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In silico evaluation of antidiabetic molecules of the seeds of *Swietenia mahagoni* Jacq

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ABSTRACT

Diabetes is a chronic metabolic disorder. WHO has projected that India will have around 57 million persons with diabetes by 2025. Swietenia mahagoni Jacq. (Meliaceae) is a large, deciduous tree whose seeds and bark were used for diabetes traditionally. The in silico hyperglycemic activity of the seeds of Swietenia mahagoni Jacq was studied by using AUTODOCK version 4.2 which reveals the putative binding sites of the compound to target protein. Homology modeling was done using MODELLER for the crystal structure of sodium/glucose co-transporter 2(SGLT2). The putative binding modes of compounds were identified using the search method of Lamarckian Genetic Algorithm (LGA).Atomic affinity and electrostatic potential grid maps were calculated using Auto Grid 4.2. From the fallout, we may scrutinize that for successful docking, intermolecular hydrogen bonding and lipophilic interactions between the ligand and the receptor are very essential. The results evolved with the least binding energy ensures that the Oleanolic showed good inhibitory activity and further work may help to develop the compound as an active therapeutic agent for the treatment of hyperglycemia.

Keywords: Diabetes mellitus, *Swietenia mahagoni* Jacq, Docking, Oleanolic acid.
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INTRODUCTION

Diabetes mellitus is a disease of civilization for over 2500 years and is one of the world's greatest social problems. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and expected to be 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people 65 years of age. World Health Organization (WHO) has projected that India will have around 57 million persons with diabetes by 2025. India already has crossed the thirty million mark and it has become a serious medical as well as a socioeconomic problem [1].

Type 2 Diabetes mellitus pathogenesis involves progressive development of insulin resistance in liver and peripheral tissues. It is also accompanied by a defective insulin secretion from pancreatic beta cells leading to hyperglycemia [2]. Though several oral hypoglycemic agents are available, only 25-50% of Type 2 diabetes mellitus are effectively treated by current available oral hypoglycaemic agent for the treatment of resistance or uncontrolled hyperglycemia immediately, continuous exploration for alternative target is being made involving the maintenance of glucose homeostasis[3].

SGLT inhibitors are the agents which inhibit the membrane protein sodium glucose co-transporter, play an important role in the reabsorption of glucose. These are compounds with the mechanism of action to interfere with sodium glucose cotransport in the S1 segment of the proximal convoluted tubule. This class of drugs target insulin

resistance and insulin deficiency, providing glucose dependent and insulin-independent pathway for antihyperglycemic action [4-5].

Approximately 90-99% blood glucose is filtered through glomeruli and reabsorbed *via* SGLT in the renal tubules. SGLT inhibitors work on urinary sugar excretory mechanism. Inhibition of SGLT leads to decreased glucose reabsorption, results in the urinary sugar excretion and normalize the blood glucose level without severe side effect [6]. Six isoforms of SGLTs (SGLT1 to SGLT6) are known [7-8]. Among these only two isoforms SGLT1 and SGLT2 are well investigated, where SGLT1 is high affinity, low capacity transporter and highly expressed in the small intestine and in kidney and SGLT2 is specially expressed in renal tubules, a low-affinity, high capacity transporter. It plays critical role in renal glucose absorption while SGLT1 helps in absorption of dietary glucose in small intestine [9-10]. It has been reported that inhibition of SGLT1 is associated with sever gastrointestinal discomfort, thus selective inhibition of SGLT2 is considered to be effective way for diabetes treatment [11].

Swietenia mahagoni Jacq. (Meliaceae) is a large, deciduous, and economically important timber tree native to the Central America and is commonly known as "Mahogany" [2]. In India, traditionally it is used for several medicinal purposes. The seeds and bark are used for the treatment of hypertension, diabetes, malaria, and in epilepsy as a folk medicine in Indonesia and India [3-4]. Traditionally the bark decoction is used orally to increase appetite, to restore strength in cases of tuberculosis, to treat anaemia, diarrhoea, dysentery, fever and toothache [5].

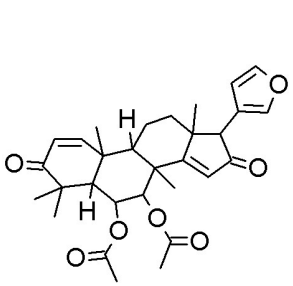
The local people of East Medinipur (West Bengal), Balasore (Orissa) traditionally use the aqueous extract of its seed and bark for curing psoriasis, diabetes, diarrhea and also used as an antiseptic in cuts and wounds [5]. The leaf decoction is used against Nerve disorders, the seed infusion against chest pain and a leaf or root poultice against bleeding [6]. Mahogany seeds have also been reported to have medicinal value for treatment of cancer, amoebiasis, coughs and intestinal parasitism [12]. The bark contains tannin and may serve as an antipyretic, tonic and astringent. It is used as a substitute for Cinchona bark in the West Indies [13]. It also yields a gum. Decoction of seeds used as abortifacient, Used by Ifugao migrants for malaria, cough and miscarriage. In Africa, bark decoction is used as febrifuge [14].

