In silico–based combinatorial pharmacophore modelling and docking studies of GSK-3β and GK inhibitors of *Hippophae*

SUSHIL KUMAR MIDDHA[1], ARVIND KUMAR GOYAL[2], SYED AHMED FAIZAN[3], NETHRAMURTHY SANGHAMITRA[3], BHARAT CHANDRA BASISTHA[4] and TALAMBEDU USHA[1,*]

[1]*DBT-BIF Facility, Department of Biotechnology & Biochemistry, Maharani Lakshmi Ammanni College For Women, Malleswaram, Bangalore 560 012, India*

[2]*Department of Botany, Molecular Cytogenetics Laboratory, University of North Bengal, Siliguri 734 013, India*

[3]*Department of Biotechnology, MS Ramaiah Institute of Technology, Bangalore 560 054, India*

[4]*Sikkim State Council of Science and Technology, Gangtok, Sikkim 737 101, India*

**Corresponding author (Email, ushatalambedu@gmail.com)*

Type 2 diabetes is an inevitably progressive disease, with irreversible β cell failure. Glycogen synthase kinase and Glukokinase, two important enzymes with diverse biological actions in carbohydrate metabolism, are promising targets for developing novel antidiabetic drugs. A combinatorial structure-based molecular docking and pharmacophore modelling study was performed with the compounds of *Hippophae salicifolia* and *H. rhamnoides* as inhibitors. Docking with Discovery Studio 3.5 revealed that two compounds from *H. salicifolia*, viz Lutein D and an analogue of Zeaxanthin, and two compounds from *H. rhamnoides*, viz Isorhamnetin-3-rhamnoside and Isorhamnetin-7-glucoside, bind significantly to the GSK-3 β receptor and play a role in its inhibition; whereas in the case of Glucokinase, only one compound from both the plants, i.e. vitamin C, had good binding characteristics capable of activation. The results help to understand the type of interactions that occur between the ligands and the receptors. Toxicity predictions revealed that none of the compounds had hepatotoxic effects and had good absorption as well as solubility characteristics. The compounds did not possess plasma protein-binding, crossing blood–brain barrier ability. Further, *in vivo* and *in vitro* studies need to be performed to prove that these compounds can be used effectively as antidiabetic drugs.

[Middha SK, Goyal AK, Faizan SA, Sanghamitra N, Basistha BC and Usha T 2013 *In silico*–based combinatorial pharmacophore modelling and docking studies of GSK-3β and GK inhibitors of *Hippophae*. *J. Biosci.* **38** 805–814] **DOI** 10.1007/s12038-013-9367-y

1. Introduction

Hippophae (family: Elaeagnaceae) are deciduous, dioecious, nitrogen fixers and non-self-fertile actinorhizal plants (Basistha *et al*. 2010). *H. rhamnoides, H. salicifolia, H. tibetiana* and *H. neurocarpa* are the four species of the genus *Hippophae* (Rousi 1971). *H. rhamnoides and H. salicifolia* are amongst the most commonly found variety in India (Goyal *et al.* 2011). In India, *Hippophae* grows in high altitudes like Himachal Pradesh, Jammu and Kashmir, Sikkim and Uttar Pradesh (Singh 1998). It is known to have medicinal and nutritional values such as vitamins (A, B, C, E and K), flavonoids, sterols, amino acids, phytosterols, polyunsaturated fatty acids, organic acids and carotenoids, and hence it is grown worldwide (Li and Schroeder 1996). For many centuries, people in central and southeastern Asia have used this plant as a traditional agent to prevent various ailments, and also in local uses such as fuel, fodder, small timber and food (Christaki 2012).

Type 2 diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM), is one amongst the most widespread diseases in the world, affecting 90% of all ages (Wild *et al*. 2004; Middha *et al*. 2011). Type 2 diabetes is the more common form of diabetes when compared to insulin-

Keywords. Actinorhizal plants; ADMET; Discovery Studio 3.5; *Hippophae*; QSAR

Published online: 1 October 2013

dependent diabetes. A high level of blood glucose in NIDDM is a result of improper usage or inappropriate production of insulin in the body. Insulin is needed to move blood sugar into cells, where the carbohydrates are reduced to glucose and glucose 6-phosphate, which are later stored in the form of glycogen and used as an energy source (American Diabetes Association 2011). Type 2 diabetes leads to insulin resistance in which liver and muscle cells do not respond correctly to insulin (Laakso and Lehto 1997). As a result, blood glucose does not get into these cells, leading to increased blood glucose concentrations (hyperglycemia). NIDDM usually occurs slowly over time. Family history, genetic makeup, low muscle or body activity, junk food or unhealthy diet, and excess body weight usually increase the risk of a person getting affected (Giugliano *et al.* 1995). Some of the long-term symptoms include deterioration of normal health, atherosclerosis, myocardial infarction and hyperosmolar nonketotic diabetic coma (Olokoba *et al*. 2012).

