Healthmed Journal of Pharmaceutical Sciences

Journal Homepage: http://ps.healthmedsci.org

Healthmed Science
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Article

Evaluation of kaempferol derivatives as a potential inhibitor of diabetes receptor – a computational drug design approach

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Manuscript received: 12 Jan 2024
Revision received: 24 March 2024
Accepted: 27 March 2024
Published: 28 March 2024

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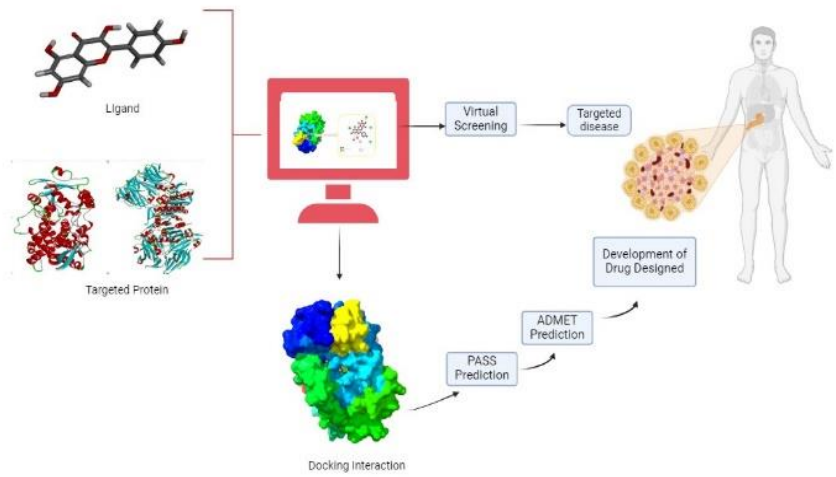
Citation:
Ahmad S, Faruk O, Rahman A. Evaluation of kaempferol derivatives as a potential inhibitor of diabetes receptor - a computational drug design approach. Healthmed J Pharm Sci 2024; 2(1):37-45.

Abstract

Diabetes mellitus, characterized by high blood sugar levels, is a growing global health problem, posing major challenges to individuals and public health systems. This study examines Kaempferol derivatives as potential inhibitors of diabetes receptors using molecular modeling techniques such as ADMET, QSAR, pLogIC50, and molecular docking. Our analysis shows that ligands 06, 07, and 09 have strong binding affinities to the human CYP3A4 enzyme bound to metformin (PDB ID: 5G5J), with values between -9.8 and -10.0 kcal/mol, and to human dipeptidyl peptidase-IV (PDB ID: 4A5S), with values between -8.3 and -8.6 kcal/mol. In comparison, Metformin has binding energies of -4.9 kcal/mol for human CYP3A4 and -5.3 kcal/mol for human dipeptidyl peptidase-IV. Drug similarity and ADMET predictions suggest that these Kaempferol derivatives are likely non-carcinogenic, non-hepatotoxic, and highly soluble. These findings indicate that Kaempferol derivatives could be promising anti-diabetic agents. However, further investigations from computational to *in vitro* or *in vivo* are required.

