ScienSage

Journal of Advanced Scientific Research

Available online through https://sciensage.info

ISSN 0976-9595

Research Article

PREDICTION OF TOXICITY, PHARMACOKINETICS OF SELECTED PHYTOCHEMICALS OF LEAF OF DRUMSTICK (*Moringa* Sp.) AND MOLECULAR DOCKING STUDIES ON TWO RECEPTORS AS INSULIN TYROSINE KINASE FOR ANTIDIABETIC POTENTIAL

Kaushick Mishra*[1], Soumendra Nath Talapatra[2]

[1]*Department of Pharmacology, R. G. Kar Medical College and Hospital, Khudiram Bose Sarani, Shyam Bazar, Kolkata, West Bengal, India*

[2]*Department of Bio-Science, Seacom Skills University, Kendradangal, Shantiniketan, Birbhum, West Bengal, India*

**Corresponding author: kaushick30@gmail.com*

Received: 26-09-2021; Revised: 21-02-2022; Accepted: 27-02-2022; Published: 31-03-2022

 https://doi.org/10.55218/JASR.202213210

ABSTRACT

The medicinal plant, *Moringa oleifera* Lam is a common tree and the leaf of this plant contains several phytochemicals that have potent anti-diabetic properties. The objective of the present study was to predict toxicity, pharmacokinetics and receptor-ligand binding energy and interaction through molecular docking for selected phytocompounds against mutated protein A and B insulin receptor tyrosine kinase (PDB IDs: 3ekk and 3ekn). *In silico* study especially molecular docking and pharmacokinetics, bioavailability, drug-likeness, and medicinal chemistry prediction was performed by using PyRx tool (Version 0.8) and Swiss ADME online tool. The molecular interaction was visualized in the molecular graphics laboratory (MGL) tool (Version 1.5.6). About 6 selected phytoconstituents and 2 nos. of synthetic medicines were taken for present prediction. Present *in silico* study especially molecular docking revealed that favourable binding energy was obtained for Serpentine and Niazirin for A receptor and Anthraquinone for B receptor when compared to synthetic medicines viz. Glibenclamide and Metformin. The pharmacokinetics, bioavailability and drug-likeness and medicinal chemistry to know lead-likeness prediction Serpentine and Niazirincan be suitable drug candidates, which may be potent antidiabetic compound. In conclusion, the binding was obtained near the active site, which may be due to competitive inhibition. Moreover, in future research this predictive data should be validated with further toxicological and pharmacological assay for confirmation of antidiabetic potential.

Keywords: *Moringa* sp.; *In silico* method; ADMET profiling; Drug candidate; Antidiabetic phytomedicine.

1. INTRODUCTION

The disease diabetes mellitus (DM) depends on metabolic syndrome, life-style pattern, non-communicable, prolonged effect, etc., which leads to increase glycaemia and other co-morbidities [1]. These complications are originating due to defect in insulin secretion, its function or may be due to tissue and vascular damage [2-7]. Moreover, the regulation of insulin-mediated glucose metabolism in peripheral tissues via insulin receptor substrate/phosphoinositide 3 kinase/protein kinase B (IRS/PI3K/Akt) signalling pathway plays a key role in the prevalence of the disease [6]. The molecular mechanisms lead to the development of insulin resistance by the proteins participated in this signalling pathway [6]. The investigators find that in individuals with insulin resistance, the expression of the insulin receptor (IR) observes reduction or absent [6, 8-9]. According to Whitehead et al. [10], insulin resistance-associated with insulin receptor substrate-1 (IRS-1) mutations, and an increasing phosphorylation of this substrate on serine residues may lead to the reduction of its tyrosine phosphorylation, ultimately develop lower insulin signalling [6,11]. It has been observed in the insulin signalling pathway that the first critical node is the receptor itself (IR), which creates two isoforms such as IRA and IRB through the alternative splicing.

In recent days, phytomedicines are of concern to prevent the DM without any side effects. In this context, natural products derived from plants may be less expensive, indigenous, etc. and can be used in drug discovery. To date, the DM cure mainly the proper

functioning of IR in DM patients, is challenging fact. Among several plant species, *Moringa oleifera* Lam. commonly called as "Sajne in Bengali" and "Drumstick in English" and found in most places of India. The extract of leaves of this plant has immense potential to prevent DM in animal studies and as per traditional knowledge [12-16]. But leaves extract contains many phytochemicals that may be allelochemicals, which are entering into the body of animals or humans and may pose toxicity [17, 18].