MATERIALS AND METHODS

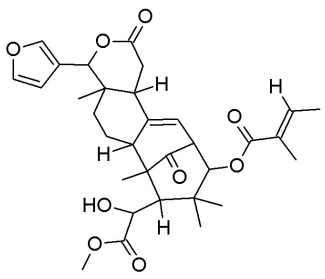
2.1 Ligand preparation

The main objective of this study is to investigate the inhibitory activity of phytoconstituents of *Swietenia mahagoni* Jacq. on Type II diabetes with the help of modern computer aided drug designing tools (Molecular docking studies) using Auto Dock Software version 4.2 and hence it would serve as a tool to design an alternative drug to diabetes. Docking studies were performed for phytoconstituents with target protein SGLT-2 by AutoDock version 4.2.

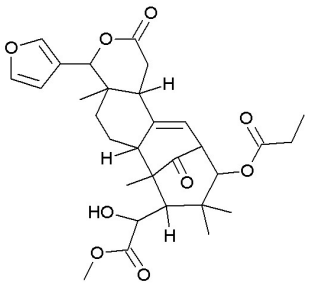
The structure of the compounds of *Swietenia mahagoni* Jacq. Mahonin, Sweitenin, Sweitenin B, Sweitenin C, Sweitenin D, Sweitenin E, Sweitenin F, Secomahoganin, Swietenollide, Swietemahonin A, Swietemahonin B, Swietemahonin C, Swietemahonin D, Swietemahonin E,Swietemahonin F,Swietemahonin G, Swietemahonolide , Oleonalic acid and Dapagliflozin {Standard Drug} were drawn by using chemsketch (ACD LABS 12.0) and converted to 3D structure with the help of 3D optimization tools.



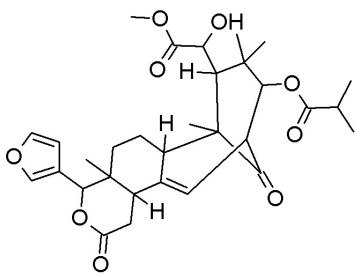
Mahonin



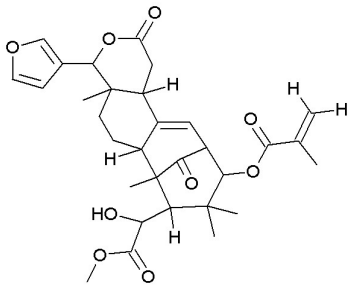
Sweitenin



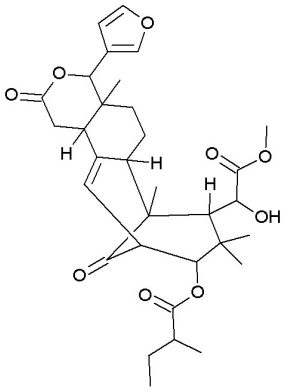
*Sweitenin **B***



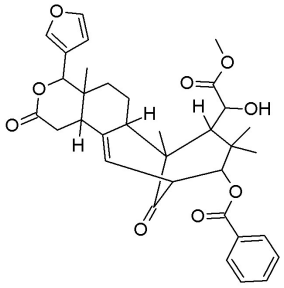
*Sweitenin**C***



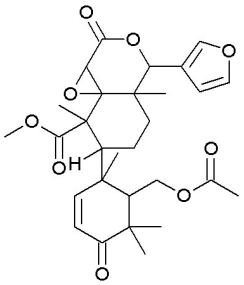
*Sweitenin**D***



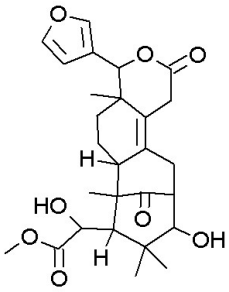
*Sweitenin**E***



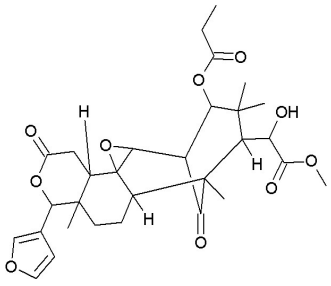
*Sweitenin**F***



Secomahoganin



Swietenollide



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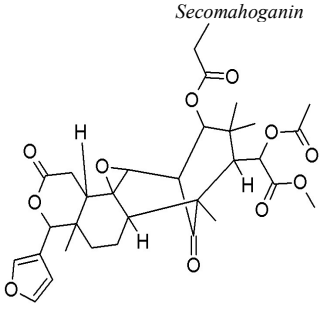
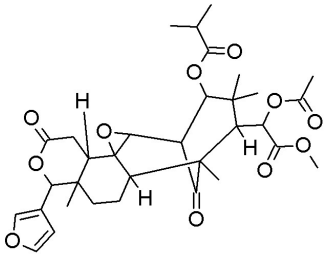
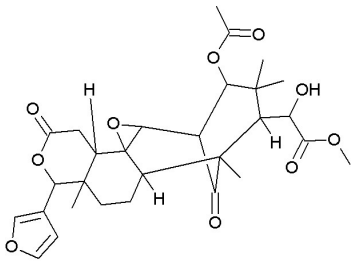


