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# In silico Comparison of Ocimum Kilimandscharicum Biomolecules as Novel Drug Targets for Diabetes

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**Abstract**

The goal of this study was to trace out apparent antidiabetic potential of different phytoconstituents of *Ocimum kilimandscharicum.* The study was also anticipated to establish a link between certain phytoconstituents and 4 receptors playing vital role in development of diabetes, using *in silico* procedures. All the phytoconstituents of *Ocimum kilimandscharicum* reported till date were screened for ADMET parameters. Selected phytoconstituents were further explored for their antidiabetic potential by molecular docking carried using Molegro virtual docker. Four PDB's including 1IR3, 1US0, 5NN6 and 2QV4 were appraised in the study for Insulin receptor, Aldose Reductase, Alpha amylase and Alpha glucose respectively. Out of total 54 phytoconstituents of *Ocimum kilimandscharicum*, 24 were selected on the basis of ADMET profile. 9 phytoconstituents reflected comparative MolDock score and higher number of hydrogen bonding in contrast to internal ligands and selected standard drugs. These compounds include Fisetin, Galuteolin, Lithospermic Acid, Rosmarinic acid, Rutin, Vanillic Acid, Turkesterone, Apigenin and Quercetin. The entire study gives understanding of the molecular relationship of the phytoconstituents with selected receptors which was found to be even better than the standard drugs available in the market and hence leads us to say that plant presumably has antidiabetic potential.

**Key Words:** Molegro Virtual Docker, Antidiabetic, rutin, turkesterone, quercetin, diabetes mellitus, ADMET

## Introduction

'*In silico*' refers to experiments carried through computer simulation, such semiconductor devices are made by using silicon and this technique is often used to replace *in vivo* and *in vitro* techniques. The '*in silico*' term's historical context is obscure, with just a few experts claiming to have had a role in its inception[1]. In the modern scenario, computational techniques like molecular docking tools are being utilized to develop new lead compounds by studying the interactions between proteins and ligand molecules [2]. Type 2 diabetes, commonly known as diabetes mellitus, is one of the most common chronic diseases and, without a doubt one of the most challenging health concerns of the twenty-first century[3]. In both developed and developing nations, it is the fifth greatest cause of mortality, and it appears to be pandemic in many countries. Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia as well as impaired glucose, protein, and fat digestion[4]. Since ancient times, the different plants have been used as medicines all across the world. Moreover, even in current times, search for alternative therapies is drawing attention of researchers for a source of newer phytomolecules. It's interesting to consider that much of the world's population is relying on plant-based products. India is home to a diverse range of plant species, some of which are well-known for their healing powers and others which are still unidentified for therapeutic values.

*Ocimum kilimandscharicum* seed, bark, fruits, leaves, and roots are used to cure a variety of diseases and illnesses. Leaves contain the majority of medicinal active substances[5]. This plant is frequently used in conventional medicine to cure a variety of illnesses such as colds, coughs, stomach aches, measles, and diarrhoea[6]. By inhaling crushed leaves or inhaling the vapor of boiling leaves, the leaves cure a congested chest, cough and cold. Measles can be cured by drinking a leaf infusion. The physiologically active components of essential oils function as insect repellents [6-8]. Some farmers also combine stored meals with dried leaves for Protection against insect pest damage in storage using Ocimum kilimandscharicum[9]. Ocimum kilimandscharicum have been reported for antioxidant, antifungal, antibacterial activity, larvicidal, anti-diarrhoeal activity, antimelanoma, radioprotective activity, antinoceptive activity and mosquito repellant activity[10].

ADMET and Molecular docking analysis are remarkable tools in the process of drug discovery[11]. By utilising *in silico* approaches like bioinformatics parameters, different types of pharmacological targets

may be categorized [12]. It is indeed used to figure out how the compounds' structural and functional relationships work[13]. Combining in-silico techniques with plant components allows for new possibilities in disease treatment. In addition, combining the databases of digital libraries with natural resources opens up new drug development pathways [14]. On the basis of traditional usage and the integrity of *in silico* analysis method, the current molecular docking study was developed to determine the antidiabetic efficacy of plant *Ocimum kilimandscharicum*.

## MATERIAL METHODS

### Software and hardware

In the present study structures of phytoconstituents were retrieved from Chemspider and Pubchem database. Further Openbabel 3.0 was used for format conversion, ADMETlab 2.0 for admet evaluation, and Molegro Virtual Docker (MVD) version for docking analysis using on a Windows 10 64-bit machine with an Intel i5 CPU 2.13 GHz and 4GB DDR4 RAM.