Few studies have been conducted to know the potential phytocompound(s) to prevent DM as molecular docking approach, predictive toxicity, and pharmacokinetics of the phytochemicals of the leaves of *M. oleifera* compared to established synthetic medicines viz. Metformin and Glibenclamide [19-22].

The predictive toxicity screening can be done through QSAR modelling by using ProTox-II webserver developed by Drwal et al. [23] and further research works done by Banerjee et al. and Ghosh et al. [24, 25] and Biswas and Talapatra [26]. Beside these, the predictive screening pharmacokinetics, bioavailability, drug-likeness, and medicinal chemistry friendliness of ligands are also important approach for drug discovery. On the other hand, molecular docking is suitable to detect favourable binding energy of ligand through receptor-ligand binding interaction in which lead molecule can easily be identified for new drug design [27].

In the present *in silico* study, predictive toxicity, pharmacokinetics, and molecular docking between two IR kinase and ligands of *M. oleifera* leaves for anti-diabetic potential were performed.

2. MATERIAL AND METHODS

2.1. Selection of plant specimen

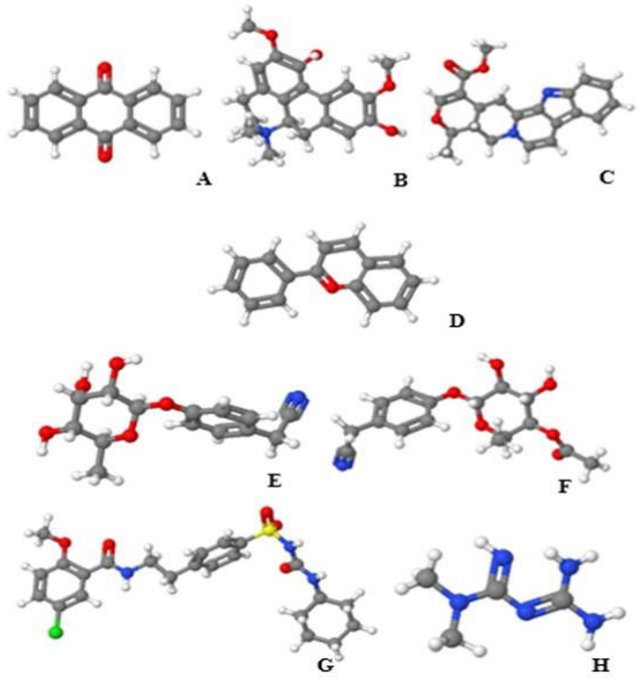
In the present *in silico* study, the plant specimen was selected as *Moringa* sp. commonly called "Drumstick" under Moringaceae family and very fast-growing tree, found in all parts of India. The phytochemicals of this tree have potential medicinal properties as per traditional knowledge [28].

2.2. Selection of phytochemicals and synthetic medicines (ligands)

All the ligands for leaf phytochemicals and synthetic medicines were selected as per literature of earlier studies [19-22, 29] and the three-dimensional (3D) structures of selected ligands are depicted in Fig 1. The SMILES (simplified molecular-input line-entry system) of selected ligands were taken from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and 3D structure were retrieved from CORINA online server (www.mn-am.com/online_demos /corina_demo).

2.3. Toxicity prediction

The toxicity screening especially rats oral acute toxicity, to know median lethal dose (LD_{50}) as mg/Kg and hepatotoxicity, immunotoxicity, cytotoxicity, mutagenicity and carcinogenicity were predicted by using ProTox-II webserver developed by Drwal et al., [23] and protocol established by Banerjee et al., [24]. The toxicity prediction was carried out for 6 phyto-ligands and 2 synthetic antidiabetic medicines.



(A = Anthraquinone; B = Laurifoline; C = Serpentine; D = Flavylium; E = Niazirin; F = Niazirinin) and synthetic medicines (G = Glibenclamide and H = Metformin)

Fig. 1: Three-dimensional ribbon structure of phytochemicals

2.4. Pharmacokinetics (ADME), bioavailability, and drug-likeness prediction of ligands

The predictive study of pharmacokinetics especially ADME, bioavailability, drug-likeness, and medicinal chemistry for lead-likeness of selected ligands were performed through Swiss ADME online tool developed by Daina et al. [30, 31] and the methodology for prediction was described in the earlier study [32]. The tool predicts bioavailability radar as per six physicochemical properties such as lipophilicity, size, polarity, solubility, flexibility, and saturation to detect drug-likeness.