Graphical Abstract



Keywords: Kaempferol, molecular docking, antidiabetic drug, pharmacokinetics

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Introduction

Diabetes is a chronic illness that is significantly impacted by daily changes in nutrition, physical activity, infection, and stress (MURUGESH SHIVASHANKAR, 2011). The personal and social toll of diabetes's growing prevalence is intolerable (Fradkin, 2012). Diabetes mellitus (DM) is one of the leading non-communicable diseases globally, significantly contributing to increasing rates of morbidity and mortality. The global impact of DM is profound, as it not only affects individuals but also places a heavy burden on healthcare systems. The chronic nature of diabetes means that individuals require continuous medical care, monitoring, and lifestyle modifications to manage the disease effectively. Moreover, DM is a major risk factor for several severe complications, including cardiovascular diseases, stroke, kidney failure, and neuropathy, further exacerbating its health toll. The prevalence of DM has been rising more rapidly in low- and middle-income countries compared to high-income nations. Currently, 537 million individuals aged 20-79 years are affected by diabetes, a number expected to soar to 783 million by 2045. This dramatic increase is driven by several factors, including urbanization, sedentary lifestyles, and dietary shifts towards high-calorie, low-nutrient foods. These lifestyle changes are particularly pronounced in developing regions where economic growth has led to significant alterations in traditional living and eating patterns. The surge in diabetes cases in these countries highlights the urgent need for targeted public health interventions and accessible healthcare solutions to manage and prevent diabetes effectively (Farhana Akter, 2022). Diabetes represents a substantial economic burden, with the International Diabetes Federation estimating that it accounts for 5–20% of all healthcare expenditures in most countries. This financial strain is due to the extensive medical needs of diabetes patients, which include regular monitoring of blood glucose levels, medications, treatment of complications, and routine healthcare visits. The indirect costs are also significant, encompassing lost productivity, absenteeism, and early retirement due to diabetes-related health issues. This dual economic impact underscores the necessity for cost-effective management strategies and innovative therapeutic approaches to alleviate the financial load on healthcare systems and improve patient outcomes (William H. Herman MD, 2016). If left untreated, complications from diabetes can be fatal (Suji G, 2003). Today's rapidly expanding world may now readily access high throughput data by transforming it into relevant datasets. This data is essential for computer-aided drug design (CADD) hypothesis optimization and drug design (Kaur P, 2021-2022). Quick screening of probable candidates is made possible by computational drug design, an effective method in contemporary pharmaceutical research. There is great promise for computational methods to expedite the drug discovery process. Several technologies that are based on computer science techniques and algorithms may be used for visualization, molecular docking and virtual screening, cavity/binding site prediction, and structural modeling (Dev Bukhsh Singh, 2020). This research focuses on kaempferol derivatives, a group of naturally occurring flavonoids found in various plants such as tea, broccoli, and grapes. These compounds are renowned for their diverse biological activities, including anti-inflammatory, antioxidant, and anti-cancer properties. Of particular interest is their potential as anti-diabetic agents. Kaempferol derivatives have been shown to modulate several biochemical pathways involved in glucose metabolism and insulin sensitivity. Their molecular structure allows for strategic chemical modifications that can enhance their bioactivity and pharmacokinetic properties. By systematically altering the chemical structure of kaempferol derivatives, researchers aim to improve their binding affinity to target receptors and enhance their therapeutic efficacy. This study endeavors to uncover the key structural elements that govern the interaction between kaempferol derivatives and diabetes-related receptors, thereby paving the way for the development of novel, more effective anti-diabetic drugs. They provide good candidates for logical drug design since their molecular structure serves as a platform for strategic alterations. Discovering the fundamental structural elements influencing the interaction between derivatives of kaempferol and the target receptor is the main goal. We aim to improve these compounds' pharmacological characteristics.

Materials and Methods

Pass prediction

The Way2Drug informational-computational platform offers computational capabilities for the prediction of biological activity of drug-like organic compounds, as well as access to data on medications authorized for medicinal use in the United States and the Russian Federation (D. S. Druzhilovskiy, 2017). The PASS prediction has been made to determine the capability of the anti-diabetic drug. The online web program PASS (Way2Drug.com, 2011 - 2024) was used to predict the anti-neoplastic, anti-diabetic, and anti-viral. The configuration of Kaempferol derivatives was illustrated first, and then they were transformed into smile forms by the addition of the free online programs provided by Swiss ADMET (SwissDrugDesign , 2017). These programs are well-known for their ability to determine the PASS spectrum by using the PASS web toll. PASS findings are represented by the probabilities Pa (probability of an active molecule) and Pi (probability for an inactive molecule). Pa and Pi grades may vary from 0.00 to 1.00, and Pa and Pi must be less than 1 since potentialities can be anticipated in whatever way the researcher chooses. The drug candidate should be potential and bioactive if the score of Pa >Pi.

Ligand optimization

The phytochemical ligands derived from Kaempferol derivatives were obtained from the PubChem database. Each molecular structure underwent thorough optimization to correct any geometric irregularities and ensure compliance with standardized structural parameters. This optimization process involved refining the geometry of the molecules and adding hydrogen atoms where necessary to accurately represent potential hydrogen bonding configurations. Subsequently, the optimized structures were saved in the Protein Data Bank (PDB) format, widely used in

computational chemistry and molecular modeling due to its compatibility with various software tools.

Protein preparation

Human CYP3A4 bound to metformin (PDB ID 5G5J) and Human dipeptidyl peptidase-IV (PDB ID: 4A5S) three-dimensional structure downloaded from the protein data bank (F.C. Bernstein). Discovery Studio 2021 Client software tools were used to delete all heteroatom and water molecules.

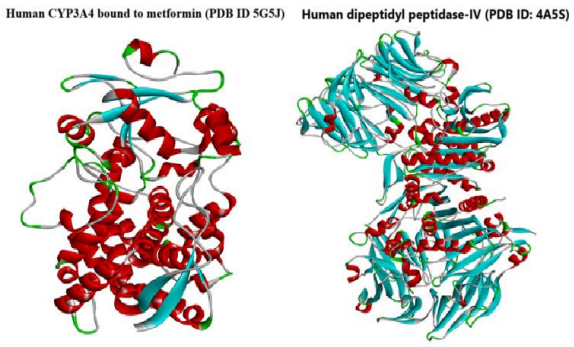


Fig. 1 Three-dimensional structure of protein.