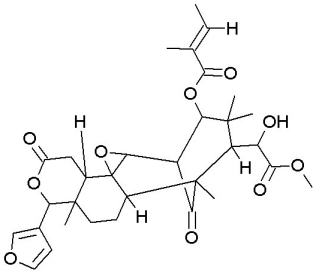
Swietemahonin B



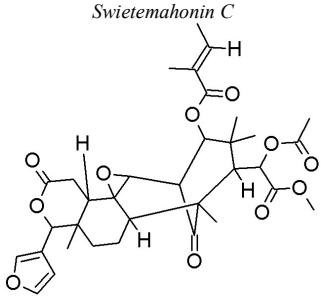
Swietemahonin C



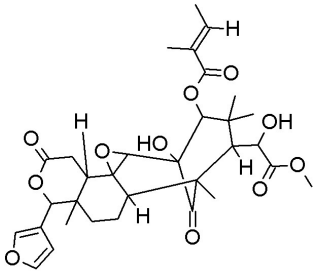
Swietemahonin D



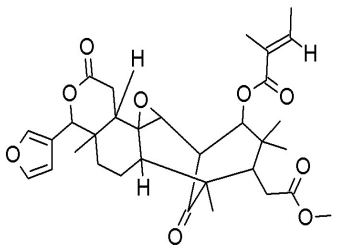
Swietemahonin E



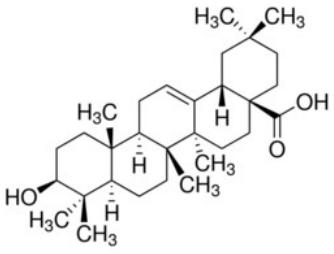
Swietemahonin F



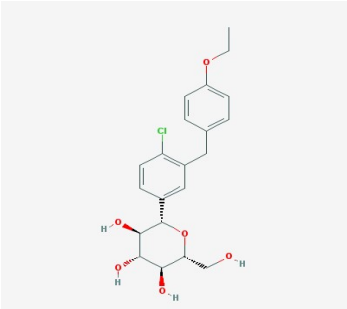
Swietemahonin G



Swietemahonolide



Oleanolic acid



Dapagliflozin {Standard Drug}

Figure 1: Ligand structure of 18 compounds from *S.mahagoni* and standard drug used in the study

2.2 Protein preparation

2.2.1 Homology modeling

MODELLER software package [15-16] was used to construct homologe models of human SGLT-2 protein. These relationships are expressed as conditional probability desity function. The spatial restraints thus derived and stereochemistry enforced by CHARMM22 force-field terms are combined into an objective function and this function is minimized by an optimization procedure during model building. A dynamic programming method (variable gap opening penalty) is used to align the target sequence with the template sequences [17]. This gap penalty avoids placing gaps in secondary structural elements and favours gap in exposed regions and curved parts of the main-chain. Since sequence-structure alignment is a vital step in the model building process, we further checked the target-template alignment manually and gaps in the middle of the helices or in the conserved loops. The resultant alignment was given as input to MODELLER to build models with 'very fast' simulated annealing protocol and 5 final models were generated. Among them the model with the lowest objective function value was selected. The loops of this model were further refined using MODELLER'S loop optimization procedure.

```
Query_67358  1    MEEHTEAGSAPEMGAQKALIDNPADILVIAAYFLLVIGVGLWSMCRTNRGTVGGYFLAGRSMVWWPVGASLFASNIGSGH  80
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3DH4_A       41   FIGMSGSGYSIGLAIASYEWMSAITLIIVGKYFLPIFIEKGIYTIPEFVEKRF-NKKLKTILAVFWISLYIFVNLTSVLY  119

Query_67358  161  SGAVFIQQALGWNIYASVIALLGITMIYTVTGGLAALMYTDTVQTFVILGGACILMGYAFHEVG---GYSGLFDKYLGAA  237
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Query_67358  238  TSLTVSEDPAVGNISSFCYRPRPDSYHLLRHPVTGDLPWPALLLG-LTIVSGWYWCSDQVIVQRCLAGKSLTHIKAGCIL  316
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Query_67358  317  CGYLKLIPMFLMVMPGMISRILYPDE-VACVVPEVCRRVCGTEV---GCSNIAYPRLVVKLMPNGLRGLMLAVMLAALMS  392
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Query_67358  393  SLASIFNSSSTILFTMDIYTR-LRPRAGDRELLLVGRLWVVFIVVVSVAWLPVVQAAQGG--QLFDYIQAVSSYLAPPVSA  469
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Query_67358  630  QEEAAAAAARRLEDISEDPSWARVVNLNALLMMAVAVFLWGFYA  672
3DH4_A       ----------------------------------------------
```

