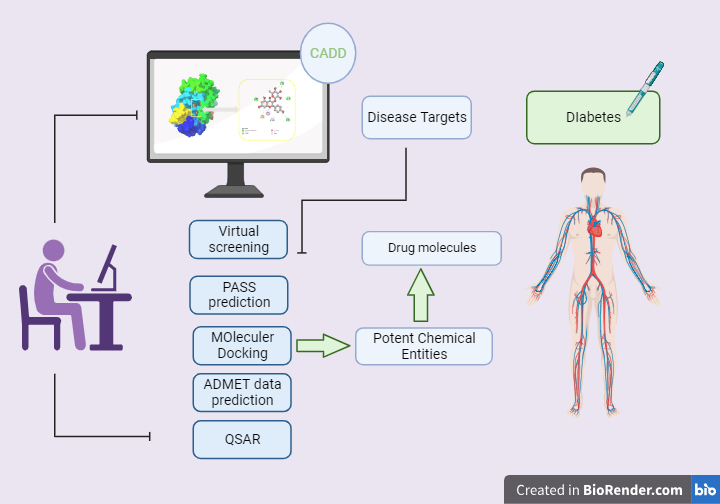
**Kaempferol derivatives as a** **potential inhibitor of Diabetes receptor by computational drug design approach**

**Abstract**

It is increasingly apparent that not only is a cure for the current worldwide diabetes epidemic required but also for its major complications, affecting both small and large blood vessels. These complications occur in the majority of individuals with both type 1 and type 2 diabetes. Among the most prevalent microvascular complications are kidney disease, blindness, and amputations, with current therapies only slowing disease progression **https://journals.physiology.org/doi/full/10.1152/physrev.00045.**This study investigates the Kaempferol derivatives as a potential inhibitor of Diabetes receptor using molecular modeling methods, including ADMET,(QSAR) and PlogIC50, molecular docking. The effectiveness of these compounds as anti-diabetic drugs was assessed using the Prediction of Activity Spectra for Substance (PASS) prediction, which demonstrated that ligand no:( 06,07,09) bind to the Crystal structure of human CYP3A4 bound to metformin (PDB ID 5G5J) with binding affinities ranging from -9.8 kcal/mol to -10.0 kcal/mol and Human dipeptidyl peptidase-IV (PDB ID: 4A5S) with binding affinities ranging from -8.3 kcal/mol to -8.6 kcal/mol. Drug similarity and ADMET prediction assessments of pharmacokinetics properties revealed that the compounds were likely non-carcinogenic, non-hepatotoxic, and rapidly soluble. The overall value of QSAR and PlogIC50 was positive and They satisfied all requirements. These findings could facilitate the discovery of new antidiabetic drugs.

**Graphical Abstract**

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**Keywords:** Kaempferol, Molecular docking, antidiabetic drug, Pharmacokinetics

1. **Introduction**

The International Diabetes Federation estimates that 366 million people had diabetes in 2011 and that by 2030, this figure will have risen to a staggering 552 million worldwide. In 2011, diabetes was the cause of 4.6 million deaths and accounted for 11 % of adult healthcare expenditure in the USA [1]. The increasing incidence of both type 1 diabetes (T1D) and type 2 diabetes (T2D) elevates the complications of diabetes as one of the most important current public health issues. quick screening of probable candidates is made possible by computational drug design, an effective method in contemporary pharmaceutical research. The focus of this research is on kaempferol derivatives, a group of naturally occurring flavonoids with a variety of bioactivities, including anti-diabetic effects. 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, enhancing their therapeutic potential by methodical chemical alterations.

**Computational method and working procedure**

**2.1 Pass prediction**

The PASS prediction has been made to determine the capability of the anti-diabetic drug. The online web program PASS <http://www.way2drug.com/passonline/index.php> 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( <http://www.swissadme.ch/> ). These programs are well-known for their ability to determine the PASS spectrum by making use of 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.

**2.2 Biological pass prediction spectrum computation of Chlorogenic acid derivatives**

The probable biological spectrum for Kaempferol derivatives has been predicted by applying the web server <http://www.way2drug.com/passonline/index.php>. 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 Chlorogenic acid 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 |

**2.3. Protein preparation and molecular docking study and visualization.**

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 <https://www.rcsb.org/> . 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)

Figure 1. Three-dimensional protein structure

|  |  |
| --- | --- |
| Human CYP3A4 bound to metformin (PDB ID 5G5J) | Human dipeptidyl peptidase-IV (PDB ID: 4A5S) |
| Ref. [1] | Ref. [2] |
|  | |

**2.4 Ligand optimization**

The chemical structure of natural compounds such as Kaempferol derivatives was drawn using the Hypercom 8.0 package after that all the structures were pre-optimized by applying the molecular mechanics force field (MH+, AMBER) Strategic [44,45]. The molecular structure was analyzed using the semi-empiricalAM-1 method to locate the homologs that had the lowest amount of energy. Then the optimized chemical structures were saved in PDB format, molecular docking, drug-likeness, ADMET, and some additional types of analysis.

