Molecular docking analysis of candidate compounds derived from medicinal plants with type 2 diabetes mellitus targets

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Abstract:
Herbal drugs are used for the treatment of diseases and disorders with its less side effects, easy availability and low cost. Several bioactive compounds have been isolated from medicinal plants such as Ficus benghalensis, Ficus racemosa, Ficus religiosa, Thespesia populnea and Ficus lacorbuch were taken for screening. This study aimed to evaluate molecular interactions of selected diabetes mellitus (DM) targets with bioactive compounds isolated from Ficus benghalensis, Ficus racemosa, Ficus religiosa, Thespesia populnea and Ficus lacorbuch. In this article, screening of the best substances as bioactive compounds is achieved by molecular docking analysis with 3 best selected DM target proteins i.e., aldose reductase (AR), Insulin Receptor (IR) and Mono-ADP ribosyltransferase-sirtuin-6 (SIRT6). In this analysis six potential bioactive compounds (gossypetin, herbacetin, kaempferol, leucoperalgonidin, leucodelphinidin and sorbifolin) were successfully identified on the basis of binding energy (>8.0 kcal/mol) and dissociation constant using YASARA. Out of six compounds, herbacetin and sorbifolin were observed as most suitable ligands for management of diabetes mellitus.

Keywords: Diabetes mellitus; in silico docking; aldose reductase; insulin receptor; SIRT-6; medicinal plants

Background:
Incidence of Diabetes Mellitus (DM) is increasing every day among every population of the world. Conferring to a report by International Diabetes Federation (2011), there are 366 million people presently suffering from DM and it would up surge to 552 million till 2030. In 2000, the pervasiveness of Type 2 Diabetes Mellitus worldwide among adults was projected to be approximately 171 million [1] whereas in 2015 this number raised up to around 415 million [2]. Diabetes Mellitus is a cluster of metabolic disorder, an illness of hyperglycemia in which person grieves from disorders like failure of pancreas to produce insulin or insensitivity of cells towards insulin (insulin resistance). Diabetes Mellitus (DM) is previously called as "Non-insulin dependent diabetes mellitus" (NIDDM) [3]. Principal symptoms of DM are polyuria (recurrent urination), polydipsia (augmented thirst) and polyphagia (amplified hunger). Common explanations of Type 2 DM are lifestyle changes, obesity (defined as body mass index greater than 30), absence of physical activity, extreme body weight, deprived diet and anxiety [4]. There are numerous synthetic drugs available such as meglitinitides, biguanides, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase-IV inhibitors for treatment of DM [5, 34]. Today, researchers emphases primarily on finding of effective, low side effect and innocent therapeutic drugs to treat of DM [6]. Medicinal plants contain chemical groups (e.g., Phenolic acids, Flavonoids, Triterpenoids, Alkaloids and Carbohydrates) that hold strong anti-diabetic properties, which can normalize blood glucose level. In traditional medicine, numerous medicinal plants were used such as Ficus benghalensis (Banyana), Ficus religiosa (Peepal), Ficus racemosa (Gular), Thespesia populnea, (Paras peepal) and Ficus lacorbuch (Pakar) that avoid difficulties in organization of Diabetes Mellitus.
There are a number of targets in the form of receptors are selected for treatment of DM such as Aldose Reductase (AR), Insulin Receptor (IR) and Sirtuin-6 or Mono-ADP ribosyltransferase-sirtuin-6 (SIRT6). Many more are still under exploring study to alleviate DM. AR (EC 1.1.1.21) is a monomeric, NADP-dependent oxidoreductase enzyme and a member of aldo-keto reductase multigene superfamily. Study presented that an upsurge in AR (aldose reductase) activity leads to an enlarged accumulation of intercellular sorbitol which outcomes in boosted complication in DM [7]. Another receptor called IR (Insulin receptor) which belongs to class of tyrosinekinase, a trans membrane receptor [8]. One of the most common causes DM is inactivation of insulin receptor function [9]. IR is activated by insulin, IGF-1(Insulin-like growth factor) and IGF-II (Insulin growth factor-II) and any inequity in production or response of these factors adds to a cause in DM [10]. Mono-ADP ribosyltransferase-sirtuin-6 (SIRT6) or Sirtuin-6 is a stress receptive protein deacetylase and mono-ADP ribosyl transferase enzyme programmed by the SIRT-6 gene. SIRT-6 plays role in numerous molecular pathways such as aging, including DNA repair, telomere maintenance, glycolysis and inflammation. Sirtuin-6 is a possible therapeutic target for DM [11].