Figure 2: Sequence alignment of SGLT2 (human) and first BLASTp hit (3DH4_A)

3DH4_A: Chain A, Crystal Structure of Sodium SUGAR SYMPORTER WITH BOUND GALACTOSE FROM Vibrio Parahaemolyticus

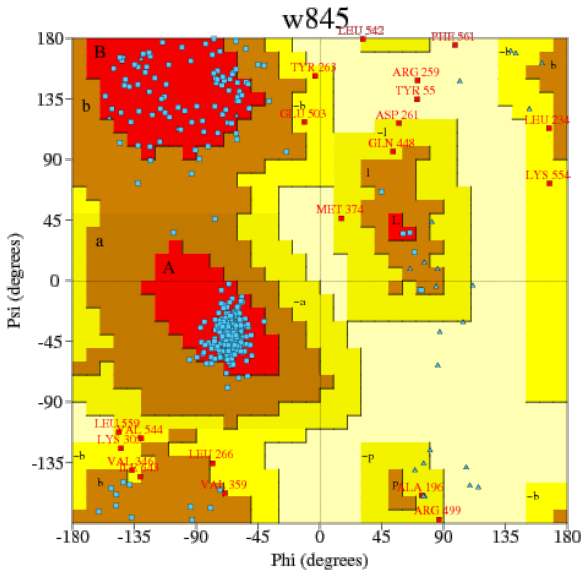


Figure 3: Ramachandran plot for generated model of SGLT2

2.2.2 Ramachandran Plot statistics

	No. of residues	%-tage
Most favoured regions [A,B,L]	470	89.5%
Additional allowed regions [a,b,l,p]	35	6.7%
Generously allowed regions [~a,~b,~l,~p]	17	3.2%
Disallowed regions [XX]	3	0.6%
Non-glycine and non-proline residues	525	100.0%
End-residues (excl. Gly and Pro)	2	
Glycine residues	61	
Proline residues	33	
Total number of residues	621	

2.3 Molecular Docking [18-19]

The program Auto Dock was used to identify putative binding modes of compounds. Auto Dock version 4.2 have a variety of search methods, including Simulated Annealing (SA), Genetic Algorithm (GA) and Larmarckian Genetic Algorithm (LGA). The most capable search method is the hybrid search method, LGA. This couples a typical Darwinian genetic algorithm for global searching with the Solis and Wets algorithm for local searching. LGA allows improvements in the phenotype (*i.e.* conformations with lower energies) to be passed on *via* the genotype (the system's translation, orientation and torsion angles) to subsequent generations: this improves the efficiency of the calculation compared with traditional GAs. Version 4.2 of Auto Dock introduces side chain flexibility into the target macromolecule. Selected side chains are allowed to change their conformations at the same time as the ligand that is being docked. However, the rest of the macromolecule remains rigid, so certain kinds of larger-scale conformational changes in the tertiary structure cannot be predicted with this method. The additional degrees of freedom added by these macromolecule side chains must also be taken into consideration when docking ligands with many rotatable bonds: the method is limited to a finite number of 32 torsions, but also by the search capabilities of the particular search method used.

The macromolecule side chains chosen to be flexible are separated from the rigid portion of the macromolecule and actually become part of the input ligand (PDBQ) file. These side chains are distinguished from the ligand by special records new to AutoDock 4.2, that indicate that these residues may only change conformation, and unlike the ligand, may neither change translation nor orientation. The remains of the rigid portion of the macromolecule is treated as before, by storing it in a PDBQS-formatted file with the corresponding Kollman united atom partial atomic charges and Stouten atomic solvation parameters. Lennard-Jones, Goodford-directional hydrogen bonding and electrostatic potential grid maps are pre-computed using Auto Grid. The moving portion includes the ligand, which may translate, change orientation and/or formation, and the flexible side chains in the macromolecule, which as just mentioned, may only change conformation. During the docking, the "docked energy" of the moving portion is computed as before. Auto Dock uses trilinear interpolation of the pre-computed AutoGrid maps between the moving and rigid portions of the system; within the moving portion, it uses the 'intramolecular' energy calculation, summing the non-bonded and electrostatic terms between atom-pairs whose separations vary depending on the selected

rotatable bonds. For each pair of atoms at the boundary between the rigid and flexible portions of the macromolecule, the vector that defines the rotatable bond emanating from the rigid region is used for rotating the side chain's atoms. These two same atoms, however, are omitted from the trilinear intermolecular non-bonded energy calculation, even though they are technically in the moving portion of the system.