Method of Molecular Docking

The goal of docking is to precisely quantify the intensity of binding and anticipate a ligand's structure within the bounds of a receptor binding site (Elizabeth Yuriev, 2013). The crystal structure of human CYP3A4 bound to metformin (PDB ID 5G5J) and the crystal structure of human dpp4 in complex with a noval heterocyclic dpp4 inhibitor (PDB ID: 4A5S) have both had their three-dimensional crystal structure downloaded from the protein data bank (RCSB PDB (RCSB.org), n.d.) Discovery Studio 2021 Client software tools were used to delete all heteroatom and water molecules. Then the targeted human CYP3A4 bound to metformin protein and human dpp4 in complex with a noval heterocyclic dpp4 inhibitor and previously natural molecules were subjected to a molecular docking investigation using PyRx version 8.0 as the software platform. The technique known as AutoDock vina wizard is used to incorporate the polar hydrogens into the protein. The grid box size on the protein was set to be center_x = 19.0878 center_y = -23.6628 center_z = 13.4752 size_x = 45.7987989521 size_y = 72.003985939 size_z = 62.0640604782 (PDB ID 5G5J) and the other protein grid box was set to be center_x = 34.1137 center_y = 71.3218 center_z = 83.6485 size_x = 85.6661769485 size_y = 68.464191246 size_z = 74.8520298767. (PDB ID: 4A5S).

ADMET, drug-likeness, and Lipinski Rule

The primary reasons why drug candidates fail clinical trials are unsatisfactory toxicity or undesirable pharmacokinetic (PK) characteristics. Ever since its inception, the notion of drug-likeness has gained significant traction as a criterion for choosing molecules with acceptable bioavailability in the early stages of drug research (Chen-Yang Jia, 2020). The drug development process must include the prediction of a pharmacological property of the molecule, such as the ADMET properties—which stand for absorption, distribution, metabolism, excretion, and toxicity to prevent failure during the clinical phases. To prevent their implosion during clinical trials, all the natural were assessed for their in silico pharmacokinetic characteristics This study utilizes in silico tools from SwissADME and pkCSM to predict the ADME/T properties of Kaempferol derivatives (Douglas E. V. Pires, 2015) was used to calculate the pharmacokinetic parameters for each natural chemical. In terms of a compound's water solubility, toxicity, metabolism, distribution, and absorption, this online database analyses its pharmacokinetics profile. The Lipinski rule, however, identifies the characteristics of any molecule that are similar to those of a medication. According to Lipinski's criteria, any biomolecule is regarded to have the potential to make a great oral drug. In the current study, the Lipinski rule computation was done using the Swiss ADME online web application (SwissDrugDesign , 2017).

Results

Biological pass prediction

The probable biological spectrum for Kaempferol derivatives has been predicted by applying the web server (Way2Drug.com, 2011 - 2024). The PASS data are summarized as Pa and Pi, which are shown in Table 1. According to the presupposition in Table 1, Kaempferol derivatives 1-9 demonstrated 0.835<Pa<0.925 for anti-neoplastic, 0.543<Pa<0.547 for anti-diabetic, 0.290<Pa<0.251 for antiviral, which indicated that the kaempferol derivatives have a greater potential as anti-neoplastic and anti-diabetic also compared to other antiviral characteristics. Although the anti-neoplastic PA score is higher, it has been largely ignored in favor of the anti-diabetic Pa score since researchers are more interested in discovering new antidiabetic drugs.

Table 1. Biological pass prediction spectrum computation of Kaempferol derivatives

Sl. No	CID	Antineoplastic		Anti-Diabetic		Antiviral	
		Pa	Pi	Pa	Pi	Pa	Pi
1	5481882	0,835	0,008	0,547	0,017	0,290	0,040
2	21310440	0,835	0,008	0,547	0,017	0,290	0,040
3	14749097	0,835	0,008	0,547	0,017	0,290	0,040
4	44258911	0,835	0,008	0,547	0,017	0,290	0,040
5	5316673	0,855	0,006	0,543	0,018	0,251	0,059
6	15558501	0,855	0,006	0,543	0,018	0,251	0,059
7	22838616	0,855	0,006	0,543	0,018	0,251	0,059
8	5835713	0,855	0,006	0,543	0,018	0,251	0,059
9	14749098	0,925	0,003	0,547	0,017	0,290	0,040

Lipinski Rule, Pharmacokinetics, and Drug Likeness

The molecular weight of the reported Kaempferol derivatives (L1-L9) was 418.35-432.38, the number of the hydrogen bond acceptor was 10, the hydrogen bond donor was 6, the Molar Refractivity was 102.17-106.97, The Consensus Log Po/w was 0.28-0.67. However, the molecules are not satisfied because the Six hydrogen bond donor groups are present in each of the nine compounds. Even though Lipinski's Rule of Five suggests that this should be cause for alarm. Additional research and testing are planned to help us narrow down our selection. This preliminary screening approach serves as a starting point for prioritizing compounds for further development.