**Materials AND Methods:**

**Receptors:**
A major database CDD Conserved Domains Database in area of structural biology and computational biology for research and education [12,13]. The three-dimensional crystal structure taken form Protein Data Bank (PDB) ie., AR (PDB ID:1US0) [14] IR (PDB ID:1IR3) [14] SIRT-6 (PDB ID: 3K35) [15] (Figure 1).

**Active site identification:**
CDD BLAST [12] and Metapocket (http://projects.biotec.tu-dresden.de/metapocket/) server were used for identification of probable active sites. Discovery Studio 3.0 developed by Accelrys, used for visualization of three-dimensional complex structures and active site residues visualization (http://accelrys.com/).

**Ligands retrieval and assessment:**
For ligand retrieval and assessment used Lipinski filter free online server services for retrieval of important molecular properties of bioactive compounds such as cLogp, hydrogen bond donors/acceptor and Molar refractivity [16]. Lipinski’s rule of five were applied for selection of ligands and ADEM-TOX -Drug3 (Free ADME-Tox Tool version 3.0) used for computational prediction of Adsorption, Distribution, Metabolism, Excretion, and Toxicity properties [17].

**Docking calculation and visualization:**
YASARA Autodock VINA tool, Yet another Scientific Artificial Reality Application (YASARA) was used for docking calculation. It is an online software for molecular graphics, modeling and simulation [18]. The docking analyses of potent ligands were visualized using Discovery Studio 3.0. Interactions were calculated on the basis of binding energy and containing receptor residues (Kcal/mol).

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**Figure 1:** 3-D Structure of AR (PDB ID: 1US0), IR (PDB ID: 1IR3) and SIRT-6 (PDB ID: 3K35) visualized by Discovery Studio 3.0.
Table 1: List of selected natural anti-diabetic compounds with plant name, common name and isolation source

| S. No | Plant Name         | Sources | Bioactive Compound Details                                                                 | References |
|-------|--------------------|---------|-------------------------------------------------------------------------------------------|------------|
| 1.    | *Ficus benghalensis* (Banyana) | Bark | 6-heptatriactone-10-one, pentatriactan-5-one, meso-inositol, 5,7-dimethyl ether of leucopergonalin-3-0-α-L-rhamnioside, 5,3-dimethyl ether of leucocyanidin, 5,7,3-trimethoxy leucodelphinidin 3-O-α-L-Rhamnoside. | [19–22]   |
| 2.    | *Ficus racemosa* (Gular) | Steam, Root, Bark, Fruit. | Campestrol, Hentriacontane, Hentriacontanol, Kaemperol, Stigmasterol, Glauanol, Glauanolactate, Esters of taraxasterol, lupeolacetate, Friedelin, Cycloartenol, Euphorbol, Hexacosanoate, Taraxerone, Tinyatoxin, Sapoparinglucanol acetate, Leucocyanidin-3-0-β-D-glucopyranoside, Leucopergonalin-3-0-α-L-rhamnopyranoside, Lupeol, Cerylbravenol, Lupeol acetate, a-amyrin acetate, Leucocyanidin-3-0-α-L-rhamnopyranoside, Leucopergonalin-3-0-α-L-Rhamnoside. | [19, 23–27] |
| 3.    | *Ficus religiosa* (Peepal) | Bark | Lupeol, Stigmasterol, Lanosterol, Campesterol. Octacosanol, Methyl oleonate, lupen-3-one. | [19, 28–30] |
| 4.    | *Thespesia populnea* (Paras peepal) | Bark | Herbacetin, Quercetin, Goosypol, Popunel Calycapterin, Thespone, Thespone, Goosypetin. | [19, 31, 32] |
| 5.    | *Ficus axor buch* (Palak) | Leave, Bark | Triterpenoids, α, β-amyrin, Lanosterol, Caffeic acid, Bergerin, Camposteer, Methyl ricinolate, Scutellarein, Scutellarein, Sorbilin, Bergapten, Bergapten. | [33] |