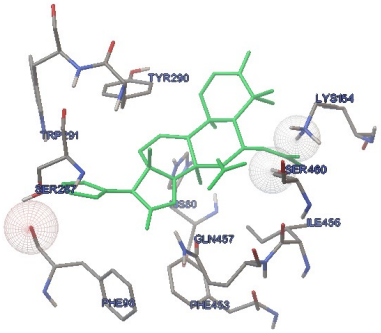
Atomic affinity and electrostatic potential grid maps were calculated using Auto Grid 4.2. A grid map with 82 X 84 X 78 points and a grid point spacing of 0.375 Å generously included the whole binding site of SGLT2. All the dockings performed in this work were carried out using the Lamarckian Genetic Algorithm (LGA). The specific Auto Dock parameters for the LGA were set as follows: the population size was 19 individual compounds, each of whose initial translations, orientations and torsions were set to random values. The limit of the number of energy evaluations was set to 1×10^6 for each docking. The maximum number of generations was set to 27,000. The mutation and crossover rates were set to 0.02 and 0.80 respectively. The maximum number of iterations per local search was set to 300, and the probability of performing such a local search on an individual was 0.06. The maximum number of consecutive successes or failures before doubling or halving the local search step size was 4. Elitism was applied, with the top-scoring individual in the current generation automatically surviving into the next generation. A set of 100 docking calculations was performed for each ligand, and the resulting docked conformations were clustered into families of like-conformations, using a root mean squared positional deviation cluster tolerance of 1.0 Å. These same docked conformations were re-clustered at a more forgiving value of 3.0 Å.

RESULTS AND DISCUSSION

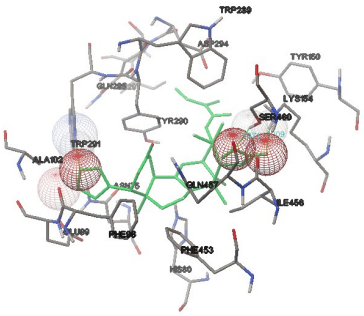
Table 2: Results for interaction of various compounds present in the seeds of *Swietenia mahagoni* Jacq with SGLT2 protein using Autodock v4.2

Sl. No.	Compound Name	Binding Energy (kCal/mol)	Ligand Efficiency	Inhibition Constant (nM)	Vdw_hb_ desol_energy	Electrostatic energy	Total internal energy	refRMS
1.	Mahonin	-10.73	-0.29	13.59	-11.62	-0.6	-1.41	59.76
2.	Sweitenin	-11.7	-0.31	490.51	-13.77	-0.42	-1.1	59.11
3.	Sweitenin B	-11.48	-0.29	3.83	-12.97	-0.42	-0.87	59.97
4.	Sweitenin C	-11.61	-0.29	3.08	-13.07	-0.03	-1.22	60.83
5.	Sweitenin D	-11.29	-0.28	5.27	-12.35	-0.44	-0.96	59.87
6.	Sweitenin E	-10.15	-0.31	36.51	-10.37	-0.06	-0-02	61.66
7.	Sweitenin F	– 11.37	-0.28	4.62	-12.6	-0.27	-1.65	59.67
8.	Secomahoganin	-9.54	-0.25	101.1	-10.89	-0.15	-1.37	57..82
9.	Swietenollide	-10.43	-0.3	22.54	-11.76	-0.66	-0.66	60.0
10.	Swietemahonin A	-9.15	-0.23	196.82	-10.86	-0.22	-0.56	61.04
11.	Swietemahonin B	-9.29	-0.22	153.85	-10.79	-0.04	-0.41	60.64
12.	Swietemahonin C	-9.66	-0.22	83.09	-11.24	-0.09	-1.78	60.74
13.	Swietemahonin D	-8.44	-0.22	646.4	-10.11	-0.17	-0.52	60.98
14.	Swietemahonin E	-9.64	-0.23	86.21	-11.13	-0.18	-0.69	60.8
15.	Swietemahonin F	-10.08	-0.22	40.75	-11.51	-0.06	-2.05	59.03
16.	Swietemahonin G	-9.6	-0.22	91.24	-10.86	-0.23	-0.97	59.28
17.	Swietemahonolide	-10.61	-0.26	16.73	-12.1	-0.29	-1.34	61.15
18.	Oleanolic acid	-12.59	-0.29	1.65	-13.94	-0.14	-0.8	60.35
19.	Dapaglifozin (Standard Drug)	-7.77	-0.28	2.03	-9.07	-0.04	-0.35	52.7