Glycogen synthase kinase (GSK-3) and Glucokinase (GK) are some of the common proteins which play a vital role in NIDDM. In mammals, GSK-3 is encoded by two known genes: *GSK-3α* and *GSK-3β*. Increased expression of GSK-3 is harmful since it causes the inactivation of multiple blood-glucose-reducing enzymes and disrupts insulin signalling. Studies have shown that introducing competitive inhibitors of GSK-3 leads to increased activity of insulin (Desbois-Mouthon *et al*. 2001).

GK occurs in cells associated with liver, pancreas and gut of humans. In each of these organs, it plays an important role in the regulation of carbohydrate metabolism (Yamashita *et al*. 2001). Mutations of the gene coding for GK can cause unusual forms of diabetes (Miller *et al*. 1999). It has a high affinity for glucose. Pancreatic GK plays an important role in modulating insulin secretion (Efanov *et al*. 2005). Hepatic GK helps to facilitate the uptake and conversion of glucose by acting as an insulin-sensitive determinant of hepatic glucose usage (Nordlie *et al*. 1999). This protein, when bound to small molecule Glucokinase activators (GKAs), leads to lowering of plasma glucose and enhancing glucose-stimulated insulin secretion; however, these proteins also carry a risk of excessively triggering GK and causing hypoglycemia (Johnson *et al*. 2007).

Considering the earlier studies, data strongly recommend that suppressing levels of GSK-3β and GK will be an effective approach for inhibiting diabetes mellitus. Computational biology helps to facilitate and reduce the time and cost of drug discovery process, which involves diverse methods to discover novel compounds (Usha *et al.* 2013). One such method utilized in the present study is active site and molecular docking analysis of GSK-3β and GK, which enabled us to identify natural inhibitors from *Hippophae*.

2. Methodology

2.1 *Preparation of ligands*

Extensive literature survey was done to collect the list of all the compounds present in *H. salicifolia* and *H. rhamnoides*, and their structures were elucidated using NMR or mass spectrometry (Heinäaho *et al.* 2009). The structures of the ligands were obtained from the Pubchem database *(http://pubchem.ncbi.nlm.nih.gov/)*. The ligand preparation included 2D–3D conversions, correcting structures, generating variations of these structures, verifying and optimizing the structures. All these tasks were performed using Marvin Sketch (ChemAxon 2010). Marvin was used for drawing, displaying and characterizing chemical structures, substructures and reactions. Quantitative structure–activity relationship (QSAR) are regression or classification models used in chemical and biological sciences to engineer drug-likeliness properties. The properties include ionization states, tautomeric variations of these structures, alternative chirality, low-energy ring conformations, filtering the structures, calculate chemical properties such as log D, molecular dynamics, orbital electronegativity, polarizability, refractivity, resonance, Huckel analysis and topology (Sharma and Naik 2013). Root mean square deviation (RMSD) values of different analogues were calculated. The Lipinski's rule of five was also used to determine the drug-like properties of the compounds (Lipinski *et al*. 2001)

2.2 *Preparing the receptors*

GSK-3β and GK were chosen as the target receptors due to their vital role in regulation of blood glucose concentration. The structures of human GSK-3β in complex with inhibitor OFT-(3z)-*N*,*N*-diethyl-3-[(3e)-3-(hydroxyimino)-1,3-dihydro-2h-indol-2-ylidene]-2-oxo-2,3-dihydro-1h-indole-5-sulphonamide and Glucokinase in complex with glucose were retrieved from the Protein Databank (PDB) (*http://www.pdb.org/*). Typically a PDB structure file consists of heavy atoms, water molecules and metal ions, and generally has no information on bond orders, topologies or formal atomic charges. It may also have misaligned amide groups, because the X-ray structure analysis cannot usually distinguish between O and NH_2. Ionization and tautomeric states are also generally unassigned (Berman 2008).

Considering all these criteria, the 3D structures of GSK-3 (PDB id: 3SAY) and Glucokinase (PDB id: 3FA6) were prepared by removing the heteroatoms and cleaned (clean geometry) using Discovery Studio 3.5 (DS) software (Accelrys Software Inc, USA, 2012). After cleaning, CHARMM force field was applied to the receptor. CHARMM is a program for macromolecular dynamics (Brooks *et al.* 2009). The PDBsum

(*http://www.ebi.ac.uk/pdbsum/*) server was used to determine the active sites of the receptors and their interactions with compounds.

