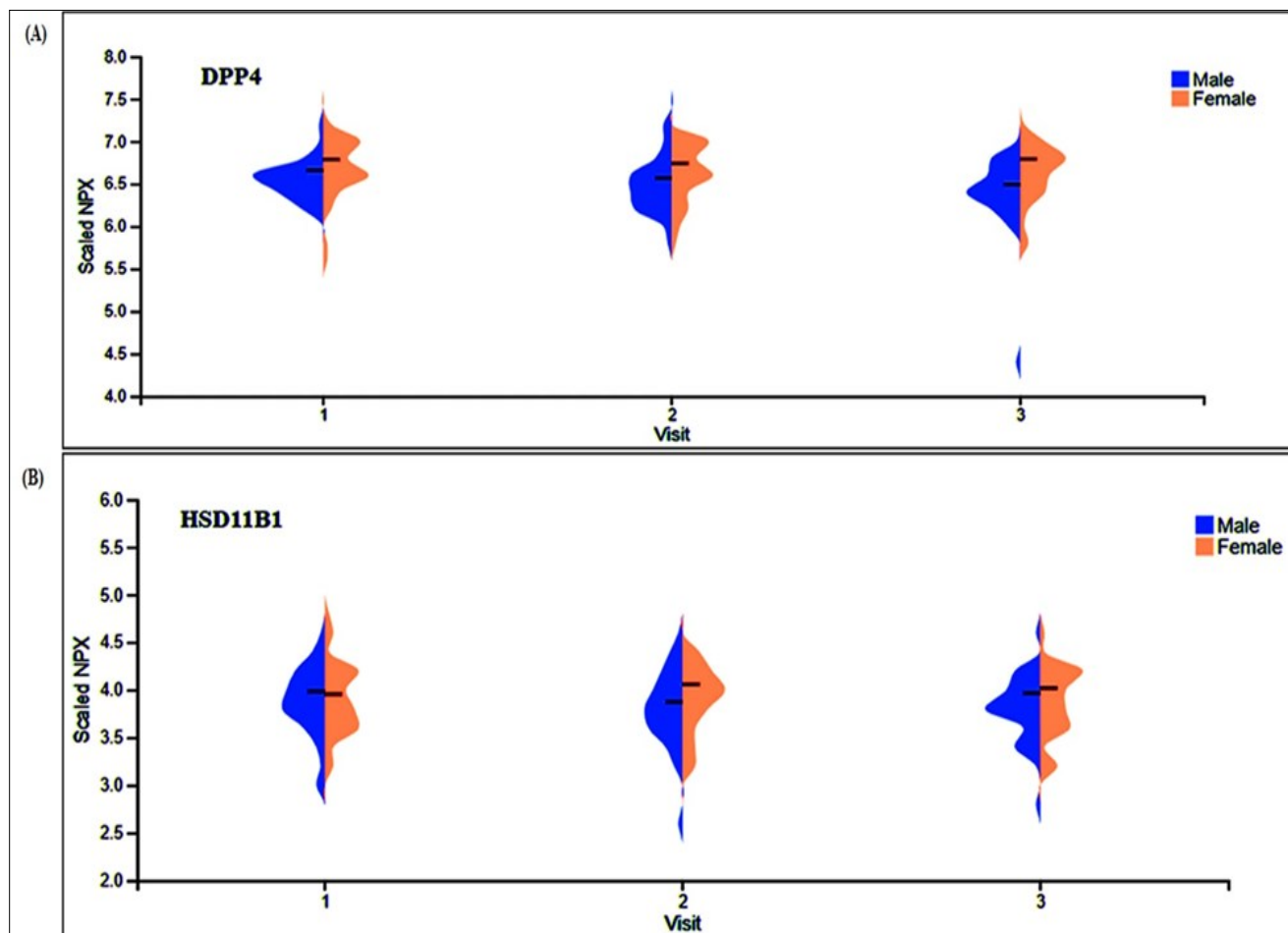


Fig. 2. Blood proximity extension assay (PEA). A: DPP4 protein; B: HSD11B1 protein.

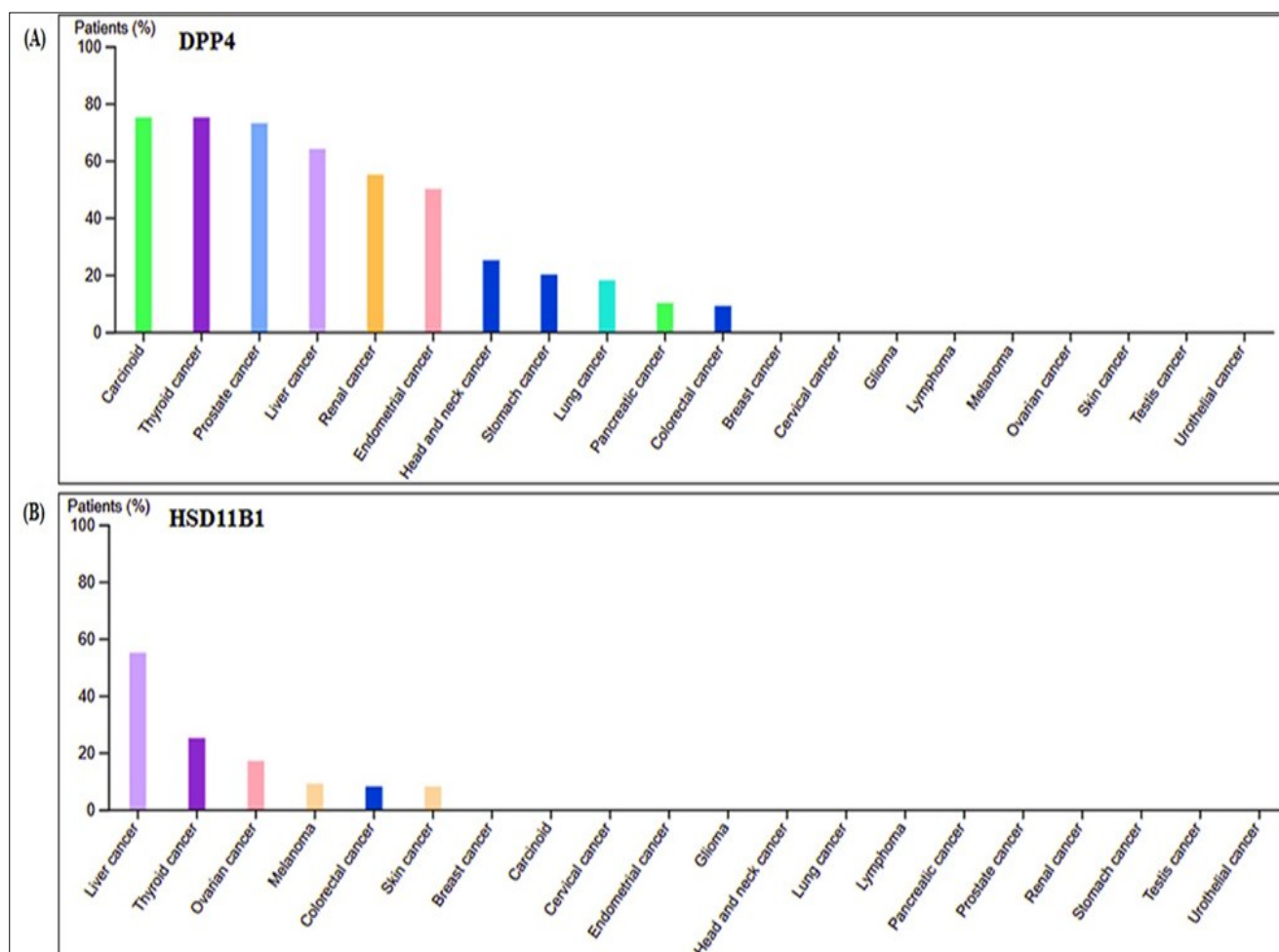


Fig. 3. Expression of protein in different cancer cells. A: DPP4 protein; B: HSD11B1 protein.

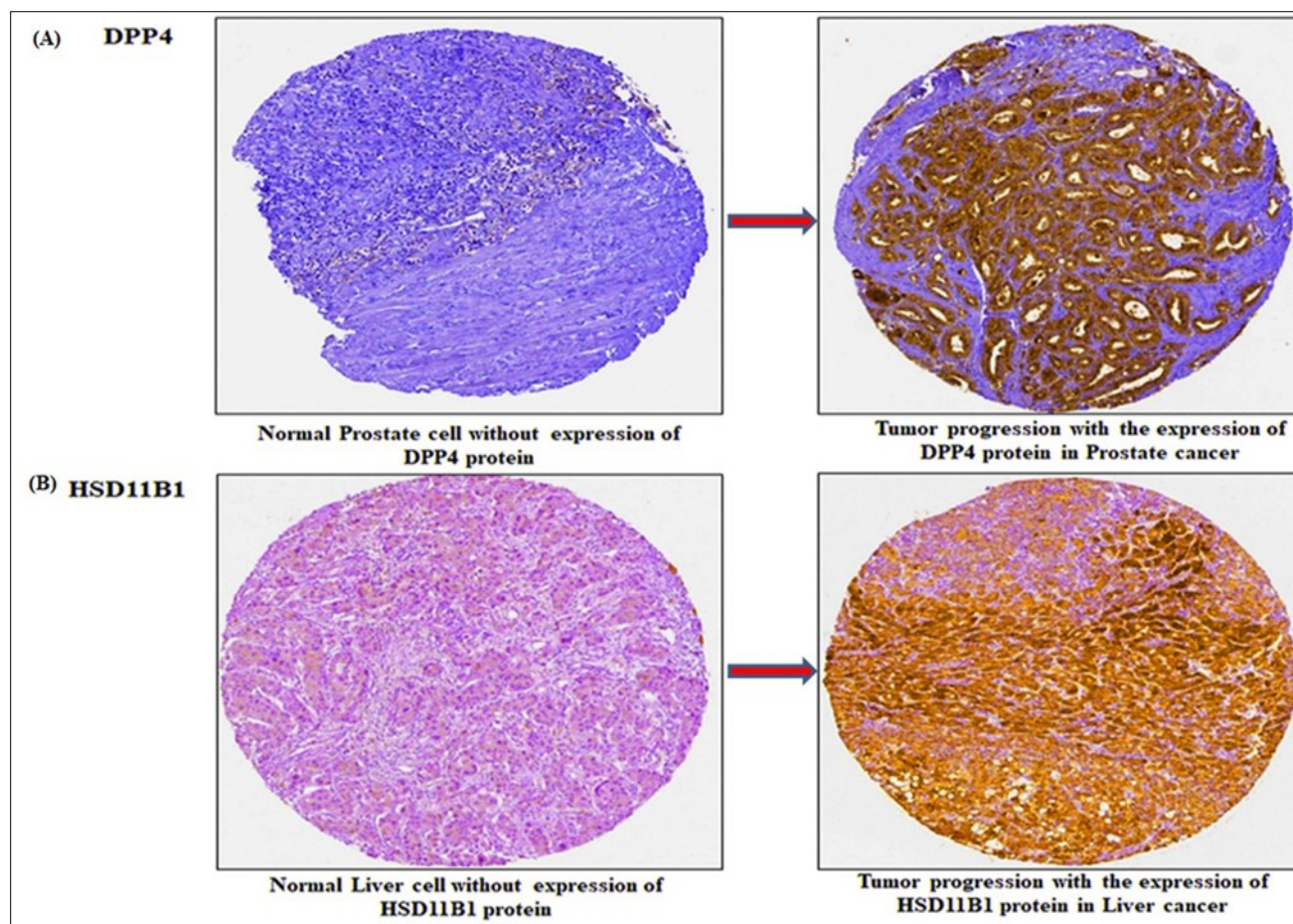


Fig. 4. Cellular changes marked without and with expression of protein in different cancer cells. A: DPP4 protein; B: HSD11B1 protein. Based on computational availability, cancer expression has been studied.