2.5. Selection of receptors

The 3D crystal structure of two proteins viz. IR tyrosine kinase A and B (PDB IDs: 3EKK and 3EKN) were downloaded from the protein data bank (www. rcsb.org). Chamberlain et al. [33, 34] experimented and deposited the X-ray diffraction crystallographic structures of two receptors at 2.10Å and 2.20 Å resolution. The three-dimensional (3-D) ribbon structure of both receptors are depicted in Fig 2A and B after visualizing in MGL tool developed by The Scripps Research Institute [35]. The attached inhibitor molecules were GS2 (2-[(2-{[1-(N,N-dimethylglycyl)-5-methoxy-1H-indol-6-yl]amino}-7H-pyrrolo[2,3-d] pyrimi-din-4-yl)amino]-6-fluoro-N-methylbenzamide) and GS3(2-fluoro-6-{[2-({2-methoxy-4-[4-(1-methylethyl) piperazin-1-yl]phenyl} amino)-7H-pyrrolo[2,3-d]pyri-midin-4-yl]amino} benzamide).

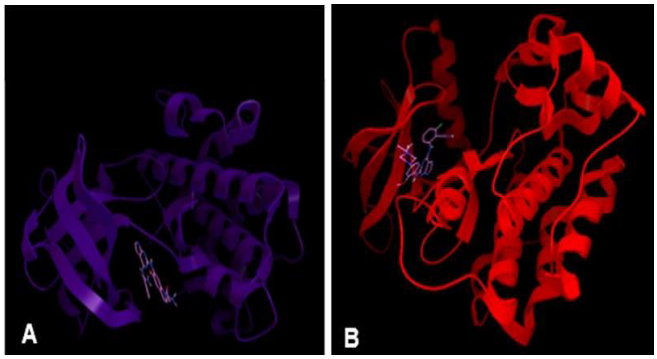


Fig. 2: Three-dimensional ribbon structure of IR tyrosine kinase attached with inhibitor molecule (A=GS2 and B=GS3) as line structure (PDB IDs: 3ekk and 3ekn)

2.6. Study of molecular docking and interaction

The molecular docking was done by using PyRx software (Version 0.8) developed by Trott and Olson [36]. The molecular docking was visualized the output. pdbqt file and the result of suitable lead was rendered by using MGL tool [35]. The docking was carried out with 6 phytoligands and 2 synthetic antidiabetic medicines on IR tyrosine kinase A and B (PDB IDs: 3EKK and 3EKN) to predict suitable binding energy value. The receptor-ligand interaction of this target receptors and ligands were identified to detect the residues involved in each case for the therapeutic efficacy of DM. The 3-D grid box size values such as X = 54.5501, Y = 53.9688 and Z = 53.1326Å and central position values viz. X = -13.869, Y= 15.1557 and Z= -17.7602Å for A and X = 54.2279, Y= 52.6583 and Z= 52.3855 and central position values viz. X = 14.3036, Y = 15.1570 and Z = 18.0052Å for B, respectively for docking site on the studied target receptors with a grid spacing of 0.375 Å. Finally, binding pose and interaction with amino acids were identified.

3. RESULTS

The results of selected phytochemicals and synthetic medicines obtained the predictive rat oral acute toxicity (LD_{50}) values (mg/Kg) along with activity or inactivity on liver toxicity, immunotoxicity, genetic toxicity end points viz. cytotoxicity, mutagenicity, and carcinogenicity (Table 1). Majority of ligands were predicted as class V (may be harmful, if swallowed ($2000 < LD_{50} \leq 5000$).