### Ligands selection and preparation

Using the Pubchem chemical database and chemspider, the structure of different phytoconstituents of *Ocimum kilimandscharicum* was obtained[15]. Chemdraw ultra software was also used to clear up the structure[16]. Openbabel software was used to acquire smile formats[17]. MarvinSketch 5.11.4 was used to create the ligands. Hydrogen explciting and conversion of 2D molecules into 3D [18]. The ligand's missing or absent bonds, charge and hybridization state, if any, was all be restored using MVD[19].

### Selection and preparation of PDB

Protein Data Bank (http://www.rcsb.org/) is being used to obtain all 3D structures of PDBs. PDBs were chosen based on resolution and a literature search for a specific target. Different PDBs for Insulin Receptor, Aldose Reductase, alpha amylase and alpha glucosidase were chosen including 1IR3, 1US0, 5NN6 and 2QV4 for their respective targets[20].

### QSAR analysis

Along with Molinspiration, Zinc15 is a free online tool that assists in tracing out critical parameters necessary for ligand selection and screening. Both are used in the study to conduct QSAR simulations and examine possible functionalities of biological objects [24].

### ADMET studies

ADMETlab 2.0 was used to conduct the ADMET investigations. The ligand structure was converted to smiles format using the Open Babel programme. Smile formats are then imported into ADMETlab 2.0. Molecular weight, Los value, log p value, HIA, PPB, NHA, NHD, TPSA, P-gp substrate and other molecular aspects of the ligand were then examined. Aside from that Lipinski rule, Pfizer rule, GSK rule and Golden Triangle rule are all taken into account. Acute Toxicity Rule and SureChEMBL Rule, as well as toxicological characteristics such as DILI, H-HT, and Carcinogenicity are all thoroughly examined[21].

### Molegro Virtual Docker

MVD is a remarkable approach for predicting interactions between proteins and ligands. It is a truly incredible cutting-edge instrument for doing professional docking evaluation review. In comparison to other readily available techniques, it produces the most promising results in terms of ligand binding tendencies. With MVD, the percentage of result was determined to be 87, FlexX2 (57.9%), Surflex (75.3%), Gold (78.2%) and Glide (81.8%) percent[22]. After removing any water and cofactors, if any, a selected PDB was imported, and protein preparation was completed by correcting any warnings detected in the structure. PDB also has internal ligands that help it identify a surface to bind with. The surface was recognized first, followed by the cavity. Cavities are grid locations where ligand is inserted.

The ligand reset view was completed after the import. The docking procedure was then carried out. The docking results were examined, and all interactions between the target and the ligand were annotated. Moldock score, number of interaction and hydrogen bonding were used to calculate the *in silico* findings of the ligand.

## RESULTS AND DISCUSSION

### Validation of docked complex

Internal ligand was obtained from the co-crystallized structure of the protein, and validation was accomplished by docking the internal ligand with a particular PDB.

### Lipinski's rule of five and ADMET studies

Total 54 phytoconstituents of *Ocimum kilimandscharicum*, were screened by ADMET filter out of which 24 followed the ADMET profile parameters (Table 1). Solubility, SA score, TPSA, PAINS, Pgp-substrate, Plasma Protein Binding, Human Intestinal Absorption, Carcinogencity, Genotoxic, and Carcinogenocity Rule were all taken into consideration while choosing phytoconstituents for docking. Fisetin, Galuteolin, Lithospermic Acid, Rosmarinic acid, Rutin, Vanillic Acid, Turkesterone, Apigenin and Quercetin gave best docking results.

### Docking Results

MVD is used to dock all of the selected phytoconstituents with four different PDBs. Moldock score, total number of ligand-protein interactions and hydrogen bonds were all used to calculate binding affinity. The length of the hydrogen bond is also considered. All of the results were based on the number of ligand-protein interactions and hydrogen bonds found to be between 1 and 21. The majority of compounds have a strong affinity for receptors. Internal ligand and phytoconstituents comparison data was shown in table 2.