Phyto-constituents from *Mangifera indica* L.

A total of 63 phyto-constituents reported from the leaf of *M. indica* L. were picked for this inquiry and literature on them was investigated. The structural information for these phytochemical compounds was obtained from the PubChem database, which provided details on their structures. Table 1 lists the phytochemicals retrieved for the study. Supplementary Table 1 provides details of the phytochemicals considered in the literature survey.

Phytocompounds followed the pharmacokinetic properties

The TargetNet web server was used to apply the Lipinski rule of five, which screened 30 of the 63 phyto compounds that met all criteria. Supplementary Table 2 reflects the results of Lipinski's rule of Five for the following compounds. Furthermore, Toxicity Checker (mcule) and Protox-II were used to validate the non-toxic status of the 30 compounds. Only 14 compounds were identified as non-toxic by both servers and qualified for further analysis. Supplementary Table 3 depicts the results for toxicity testing of compounds. Table 2 gives the list of phytoconstituents of *M. indica* L., following Lipinski's rule of Five and Non-Toxic in nature.

Active site detection

The assent reverberation of CASTp and GheCom web servers delineated the active site of each selected target protein. The active site of DPP4 protein was formed by the residues Ser108,

Pro109, Ile114, Leu115, Leu116, Glu117, His126, Ser127, Trp215, Trp216, Pro218, Asn219, Cys301, Asp302, Val303, Thr304, Trp305, Ala306, Phe357, Arg358, Pro359, Leu366, Phe371, Phe396, Ile405, Gly406, Thr411, Ser412, Ser458, Val459, Ser460, Phe461, Ser462, Lys463 and Glu464. Similarly, in HSD11B1 protein active sites are Thr40, Gly41, Ser43, Lys44, Gly45, Ile46, Gly47, Arg48, Thr64, Ala65, Arg66, Ser67, Gly91, Ser169, Leu171, Ala172, Tyr177, Pro178, Val180, Tyr183, Thr220, Glu221, Thr222, Ala223, Lys225, Ala226, Val227, Val231 and Lys238.

Molecular docking

Molecular docking is crucial in structural molecular biology and computer-assisted drug development, aiming to determine the principal binding modes of a ligand with a known protein structure. In the current molecular docking simulation, AutoDock 4.2 and AutoDock Vina are used to obtain results throughout the docking process. Using AutoDock 4.2, Kollman charges were initially assigned to the selected proteins. Subsequently, Gasteiger partial charges were delegated to the inhibitors to set out the grid box value. AutoDock vina was employed to perform molecular docking analysis of all 14 screened phytoconstituents against DPP4 and HSD11B1 as T2DM targets. The binding free energy of all the interaction complexes is presented in Table 3. Only one of the most advantageous perspectives, with enhanced binding energy and more H-bonds, was considered to assess intramolecular

Table 2. List of phytoconstituents of *Mangifera indica* L., following Lipinski's rule of five and non-toxic in nature

Plant name	Phytocompounds following Lipinski's rule of five and non-toxic in nature
<i>M. indica</i> L.	Alpha-cadinene, Alpha-eudesmol, Alpha-gurjunene, Alpha-pinene, Alpha-panasinsen, Alpha-terpineol, Apigenin, Borneol, Delta-3-carene, Globulol, Guaiol, Kaempferol, Palustrol, Viridiflorol

Table 3. Molecular docking of 14 screened phyto-constituents from *M. indica* L. leaf and Metformin (standard) against DPP4 and HSD11B1 targets of T2DM

Target	Compound	Binding energy (kcal/mol)
DPP4	Alpha-Cadinene	-5.9
	Alpha-Eudesmol	-6.0
	Alpha-Gurjunene	-6.0
	Alpha-Pinene	-4.8
	Alpha-Panasinsen	-6.1
	Alpha-Terpineol	-5.1
	Apigenin	-7.5
	Borneol	-5.0
	Delta-3-Carene	-4.9
	Globulol	-6.2
	Guaiol	-6.2
	Kaempferol	-7.6
	Palustrol	-5.8
	Viridiflorol	-6.1
	Metformin (marketed)	-5.2
	Alpha-Cadinene	-7.3
	Alpha-Eudesmol	-7.5
	Alpha-Gurjunene	-7.4
	Alpha-Pinene	-5.5
	Alpha-Panasinsen	-7.0
	Alpha-Terpineol	-5.9
	Apigenin	-8.8
	Borneol	-6.0
	Delta-3-Carene	-5.5
HSD11B1	Globulol	-7.4
	Guaiol	-7.5
	Kaempferol	-9.0
	Palustrol	-7.5
	Viridiflorol	-7.5
	Metformin (marketed)	-7.7

interactions among the ten conformations retained from the docking studies. The grid was made up of the following dimensions, spaces and parameters: x-centering: 18.793, y-centering: 14.39 and z-centering: 54.227 for DPP4 protein and x-centering: 7.564, y-centering: -3.518 and z-centering: 21.035 for HSD11B1 protein, to facilitate a fully extended conformation of the

ligands/compounds. The docking study revealed Kaempferol as the top-scored compound with a binding energy of $-7.6 \text{ kcal mol}^{-1}$ against the DPP4 protein, followed by other compounds. Subsequently, for the HSD11B1 protein, the same compound, Kaempferol, again had the highest binding energy, -9.0 kcal/mol . Whereas a well-reported drug, i.e., Metformin (considered a standard), which is mostly prescribed for T2DM therapy, showed binding energies of $-5.2 \text{ kcal mol}^{-1}$ and $-7.7 \text{ kcal mol}^{-1}$ against the selected targets, DPP4 and HSD11B1, respectively. Fig. 5 and 6 show the 2D and 3D molecular docking interactions of the high-scoring phyto-compound Kaempferol with the DPP4 and HSD11B1 proteins. Contingent on the Average Distance of H-bonds, intermolecular hydrogen (H)-bonds and binding energy values, the best-docked complexes have been reported and analysed to facilitate further computational investigation. The existence of intermolecular associations between protein-drug/compound complexes has been demonstrated by implementing LigPlot+ (38). Fig. 7 shows a heat map of changes in protein pathogenicity upon application of phytochemicals.

Quantum chemical simulation

In addition to the implications of quantum computation, quantum chemistry was utilised in investigating cutting-edge molecular characterisation, like HOMO and LUMO, gap energy, Electronic Energy (eV), Potential Energy (eV), Kinetic Energy (eV) and dipole moment for the phytochemicals, which showed better binding effects against the T2DM. The docking simulation showed that, among the 14 selected compounds, the phyto-compound Kaempferol frequently yielded the optimised results. So, quantum computation was performed only for this phyto-compound and the standard Metformin. Table 4 reflects the quantum computation results. The effective reactivity of the two compounds was characterized by a band energy gap (ΔE), i.e., the difference between ELUMO and EHOMO. The results showed higher reactivity of the

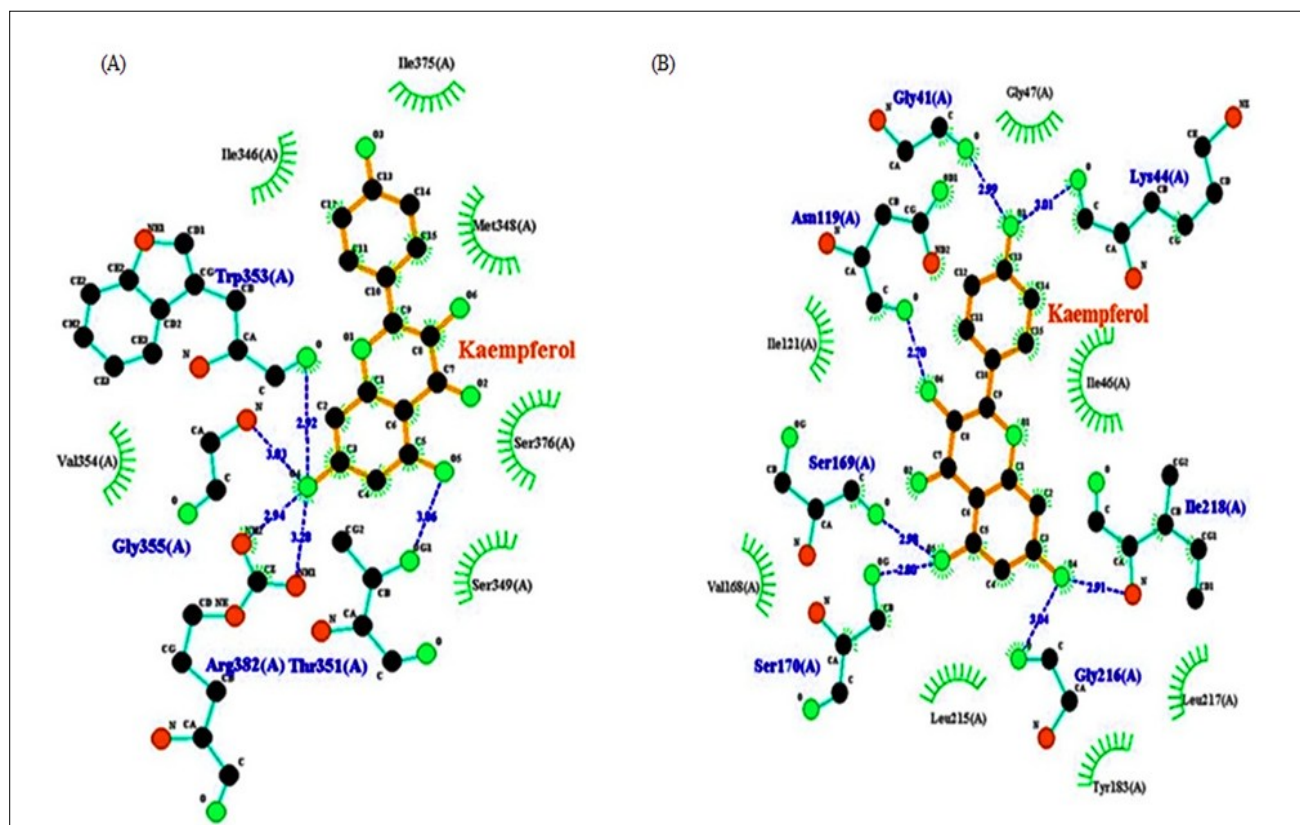


Fig. 5. 2D molecular docking interactions. A: DPP4-Kaempferol complex; B: HSD11B1-Kaempferol complex.