2.2.1 *Docking using Discovery Studio (DS):* The protocol of docking of ligands with the receptors was performed using DS 3.5 suite. Docking is virtual screening of a database of compounds and predicting the strongest binders based on various scoring functions. Accelrys Discovery Studio 3.5 was used for docking. In the process, first, a ligand library was generated by placing the ligand PDB files in a single discovery studio file (.dsv). The preparation of the library helps in simultaneous docking of multiple ligands against the receptor and in making an easy comparative study between the ligands. Before docking, the ligands were prepared using the 'Prepare Ligand' module, which cleans the geometry of the ligands and distributes the uneven charges throughout using CHARMM. Force fields applied in CHARMM are the energies and forces on each particle of the system and also defines the positional relationships between atoms that determine their energy. The ligands were primarily positioned in the binding site using LibDock and then they were docked with both the receptors to understand the mechanism of GSK-3β and GK catalysed enzymatic reactions. A comparative analysis of LibDock scores and the binding energies was also done to examine the role of bioactive compounds interaction with active site residues (Patil *et al*. 2010).

2.3 *ADMET predictions*

ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) prediction and significant descriptors of drug-likeness such as mutagenicity, toxicological dosage level for different organs and pharmaceutically relevant properties of the compounds was predicted using PreADMET server (*http://preadmet.bmdrc.org/*). PRODRG server (*http://davapc1.bioch.dundee.ac.uk/prodrg/*) was utilized to obtain the various topologies and energy minimized coordinates. PRODRG server takes a description of the compound submitted (as PDB coordinates/MDL Molfile/SYBYL Mol2 file/textdrawing) and, from it, generates a variety of topologies using various programs, as well as energy-minimized coordinates in a variety of formats (Van-Aalten *et al.* 1996).

3. Results and discussion

In the present docking studies, we identified that the effective binding site of GSK-3β antagonists occur in the chain A. PDB structure of GSK-3β is in complex with the ligand OFT-(3z)-*N*,*N*-diethyl-3-[(3e)-3-(hydroxyimino)-1,3-dihydro-2h-indol-2-ylidene]-2-oxo-2,3-dihydro-1h-indole-5-sulphonamide. The PDBsum active site analysis revealed that the ligand formed hydrogen bonds with Val135(A), Asp133(A) and Lys85(A) of the β strand of the receptor. It also showed hydrophobic interactions with Phe67(A), Asp200(A), Val70(A), Gln185(A), Arg141(A), Pro136(A), Tyr134(A), Leu188(A), Ala83(A), Asn186(A), Leu132(A) and Cys199(A) of the β strand and α helices. Most of the aliphatic amino acids showed interactions with ligand. The active site of the second receptor GK considered for the study consists of two domains, namely small and a large domain, and the ligand D-glucose is completely buried in the catalytic site. D-glucose has shown seven hydrophilic and six hydrophobic interactions with GK. Residues whose side-chain faces the substrate-binding pocket are Thr186(A), Glu256(A), Asn204(A), Asp205(A), Lys169(A), Glu290(A), Asn231(A), Gly229(A), Thr206(A), Ile225(A), Ser151(A), Pro153(A) and Phe152(A). Notably, almost all the residues predicted to be involved in D-glucose binding are located in the secondary structures like β strand, β turn, β hairpin, γ turns and α helices.

All compounds collected from the literature (Heinäaho *et al.* 2009) were considered for docking studies, since some of the earlier studies showed that 66% of approved drugs in the

Table 1. The RMSD values of Zeaxanthin analog

Zeaxanthin compared with	RMSD (Å)
Analog I	3.003085
Analog II	2.558529
Analog III	1.896550
Analog IV	2.037715
Zeaxanthin analog I compared with	
Zeaxanthin	3.003085
Analog II	1.753791
Analog III	2.640960
Analog IV	2.724717
Zeaxanthin analog II compared with	
Zeaxanthin	2.558529
Analog I	1.753791
Analog III	2.094065
Analog IV	2.388945
Zeaxanthin analog III compared with	
Zeaxanthin	1.896550
Analog I	2.640960
Analog II	2.094065
Analog IV	1.388740
Zeaxanthin analog IV compared with	
Zeaxanthin	2.037715
Analog I	2.724717
Analog II	2.388945
Analog III	1.388740