### Insulin Receptor (IR)

Moldock score value for internal ligand (ANP) was found to be -141.83 with 7 hydrogen bonds and standard drug Glibenclamide showed -125.221 with 5 H-bonds with Insulin Receptor. On the other hand selected phytoconstituents Apigenin, Fisetin, Galuteolin, lithospermic acid, rosmarinic acid, rutin, turkesterone, quercetin and vanillic acid showed comparable results for moldock score and hydrogen bond as -91.7(4), -93.57(6), -111.63(11), -167.96(11), -123.945(9), -144.004(11), -119.00(8), -97.9(7) and -65.6219(4) respectively. Galuteolin, lithospermic acid and rutin exhibited remarkable 11 hydrogen bonds with highest moldock shown by lithospermic acid (Figure 1) in contrast to that of standard drug Glibenclamide and internal ligand.

### Aldose Reductase (AR)

Internal ligand (LDT_320) gives the value of Moldock score -147.84 with Aldose Reductase. Whereas Tolrestat have moldock score -128.43 with 7 hydrogen bond. In contrast to internal ligand and standard drug selected phytoconstituents Apigenin, Fisetin, Galuteolin, lithospermic acid, rosmarinic acid, rutin, turkesterone, quercetin and syringic acid showed comparable results for moldock score and hydrogen bond as -137.39(7), -131.10(10), -144.20(19), -17.24(9), -176.16(13), -170.26(11), -131.9(8), -144.06(8) and -113.60(7) respectively. Maximum 19 interactions were shown by Galuteolin (Figure 2).

### Alpha glucosidase 5NN6

Moldock score for the internal ligand 5nn6 was found to be -119. Whereas, Acarbose have value for moldock score as -78.0998 with 11 hydrogen bonds. In contrast to internal ligand and standard drug selected phytoconstituents Apigenin, Fisetin, Galuteolin, lithospermic acid, rosmarinic acid, rutin, turkesterone, Quercetin and vanillic acid exhibited comparable results for moldock score and

hydrogen bond as -69.23(5), -87.6257(6), -55.1833(7), -85.6225(5), -110.689(10), -80.6478(9), -83.9186(8), -73.23(5) and -57.1733(4) respectively. Turkesteron formed shortest bond length of 1.63 Å given in figure 3.

**Alpha amylase**

Moldock score for the internal ligand 2QV4 NAG_497 was found to be -65.54 with 7 hydrogen bonds. Whereas Acarbose have value for moldock score as -78.0998 and 8 hydrogen bonds. In contrast to internal ligand and standard drug selected phytoconstituents Apigenin, Fisetin, Galuteolin, lithospermic acid, rosmarinic acid, rutin, turkesterone, Quercetin and caffeic acid showed comparable results for moldock score and hydrogen bond as -87.47(5), -81.5995(6), -138.578(8), -119.084(7), -67.5915(9), -102.751(13), -106.572(5), -91.46(5) and -82.65 (6) respectively. Rutin showed max interaction 13 (figure 4) where as shortest bond was formed by Syringic acid with bond length 1.72 Å.

**Table 1: ADMET profile of selected Phytoconstituents of *Ocimum kilimandscharicum***

| Sr.no. | name | **LogS** | **LogP** | **Pgp-sub** | **MW** | **nHA** | **nHD** | **TPSA** | Lipinski | Pfizer | GSK | GoldenTriangle |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Apigenin | -3.606 | 3.307 | 0.82 | 270.05 | 5 | 3 | 90.9 | + | + | + | + |
| 2 | turkesterone | -2.766 | 0.559 | 0.997 | 496.3 | 8 | 7 | 158.68 | + | + | - | + |
| 3 | FISETIN | -3.704 | 2.428 | 0.008 | 286.05 | 6 | 4 | 111.13 | + | + | + | + |
| 4 | galuteolin | -3.842 | 0.548 | 0.954 | 448.1 | 11 | 7 | 190.28 | - | + | - | + |
| 5 | lithospermic acid | -4.061 | 1.951 | 0.004 | 538.11 | 12 | 7 | 211.28 | - | + | - | - |
| 6 | rosmarinic acid | -2.432 | 1.775 | 0.004 | 360.08 | 8 | 5 | 144.52 | + | + | + | + |
| 7 | rutin | -3.742 | -0.038 | 0.997 | 610.15 | 16 | 10 | 269.43 | - | + | - | - |
| 8 | vanillic acid | -1.771 | 1.396 | 0.003 | 168.04 | 4 | 2 | 66.76 | + | + | + | - |
| 9 | quercetin | -3.671 | 1.767 | 0.005 | 302.04 | 7 | 5 | 131.36 | + | + | + | + |
| 10 | stigmasterol | -6.736 | 7.5 | 0.936 | 412.37 | 1 | 1 | 20.23 | + | - | - | - |
| 11 | caffeic acid | -1.118 | 1.43 | 0.024 | 180.04 | 4 | 3 | 77.76 | + | + | + | - |