Table 2: List of selected anti-diabetic compounds and their details

| S.N. | Compounds | PubChem CID | Molecular Formula | Molecular Weight (g/mol) | Canonical SMILES |
|------|-----------|-------------|------------------|-------------------------|-----------------|
| 1.   | 6-heptatriactone-10-one | 56613778 | C₅₆H₇₀O₂ | 532.982 | 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Table 3: Drug Likeness using Lipinski’s rule

| S. No. | Compounds | Molecular mass less than 500 | Hydrogen bond donor less than 5 hydrogen bond donors | Hydrogen bond acceptor less than 10 hydrogen bond acceptors | LogP | High lipophilicity expressed as log P less than 5 | Molar refractivity less should be between 40-130 | Status |
|--------|-----------|-----------------------------|-------------------------------------------------------|----------------------------------------------------------|------|------------------------------------------------|-----------------------------------------------|--------|
| 1.     | 6-heptatriacontene-10-one | 532.000 | 0 | 1 | 13.634 | 173.239 | Not accepted |
| 2.     | Pentatriacontan-5-one | 506.000 | 0 | 1 | 13.078 | 164.099 | Not accepted |
| 3.     | Meso-inositol | 180.000 | 6 | 6 | -3.825 | 36.041 | Not accepted |
| 4.     | Leucoperagalolin | 290.000 | 5 | 6 | 1.331 | 72.714 | Accepted |
| 5.     | Leucocyanidin | 306.000 | 6 | 7 | 1.037 | 73.879 | Not accepted |
| 6.     | Leucodelphinidin | 322.000 | 7 | 8 | 0.743 | 75.543 | Accepted |
| 7.     | α-amin | 426.000 | 1 | 1 | 8.105 | 130.674 | Not accepted |
| 8.     | Lipol | 409.000 | 1 | 1 | 8.925 | 130.649 | Not accepted |
| 9.     | Stigmasterol | 412.000 | 1 | 1 | 7.800 | 128.123 | Not accepted |
| 10.    | Lanosterol | 426.000 | 1 | 1 | 8.479 | 132.879 | Not accepted |
| 11.    | Octacosanol | 410.000 | 1 | 1 | 10.141 | 132.802 | Not accepted |
| 12.    | Methyl oleate | 286.000 | 2 | 2 | 6.197 | 91.407 | Not accepted |
| 13.    | Liposorone | 323.000 | 3 | 5 | -0.953 | 77.146 | Not accepted |
| 14.    | Campesterol | 400.000 | 1 | 1 | 7.635 | 123.599 | Not accepted |
| 15.    | Henricotane | 436.000 | 0 | 0 | 12.339 | 145.241 | Not accepted |
| 16.    | Henricotanol | 452.000 | 1 | 1 | 11.311 | 146.653 | Not accepted |
| 17.    | Kaeppelrol | 286.000 | 4 | 6 | 2.305 | 72.386 | Accepted |
| 18.    | Glaconol | 428.000 | 0 | 2 | 7.793 | 126.509 | Accepted |
| 19.    | Esters of taraxasterol | 428.00 | 1 | 1 | 8.105 | 130.674 | Not Accepted |
| 20.    | Lupoolactate | 468.00 | 0 | 2 | 8.506 | 140.197 | Not accepted |
| 21.    | Friedelin | 426.00 | 0 | 1 | 8.457 | 129.744 | Not accepted |
| 22.    | Cyclartanol | 426.00 | 1 | 1 | 8.169 | 130.719 | Not accepted |
| 23.    | Euphorbol | 440.00 | 1 | 1 | 8.725 | 137.426 | Accepted |
| 24.    | Hexacosanone | 424.00 | 0 | 2 | 9.932 | 133.115 | Not accepted |
| 25.    | Tarasorone | 424.00 | 0 | 1 | 8.327 | 129.719 | Not accepted |
| 26.    | Hixaloxin | 398.00 | 2 | 8 | 4.946 | 103.141 | Not accepted |
| 27.    | Leucoanthocyanidin | 242.00 | 2 | 3 | 2.215 | 67.219 | Accepted |
| 28.    | Herbactein | 302.00 | 5 | 40 | 2.011 | 74.090 | Not accepted |
| 29.    | Gossypol | 518.00 | 6 | 8 | 3.846 | 139.167 | Not accepted |
| 30.    | Populiferol | 242.00 | 1 | 3 | 3.174 | 3.174 | Accepted |
| 31.    | Calycaperin | 374.00 | 2 | 8 | 2.714 | 94.757 | Accepted |
| 32.    | Thespeson | 257.00 | 0 | 4 | 2.141 | 68.630 | Accepted |
| 33.    | Thespone | 240.00 | 0 | 3 | 3.218 | 68.676 | Accepted |
| 34.    | Gossypetin | 318.00 | 6 | 8 | 1.716 | 75.715 | Accepted |
| 35.    | Triterpenes | 366.00 | 5 | 5 | 5.345 | 180.92 | Not accepted |
| 36.    | β-amin | 426.00 | 1 | 1 | 8.169 | 130.719 | Not accepted |
| 37.    | Bergopterin | 328.00 | 5 | 9 | -1.301 | 72.240 | Not accepted |
| 38.    | Caffic acid | 179.00 | 2 | 4 | -0.139 | 43.812 | Not accepted |
| 39.    | Methyl ricinolate | 312.00 | 1 | 3 | 5.168 | 92.859 | Accepted |
| 40.    | Scutellarin | 461.00 | 6 | 12 | -1.644 | 103.130 | Not accepted |
| 41.    | Sorbilin | 301.00 | 3 | 6 | 2.428 | 77.366 | Accepted |
| 42.    | Bergapten | 216.00 | 0 | 4 | 2.373 | 57.435 | Accepted |
| 43.    | Bergaptenol | 202.00 | 1 | 4 | 2.071 | 52.548 | Accepted |