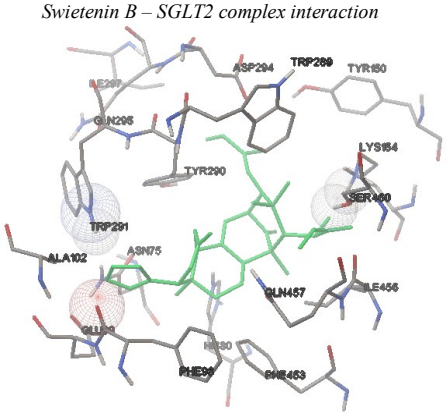
Mahonin – SGLT2 complex interaction



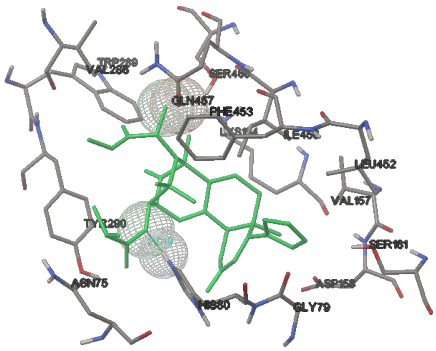
Swietenin – SGLT2 complex interaction



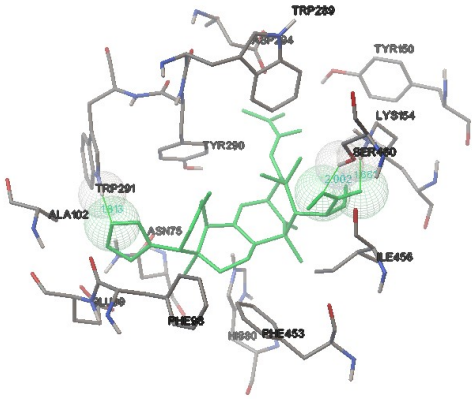
Swietenin B – SGLT2 complex interaction



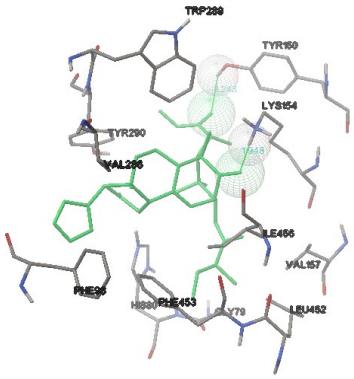
Swietenin C – SGLT2 complex interaction



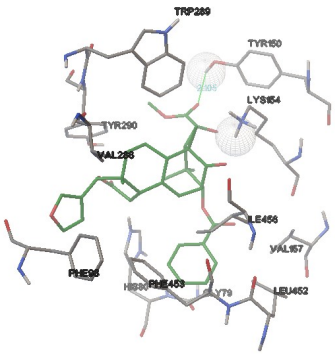
Swietenin D – SGLT2 complex interaction



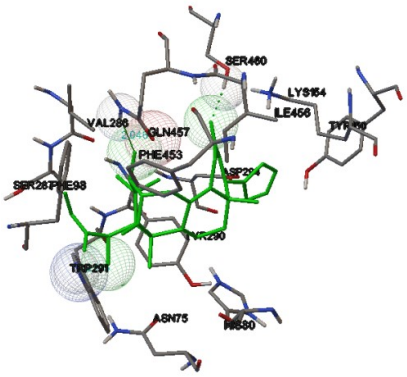
Swietenin E – SGLT2 complex interaction



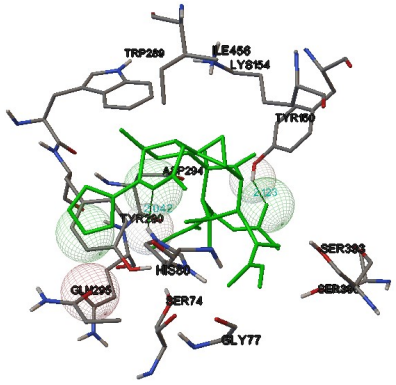
Swietenin F – SGLT2 complex interaction



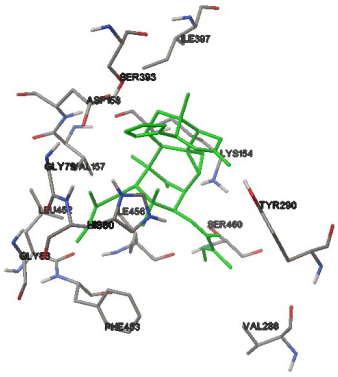
Swietenollide – SGLT2 complex interaction