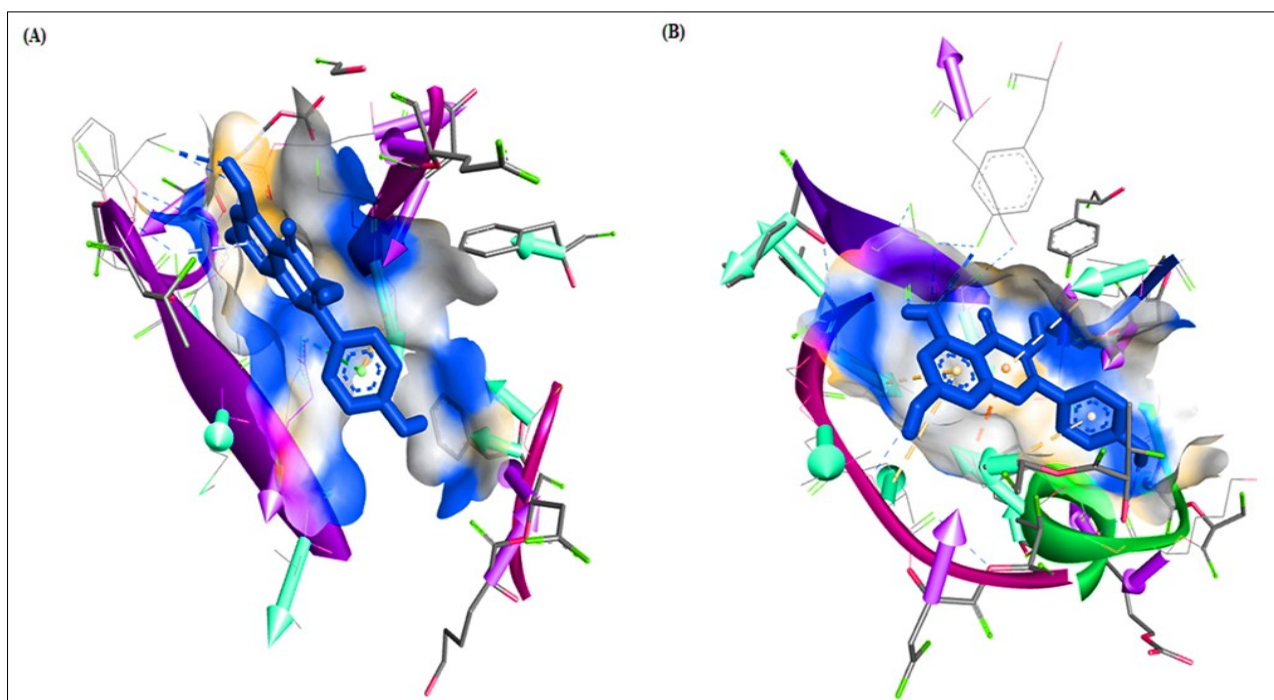


Fig. 6. 3D molecular docking interactions. A: DPP4-Kaempferol complex; B: HSD11B1-Kaempferol complex.

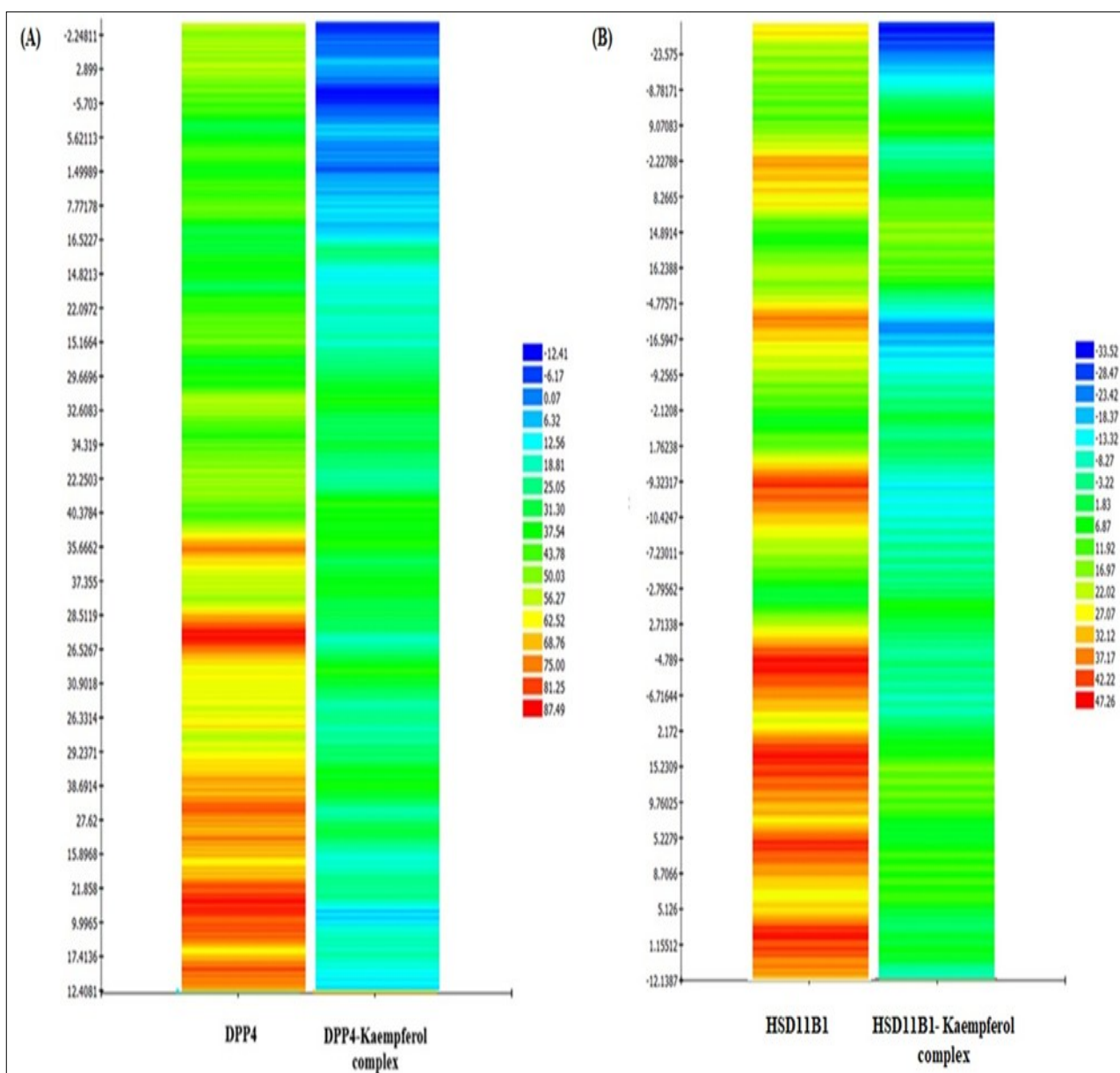


Fig. 7. Heat maps. A: DPP4 - Kaempferol complex; B: HSD11B1 - Kaempferol complex.

Table 4. DFT results of the best phytocompound selected from *M. indica* L. leaf showing better results against different targets of T2DM

Sl. No.	Phytochemical name	Electronic energy (eV)	Potential energy (eV)	Kinetic energy (eV)	LUMO (eV)	HOMO (eV)	GAP energy (eV)
1.	Kaempferol	-70771.00004	-55518.42058	27702.09500	2.141	-8.742	10.883
2.	Metformin	-17810.66493	-19095.38413	9522.56036	4.681	-8.816	13.497

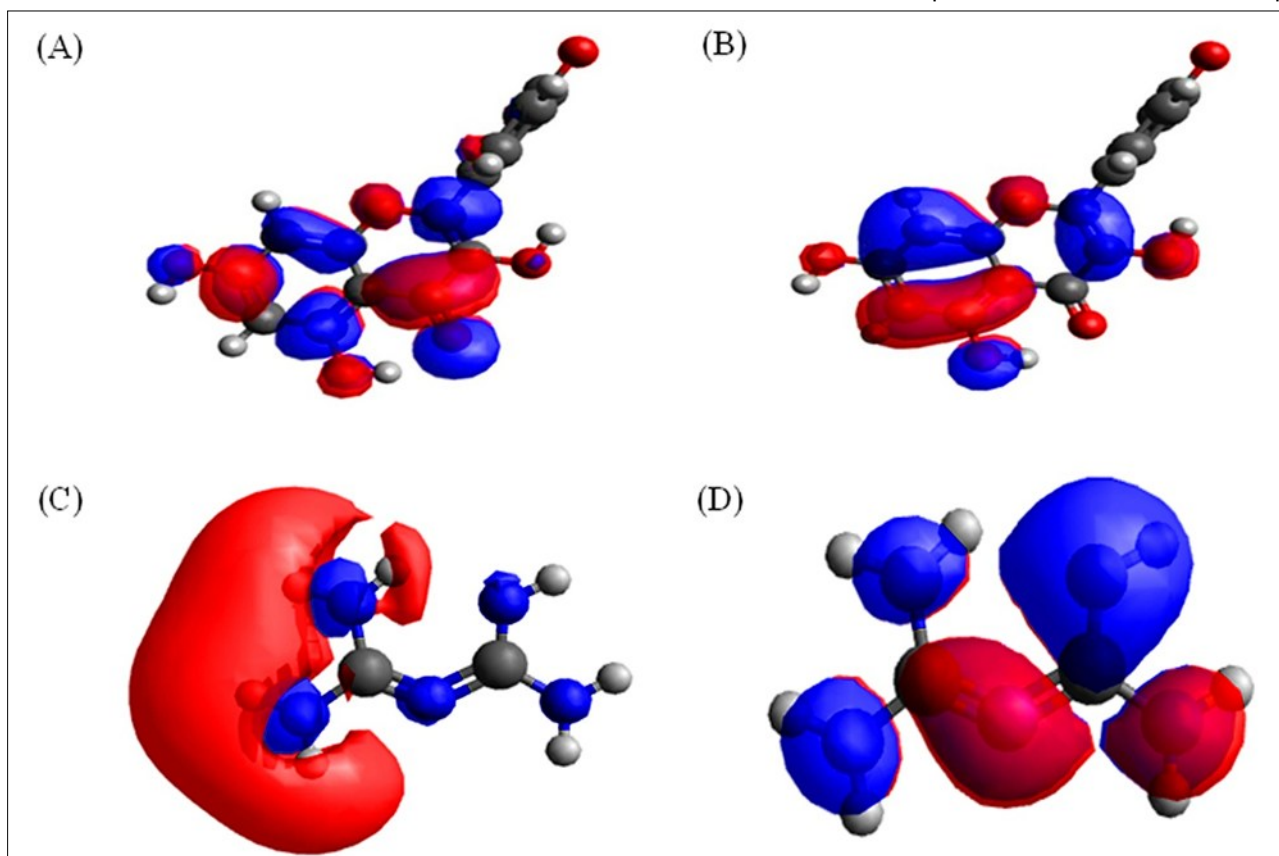
Kaempferol compound, with optimal performance relative to standard drugs, as indicated by its lowest band energy gap. For T2DM, the investigational targets were DPP4 and HSD11B1 and the phytocompound Kaempferol showed the highest docking affinity in DFT calculations, with a gap energy of 10.883 eV; metformin was used as a standard, with a gap energy of 13.497 eV. These results indicate that the phyto-compound Kaempferol is more reactive than the standard drug against their respective protein targets in T2DM. Fig. 8 reflects the results of the LUMO and HOMO energies of these compounds. Red illustrates a positive concentration of electrons, while blue expresses a negative concentration of electrons.