Table 4: FAF Drug Results: Best selected compounds on the basis of adsorption, distribution, metabolism, excretion and toxicity.

| S. No. | Compound Name | Heavy atom | Hetero atom | Solubility (mg/L) | Oral (Bioavailability) (EGAN) | Oral (Bioavailability) (VEBER) | Ratio (H/C) | 3-75 | Status |
|--------|---------------|------------|-------------|-------------------|-----------------------------|-------------------------------|-------------|------|--------|
| 1.     | Leucoperagalolin | 21 | 6 | 3803.51 | Good | Good | 0.40 | Good | Accepted |
| 2.     | Leucodelphinidin | 23 | 8 | 444470.47 | Good | Good | 0.53 | Good | Accepted |
| 3.     | Kaeppelrol | 21 | 6 | 12543.68 | Good | Good | 0.40 | Good | Accepted |
| 4.     | Leucoanthocyanidin | 18 | 3 | 17228.74 | Good | Good | 0.20 | Warning | Accepted |
| 5.     | Herbacitin | 22 | 7 | 10539.43 | Good | Good | 0.46 | Good | Accepted |
| 6.     | Populiferol | 18 | 3 | 7599.60 | Good | Good | 0.20 | Bad | Accepted |
| 7.     | Calycaperin | 27 | 8 | 6456.43 | Good | Good | 0.42 | Warning | Accepted |
| 8.     | Thespeson | 19 | 4 | 19306.11 | Good | Good | 0.27 | Warning | Accepted |
| 9.     | Thespone | 18 | 3 | 7740.16 | Good | Good | 0.20 | Warning | Accepted |
| 10.    | Gossypetin | 23 | 15 | 12386.97 | Good | Good | 0.53 | Good | Accepted |
| 11.    | Methyl ricinolate | 22 | 3 | 3645.68 | Good | Good | 0.16 | Bad | Accepted |
Table 5: YASARA Docking Calculation: Binding Energy (Kcal/mol) of receptors and ligands complexes.