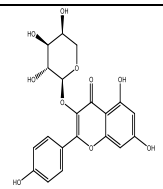
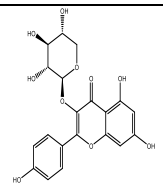
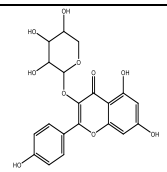
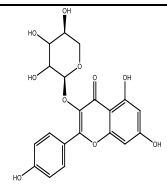
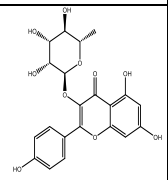
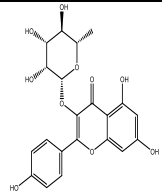
Table 2. Data of the Lipinski rule, Pharmacokinetics, and Drug likeness

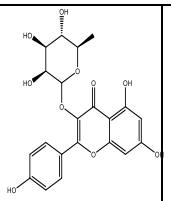
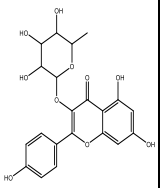
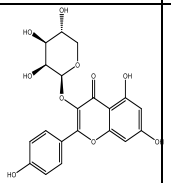
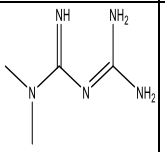
Ligand No	CID	Molecular weight	Hydrogen bond acceptor	Hydrogen bond donor	Molar Refractivity	Consensus Log Po/w	Lipinski rule	
							Result	violation
L01	5481882	418.35 g/mol	10	6	102.17	0.35	yes	1 violation
L02	21310440	418.35 g/mol	10	6	102.17	0.38	yes	1violation
L03	14749097	418.35 g/mol	10	6	102.17	0.24	yes	1 violation
L04	44258911	418.35 g/mol	10	6	102.17	0.32	yes	1 violation
L05	5316673	432.38 g/mol	10	6	106.97	0.67	yes	1 violation
L06	15558501	432.38 g/mol	10	6	106.97	0.57	yes	1 violation
L07	22838616	432.38 g/mol	10	6	106.97	0.61	yes	1 violation
L08	5835713	432.38 g/mol	10	6	106.97	0.60	yes	1 violation
L09	14749098	418.35 g/mol	10	6	102.17	0.28	yes	1 violation

Chemical structure with molecular docking score

Human CYP3A4 bound to metformin (PDB ID 5G5J) and Human dipeptidyl peptidase-IV (PDB ID: 4A5S) were docked with Kaempferol nine selected derivatives. The docked complex was compared with the standard drug Metformin to justify the significance of conducting this study. According to the molecular docking rules, a stable protein-ligand complex should express minimum binding affinity of the ligand with the receptor protein. Metformin binding energy of -4.9 kcal/mol for the Human CYP3A4 bound to metformin (PDB ID 5G5J and -5.3 kcal/mol for Human dipeptidyl peptidase-IV (PDB ID: 4A5S). However, the nine selected Kaempferol derivatives express higher binding affinity than the standard drug. Those docking scores indicate that ligand no:(06,07,09) have bound much more strongly than Metformin with the Human CYP3A4 bound to metformin (PDB ID 5G5J) and Human dipeptidyl peptidase-IV (PDB ID: 4A5S). AS stronger binding has a positive correlation with forming a more stable receptor-ligand complex, we can suppose that our selected compounds will have a better role in stabilizing the target protein than the standard drug.

Table 1. Molecular docking score

Sl. No.	Drug Molecules No	Chemical structure	Human CYP3A4 bound to metformin (PDB ID 5G5J)	Human dipeptidyl peptidase-IV (PDB ID: 4A5S)
			Binding Affinity(kcal/mol)	Binding Affinity(kcal/mol)
1	5481882		-9.6	-8.3
2	21310440		-9.7	-7.8
3	14749097		-9.6	-9.1
4	44258911		-9.6	-8.4
5	5316673		-9.7	-8.5
6	15558501		-9.8	-8.6

7	22838616		-10.0	-8.5
8	5835713		-9.3	-9.1
9	14749098		-9.9	-8.3
10	Standard (Metformin)		-4.9	-5.3