Trajectory analysis of molecular dynamics simulation

To understand how atoms and molecules physically interact within a system and to examine correlations between macromolecular structure and function, the highly sophisticated computational technique known as MD is used. The atoms and molecules were allowed to interact for a specified period, indicating the evolution of the multifaceted system. A 100 ns MD simulation, encompassing structural rearrangements of molecules and receptors, was performed to assess the stability of the docked complex. The dynamics and stability of Apo and Holo systems (DPP4: Apo; Holo1: DPP4-Kaempferol complex; Holo2: DPP4-Metformin complex; Holo3: HSD11B1-Kaempferol complex; Holo4: HSD11B1-Metformin complex) were evaluated using the Desmond suite to elucidate the

dynamic behaviour and bonding mechanism. For the DPP4 and HSD11B1 proteins, the dynamic rigidity of both systems (Apo and Holo) was evaluated using the RMSD profile of the backbone atoms at 100 ns. The results are displayed in Fig. 9.

The backbone RMSD graph of Holo1 state: DPP4-Kaempferol complex revealed a stable RMSD during 15 to 70 Nanosecond (ns) analogized to its Apo state with values between ~0.4 to ~0.7 Å in the initial stage and after that second stable RMSD found during 85 ns to 95 ns, whereas in Holo2: DPP4-Metformin complex conveyed unstable avenues throughout the simulation cycle upon analogization to its Apo state MD simulations. In the case of Holo3 for the HSD11B1-Kaempferol complex, stable avenues were found in the early simulation period, from five ns to 100 ns, with RMSD values ~1.7 Å to ~2.4 Å and in the case of Holo4 for the HSD11B1-Kaempferol complex, depicted unstable MD simulations trajectories throughout the simulation process, which are more fluctuating than its Apo state. The backbone atoms' RMSD profile at 100 ns is shown in Fig. 9, illustrating the dynamic stability of both the Apo and Holo systems when ligands form complexes with the DPP4 and HSD11B1 proteins. Taking together the RMSD values of all four Holo states for DPP4, Holo1 showed minor deviations and a stable trajectory, followed by Holo2. Holo3 showed a more stable trajectory than Holo 4. This suggests that the compound Kaempferol could inhibit DPP4 and HSD11B1 and help maintain rigidity by tailoring its molecular framework compared to Metformin. Root mean square

**Fig. 8.** Plots of LUMO and HOMO orbitals of phytocompounds. A: Kaempferol: LUMO; B: Kaempferol: HOMO; C: Metformin: LUMO; D: Metformin: HOMO.

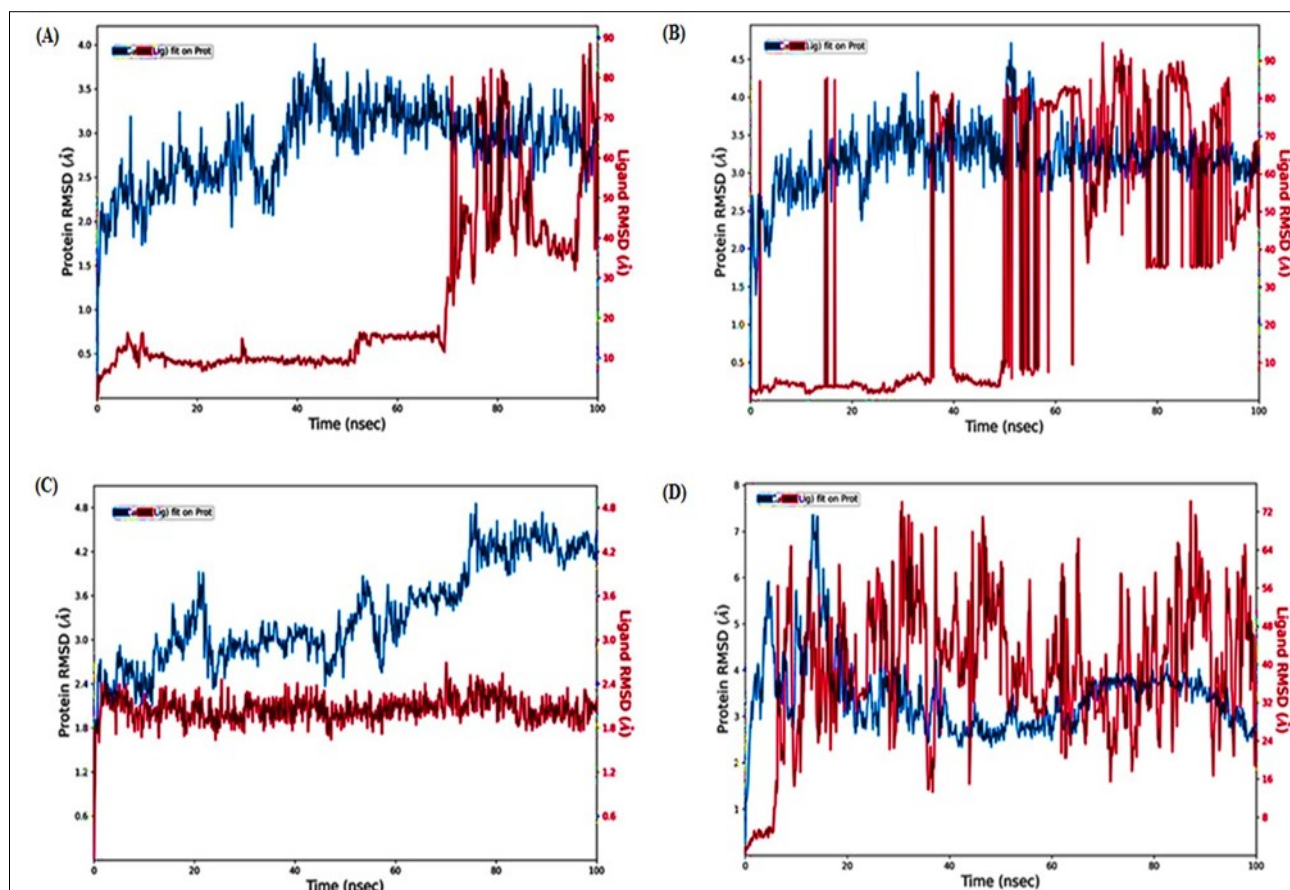


Fig. 9. The structural rigidity of the Apo and Holo states of DPP4 and HSD11B1 protein of T2DM throughout a 100-nanosecond (ns) time period of MDS Backbone-RMSD. A: DPP4-Kaempferol complex; B: DPP4-Metformin complex; C: HSD11B1-Kaempferol complex; D: HSD11B1-Metformin complex.

fluctuation, which tracks residue fluctuations, provided additional support for the RMSD result. The dispersion across various residues has been monitored in each state using RMSF plots. Thus, comparable to the Holo states, the Apo state exhibited more extensive fluctuations in the DPP4 and HSD11B1 proteins, indicating constrained motions in the simulation. The amino acid residues aligning at 180–280 (Holo1), 90–150 (Holo2), 130–200 (Holo3) and 50–120 (Holo4) displayed more significant variations in their C α atoms than at alternate locations. The relationship between components may be a consequence of the volatility. Protein residues that interact with the ligand are marked with green-coloured vertical bars. The findings confirm that binding could render residues in the Holo state more stationary than in the Apo state. Fig. 10 depicts the RMSF results.

Attributes, notably the radius of gyration (rGyr), were used to characterise aggregate compactness and resilience in the binding pockets of DPP4 and HSD11B1 proteins during the 100 ns simulation. A ligand's essential moment of rigidity, or radius of gyration (rGyr), is a technique to quantify how "extended" it is.

The rGyr fluctuation graphs versus the simulation timeframe for DPP4 confirm that rGyr remains constant between 65 and 100 ns. Holo1 depicted rGyr appraises ~3.60 to ~3.70 Å, Holo2 evince rGyr values ~2.14 to ~2.27 Å. For HSD11B1, rGyr remained constant between 85 and 100 ns. Holo3 manifested the rGyr values ~3.66 to ~3.76 Å and Holo4 exhibited rGyr values between ~1.14 to ~2.26 Å.

Rigidity and rGyr values are inversely correlated: lower rGyr values indicate greater rigidity and vice versa. The rGyr value of Holo1 was found to be lower than that of Holo2, defining its rigidity and Holo1 indicates that the ligands could potentially interact more

with DPP4. Subsequently, for HSD11B1, Holo 3 has lower rGyr values, indicating a more compact state than Holo 4. The RMSF assessment affords substantial evidence for these rGyr accomplishments. Fig. 11 depicts the rGyr results.

Solvents expose amino acids through hydrophobic interactions, with solvent-accessible surface area (SASA) correlated with the frequency of these interactions between solvent and core protein residues. The SASA study shows that binding of anti-diabetic compounds can alter hydrophilic and hydrophobic interaction areas, potentially affecting protein veneer orientations due to amino acid residue shifts during 70 ns to 100 ns simulations for DPP4. SASA was portrayed by the Holo1 state, comprising ~280 Å² to ~450 Å². In contrast, for Holo2, the SASA ranged from ~60 Å² to ~250 Å², comparable to the HSD11B1 amino acid residue shift observed during the 65–100 ns simulation. SASA values for Holo3 ranged from ~10 Å² to ~30 Å², whereas for Holo4, the SASA values were ~120 Å² to ~250 Å². This indicates that the shift in the protein's exterior symmetry could arise from amino acid residues in the Holo state migrating from the visible region to the concealed region. Reduction in the attainable solvent surface in the Holo states was demonstrated in Fig. 12.