Table 1: Prediction of oral acute toxicity, classes, and accuracy of different ligands

Sl. No.	Ligands	Oral LD50 value (mg/Kg)	Predicted toxicity class	Prediction accuracy (%)
1.	Anthraquinone	5000	V	100.0
2.	Laurifoline	450	IV	72.9
3.	Flavylium	2500	V	69.26
4.	Serpentine	215	III	54.26
5.	Niazirin	3750	V	69.26
6.	Niazirinin	4000	V	70.97
7.	Glibenclamide	3250	V	100.0
8.	Metformin	680	IV	54.26

Class III: toxic if swallowed ($50 < LD_{50} \leq 300$); Class IV: harmful if swallowed ($300 < LD_{50} \leq 2000$); Class V: may be harmful if swallowed ($2000 < LD_{50} \leq 5000$) and Class VI: non-toxic ($LD_{50} > 5000$)

All ligands were predicted hepatotoxic and cytotoxic inactive while majority of ligands were non-immunotoxic, non-mutagenic and non-carcinogenic (inactive) except Laurifoline and Serpentine were immunotoxic, Anthraquinone was mutagenic and Flavylium was predicted both mutagenic and carcinogenic active (Table 2 and 3).

The results on predictive values for pharmacokinetics especially ADME (absorption, distribution, metabolism and excreation), bioavailability, drug-likeness, and

medicinal chemistry data on studied phyto and synthetic ligands (Table 4). For pharmacokinetics prediction, the GI absorptionrate was obtained higher in all ligandswhile lower for Glibenclamide drug. No blood-brain permeability was observed for Niazirin, Niazirinin, Glibenclamide and Metformin while rest ligands obtained BBB positive. In case of skin permeation (log Kp, cm/s), higher negative value was obtained for Metformin followed by Niazirinin and lower for Anthraquinone and Flavylium. All the ligands did not show p-glycoprotein substrate activity except Laurifoline and Flavylium (Table 4).

Table 2: Prediction of hepatotoxicity and immunotoxicity of different ligands

Sl. No.	Ligands	Hep	P (%)	Imm	P (%)
1.	Anthraquinone	I	72	I	98
2.	Laurifoline	I	96	A	99
3.	Flavylium	I	74	I	99
4.	Serpentine	I	79	A	82
5.	Niazirin	I	73	I	87
6.	Niazirinin	I	69	I	51
7.	Glibenclamide	I	63	I	73
8.	Metformin	I	74	I	99

Hep = Hepatotoxicity; Imm = Immunotoxicity; I = Inactive; A = Active and P = Probability

Table 3: Prediction of cytotoxicity, mutagenicity and carcinogenicity of different ligands

Sl. No.	Ligands	Cyt	P (%)	Mut	P (%)	Crc	P (%)
1.	Anthraquinone	I	85	A	83	I	74
2.	Laurifoline	I	69	I	59	I	64
3.	Flavylium	I	75	A	56	A	56
4.	Serpentine	I	66	I	53	I	52
5.	Niazirin	I	77	I	74	I	64
6.	Niazirinin	I	78	I	77	I	64
7.	Glibenclamide	I	77	I	80	I	76
8.	Metformin	I	69	I	59	I	68

Cyt = Cytotoxicity; Mut = Mutagenicity; Crc = Carcinogenicity; I = Inactive; A = Active and P = Probability

Table 4: Prediction of Pharmacokinetics of phyto and synthetic ligands

Ligands	GI absorption	BB permeant	PGP substrate	CYP450 1A2 inhibitor	CYP450 2C19 inhibitor	CYP450 2C9 inhibitor	CYP450 2D6 inhibitor	CYP450 3A4 inhibitor	Skin permeation as log Kp (cm/s)
Anthraquinone	High	Yes	No	Yes	Yes	No	No	No	-5.16
Laurifoline	High	Yes	Yes	Yes	No	No	No	Yes	-6.44
Flavylium	High	Yes	Yes	Yes	No	No	Yes	No	-5.16
Serpentine	High	Yes	No	No	Yes	No	Yes	Yes	-6.59
Niazirin	High	No	No	No	No	No	No	No	-8.27
Niazirinin	High	No	No	No	No	No	No	No	-7.91
Glibenclamide	Low	No	No	No	Yes	Yes	Yes	Yes	-5.90
Metformin	High	No	No	No	No	No	No	No	-7.99

GI = Gastro-intestinal; BB = Blood-brain; PGP = p-Glycoprotein

To detect inhibitory activity for cytochrome p450 as CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 inhibitors, Anthraquinone, Laurifoline and Flavylium were obtained inhibitors for CYP1A2, Anthraquinone, Serpentine and Glibenclamide were found inhibitors for CYP2C19, Glibenclamide was only obtained inhibitor for CYP2C9, Flavylium, Serpentine and Glibenclamide were found inhibitors for CYP2D6 and Laurifoline, Serpentine and Glibenclamide were found inhibitors for CYP3A4. The prediction of bioavailability score was same for all ligands (0.55) except Serpentine (0.85). Regarding the water solubility, three ligands viz.