**Table 2: Docking results of selected phytoconstituents of *Ocimum kilimandscharicum***

| **Sr no** | **Ligand/Internal ligand** | **PDB** | **MolDock Score** | **Interaction** | **HBond** |
|---|---|---|---|---|---|
| **1.** | Anp | 1IR3 | -141.83 | -144.151 | -7.94 |
| 2. | Apigenin | 1IR3 | -91.7 | -107.01 | -9.36 |
| 3. | Turkesterone | 1IR3 | -119.00 | -132.224 | -14.716 |
| 4. | Fisetin | 1IR3 | -93.57 | -111.239 | -10.9924 |
| 5. | Galuteolin | 1IR3 | -111.635 | -135.558 | -21.3309 |
| 6. | Lithospermic acid | 1IR3 | -167.962 | -154.807 | -18.5246 |
| 7. | Rosmarinic acid | 1IR3 | -123.947 | -130.665 | -16.4972 |
| 8. | Rutin | 1IR3 | -144.004 | -166.178 | -17.3323 |
| 9. | Vanillic acid | 1IR3 | -65.6219 | -72.2069 | -6.20041 |
| 10. | Quercetin | 1IR3 | -97.9 | -118.57 | -11.74 |
| 11. | Glibenclamide | 1IR3 | -125.221 | -134.111 | -5.717 |
| 12. | Ldt_320 | 1US0 | -147.84 | -167.06 | -4.33 |
| 13. | Apigenin | 1US0 | -137.39 | -153.46 | -5.9 |
| 14. | Turkesterone | 1US0 | -131.927 | -157.893 | -12.3321 |
| 15. | Fisetin | 1US0 | -131.108 | -150.354 | -14.1572 |
| 16. | Galuteolin | 1US0 | -144.206 | -173.878 | -24.3734 |

| Sr no | Ligand/Internal ligand | PDB | MolDock Score | Interaction | HBond |
|---|---|---|---|---|---|
| 17. | Lithospermic acid | 1US0 | -17.2462 | -55.1767 | 12.003 |
| 18. | Rosmarinic acid | 1US0 | -176.162 | -186.561 | -20.0071 |
| 19. | Rutin | 1US0 | -170.262 | -200.918 | -18.2392 |
| 20. | Vanillic acid | 1US0 | -92.8811 | -99.5105 | -8.68767 |
| 21. | Quercetin | 1US0 | -144.06 | -163.27 | -10.27 |
| 22. | Tolrestat | 1US0 | -128.43 | -152.935 | -7.84604 |
| 23. | Nag nag bma | 5NN6 | -119 | -157.12 | -19.9 |
| 24. | Apigenin | 5NN6 | -69.23 | -85.68 | -8.42 |
| 25. | Turkesterone | 5NN6 | -83.9186 | -103.714 | -11.8857 |
| 26. | Fisetin | 5NN6 | -87.6257 | -105.89 | -9.63057 |
| 27. | Galuteolin | 5NN6 | -55.1833 | -80.6399 | -13.0276 |
| 28. | Lithospermic acid | 5NN6 | -85.6225 | -106.726 | -9.65703 |
| 29. | Rosmarinic acid | 5NN6 | -110.689 | -123.805 | -16.7732 |
| 30. | Rutin | 5NN6 | -80.6478 | -123.336 | -12.8825 |
| 31. | Vanillic acid | 5NN6 | -57.1733 | -63.7988 | -7.5 |
| 32. | Quercetin | 5NN6 | -73.23 | -96.01 | -10.52 |
| 33. | Acarbose | 5NN6 | -78.0998 | -118.599 | -16.1161 |
| 34. | Nag_497 | 2QV4 | -65.54 | -75.16 | -7.84 |
| 35. | Apigenin | 2QV4 | -87.47 | -103.22 | -4.82 |
| 36. | Turkesterone | 2QV4 | -106.572 | -118.412 | -7.63668 |
| 37. | Fisetin | 2QV4 | -81.5995 | -101.794 | -8.41078 |
| 38. | Galuteolin | 2QV4 | -138.578 | -163.815 | -14.3805 |
| 39. | Lithospermic acid | 2QV4 | -119.084 | -119.869 | -10.0401 |
| 40. | Rosmarinic acid | 2QV4 | -67.5915 | -70.9881 | -12.8987 |
| 41. | Rutin | 2QV4 | -102.751 | -121.973 | -17.0039 |
| 42. | Vanillic acid | 2QV4 | -72.3258 | -82.3273 | -7.49828 |
| 43. | Quercetin | 2QV4 | -91.46 | -113.91 | -8 |
| 44. | Acarbose | 2QV4 | 18.4527 | -18.4815 | -18.5693 |