H-bond analysis

Schrödinger Release 2022–24 was utilised in MD simulations to illustrate intermolecular hydrogen bonds, identify variables and determine the stability of the drug-target complex. The intermolecular hydrogen bonds of the Holo states were hounded. The stacked bar chart of Holo1 in Fig. 9A shows that amino acid residues of Post MD DPP4-Kaempferol complex intermolecular Hydrogen bonds formed with Asp230, Thr231, Ser292, Arg317,

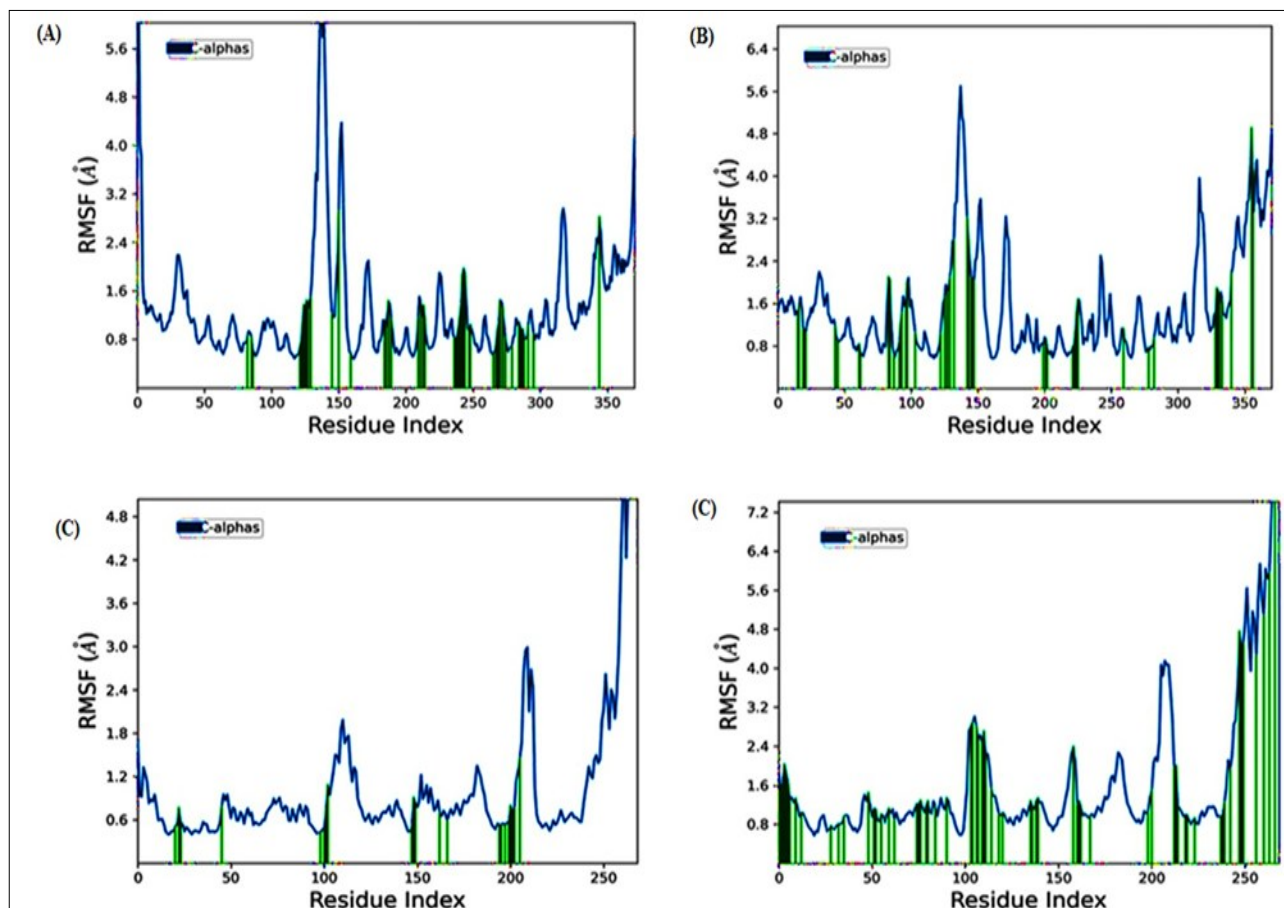


Fig. 10. C α -RMSF profile of the Apo and Holo states of the AMY2A protein of T2DM across a 100 ns period of MDS. A: DPP4-Kaempferol complex; B: DPP4-Metformin complex; C: HSD11B1-Kaempferol complex; D: HSD11B1-Metformin complex.

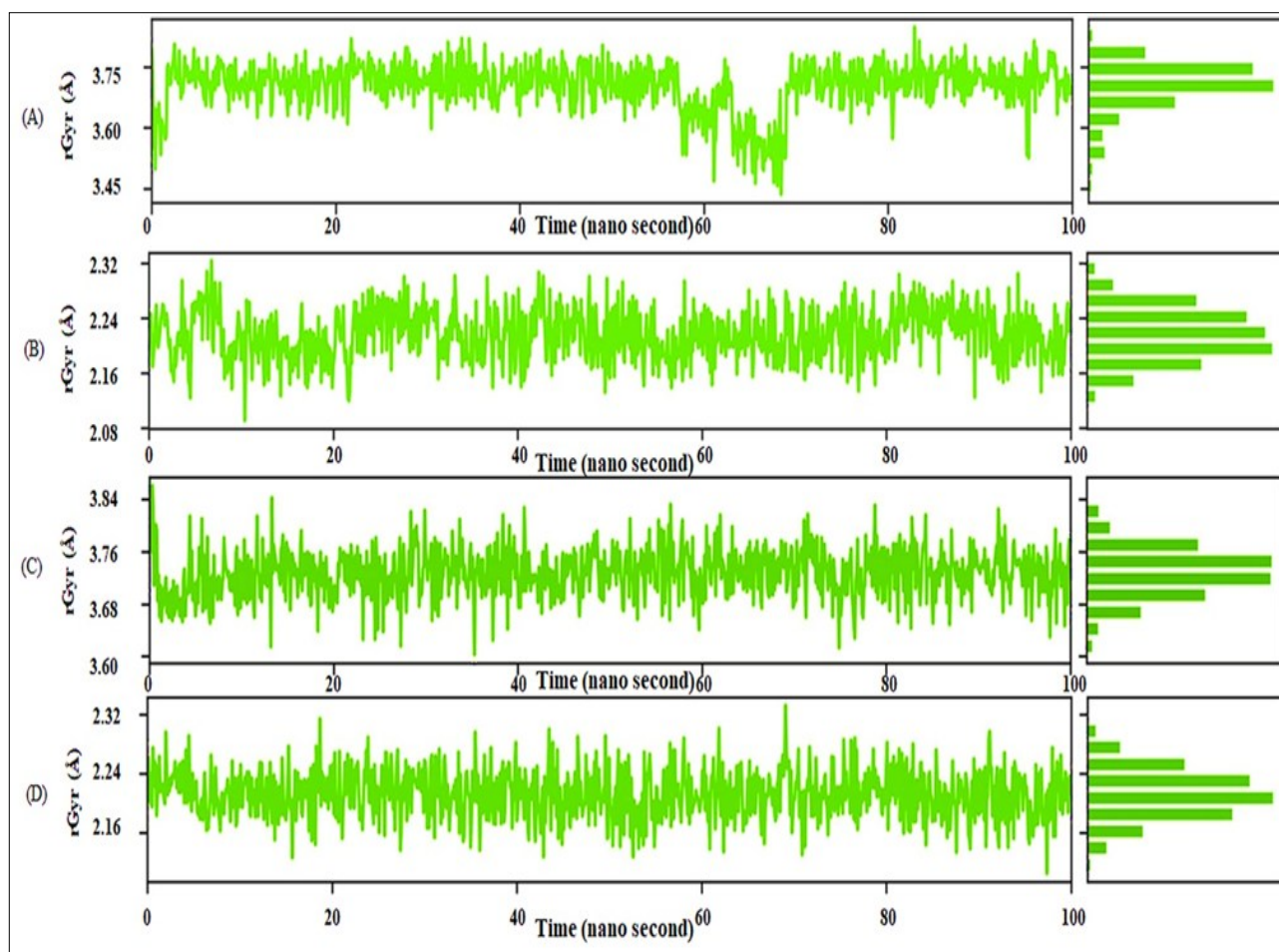


Fig. 11. Radius of gyration (Rg) profile of the Apo and Holo states of the DPP4 and HSD11B1 proteins of T2DM across a 100 ns period of MDS. A: DPP4-Kaempferol complex; B: DPP4-Metformin complex; C: HSD11B1-Kaempferol complex; D: HSD11B1-Metformin complex.

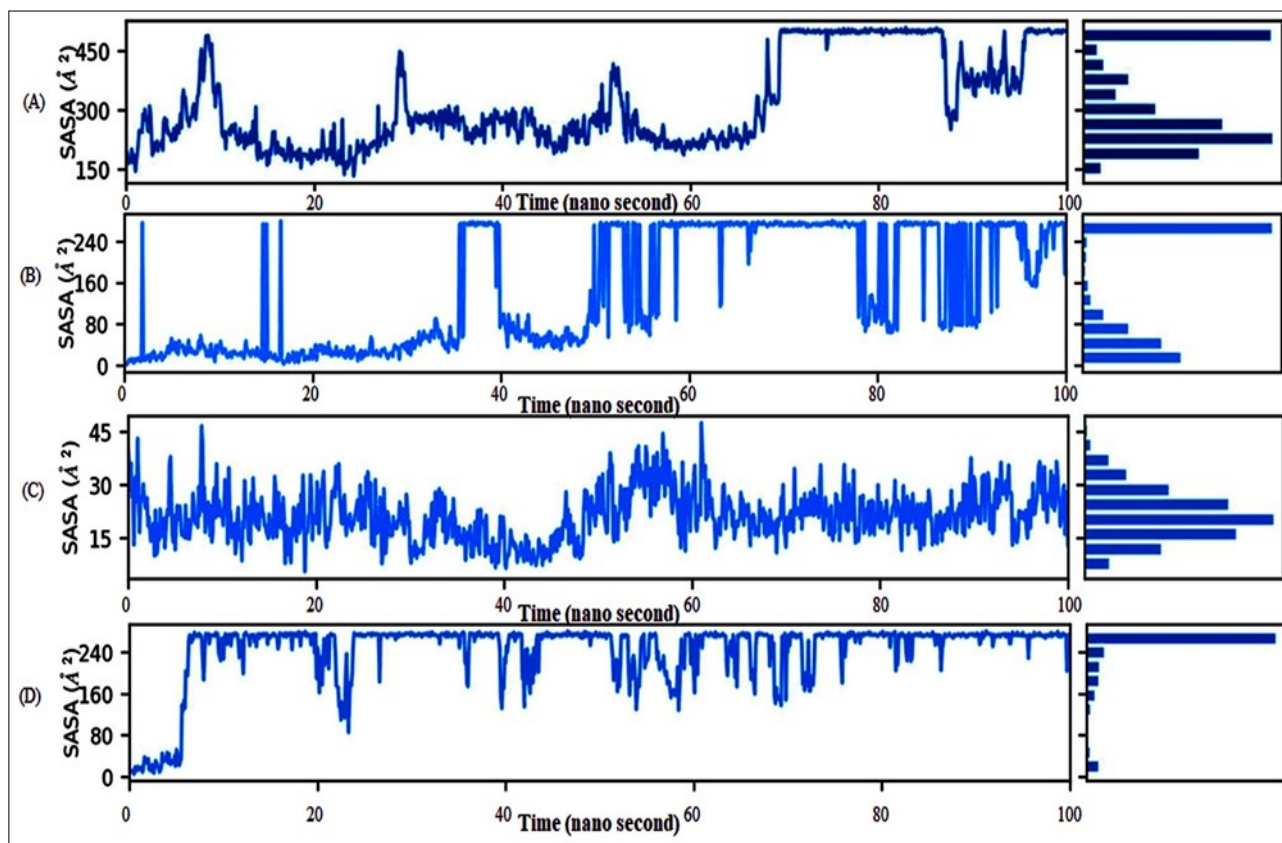


Fig. 12. Assessment of the DPP4 and HSD11B1 proteins' solvent accessible surface (SASA) throughout a 100 ns MD simulation. A: DPP4-Kaempferol complex; B: DPP4-Metformin complex; C: HSD11B1-Kaempferol complex; D: HSD11B1-Metformin complex.