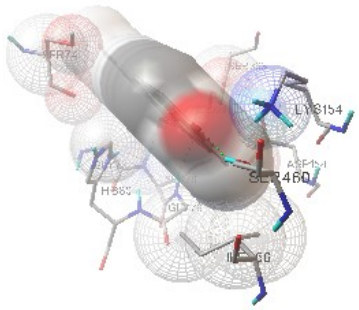


Swietemahonin F – SGLT2 complex interaction

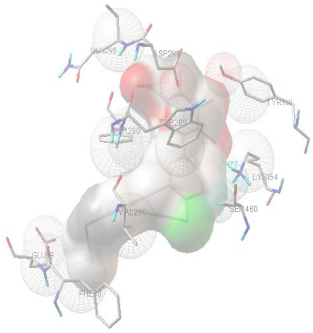


Swietemahonolide – SGLT2 Complex interaction





Oleanolic acid – SGLT2 complex interaction



Dapaglifozin – SGLT2 complex interaction

Mahonin interacts with SGLT2 protein with a binding energy of -10.73 kCal/mol. The ligand forms hydrogen bond with protein residues Lys154, Ser460 and Ser287. It also interacts hydrophobically with Tyr290, Ile456, Gln457, Phe453, Phe96, Trp291 and His80. Sweitenin interacts with SGLT2 protein with a binding energy of - 11.7 kCal/mol. The ligand forms hydrogen bond with protein residues Lys154, Ser460, Trp291 and Ala102. It also interacts hydrophobically with Gln295, Trp289, Asp294, Tyr150, Tyr290, Gln457, Ile456, Phe453, His80, Phe98, Glu99 and Asn175. SweiteninB interacts with SGLT2 protein with a binding energy of -11.48kCal/mol. The ligand forms hydrogen bond with proteins residues Lys154, Ser460, Trp291, Glu99 and Ala102. It also interacts hydrophobically with Gln295, Trp289, Asp294, Tyr150, Tyr290, Gln457, Ile297, Ile456, Gln457, Phe453, Phe98, and Glu99.

Sweitenin C interacts with SGLT2 protein with a binding energy of -11.61kCal/mol. The ligand forms hydrogen bond with proteins residues Tyr290 and Gln457. It also interacts hydrophobically with Val288, Asp294, Asn75, Asp158, Ser161, Val157, Leu452, Ile450, Ser490, His80 and Gly79. SweiteninD interacts with SGLT2 protein with a binding energy of -10.15 kCal/mol. The ligand forms hydrogen bond with protein residues Lys154, Ser460 and Trp291. It also interacts hydrophobically with Trp289, Asp294, Tyr150, Tyr290, Ala102, Glu99, Phe98, Phe453 and Ile456. SweiteninE interacts with SGLT2 protein with a binding energy of -11.29kCal/mol. The ligand forms hydrogen bond with proteins residues Lys154 and Tyr150. It also interacts hydrophobically with Trp289, Asp294, Val286, Tyr290, Phe98, Glu99, Leu452, Val157, Phe453 and Ile456. SweiteninF interacts with SGLT2 protein with a binding energy of -11.37kCal/mol. The ligand forms hydrogen bond with proteins residues Lys154 and Tyr150. It also interacts hydrophobically with Trp289, Asp294, Val286, Tyr290, Phe98, Glu99, Leu456, Val157, Leu452 and Ile456.

Swietenollide interacts with SGLT2 protein with a binding energy of -10.43 kCal/mol. The ligand forms hydrogen bond with protein residues Trp291, Val286, Gln457, Phe453 and Ser460. It also interacts hydrophobically with Ser287, Phe98, Asn75, His80, Tyr290, Asp294, Ser460, Lys154, Ile456 and Tyr459. Swietemahonin F interacts with SGLT2 protein with a binding energy of -10.08 kCal/mol. The ligand forms hydrogen bond with protein residues, Gln295, Asp294 and Tyr 290. It also interacts hydrophobically with Ser74, His80, Gly77, Gly79, Ser393, Ser396, Lys 154, Tyr150, Ile 456 and Trp289. Swietemahonolide interacts with SGLT2 protein with a binding energy of -10.61 kCal/mol. The ligand shows no hydrogen bonding. It interacts hydrophobically with Leu452, Gly79, Val157, Ser460, Val286, Phe453, Val157, Tyr290, Lys 154, Ser 393, Gly88, Ile 397, Asp158 and Ile456. Oleanolic acid interacts with SGLT2 protein with a binding energy of -12.59 kCal/mol. The ligand forms hydrogen bond with protein residues Lys154 and Ser460. It also interacts hydrophobically with Ser 393, Asp 154, Ile 456 and Gly79.

Dapaglifozin (Standard Drug) interacts with SGLT2 protein with a binding energy of -7.77 kCal/mol. The ligand forms hydrogen bond with protein residues Gln295, Tyr134, Trp289, Tyr290, Lys154, Ser460, Val286, Glu99 and Phe98. It also interacts hydrophobically with Asp294.

The newly marketed SGLT2 inhibitor, Dapagliflozin was taken as standard and its least binding energy was calculated as -7.77 kcal/ mol and compared with series of compounds of the seeds of *Swietenia mahagoni* Jacq. (-12.59 kcal/mol to -9.15 kcal/mol).