Niazirin, Niazirinin and Metformin data were obtained soluble (Table 5). In case of bioavailability for other parameters such as iLOGP, XLOGP3 and WLOGP, data were also predicted. For iLOGP, higher value for Serpentine and lower value for Flavylium was obtained. For XLOGP3 and WLOGP, higher value for Glibenclamide and lower value for Metformin was obtained (Table 5). Other bioavailability parameters viz. MLOGP, higher value for Flavylium and lower value for Laurifoline was obtained. For SILCOS-ST, higher value for Anthraquinone and lower value for Metformin was obtained (Table 5).

For drug-likeness prediction, all the ligands were found under Lipinski rule with 0 violation. For Ghose filter, Veber filter, Egan filter and Muegge filter were found suitable except the synthetic ligands (Table 7). In case of medicinal chemistry prediction, Niazirin and Niazirinin followed by Laurifoline and Serpentine obtained suitable lead-likeness, Pan assay interface structure and Brenk structural alert. Synthetic accessibility score showed higher in Serpentine followed by Niazirin and Niazirinin compared to synthetic ligands (Table 7).

The bioavailability radar (Fig 3) for oral bioavailability prediction for specific ligands viz. Laurifoline, Serpentine, Niazirin, Niazirinin and Glibenclamide showed with the range of LIPO as XLOGP3, the SIZE as molecular weight (gm/mol), the POLAR as TPSA (Å²), the INSOLU Logs (ESOL) values, the INSATU (insaturation) as per Csp3 data, and the data for FLEX as per no. of rotable bonds, respectively.

Table 5: Prediction of bioavailability of phyto and synthetic ligands

Ligands	Bioavailability score	Water solubility as logS& SILICOS-IT	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT
Anthraquinone	0.55	MS, -5.25	1.94	3.39	2.46	1.86	3.56
Laurifoline	0.55	MS, -5.69	-0.43	2.74	2.31	-1.71	3.01
Flavylium	0.55	MS, -5.32	-0.68	3.39	4.38	3.28	2.79
Serpentine	0.85	MS, -4.92	3.34	2.58	3.45	2.21	2.78
Niazirin	0.55	S, -1.26	1.68	-0.37	-0.04	-0.51	0.25
Niazirinin	0.55	S, -1.90	2.43	0.49	0.53	-0.08	0.71
Glibenclamide	0.55	PS, -7.71	2.81	4.81	4.72	2.58	3.00
Metformin	0.55	S, 0.58	0.34	-1.27	-1.24	-0.56	-1.74