Protein-ligand interaction and Molecular docking poses

Ligand 6 docked with Human CYP3A4 bind to metformin (PDB ID 5G5J) and displayed a variety of interactions, including the following Conventional Hydrogen bond with ARG A:212, ARG A:372 and Pi-Alkyl with ARG A:105, ARG A:106 and Pi-Pi Stacked with PHE A:215, Pi-Anion with GLU A:374. For ligand 7 docked with Human CYP3A4 bond to metformin (PDB ID 5G5J) and showed different types of interaction including following Conventional Hydrogen Bond GLU A:374, ARG A:212, ALA A:370, SER A:119 and Alkyl bond with ARG A:105 same for Pi-Alkyl, Pi-Pi Stacked with PHEA:215, Pi-Cation with ARG A:106, The Pi-Anion bond same as Pi-Cation. When Ligand 9 was docked with the Human CYP3A4 molecule that binds to metformin (PDB ID 5G5J), it displayed a variety of interactions, including a conventional hydrogen bond with GLU A:374, ARG A:212, ALA A:370, and SER A:119. PHE A:215 and Pi-Pi combined. ARG A:105, 106 for Pi-Alkyl. Pi-Anion containing GLU A:374. On the other hand, Ligand docked with Human dipeptidyl peptidase-IV (PDB ID: 4A5S) also showed different types of interaction including the following Conventional Hydrogen Bond SER B:209, ARG B:125. Pi-Pi stacked PHE B:357, Pi-Pi T Shaped same as Pi-Pi Stacked. Pi-Anion with GLU B:205. Pi-Donor Hydrogen Bond with TRY B:666. Ligand 7 docked with Human dipeptidyl peptidase-IV (PDB ID: 4A5S) showed also different types of interaction such as Conventional Hydrogen Bond with ARG A:125. Pi-Pi Stacked and Pi-Pi T Shaped interact with TYR B:662, TYR b:666. The Carbon Hydrogen Bond and Pi-Donor Hydrogen Bond with SER B:630, TYR B:547. Also, when Ligand 9

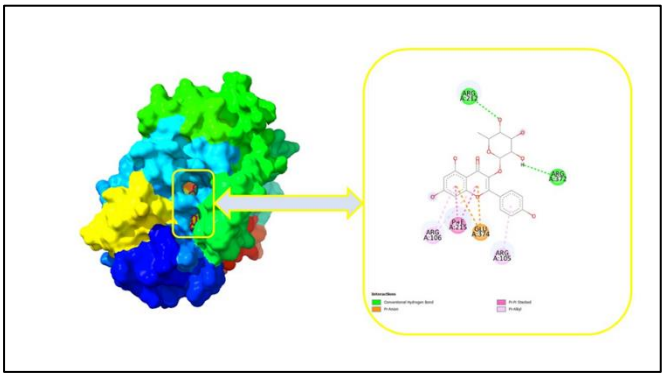


Figure 1. Ligand 6 Docking interactions between protein Human CYP3A4 bound to metformin (PDB ID 5G5J), showing key binding sites and molecular interactions.

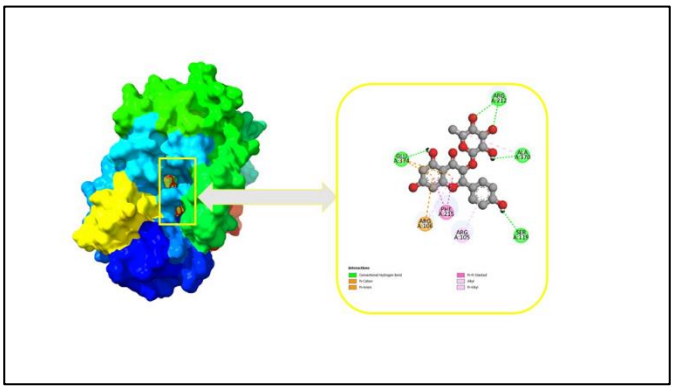


Figure 2. Docking interactions of Ligand 7 with human CYP3A4 bound to metformin (PDB ID 5G5J).

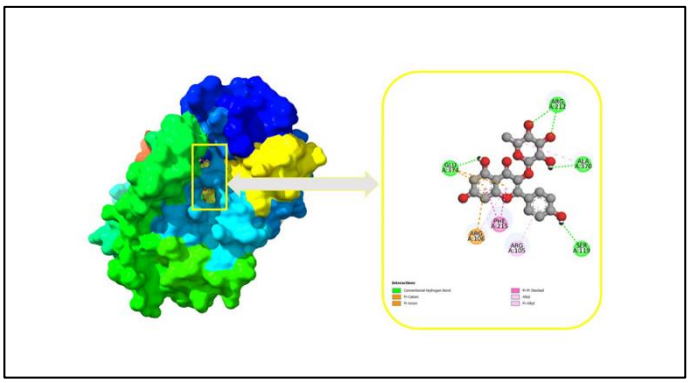


Figure 3. Docking interaction of ligand 9 with Human CYP3A4 bound to metformin (PDB ID 5G5J), illustrating significant binding interactions and stabilization effects.