**2.5 ADMET, drug-likeness, and Lipinski Rule**

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. The web server <https://biosig.lab.uq.edu.au/pkcsm/> 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 <http://www.swissadme.ch/>

**3. Result and Discussion**

**3.1 Lipinski Rule, Pharmacokinetics, and Drug Likeness**

Most drug candidates either fail to advance through the clinical or preclinical phases for several reasons or never reach the market. The creation of reliable computational methods for the assessment of a novel drug candidate's drug-likeness is crucial to raising the success rate of drug research and development efforts during the trial stage. Christopher A. Lipinski created the drug-likeness prediction model in 1997, which contained molecular descriptors linked to the many variables that can distinguish between potential drugs and non-drugs. Topological polar surface area, the number of rotatable bonds, the hydrogen bond acceptor and donor, and molecular weight are some of these elements. 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 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 |

**3.2 Molecular docking against targeted protein**

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 3:** Molecular docking score

|  |  |  |
| --- | --- | --- |
| Drug Molecules No | Human CYP3A4 bound to metformin (PDB ID 5G5J) | Human dipeptidyl peptidase-IV (PDB ID: 4A5S) |
|  | Binding Affinity(kcal/mol) | Binding Affinity(kcal/mol) |
| 5481882 | -9.6 | -8.3 |
| 21310440 | -9.7 | -7.8 |
| 14749097 | -9.6 | -9.1 |
| 44258911 | -9.6 | -8.4 |
| 5316673 | -9.7 | -8.5 |
| 15558501 | -9.8 | -8.6 |
| 22838616 | -10.0 | -8.5 |
| 5835713 | -9.3 | -9.1 |
| 14749098 | -9.9 | -8.3 |

**Table 4: Chemical structure with 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** |

**3.4 Protein-ligand interaction and Molecular docking poses**

A ligand's affinity for a receptor is significantly influenced by the interactions that are the main factors in molecular docking, which enables prediction or research of these interactions. Molecular docking studies suggest that the receptor-ligand complex with the lowest excretion of energy has the maximum binding affinity. From the previous step, we selected ligand no: (06,07,09) as the most suitable ligands with the lowest binding energy and the highest binding affinity score for selected proteins. The receptor protein-ligand docked complex is shown in Figure 4

# Figure 4. Docking interactions between the proposed compound

|  |
| --- |
|  |
| Ligand 6 Docking interactions between protein Human CYP3A4 bound to metformin (PDB ID 5G5J) |

|  |
| --- |
|  |
| * **Ligand 7** **Docking interactions between protein Human CYP3A4 bound to metformin (PDB ID 5G5J)** |

|  |
| --- |
|  |
| * **Ligand 9** **Docking interactions between protein Human CYP3A4 bound to metformin (PDB ID 5G5J)** |

|  |
| --- |
|  |
| Ligand 6 Docking interaction between Human dipeptidyl peptidase-IV (PDB ID: 4A5S) |

|  |
| --- |
|  |
| Ligand 7 Docking interaction between Human dipeptidyl peptidase-IV (PDB ID: 4A5S) |

|  |
| --- |
|  |
| Ligand 9 Docking interaction between Human dipeptidyl peptidase-IV (PDB ID: 4A5S) |

* 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 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

**3.8 Computational ADMET Data Prediction**

Since more than 50% of medications never make it to clinical trials due to having the wrong ADMET features, predicting ADMET qualities is crucial to ensure the overall effectiveness and safety of medicinal compounds. For the chosen medicinal compounds, pkCSM's innovative graph-based technique accurately predicted crucial ADMET features Drug development has a high attrition rate, with poor pharmacokinetic and safety properties a significant hurdle. Computational approaches may help minimize these risks. <http://structure.bioc.cam.ac.uk/pkcsm>

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.

Table 5:

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | CID | **Absorption** | | **Distribution** | | **Metabolism** | | **Excretion** | | **Toxicity** | | |
| SI No | 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 |

**3.9 Quantitative structure-activity relationship (QSAR) and PlogIC50**

Table:6

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Data of QSAR | | | | | | | | | | |
| **Ligand** | **CID** | **Chiv5** | **bcutm1** | **(MRVSA9)** | **(MRVSA6)** | **(PEOEVSA5)** | **GATSv4** | **J** | **Diametert** | **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 |

**QSAR** is one of the frequently used techniques in Ligand-based design. QSAR utilizes the computational method and multiple linear regression (MLR) to determine the relationship between the chemical compound’s biological and structural activity. The standard ranges of QSAR are considered below 10. Any molecule lower than 10 is potential, according to theory [153] [137]. The overall value of QSAR and PlogIC50 was positive (Table:6). They satisfied all requirements. The highest and lowest result of PlogIC50 is 4.88 and 4.89, respectively. The outcome of PlogIC50 suggests that the compound might be therapeutically effective against the targeted disease.

**4.0 Conclusion**

The application of advanced computational strategic and combined drug design approaches, such as ADMET evaluation, ligand drug-likeness quantification, and molecular docking analysis, has led to the identification and characterization of potential inhibitors of Diabetes receptors. Through these methods, a total of 9 Kaempferol derivatives have been demonstrated to have high potency against the target protein, outstanding drug-like properties, and no toxic effect. Moreover, the binding affinities of the selected natural biomolecules were measured using the AutoDock Vina tool, resulting in the of -9.3 kcal/mol to -10.0 kcal/mol against Human CYP3A4 bound to metformin (PDB ID 5G5J) and -7.8 kcal/mol to -9.1 kcal/mol against Human dipeptidyl peptidase-IV (PDB ID: 4A5S) All of the drug candidates were found to have the following qualities: improved water solubility, lack of harmful effects, high rate of gastrointestinal (G.I.) absorption, fulfillment of the Lipinski rule, and attributes that were similar to drugs. The overall value of QSAR and PlogIC50 was positive and They satisfied all requirements. As a result, it has been established that the aforementioned drug candidates are effective antidiabetic medications. Our computational data also suggests that these pharmaceuticals will have significantly fewer side effects than those of established medications if they are tested in clinical trials or laboratory settings for designing and developing newer and safer drugs from natural sources, these phytochemical compounds should be carried out from computational (in vitro and in vivo), preclinical, and clinical trials, to find out their practical value.

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