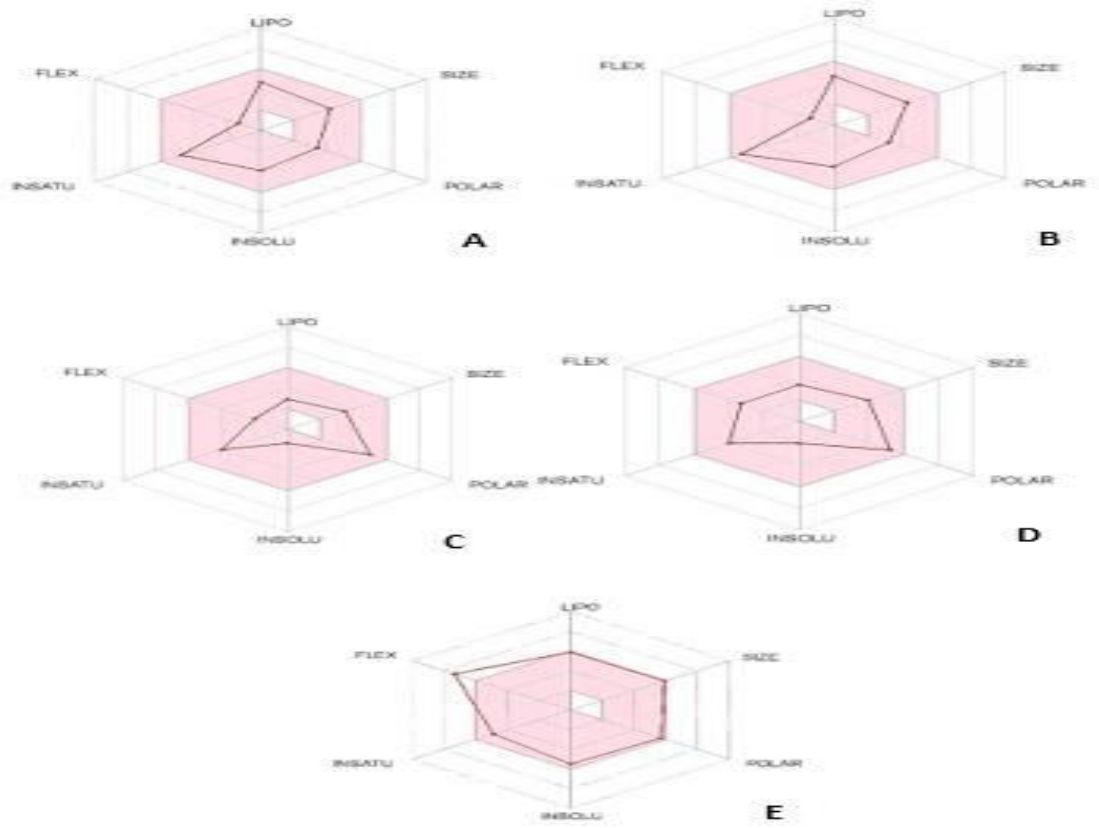
S = Soluble; MS = Moderately soluble; PS = Poorly soluble; V = Violation

Table 7: Prediction of drug-likeness of phyto and synthetic ligands

Ligands	Lipinski rule	Ghose filter	Veber filter	Egan filter	Muegge filter
Anthraquinone	Yes, 0 V	Yes	Yes	Yes	Yes
Laurifoline	Yes, 0 V	Yes	Yes	Yes	Yes
Flavylium	Yes, 0 V	Yes	Yes	Yes	No, 1 V
Serpentine	Yes, 0 V	Yes	Yes	Yes	Yes
Niazirin	Yes, 0 V	Yes	Yes	Yes	Yes
Niazirinin	Yes, 0 V	Yes	Yes	Yes	Yes
Glibenclamide	Yes, 0 V	No, 1 V	No, 1 V	Yes	Yes
Metformin	Yes,0 V	No, 3 V	Yes	Yes	No, 2 V

V = Violation

The inbuilt BOILED-Egg model is represented in which 2 phytochemicals viz. Niazirin and Niazirinin showed the capability of GI absorption while blood-brain barrier penetration was not found for these ligands related to synthetic medicines. These two ligands were found PGP negative as non-substrate in predictive model like 2 synthetic ligands (Fig 4).



A = Laurifoline, B = Serpentine, C = Niazirin, D = Niazirinin and E = Glibenclamide [LIPO = lipophilicity as XLOGP3; SIZE = size as molecular weight; POLAR = polarity as TPSA (topological polar surface area); INSOLU = insolubility in water by log S scale; INSATU = insaturation as per fraction of carbons in the sp3 hybridization and FLEX = flexibility as per rotatable bonds]

Fig. 3: Molecular structure and bioavailability radar (pink area exhibits optimal range of particular property) for studied small molecules