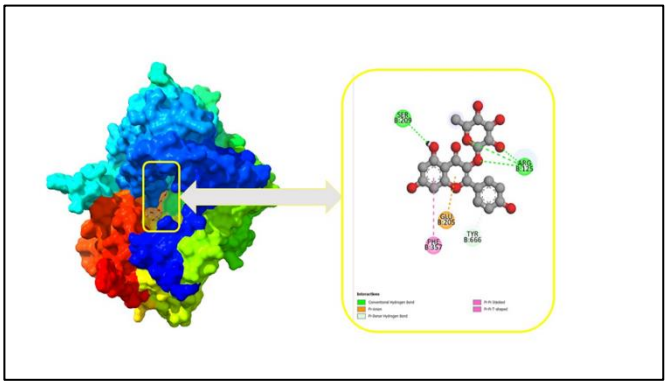


Figure 4: Molecular docking interactions of Ligand 6 with Human dipeptidyl peptidase-IV (PDB ID 4A5S), detailing binding modes and interaction sites.

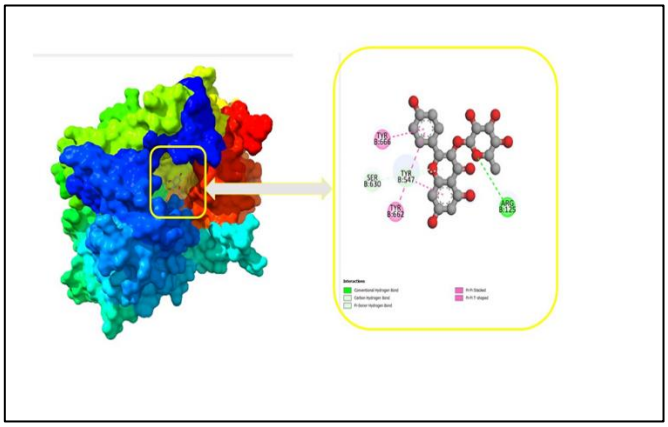


Figure 5: Docking interaction of Ligand 7 with Human dipeptidyl peptidase-IV (PDB ID: 4A5S), depicting key binding interactions and potential efficacy.

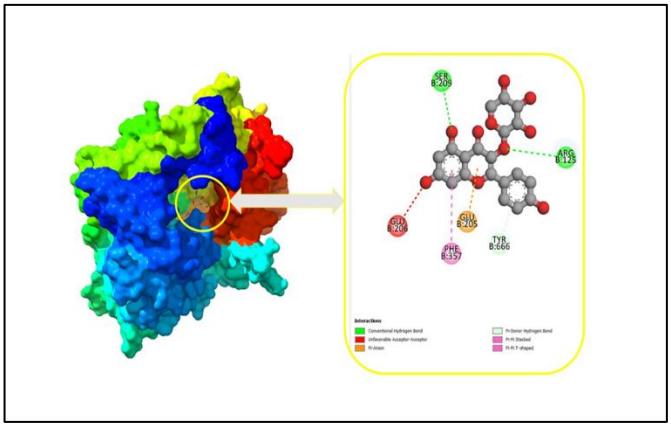


Figure 6: Docking internations of ligand 9 with human dipeptidyl peptidase-IV (PDB ID: 4A5S), outlining critical binding interactions and implications for drug design.

docked with Human dipeptidyl peptidase-IV (PDB ID: 4A5S) it showed different types of interaction including following Conventional Hydrogen Bond SER B:209, ARG B:125. Unfavorable Acceptor-Acceptor with GLU B:206. Pi-Anion with GLU B:205. Pi-Donor Hydrogen Bond TYR B:666. Pi-Pi Stacked and Pi-Pi T Shaped with PHE B: 357.