| S.N. | Compound Name (CID NO.) | AR | IR | SIRT-6 |
|------|--------------------------|----|----|--------|
| 1.   | Gossypetin (5280647)     | 000008.006 | 000008.429 | 000008.569 |
| 2.   | Herbacetin (5280844)     | 000009.623 | 000008.165 | 000008.632 |
| 3.   | Kaempferol (5280863)     | 000010.034 | 000007.881 | 000008.533 |
| 4.   | Leucodelphinidin (440835) | 000008.012 | 000007.915 | 000008.234 |
| 5.   | Leucoperalgonidin (3286789) | 000009.029 | 000007.756 | 000007.874 |
| 6.   | Sorbitolin (3084390)     | 000009.391 | 000008.063 | 000008.697 |

Table 6: Interacted, Reported, Predicted active site residues of AR and compounds.

| S.N. | Compound Name | Interacted Residues | Reported Active Site Residues | Predicted Active Site Residues | Common Residues |
|------|---------------|----------------------|------------------------------|-------------------------------|-----------------|
| 1.   | Gossypetin    | Trp5, Val12, Tyr12, Glu19, Ser20, His21, Thr22, Phe23, Ala24, Leu25, Cys26, Tyr27, Phe28 | Gly32, Thr33, Trp34, Ile35, Tyr36, Lys37, His38, Thr39, Ser40, Arg41, Gly42, Thr43, Ala44, Pro45 | Trp50, Lys51, Pro52, Trp53, Trp54, Cys55, Trp56, Thr57, Phe58, Ala59, Leu60, Tyr61, Phe62 | Trp50, Tyr63, His64, Trp65 |
| 2.   | Herbacetin    | Trp3, Val12, Tyr12, Trp23, Cys24, Ala25, Ser26, Leu27, Cys28, Tyr29, Pro30, Phe31 | Gly32, Thr33, Trp34, Ile35, Tyr36, Lys37, His38, Thr39, Ser40, Arg41, Gly42, Thr43, Ala44, Pro45, Cys46, Tyr47 | Trp50, Lys51, Pro52, Trp53, Trp54, Cys55, Trp56, Thr57, Phe58, Ala59, Leu60, Tyr61, Phe62 | Trp50, Tyr63, His64, Trp65 |
| 3.   | Kaempferol    | Trp3, Val12, Tyr12, Trp23, Cys24, Ala25, Ser26, Leu27, Cys28, Tyr29, Pro30, Phe31 | Gly32, Thr33, Trp34, Ile35, Tyr36, Lys37, His38, Thr39, Ser40, Arg41, Gly42, Thr43, Ala44, Pro45, Cys46 | Trp50, Lys51, Pro52, Trp53, Trp54, Cys55, Trp56, Thr57, Phe58, Ala59, Leu60, Tyr61, Phe62 | Trp50, Tyr63, His64, Trp65 |
| 4.   | Leucodelphinidin | Trp3, Val12, Tyr12, Trp23, Cys24, Ala25, Ser26, Leu27, Cys28, Tyr29, Pro30, Phe31 | Gly32, Thr33, Trp34, Ile35, Tyr36, Lys37, His38, Thr39, Ser40, Arg41, Gly42, Thr43, Ala44, Pro45, Cys46, Tyr47 | Trp50, Lys51, Pro52, Trp53, Trp54, Cys55, Trp56, Thr57, Phe58, Ala59, Leu60, Tyr61, Phe62 | Trp50, Tyr63, His64, Trp65 |