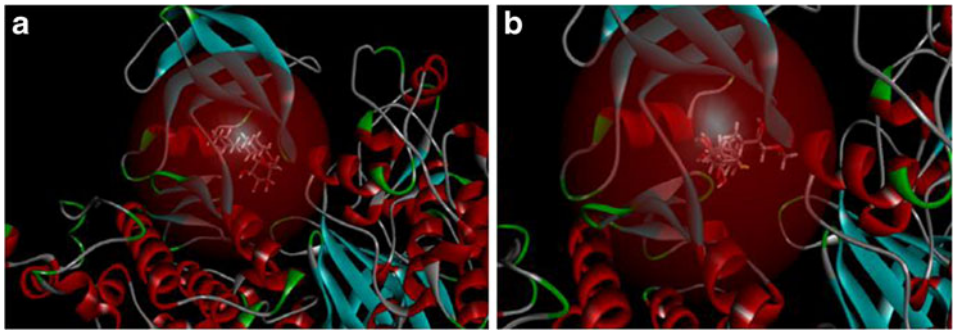

Figure 1. (**a**) Isorhamnetin 3-rhamnoside and (**b**) Isorhamnetin 7-glucoside binding to the active site of GSK-3β.

MDL drug data report (MDDR) database violate Lipinski's rule of five (Khanna and Ranganathan 2009).

3D QSAR pharmacophore generation can be used to predict the activity of new ligand candidates and guide lead optimization to improve the activity of existing ligands. Hence, a few analogues of Zeaxanthin and vitamin C that accept the rule of five were also analysed to illustrate the importance of pharmacophore modelling in the process of rational drug designing.

RMSD, or root mean square deviation, is the measure of the average distance between the atoms (usually the backbone atoms) of superimposed proteins. RMSD is used to make a quantitative comparison between the structures of partially folded proteins with that of their native structures.

The RMSD values were calculated in order to estimate the similarity between the structures and find out their identity. The RMSD values of the analogues calculated using DS helped in defining the conformational accuracy, as tabulated in table 1. The difference in these values could result in altered effects and varied functioning of the compound (Sharma and Naik 2013).

Through our study it was seen that Zeaxanthin directly did not bind to the receptors. However, when analogues of Zeaxanthin were created, the first analogue of Zeaxanthin showed good binding energy. A comparison of the RMSD values is shown in Table 1. The docking was carried out with all the analogues generated. Only the first analogue showed good binding energy with GSK-3β. When this phenomenon was investigated, it was seen that the deviation of other analogues created was greater than 1 Å, which led to their failure in binding with the receptors.

Docking results tabulated between GSK-3β receptor and the compounds of *H. salicifolia* and *H. rhamnoides* (table 1) as well as with the analogues are shown along with the modifications within them. Leutein D, Zeaxanthin analogue I, Isorhamnetin 3-rhamnoside and Isorhamnetin 7-glucoside on docking with GSK-3β receptor produced least energy values of −11.8885, −9.68933, −16.7087 and −16.3365 respectively. The lowest-energy docking poses for the ligands is the Domain A and B of chain A of GSK-3β (figure 1 and 2).

Zeaxanthin I analogue in comparison with Zeaxanthin showed a decrease in the libdock score, (table 2), which

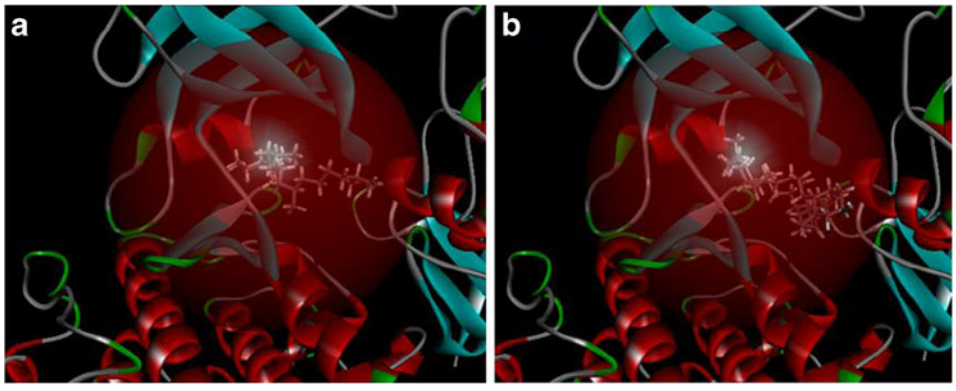

Figure 2. (**a**) Leutein-D and (**b**) Zeaxanthin binding to the active site of GSK-3β.