Computational ADMET data prediction

In the last five years, the pharmaceutical industry has uniformly adopted the integration of ADMET (absorption, distribution, metabolism, excretion, and toxicity) research into the early stages of drug discovery (Clark, 2005). Because unfavorable pharmacokinetics and toxicity are major causes of drug development's failure at the expensive late stage (Fengxu Wu, 2020). Computational approaches may help minimize these risks. (Douglas E. V. Pires, 2015) To avoid these complications, the most important ADMET properties for selected Kaempferol derivatives. To understand the absorption aspect, selected the following two parameters: water solubility and human intestinal absorption. According to the data collected from the pkCSM server, The standard drug Metformin has a low human intestine absorption rate of only 59.401%. In contrast to that, four of our proposed compounds have higher human interest in absorption rate whereas compounds 06 and 08 showed the highest score of 82.505%. According to the water solubility test (calculated in Log S), the range from highly soluble compounds to insoluble compounds is <-10 poorly <-6 moderately <-4 soluble <-2 very <0 < highly. The nine selected derivative compounds were declared as very soluble, showed no skin sensitization and hepatoxicity.

Table 2. ADMET Data Prediction

SI No	CID	Absorption		Distribution		Metabolism		Excretion		Toxicity		
		Water solubility Log S	Human Intestinal Absorption (%)	VDss (log L/kg)	BBB Permeability	CYP450 1A2 Inhibitor	CYP450 2C9 Substrate	Total Clearance (ml/min/kg)	Renal OCT2 substrate	Max. tolerated dose (Log mg/kg/day)	Skin Sensitization	Hepatotoxicity
01	5481882	-2.967	59.181	1.135	-1.243	No	No	0.431	No	0.543	No	No
02	21310440	-2.967	59.181	1.135	-1.243	No	No	0.431	NO	0.543	No	No
03	14749097	-2.967	59.181	1.135	-1.243	No	No	0.431	No	0.543	No	No
04	44258911	-2.967	59.181	1.135	-1.243	No	No	0.431	No	0.543	No	No
05	5316673	-2.969	60.006	1.15	-1.265	No	No	0.431	No	0.544	No	No
06	15558501	-2.892	82.505	0.011	0.142	Yes	No	-35.249	No	0.438	No	No
07	22838616	-2.969	60.006	1.15	-1.265	No	NO	0.431	No	0.544	No	No
08	5835713	-2.892	82.505	0.011	0.142	Yes	No	-35.249	No	0.438	No	No
09	14749098	-2.967	59.181	1.135	-1.243	No	No	0.431	No	0.543	No	No

Table 3. Data of (QSAR) and PlogIC50

Ligand	CID	Chiv5	bcutm1	(MRVSA9)	(MRVSA6)	(PEOEVSA5)	GATSv4	J	Diameter	PIC50
01	5481882	2.151	4.119	10.969	46.622	0.0	0.957	1.551	12.0	4.88
02	21310440	2.151	4.119	10.969	46.622	0.0	0.957	1.551	12.0	4.88
03	14749097	2.151	4.119	10.969	46.622	0.0	0.957	1.551	12.0	4.88
04	44258911	2.151	4.119	10.969	46.622	0.0	0.957	1.551	12.0	4.88
05	5316673	2.292	4.119	10.969	46.622	0.0	1.003	1.567	12.0	4.89
06	15558501	2.292	4.119	10.969	46.622	0.0	1.003	1.567	12.0	4.89
07	22838616	2.292	4.119	10.969	46.622	0.0	1.003	1.567	12.0	4.89
08	5835713	2.292	4.119	10.969	46.622	0.0	1.003	1.567	12.0	4.89
09	14749098	2.151	4.119	10.969	46.622	0.0	0.957	1.551	12.0	4.88

Quantitative structure-activity relationship (QSAR) and PlogIC50

Drug development has been altered by computational technologies in several ways (Areej Abuhammad, 2016). QSAR utilizes the computational method and multiple linear regression (MLR) to determine the relationship between the chemical compound's biological and structural activity. Through the use of computer-aided drug design tools, this QSAR study allowed researchers to examine the impact of very basic and straightforward descriptors in determining biological activities. The results provided insight into the critical elements that support the creation of innovative, powerful compounds (David Ebuka Arthur, 2020). The standard ranges of QSAR are considered below 10. Any molecule lower than 10 is potential. The overall value of QSAR and PlogIC50 was positive (Table 5). They satisfied all requirements. The highest and lowest results of PlogIC50 are 4.88 and 4.89, respectively. The outcome of PlogIC50 suggests that the compound might be therapeutically effective against the targeted disease.

Discussion

Our study showed that Kaempferol derivatives had promising as an anti-diabetic agent, with Pa scores ranging from 0.543 to 0.547. These scores suggest that these compounds could be effective in developing new treatments for diabetes. Given the rising number of diabetes cases and the need for safer, more effective medications, Kaempferol derivatives offer a valuable alternative to synthetic drugs. Future research should focus on understanding how these compounds work to optimize their use in managing diabetes.