Asn321, Ile346, Ser348, Asp392 and Cys394 may play a vital role in the binding and regulation of the protein. In the case of the Holo2 state in Fig. 9B for the DPP4-Metformin Post MD complex, intermolecular Hydrogen bonds were formed with Asp192, Tyr195, Thr199, Glu204 and Glu332, indicating that Metformin is less stable with DPP4. In the case of Holo3 state in Fig. 9C for HSD11B1-Kaempferol Post MD complex intermolecular Hydrogen bonds formed with higher interactions fraction with Lys44, Asn119, Lys187 and Gly216 playing a vital role in the binding and regulation of the protein whereas in case of Holo4 state in Fig. 9D for HSD11B1-Metformin Post MD complex intermolecular Hydrogen bonds formed with the lesser value of interaction fraction with Ser125, Asp132, Met179 and Glu240 defining its lesser stability. Fig. 13 depicts the results.

The simulation of the Holo1 state (DPP4-Kaempferol complex) showed a consistent number of intermolecular hydrogen bonds throughout the simulation, with minimal deviation, whereas the Holo2 state (DPP4-Metformin complex) exhibited inconsistent H-bonds. In the case of the Holo3 state (HSD11B1-Kaempferol complex), consistent and intensified H-bonds were obtained with no deviation. In contrast, the Holo4 state (HSD11B1-Metformin complex) has deviated significantly and less-intense intermolecular hydrogen bonding is observed. Fig. 14 shows the results for the stabilized hydrogen bonding interactions. Fig. 15 shows the post-MD protein-ligand interactions for all Holo states.

Principal component analysis

In every simulated protocol, the flexibility of the Apo and Holo states originates and is determined by the trace values of the covariance matrix of the backbone atoms. The transient nature of the states is illustrated in phase space by the projections of the trajectories onto PC1 and PC2. The transference of itineraries onto the first two principal components (PC1 and PC2) confirmed the relative mobility

of the Apo and Holo states of the wild-type and mutant protein-ligand complexes in the spectrum of phases. The PCA plots' cloud of points indicates that the DPP4 protein is more flexible in the Holo1: DPP4-Kaempferol complex, followed by the Holo2: DPP4-Metformin complex. The HSD11B1 protein is more flexible with Holo3: HSD11B1-Kaempferol complex, followed by Holo4: HSD11B1-Metformin complex. The motion and re-motion of atomic configurations during the dual 100 ns simulation period could be the root of the flexibility. Fig. 16 shows a curtailment in the principal component in the Holo states. The clouds exemplify the protrusion of trajectories (PC1 and PC2).

The "Cross-correlation matrix" of the α -displacement showed all residues in the "DPP4 and HSD11B1" proteins. Both negatively (blue) and positively (red) associated motions support the protein's random movement. Holo1 was found to have higher and denser positively associated motions, whereas Holo2 depicted higher negatively associated motions for DPP4. In the case of HSD11B1, Holo3 showed higher positively associated motions, whereas Holo4 showed higher negatively associated motions. Fig. 17 shows comparative Cross-correlation matrices of the Holo-state backbones of DPP4 and HSD11B1.

The vectorial portrayal of each component showed the direction of motion, while the projection vectors revealed internal and external motions. After graphing, sharp porcupine plot curves were obtained. The porcupine's protrusion introduces a shift in proposition and flexibility by showing both veiled and façade projection/motion in the Holo phases. This could result from atomic configurations changing over the 100 ns simulation. Fig. 18 shows comparative porcupine plots of vectorial motion in the Holo states of DPP4 and HSD11B1 proteins.

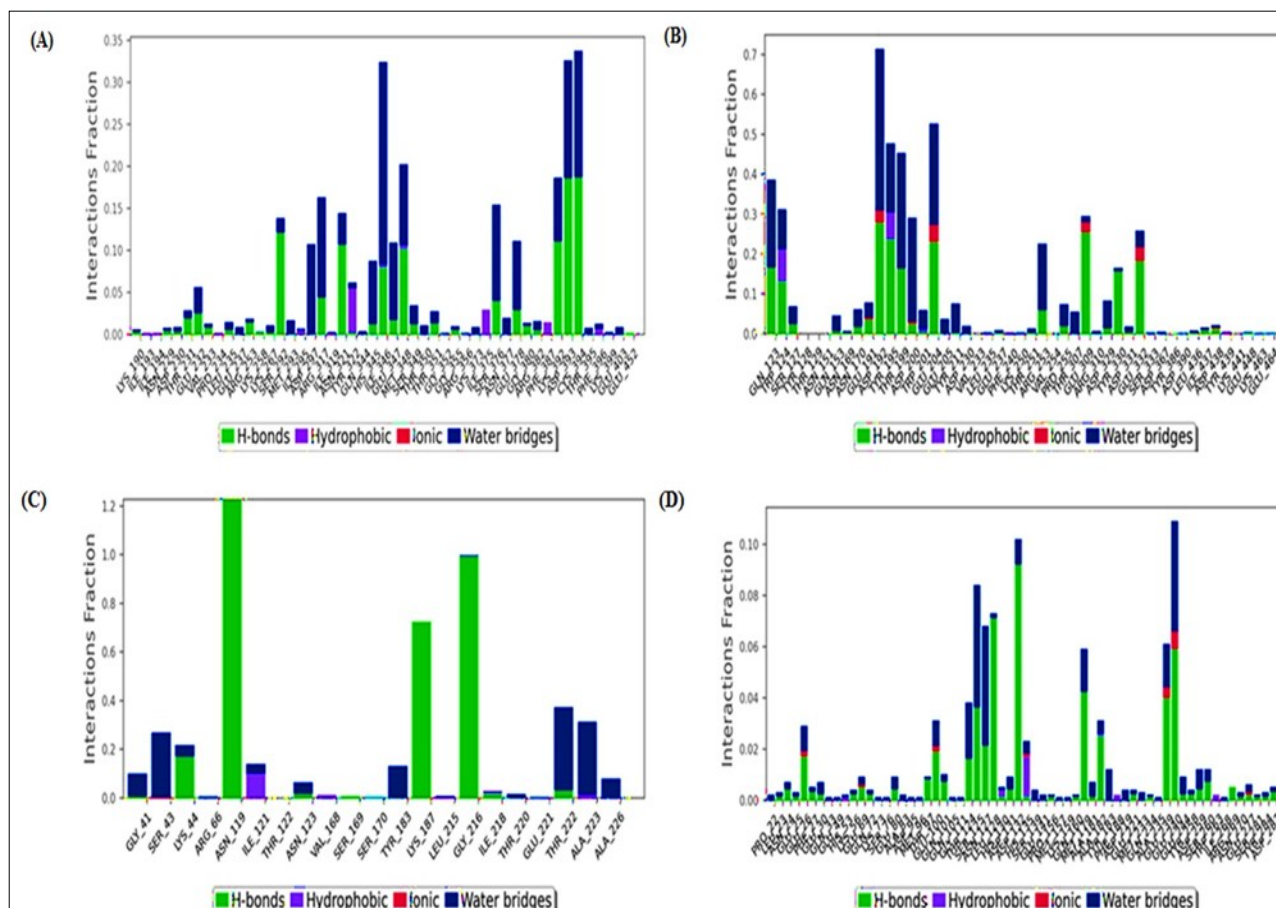


Fig. 13. Stacked bar chart plot showing protein ligand contacts during the simulation of 100 ns. A: DPP4-Kaempferol complex; B: DPP4-Metformin complex; C: HSD11B1-Kaempferol complex; D: HSD11B1-Metformin complex.

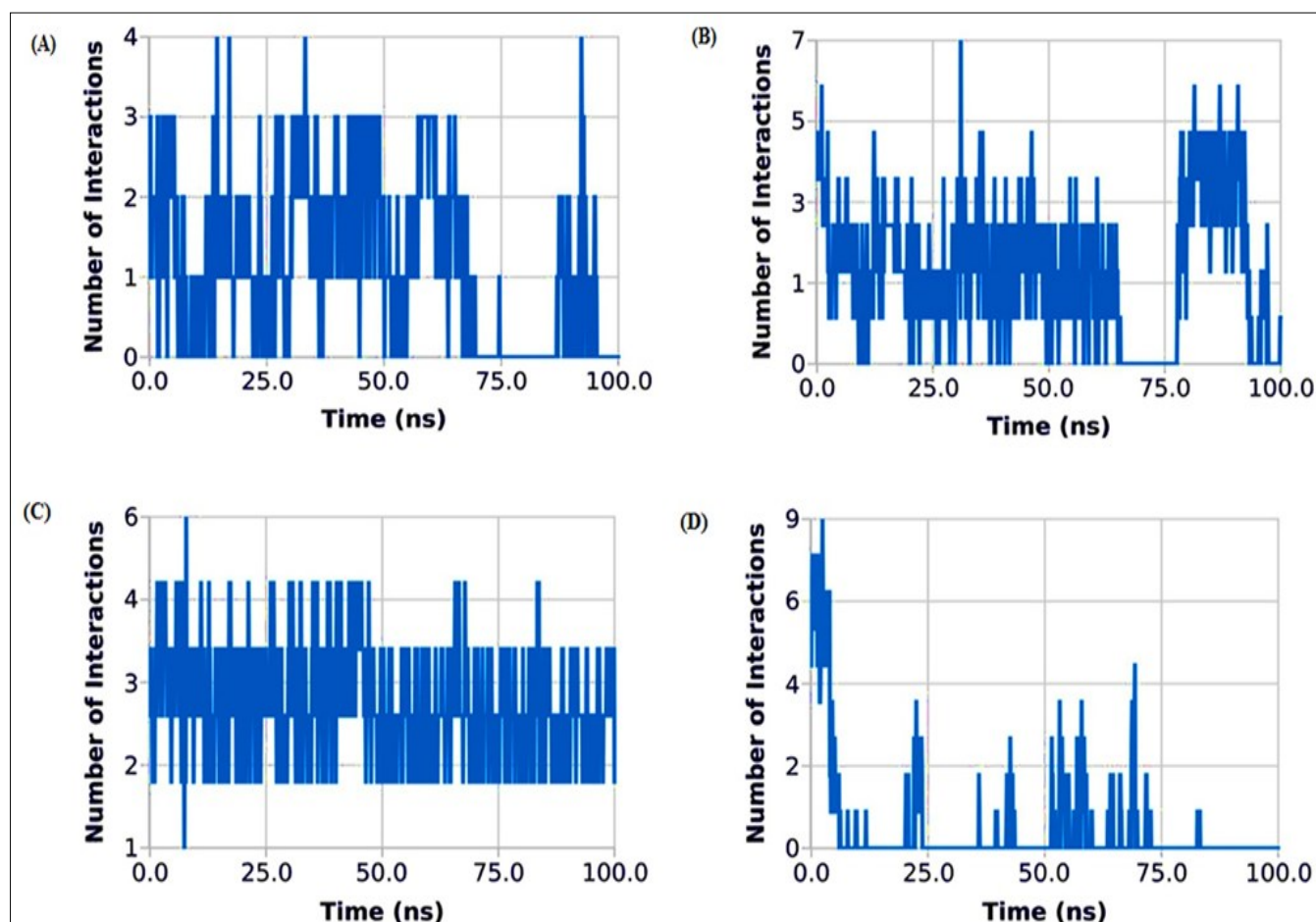


Fig. 14. Deviation of H-bonds contributed to the interaction during the 100 ns simulation. A: DPP4-Kaempferol complex; B: DPP4-Metformin complex; C: HSD11B1-Kaempferol complex; D: HSD11B1-Metformin complex.