Table 2. DS binding energies of best docked poses for *Hippophae* compounds with GSK-3 β and GK

S. No.	Compound name	Binding energy (kcal/mol)	
		GSK-3 β	GK
	H. salicifolia		
1.	Alpha Carotene	4.62E+10	NB
2.	Beta Cryptoxanthin	4.76E+09	NB
3.	Beta Carotene	4.19259	NB
4.	Gamma Carotene	−5.6606	NB
5.	**Lutein D**	**−11.8885**	NB
6.	Lycopene	13.9054	NB
7.	Translutein	1.83E+06	NB
8.	Zeaxanthin	19,231.20	NB
9.	**Zeaxanthin Analog I**	**−9.68933**	NB
10.	Zeaxanthin Analog II	4.83618	NB
11.	Zeaxanthin Analog IV	4.63558	NB
12.	Zeaxanthin Analog V	5,287.49	NB
13.	Zeaxanthin Analog VI	341.378	NB
14.	Zeaxanthin Analog VII	23.1747	NB
15.	Zeaxanthin Analog VIII	1.49E+10	NB
16.	Zeaxanthin Analog IX	0.17155	NB
	H. rhamnoides		
1.	Isorhamnetin 3-glucoside	−3.37217	NB
2.	**Isorhamnetin 3-rhamnoside**	**−16.7087**	NB
3.	Isorhamnetin 5-glucoside	−1.28277	NB
4.	**Isorhamnetin 7-glucoside**	**−16.3365**	NB
5.	Isorhamnetin 7-rhamnoside	1.41165	NB
6.	Quercetin 3-glucoside-7-rhamnoside	1.28844	NB
7.	Quercetin 3-glucoside	−10.2054	NB
8.	Vitamin C	5.52756	−19.7344
9.	Vitamin E	12.6852	NB

The bold italicized words indicate the plant species and the non-italicized words indicate the compounds having the best binding energies, whereas bold non-italicized words indicate best binding energy (kcal/mol).

NB = Not-binding (i.e., docking energy positive).

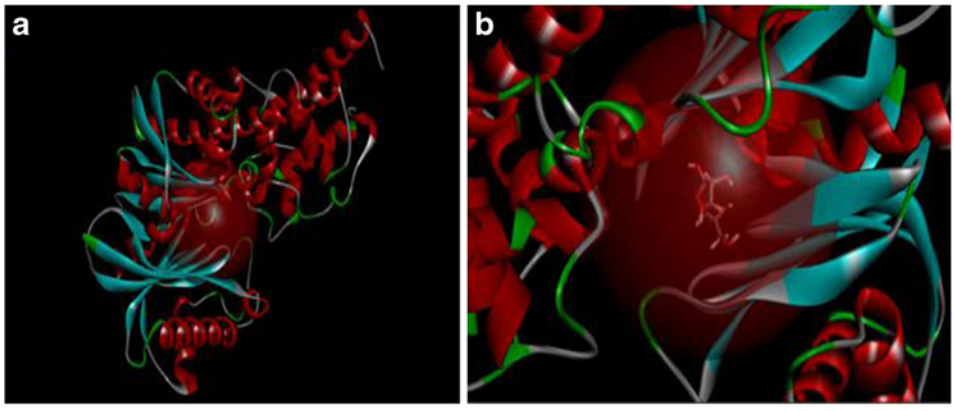

Figure 3. (**a**) X-ray crystallography structure of Glukokinase with the binding site highlighted. (**b**) GK receptor with the docked ligand vitamin C.