| 5.   | Leucoperalgonidin | Trp3, Val12, Tyr12, Trp23, Cys24, Ala25, Ser26, Leu27, Cys28, Tyr29, Pro30, Phe31 | Gly32, Thr33, Trp34, Ile35, Tyr36, Lys37, His38, Thr39, Ser40, Arg41, Gly42, Thr43, Ala44, Pro45, Cys46, Tyr47 | Trp50, Lys51, Pro52, Trp53, Trp54, Cys55, Trp56, Thr57, Phe58, Ala59, Leu60, Tyr61, Phe62 | Trp50, Tyr63, His64, Trp65 |
| 6.   | Sorbitolin    | Trp3, Val12, Tyr12, Trp23, Cys24, Ala25, Ser26, Leu27, Cys28, Tyr29, Pro30, Phe31 | Gly32, Thr33, Trp34, Ile35, Tyr36, Lys37, His38, Thr39, Ser40, Arg41, Gly42, Thr43, Ala44, Pro45, Cys46, Tyr47 | Trp50, Lys51, Pro52, Trp53, Trp54, Cys55, Trp56, Thr57, Phe58, Ala59, Leu60, Ty
| S.N | Compound Name | Interacted Residues | Reported Active Site Residues | Predicted Active Site Residues | Common Residues |
|-----|---------------|---------------------|-----------------------------|--------------------------------|----------------|
| 1.  | Gossypetin     | Lys1 Gly2 Ala5 Phe6  | Gly12 Ser18 Thr14 Phe20 Arg26 His29 Glu31, Asn33 Asp34 Gly35 Glu36 Tyr20 | Val26 Trp27 Gly23 His28 Met214 | Leu187, Gly210, Met216, Asp218 Arg212 |
| 2.  | Herbacetin     | Lys1 Gly2 Ala5 Phe6  | Gly12 Ser18 Thr14 Phe20 Arg26 His29 Glu31, Asn33 Asp34 Gly35 Glu36 Tyr20 | Val26 Trp27 Gly23 His28 Met214 | Leu187, Gly210, Met216, Asp218 Arg212 |
| 3.  | Kaempferol     | Lys1 Gly2 Ala5 Phe6  | Gly12 Ser18 Thr14 Phe20 Arg26 His29 Glu31, Asn33 Asp34 Gly35 Glu36 Tyr20 | Val26 Trp27 Gly23 His28 Met214 | Leu187, Gly210, Met216, Asp218 Arg212 |
| 4.  | Leucodelphinidin | Gly25 Ala36 Phe46 Arg6 | Gly12 Ser18 Thr14 Phe20 Arg26 His29 Glu31, Asn33 Asp34 Gly35 Glu36 Tyr20 | Val26 Trp27 Gly23 His28 Met214 | Leu187, Gly210, Met216, Asp218 Arg212 |
|      | 5. Leucoperagonidin | 6. Sorbilin |
|------|---------------------|-------------|
|      | Leu<sup>69</sup>, Gln<sup>111</sup>, Asn<sup>112</sup>, His<sup>131</sup>, Leu<sup>184</sup>, Asp<sup>185</sup>, Trp<sup>186</sup>, Asp<sup>188</sup>, Thr<sup>213</sup>, Ile<sup>217</sup> | Phe<sup>62</sup>, Gln<sup>111</sup>, Asn<sup>112</sup>, Val<sup>113</sup>, His<sup>131</sup>, Leu<sup>184</sup>, Asp<sup>185</sup>, Trp<sup>186</sup>, Leu<sup>190</sup>, Gly<sup>212</sup>, Thr<sup>213</sup>, Ser<sup>214</sup>, Ile<sup>217</sup> |