The derivatives (L1-L9) have molecular weights of 418.35-432.38, 10 hydrogen bond acceptors, 6 hydrogen bond donors, molar refractivity of 102.17-106.97, and consensus Log Po/w values of 0.28-0.67. However, having six hydrogen bond donors does not align with Lipinski's Rule of Five, raising concerns about bioavailability. Despite this, their potential benefits justify further research. Additional testing will help refine the selection and address these issues. This initial screening lays the groundwork for developing effective anti-diabetic drugs.

In the molecular docking study, the binding affinities of Metformin and nine Kaempferol derivatives to Human CYP3A4 and Human DPP-IV were compared. The results revealed that specific Kaempferol derivatives (06, 07, and 09) exhibited higher binding affinities than Metformin. This suggests the potential for these derivatives to form more stable complexes with the target proteins, indicating promise for drug development. However, it's important to note that further experimental validation is required to confirm their pharmacological relevance. Overall, the study underscores the importance of exploring natural compounds such as Kaempferol for enhancing therapeutic options in managing diabetes.

In the docking analysis, Ligand 6 formed Conventional Hydrogen Bonds and Pi-Alkyl bonds with Human CYP3A4, Ligand 7 exhibited Conventional Hydrogen Bonds and Pi-Pi Stacked interactions, and Ligand 9 showed Conventional Hydrogen Bonds, Pi-Pi stacking, and Pi-Alkyl bonds. For Human DPP-IV, Ligand 6 displayed Conventional Hydrogen Bonds, Pi-Pi stacking, and Pi-Anion bonding. Ligand 7 formed Conventional Hydrogen Bonds, Pi-Pi stacking, and Carbon Hydrogen Bonds. Ligand 9 showed Conventional Hydrogen Bonds, Pi-Pi stacking, and some unfavorable Acceptor-Acceptor interactions. These results suggest that Kaempferol derivatives could form more stable and effective complexes with target proteins than Metformin, potentially leading to better therapeutic options for diabetes management with fewer side effects.

Metformin has a low intestinal absorption rate of 59.401%. In comparison, four of our proposed compounds show higher absorption rates, with compounds 06 and 08 achieving the highest at 82.505%. All nine derivatives are very soluble in water, showing no skin sensitization or hepatotoxicity. This indicates that they could be more effective and safer alternatives to Metformin.

The findings highlight key factors essential for developing innovative and potent compounds. A QSAR value below 10 is considered indicative of potential effectiveness. In this study, both QSAR and PlogIC50 values were positive (Table 5) and met all criteria. The PlogIC50 values ranged from 4.88 to 4.89, suggesting the compounds may be therapeutically effective against the target disease.

Conclusion

Integrating advanced computational methodologies in drug design, such as ADMET evaluation, ligand drug-likeness quantification, and molecular docking analysis, has unveiled potential inhibitors for diabetes receptors. Nine Kaempferol derivatives have emerged as promising candidates, demonstrating potent activity against target proteins, favorable drug-like properties, and minimal toxicity. By employing AutoDock Vina, the binding affinities of these derivatives were evaluated against Human CYP3A4 and Human dipeptidyl peptidase-IV (DPP-IV), revealing strong binding with energies ranging from -9.3 kcal/mol to -10.0 kcal/mol for CYP3A4 and -7.8 kcal/mol to -9.1 kcal/mol for DPP-IV. Remarkably, all compounds exhibited improved water solubility, high gastrointestinal absorption rates, and compliance with Lipinski's rule, indicating their drug-like characteristics. Positive QSAR and PlogIC50 values further endorse the efficacy of these compounds as potential antidiabetic agents. The computational data suggests a potential for reduced side effects compared to existing medications, necessitating further exploration through clinical trials and laboratory experiments. This study lays the groundwork for further research, extending from computational analyses to in vitro and in vivo investigations. These steps are essential to fully explore these promising Kaempferol derivatives' therapeutic potential and safety.

Data Availability Statement

The data relevant to the study are either included in the article or provided as supplementary material. To download high-resolution versions of the figures, tables, and other raw data, kindly visit the provided link https://drive.google.com/drive/folders/13rtSrrzOsJsPM0IU6dVxM0E7SFRYorxo?usp=sharing

Authors Contributions

Research design, planning, data collection, analysis, interpretation and manuscript draft preparation was performed by SA. OF and AR contributed to data collection, analysis, and reviewed the manuscript. All authors contributed to drafting the manuscript and approved the final version for submission.

Acknowledgements

The authors are grateful to Mr. Shopnil Akash, Department of Pharmacy, Daffodil International University, Bangladesh for his valuable suggestions, guidance and help in the collection, analysis and interpretation of data and writing of manuscript.

Conflict of Interest

The authors declare no conflicts of interest regarding the research conducted and the publication of this study.

Funding Information

This research was not supported by any external funding sources.

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