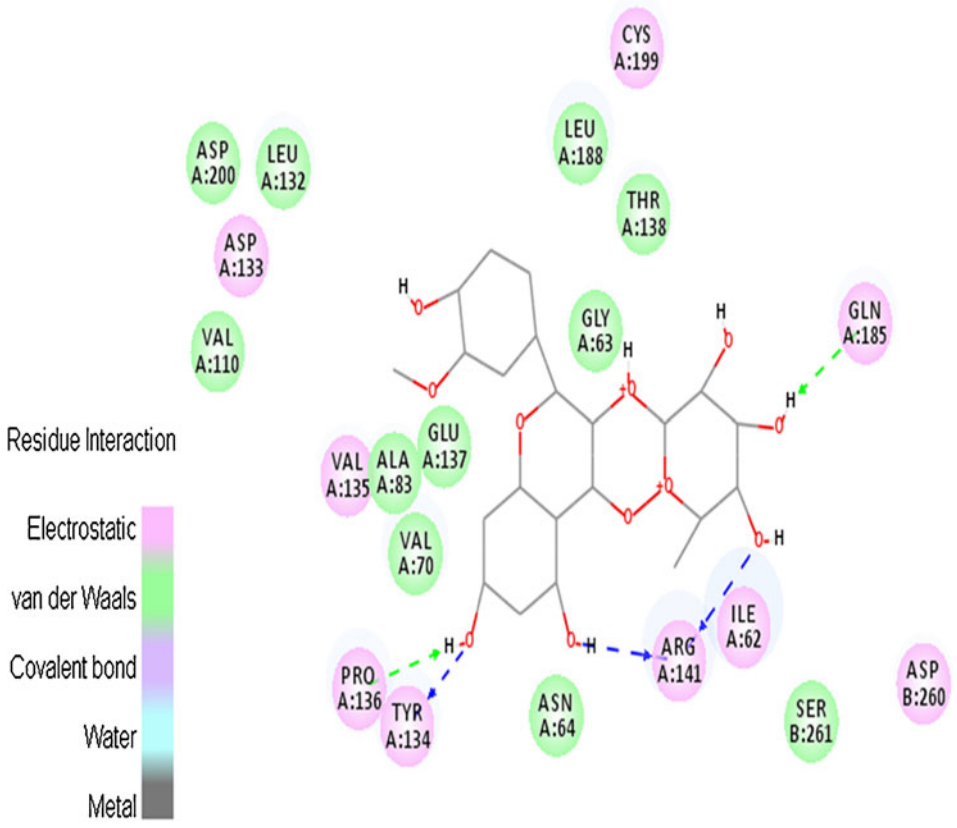

Figure 4. Schematic representation of Isorhamnetin 3-rhamnoside interactions with the residues of GSK-3β.

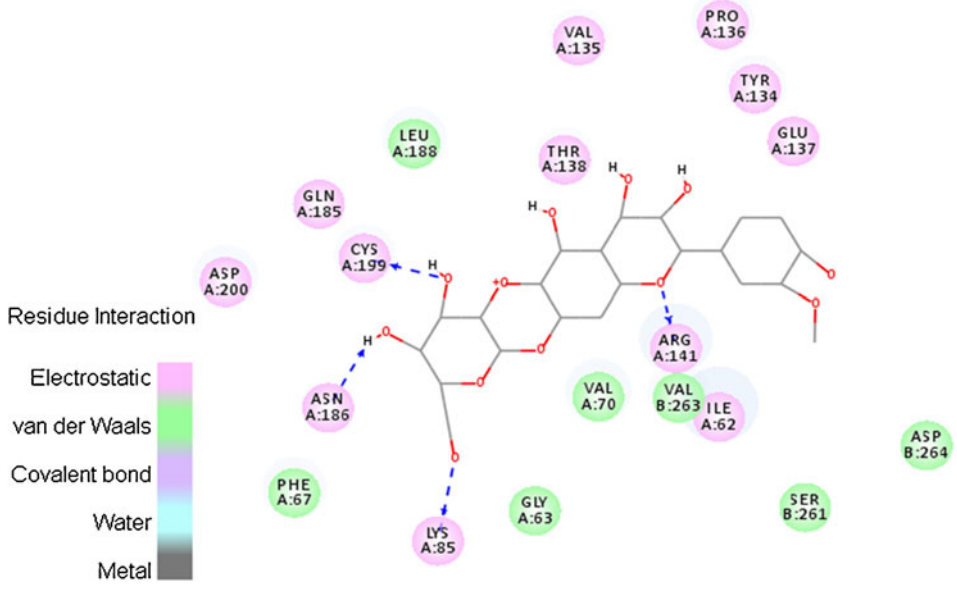

Figure 5. Schematic representation of Isorhamnetin 7-glucoside interactions with the residues of GSK-3β.

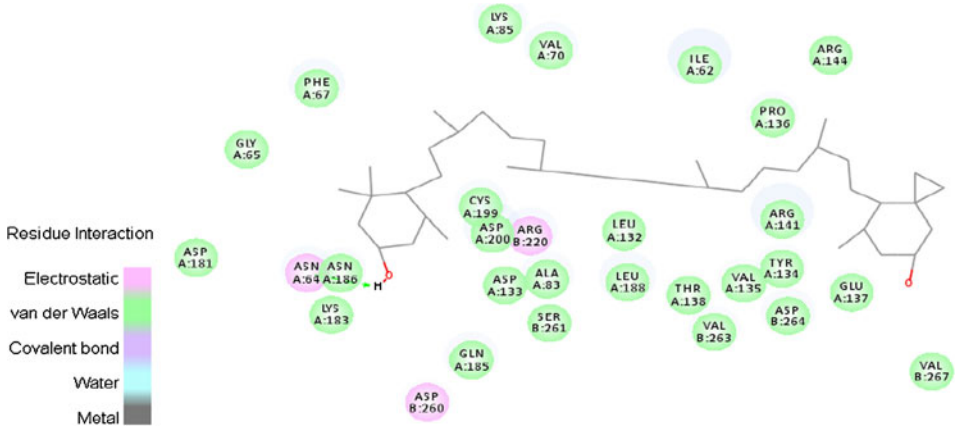

Figure 6. Schematic representation of Lutein-D interactions with the residues of GSK-3β.