**Figure 2:** 3D structure of herbacetin with AR (PDB ID: 1US0), IR (PDB ID: 1IR3) and SIRT-6 (PDB ID: 3K35)
Results & Discussion:
From five medicinal plants, 43 bioactive compound and their isolated parts (Table 1) were selected for docking calculation. All reported compounds with pubchem CID no, molecular formula, molecular weight, Conical smile (Table 2) Lipinski filter server was used to find drug likeness of selected bioactive compounds (Table 3). The anti-diabetic compounds that showed good drug likeness properties were further used for computational screening using FAF Drug server 3 (Table 4). Total selected compounds as ligand were used for docking calculation with AR, IR, SIRT-6 receptors and docking was performed by YASARA tool. Out of 43 compounds, mainly 6 compounds (Gossypetin, Herbacetin, Kaempferol, Leucodelphinidin, Leucoperagonalidin, Sorbifolin) were observed as best compounds on the basis of Energy (Table 5). Docking results obtained for each ligand with the receptor were analyzed on the basis of docking energy (Kcal/mol) and interaction of each ligand with the functional residues of AR (PDB ID:1USO), IR (PDB ID: 1IR3), SIRT-6 (PDB ID:3K35) (Figure 1) with Herbacetin and Sorbifolin respectively (Figure 2 and Figure 3). Out of six ligands Herbacetin and Sorbifolin were found best suitable ligands. In docking calculation of AR receptor and 6 ligands Trp20, Tyr48, His110, Trp111 are the most prominent binding residues (Table 6) and In case of IR, Leu1002, Met1079, Asp1150 are the most prominent binding residues with 6 ligands (Table 7) and In SIRT-6 Phe62, Gln111, Ile217, Asn112 are found to be the most prominent binding sites (Table 8). Herbacetin and Sorbifolin were observed most suitable ligands that is found in Thespesia populnea and Ficus lacor buch respectively. Leucoperagonalidin and Kaempferol were showing best docking with AR, mainly found in F. benghalensis and F. recemosa respectively.

Figure 3: 3D structure of sorbifolin with AR (PDB ID: 1US0), IR (PDB ID: 1IR3) and SIRT-6 (PDB ID: 3K35)
In Ayurvedic literature, Bark of *F. benghalensis*, *F. racemosa*, *F. religiosa*, *T. populnea* and *F. lacor buch* are frequently known as Panchvalkala [33]. *F. benghalensis* is mainly found in India, Bangladesh, Sri Lanka and used to treat diarrhea, dysentery, piles, teeth disorders, rheumatism, skin disorders and diabetes. Bark of *F. benghalensis* has been appraised in numerous animal models by inducing diabetes using alloxan and streptozotocin. It was established that aqueous extract of bark exhibited a strong *in vitro* inhibitory activity against α-amylase and α-glucosidase enzymes. The ethanol extract of their leaves successfully reduced the blood glucose, triglycerides and cholesterol levels in alloxan-induced diabetic rats [19–22]. In the traditional systems of medicine, *F. racemosa* is found all over India, Northern Australia and other parts of Asia. In this plant (leaves, fruits, bark, latex, and sap of the root) are used for treatment of diabetes. Mainly bark is used for skin diseases, ulcers, diabetes, piles, dysentery, asthma, gonorrhea, leucorrhoea and urinary disease. The methanol extract of bark also presented an anti-diabetic effect in Streptozotocin and alloxan-induced diabetic rats [19, 23–27]. *F. religiosa* is mainly found in the sub-himalayan tract, Bengal and central India. It has been commonly used for the treatment of various disorder such as diabetes, atherosclerosis, Alzheimer’s disease, gastritis, cancer and AIDS [19, 28–30]. *Thespesia populnea* from Malvaceae family has been reported to posses anti-diabetic compounds. Various experimental findings reveal that *T. populnea* has anti-diabetic properties. Ethanol and aqueous extract of *T. populnea* exhibited noteworthy anti-hyperglycemic and anti-hyperlipidemic effects on alloxan-induced diabetic rats [19, 31, 32]. *Ficus lacor buch* is usually known as Java fig, Pakar or Pakadi. It is found in the temperate climate of India. It is used for treatment of bleeding disorders, herpes, wound, mouth ulcers, diarrhea and leucorrhoea.

**Conclusion:**
ARJR, SIRT-6 used as prominent target proteins to study the interaction of selected anti-diabetic compounds isolated from various medicinal plants through the *in-silico* screening. A total of 6 anti diabetic compounds were selected out of 43 compounds isolated from five medicinal plants. Based on parameters like good oral bioavailability, Non-toxicity and Drug likeness Adsorption and Distribution, Metabolism, Excretion, Toxicity showing strong binding affinity with prominent binding site residues, only six compounds was selected as the best possible ligands which can be used for treatment of Type 2 Diabetes Mellitus. Leucoperalgonidin and Kaempferol were showing best docking with AR, mainly found in *F. benghalensis*. and *F. racemosa*, respectively.

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