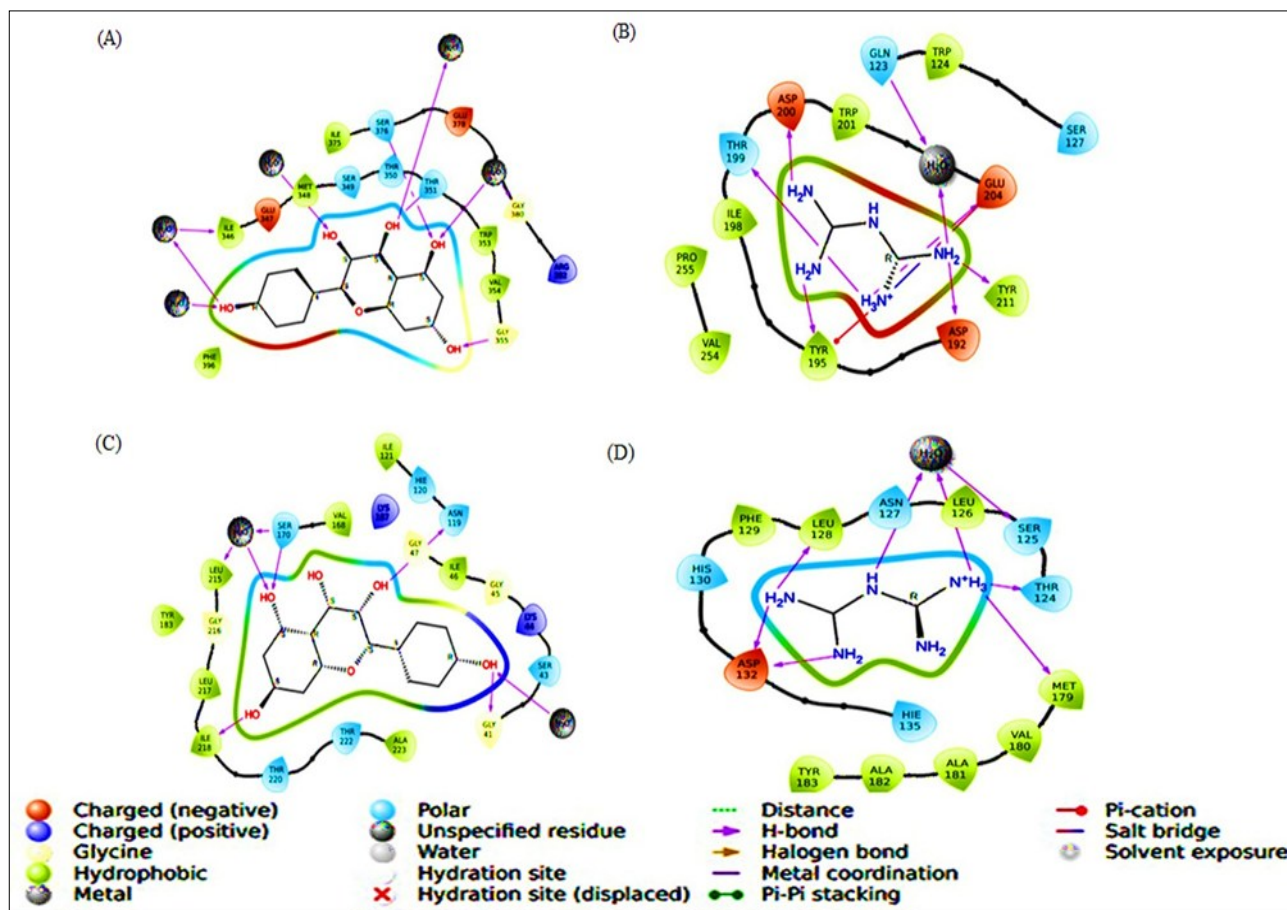


Fig. 15. Post-MD simulations intermolecular hydrogen bonding, electrostatic and hydrophobic contacts formed between post-MD. A: DPP4-Kaempferol complex; B: DPP4-Metformin complex; C: HSD11B1-Kaempferol complex; D: HSD11B1-Metformin complex.

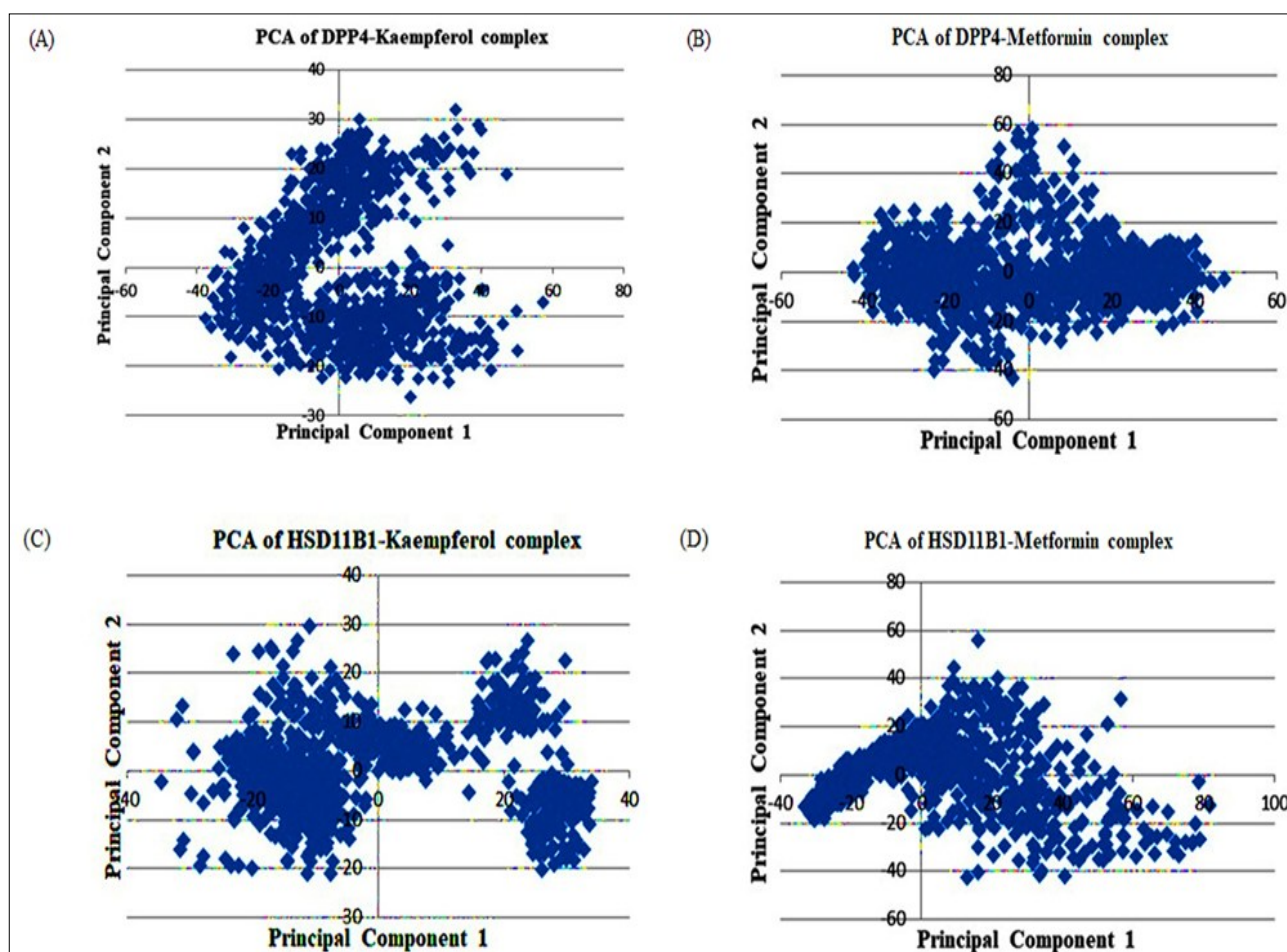


Fig. 16. PCA of the T2DM proteins complexes. A: DPP4-Kaempferol complex; B: DPP4-Metformin complex; C: HSD11B1-Kaempferol complex; D: HSD11B1-Metformin complex.

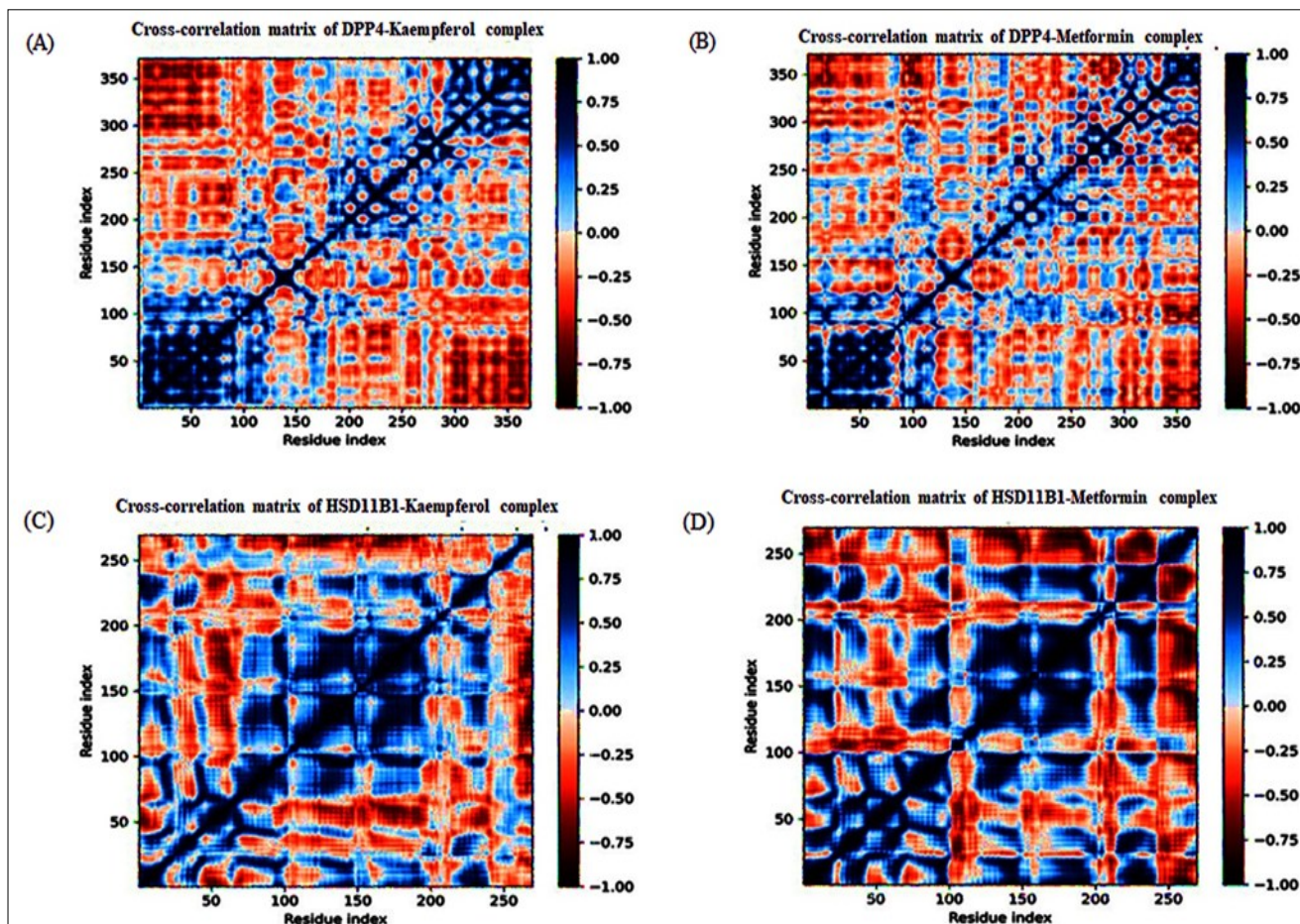


Fig. 17. DPP4 and HSD11B1 proteins' cross-correlation matrices. A: DPP4-Kaempferol complex; B: DPP4-Metformin complex; C: HSD11B1-Kaempferol complex; D: HSD11B1-Metformin complex.