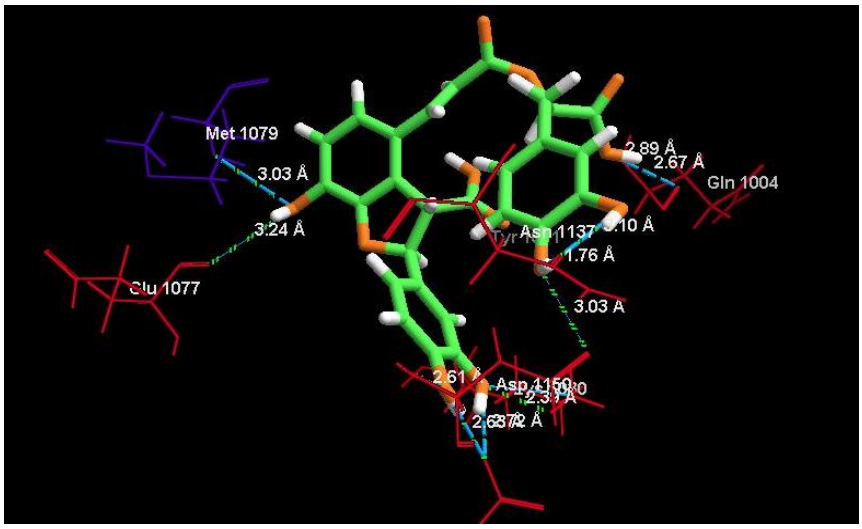


**FIG. 1: PDB-1IR3, Ligand Lithospermic acid**

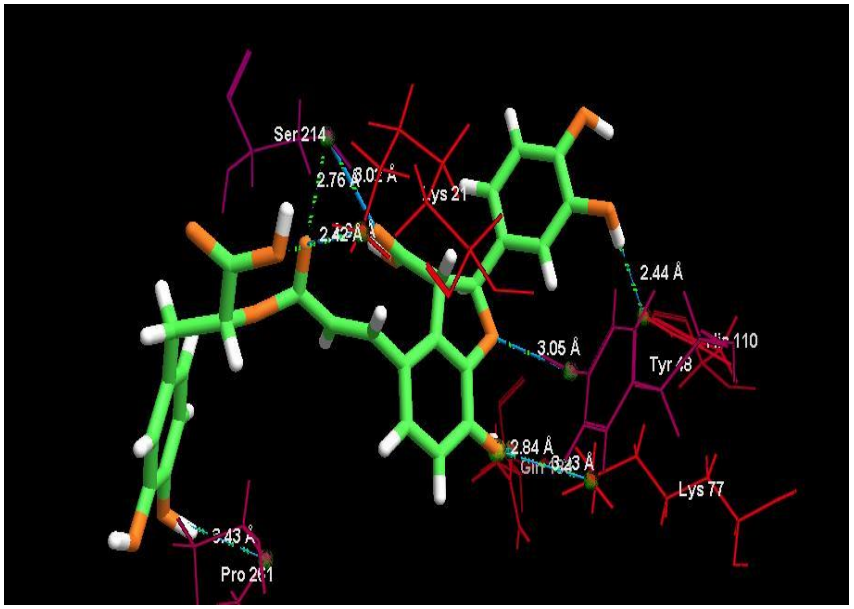


**FIG. 2: PDB-1US0, Ligand Galuteolin**

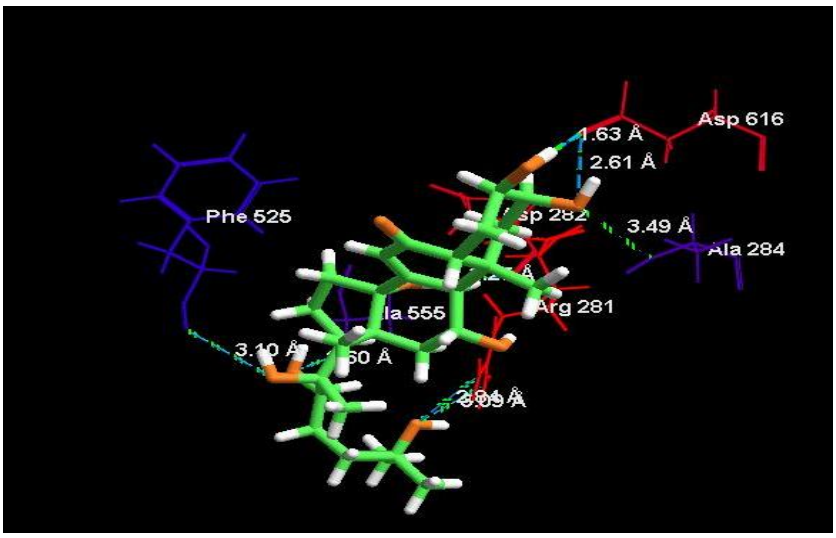


**FIG. 3: PDB-5NN6, Turkesterone**

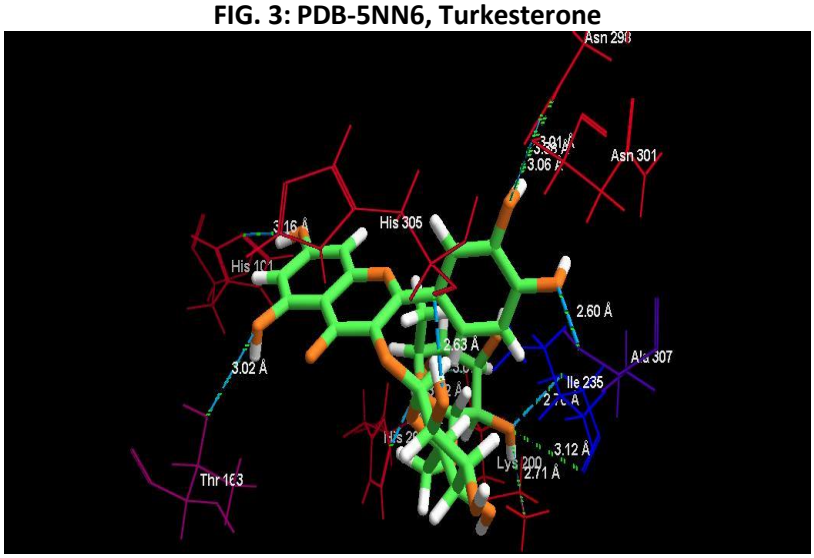


**FIG. 4: PDB-5NN6, Ligand rutin**

**Conclusion**

The goal of this work was to use molecular docking analysis to determine the antidiabetic potential of several phytoconstituents of *Ocimum kilimandscharicum*. The ADMET profile of each phytoconstituent was deeply analyzed prior to docking analysis. The ADMET data from ADMETlab 2.0 provides a detailed picture of absorption, dissolution, metabolism, excretion, and toxicity characteristics. These criteria help to assess the chosen phytoconstituent's drug likeliness. Total 54 molecules taken for study ADMET profile, out of which, 24 were selected on the basis of ADMET study. 9 phytoconstituents reflected best MolDock score and higher number of hydrogen bonding in contrast to internal ligands and selected standard drugs.

From all interpretations, it was determined that 9 of the selected 24 compounds, namely Apigenin, Fisetin, Galuteolin, lithospermic acid, rosmarinic acid, rutin, turkesterone, quercetin and vanillic acid have high affinity for all of the receptors studied. Surprisingly Galuteolin, lithospermic acid, rosmarinic acid, rutin and turkesterone exhibited equivalent or even higher number of interactions and Moldock score in contrast to that of standard drugs for all receptors. In case of Insulin receptor, lithospermic acid exhibited 11 hydrogen bonds with -167.96 Moldock score, rutin 11 with -144.00 in contrast to standard drug Glibenclamide which exhibited 5 hydrogen bonds with 125.22 Moldock score. Similarly these selected ligands expressed better interaction and Moldock score in contrast to other standard drugs including Tolrestat and Acarbose. Future research and investigation is suggested for selected 9 phytoconstituents of *Ocimum kilimandscharicum,* as these can act as new lead for treatment of diabetes mellitus. Looking at the results of *in silico* studies, it appears that the majority of ligands exhibit exceptional binding affinity for various receptors, implying a fundamental role in Diabetes mellitus.

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21. Https://zinc15.Docking.Org/.
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