indicates that the analogue binding is superior with the receptor. However, the binding site of the analogue was similar to that of its predecessor, which means that functional groups involved in the interaction were the same as by pharmacophore modelling, and only the steric compatibility was increased (Long *et al*. 2012).

Docking simulations with GK-bound ligand vitamin C (figure 3) resulted in a dock score of −19.7344. GK receptor did not show binding interactions with any other compound, which may be due to smaller catalytic site as shown in table 1 (Khanna and Ranganathan 2009).

A detailed comparison of interaction pattern from the docking results for the compounds that showed least binding energy with GSK-3β is summarized in figures 4–7. The result of the docking analysis suggested that all ligands adopted similar binding poses in GSK-3β, and some common interaction specificities were observed with residues like Val135(A), Asp200(A), Val70(A), Gln185(A), Arg141(A), Pro136(A), Tyr134(A), Leu188(A), Asn186(A) and Cys199(A).

The ligands vitamin C and D-glucose preferentially occupy different locations of receptor GK as depicted in figure 8. It also suggests that the residues Asp 205(A), Lys169(A), Ile225(A) and Ser151(A) may play a vital role in inhibitory activity.

3.1 *Toxicity studies*

Toxicity studies deal with the adverse effects of the drugs on animal models or living organisms. There is prediction that around 50% of the drugs fail during the clinical trials

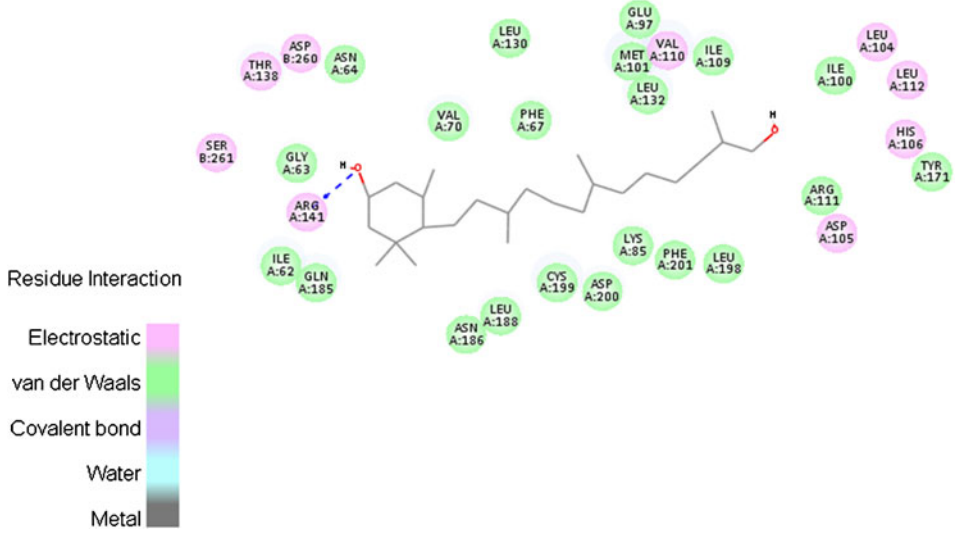

Figure 7. Schematic representation of Zeaxanthin interactions with the residues of GSK-3β.