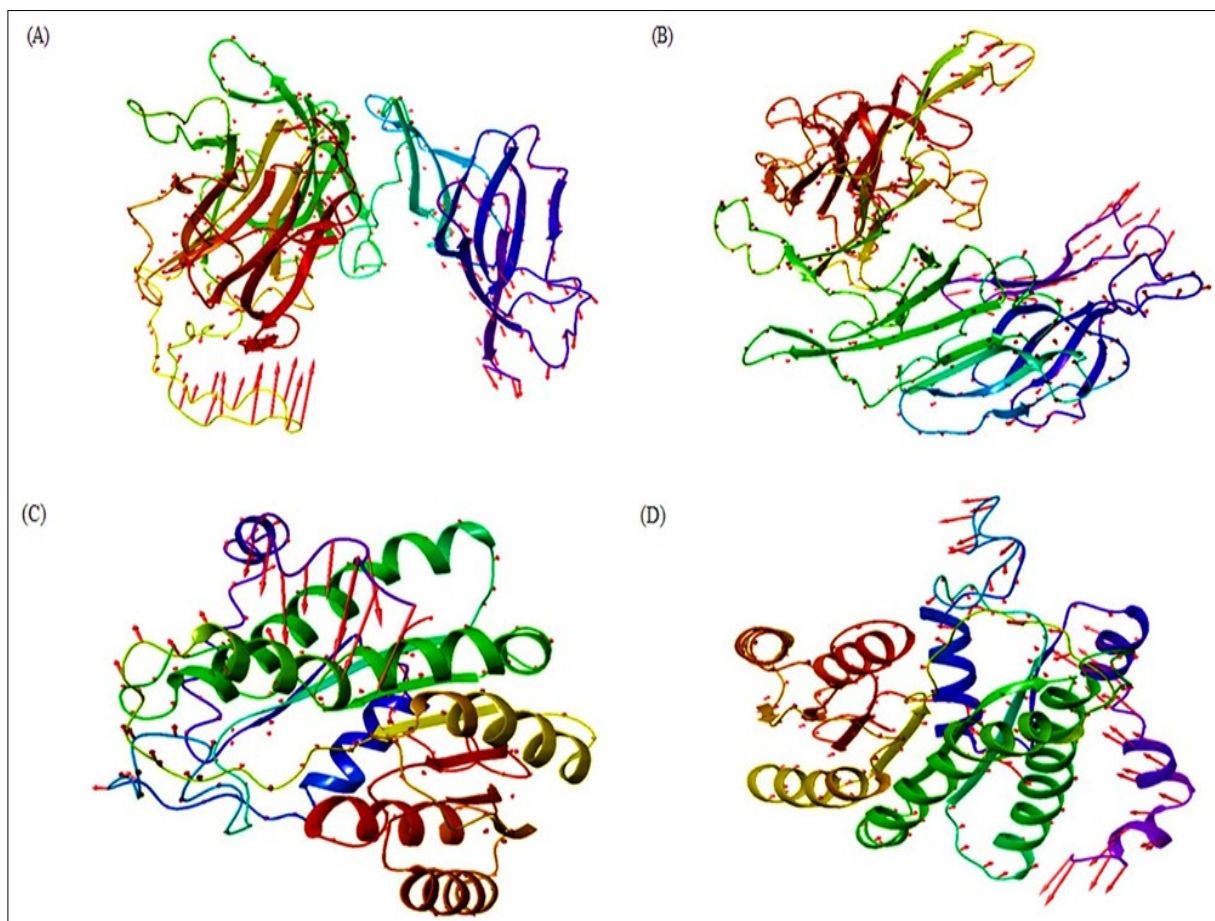


Fig. 18. Porcupine plot of DPP4 and HSD11B1 proteins. A: DPP4-Kaempferol complex; B: DPP4-Metformin complex; C: HSD11B1-Kaempferol complex; D: HSD11B1-Metformin complex.

Discussion

Metabolic disorders like T2DM are usually caused by consuming a substantial number of calories relative to energy expended. It is rapidly spreading to other parts of the world. Due to an ageing population, the impact is predicted to affect nearly twice as many individuals in the decade ahead. This will exacerbate the immense strain on healthcare providers, particularly in developing economies. The International Diabetes Federation estimates that the number of people diagnosed with diabetes will increase from 10.5 % in 2021 to 11.3 % by 2030 and 12.2 % by 2040 (39). The current *in silico* investigation aims to identify potential therapeutic solutions for critical conditions in T2DM in humans, a very common lifestyle disorder worldwide. To intervene, this investigation includes the typically implicated genes in T2DM (DPP-4 and HSD11B1), which are well known for their pivotal role in T2DM and involvement in many other diseases, including cancer. DPP-4 is essential for controlling how the body uses glucose. Orally administered synthetic DPP-4 inhibitors are effective hypoglycaemic medications for type 2 diabetes but have other side effects, such as acute pancreatitis caused by saxagliptin, complicated pancreatitis caused by sitagliptin and toxicity issues caused by denagliptin (40). A substantial body of clinical and experimental evidence also points to enhanced islet function as the primary mechanism underlying DPP-4i's inhibitory hypoglycaemic action, linked to both elevated insulin secretion and suppression of glucagon secretion. So, the search for plant-based DPP4-inhibitory phytochemicals could be a sustainable alternative for managing Type II diabetes mellitus.

PPAR- γ agonists, insulin sensitizers, statins and other traditional medications are now used to treat T2DM. However, these drugs target a single protein molecule that may change the homeostatic pathways and have several negative effects, including pancreatitis, genital mycosis, ketoacidosis, neuropathy risk, nausea and vomiting (41, 42). Complex disorders, including type 2 diabetes, may benefit from a combinatorial therapy that limits the utility of single drug molecules at high dosages. Because of the complex combination of secondary metabolites in herbal plants and their modulation of corresponding molecular protein targets, bioactive compounds from plants are important in the management of type 2 diabetes (43). The concept of multi-drug, multi-target and multi-pathway interactions in network pharmacology has recently provided new, systematic insights into the overall molecular understanding of the effects of herbal compounds. These insights may also pave the way for the development of effective drug contestant to treat complex afflictions such as obesity and T2DM (44).

Mangifera indica L., typically referred to as the mango tree, is often found in almost all places around the world. As reported by a study, a hydroalcoholic extract from the leaves of the *M. indica* L. cultivar Anwar Ratol incorporates iriflophenone 3-C- β -D-glucoside and mangiferin. It also demonstrated excellent antidiabetic effectiveness by diminishing postprandial blood glucose concentrations (45). Mangiferin, as well as foliamangiferosides, has been demonstrated in previous investigations to provide antidiabetic benefits by enhancing insulin sensitivity and diminishing alpha-glucosidase activity (46). Prior research has shown that chlorogenic acid reduces the body's use of fat and glucose after a diet. Chlorogenic acid promoted fat oxidation and diminished LDL levels. Furthermore, high-polyphenol coffee extract has been implicated in glucagon-like peptide attenuation (47). Gallic acid has been observed to improve glucose absorption by stimulating

GLUT4. By inhibiting pancreatic lipase and alpha-glucosidase, phenolic compounds have been found to prevent increases in blood glucose levels. By safeguarding the pancreas from damage and strengthening the body's antioxidant defenses, quercetin exhibits antidiabetic activity. Therefore, it may be assumed that the extract's hypoglycemic action could be credited to mangiferin, iriflophenone 3-C- β -D-glucoside, quercetin and other polyphenols identified in the plant leaves (48).

Owing to their medicinal value, the phytochemicals in leaf extracts were investigated for their anti-diabetic properties. The reported phytochemicals were identified through a literature review and subjected to pharmacokinetic property assessments. Out of 63 collected compounds, only 14 screened compounds were further processed for molecular docking and only two (Kaempferol: Test and Metformin: standard) were assessed for DFT calculations and MD simulations. In the DFT study, the LUMO-HOMO gap energy indicated that a lower gap energy is associated with a higher reactivity rate. Here, the compound kaempferol has a relatively lower gap energy than metformin, indicating its greater reactivity in the body due to higher electronic, potential and kinetic energies, implying the potential for the drug to bind to receptors with greater stability. Kaempferol showed the best docking and reactivity scores among the selected proteins for T2DM. This resulted in compounds obtained with higher binding value, reactivity and stable behaviour in the dynamics simulation than the respective standard drugs. In addition, previous research findings emphasise the effect of the compound kaempferol in promoting GLP-1 and insulin production in *in vivo* studies (49). The study with preliminary findings from the *in vivo* approach indicates that the compound kaempferol has not only anti-diabetic but also anti-obesity properties (50). This leads to this phyto-compound for further efficacy studies through *in vitro* and *in vivo* approaches. This research study suggests that the mango leaf's medicinal properties warrant further study.

Conclusion

Continued consumption of unhealthy, carbohydrate-containing food and lack of physical exercise in daily life are risk factors for T2DM and increase the risk of associated diseases. Here, phytochemicals from mango tree leaves are used as a natural source of compounds and the proteins DPP4 and HSD11B1 are associated with T2DM. Here, an *in silico* process was used to assess ADMET properties and selected compounds were docked to the targets to evaluate their efficacy. The DFT method was applied to study reactivity and relative stability and a simulation was employed to study the natural compound with selected genes. Based on these results, it can be stated that the selected natural compounds from mango leaves could be promising targets for T2DM management, with *in vitro* and *in vivo* approaches and could reduce the number of experimental steps in drug design and discovery.

Acknowledgements

We appreciate the permission to conduct the study and the support provided by Centurion University of Technology and Management, Odisha, India and the National Institute of Pharmaceutical Education and Research, Ahmedabad, India.

Authors' contributions

CST carried out data collection, computational work, manuscript preparation, formatting and writing. SKB and AKP assisted in data collection, computational analysis and writing. SP designed the study and conceived the manuscript, as well as contributed to its writing, correction and analysis. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interest to declare.

Ethical issues: None

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Peer review: Publisher thanks Sectional Editor and the other anonymous reviewers for their contribution to the peer review of this work.

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