CONCLUSION

We carried out docking analysis especially for the glucose uptake property for the isolated compounds from the seeds of *Swietenia mahagoni* Jacq using the target protein SGLT-2. Among all the compounds Mahonin, Sweitenin, Sweitenin B, Sweitenin C, Sweitenin D, Sweitenin E, Sweitenin F, Swietenollide, Swietemahonin F,

Swietemahonolide and Oleanolic acid have higher inhibitory activity, as least binding energy is related with higher activity. The maximum least binding energy of the oleanolic acid is found to be -12.59 Kcal/mol when compared to standard (-7.77 kcal/mol). Use of extract from the seeds of *Swietenia mahagoni* Jacq provide a way to natural remedy for diabetes overcoming the toxicity issues associated with synthetic drugs.

REFERENCES

[1] Sarh Wild, Gojka Roglic. 2004; 27.
[2] Anonymous (1976). The Wealth of India –Raw Materials, Publications and Information Directorate, Council of Scientific and Industrial Research, New Delhi. Reprint edition 2005; 10 (Sp-W):84-87.
[3] Nagalakshmi MAH, Thangadurai D,Muralidara D. &Pullaiah RT. Phytochemical and antimicrobial study of Chukrasiatabularis leaves. *Fitoterapia* 2001;72: 62–64.
[4] Khare CP. Indian Medicinal Plants – an Illustrated Dictionary. Springer 2007; New Delhi, 633–634.
[5] Miroslav MG. Elsevier's Dictionary of Trees.London: Elsevier Inc., 2005; I: 381.
[6] Ohsumi K, Matsueda H, Hatanaka T. Pyrazole-O-Glucosides as Novel Na+-Glucose Cotransporter (SGLT) Inhibitors; Bioorganic& Medicinal Chemistry Letters. 2003;13:2269– 2272.
[7] Rajesh R, Naren P, Vidyasagar S, Unnikrishnan, Pandey S, Varghese M et al. Sodium Glucose Co transporter 2 (SGLT2) Inhibitors: A New Sword for the Treatment of Type 2 Diabetes Mellitus. International Journal of Pharma Sciences and Research. 2010; 2:139-147.
[8] Grempler R, Augustin R, Froehner S, Hildebrandt T, Simon E, Mark M et al. Functional characterization of human SGLT-5 as a novel kidney-specific sodium-dependent sugar transporter. FEBS Letters. 2012; 586:248–253.
[9] Zhanga W, Welihinda A, Mechanic J, Ding H, Zhu L, Lu Y et al. EGT1442, a potent and selective SGLT2 inhibitor, attenuates blood glucose and HbA1c levels in db/db mice and prolongs the survival of stroke- prone rats. Pharmacological Research 2011; 63:284–293.
[10] Idris I, Donnelly R. Sodium-glucose co-transporter -2 inhibitors: An emerging new class of oral antidiabetic drug. Diabets obes Metab 2009; 11:79-88.
[11] Kanai Y, Lee W S, You G, Brown D, Hediger M A, Brown D et al. The human kidney low affinity Na/ glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D- glucose. J Clin Invest. 1994; 93:397–404.
[12] Pallab K. Haldar, Soumitra Adhikari, Samit Bera, Sanjib Bhattacharya, Siva P. Panda, Chandi C. Kandar. Hepatoprotective Efficacy of *Swieteniac*q. (Meliaceae) Bark against Paracetamolinduced Hepatic Damage in Rats. Ind J Pharm Edu Res. 2011; 45(2):108–113.
[13] Bacsal K, Chavez L, Diaz I, *et al.* The Effect of *SwieteniaMahogani*(Mahogany) Seed Extract On Indomethacin-Induced Gastric Ulcers In Female Sprague- Dawley Rats. *Acta Medica Philippina* 1997;3, 127–139.
[14] Jasper Wester, The use of medicinal plants by Ifugao-migrants in the foothills of the Sierra Madre mountain range.
[15] Eswar N, Webb B, Marti-Renom MA, Madhusudhan MS, Eramian D, Shen MY, Pieper U, Sali A*Comparative protein structure modeling using MODELLER.* Curr Protoc Protein Sci, 2007. Chapter 2: p. Unit 2 9.
[16] Sali, A. and T.L. Blundell, *Comparative protein modelling by satisfaction of spatial restraints.* J Mol Biol, 1993. 234(3): p. 779-815.
[17] Faham S, Watanabe A, Besserer GM, Cascio D, Specht A, Hirayama BA, Wright EM, Abramson J *The crystal structure of a sodium galactose transporter reveals mechanistic insights into Na+/sugar symport.* Science, 2008. 321(5890): p. 810-4.
[18] Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ *AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility.* J Comput Chem, 2009. 30(16): p. 2785-91.
[19] Morris GM., Goodsell DS, Halliday RS, Huey R., Hart WE, Belew RK. Olson AJ *Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function.* Journal of Computational Chemistry, 1998. 19(14): p. 1639-1662.