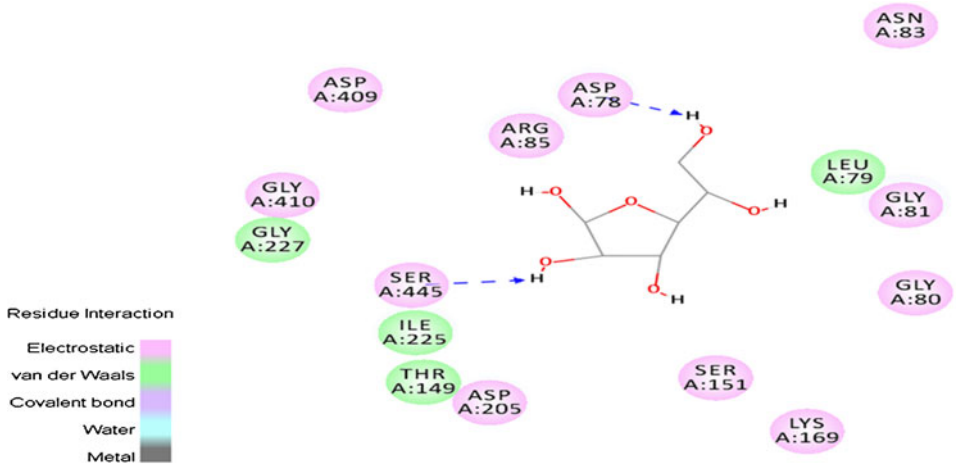

Figure 8. Schematic representation for the interactions of vitamin C with Glucokinase.

because of their toxicity represented as ADME/Tox properties. Failure of drugs at this stage proves very expensive in the drug development process (Hodgson 2001). *In silico* ADME/Tox tools present an array of opportunities that helps in accelerating the discovery of new targets and ultimately lead to compounds with predicted biological activity (Ekins and Swaan 2004). Thus, predicting ADME/Tox information at early stages would offer enormous benefits. Table 3 depicts the ADME/Tox properties of compounds with least binding energies predicted using DS toxicity prediction module. Aqueous solubility or absorption is a chief indicator for solubility in the intestinal fluids, an influential descriptor of bioavailabity issues (Cheng and Merz 2003). The solubility levels of the four compounds fall in the range 0–5, indicating good oral bioavailability. Blood–brain barrier (BBB) separates brain from systemic blood and maintains homeostasis of central nervous system (CNS). Low penetration of non-CNS drugs is desirable to minimize CNS related side-effects. All the test compounds demonstrated a low penetration value of 4. The reported incidence of drug-related hepatotoxicity is difficult to determine because of factors like underreporting, difficulties in detection and incomplete observations (Larrey 2002). Hepatotoxicity was considered as one of the parameters, because in majority of the cases, there is no successful treatment apart from stopping the drug. All the compounds display no hepatotoxicity, and Zeaxanthin analogue I shows the least hepatotoxicity level. Lutein D and Zeaxanthin analogue possess the ability to bind to plasma protein, indicating that they can bind efficiently to the proteins available in the blood. However, it may reduce the concentration of the drug at the original site of action. Isorhamnetin 3-rhamnoside, Isorhamnetin 7-glucoside and vitamin C showed partial plasma protein binding ability. Previous studies reveal that the unbound fraction of the drug exhibits good pharmacological effects and are easily eliminated from the body (Korstanje *et al.* 2011; Suri and Naik 2012).

Table 3. The toxicity prediction of the compounds present in the *Hippophae* and their analogs

Parameters Considered	Isorhamnetin-3-rhamnoside	Isorhamnetin-7-glucoside	Lutein D	Zeaxanthin Analog 1	Vitamin C
Absorption level	3	3	3	3	3
Solubility level	4 (−1.545)	4 (−1.096)	0 (−8.058)	0 (−5.708)	5 (2.343)
Blood–brain barrier level	4	4	4	4	4
Hepatotoxicity prediction	False−4.48416	False−4.83936	False−12.9983	False−13.1725	False−4.75895
Plasma protein binding prediction	False	False	True	True	False

4. Conclusion

In conclusion, few compounds of *Hippophae* like Lutein D, Zeaxanthin analogue I, Isorhamnetin 3-rhamnoside and Isorhamnetin 7-glucoside could prove to be successful drug candidates as they are a class of novel, potent, selective, orally bioavailable and nontoxic GSK-3β inhibitors and Vitamin C, being an exclusive inhibitor of GK with all of the above having reasonable binding energies and strong quantitative correlations. Small active sites (cavity or binding site) could be the probable reason for the GK not showing any interaction with other molecules. The binding interactions exhibited by various compounds and analogues of *Hippophae* signify the importance of specific amino acid residues in the active site of both GSK-3β and GK. Therefore, the present study illustrates the efficacy of computational rational drug designing in drug discovery. It also warrants the need of further *in vitro* and *in vivo* studies for development of potent inhibitors of the receptors for treatment of diabetes.

Acknowledgements

The authors wish to thank the Deanship of Life Science Research, DBT-Bioinformatics Infrastructure Facility, and BT-Finishing School, at Maharani Lakshmi Ammanni College for Women, for providing infrastructure and the licensed software to carry out the project.

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