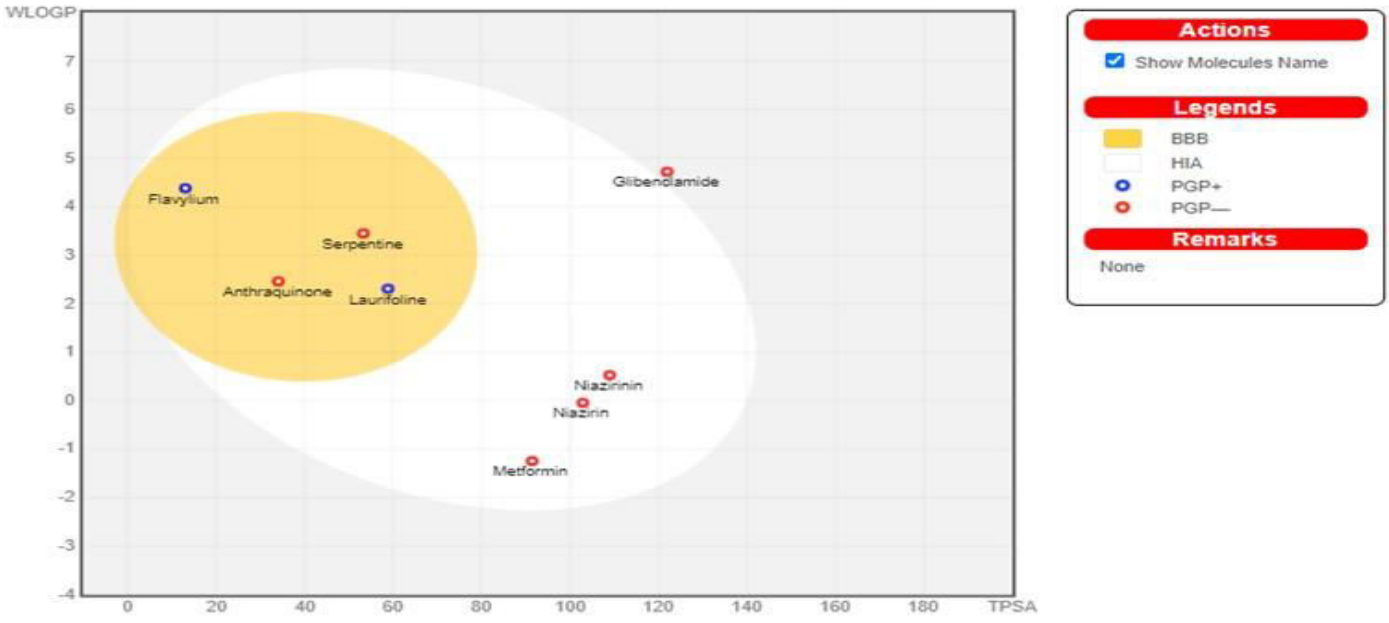


Fig. 4: The BOILED-Egg represents for intuitive evaluation of passive gastrointestinal absorption (HIA) white part and brain penetration (BBB) yellow part as well as blue and red points PGP positive and negative in function of the position of the small molecules in the WLOGP-versus-TPSA graph

In Table 8, the data of favourable binding energy, predicted values for two phytoligands viz. Serpentine of about -7.9Kcal/mol and Niazirin of about-7.5Kcal/mol, respectively when compared to synthetic medicine viz. Glibenclamide (-8.2 Kcal/mol) on IR tyrosine kinase A (PDB ID: 3EKK). The data of favourable binding energy predicted value of one phytoligand viz. Anthraquinone of about -7.9 Kcal/mol when compared to synthetic medicine viz. Glibenclamide (-8.0 Kcal/mol) on IR tyrosine kinase B (PDB ID: 3EKN).

In case of the receptor-ligand binding pose and interaction study on IR tyrosine kinase A, the contact residues such as ARG1089, LYS1085 and GLU1096 with a hydrogen bonding with residue ALA1095 were obtained for Serpentine while contact residues such as ARG1089, LYS1085 without hydrogen bonding were obtained for Niazirin. In comparison with Glibenclamide, the contact residues such as TYR1087, SER1090, SER1086, ASN1097, GLU1096, GLU1094 and ARG1089 without hydrogen bonding were obtained. In three ligands, the common contact residue was ARG1089. The pose and interaction for each ligand is depicted in Fig 5A-C.

Table 8: Binding energy of receptor-ligand binding

Sl. No.	Ligands	Binding energy (Kcal/mol) PDB ID: 3ekk	Ligands	Binding energy (Kcal/mol) PDB ID: 3ekn
	Phytochemicals		**Phytochemicals**	
1.	Serpentine	-7.9	Anthraquinone	-7.4
2.	Niazirin	-7.5	Laurifoline	-7.3
3.	Flavylium	-7.4	Flavylium	-7.1
4.	Laurifoline	-7.1	Serpentine	-6.8
5.	Anthraquinone	-6.9	Niazirin	-6.6
6.	Niazirinin	-6.8	Niazirinin	-6.0
	Synthetic medicines		**Synthetic medicines**	
1.	Glibenclamide	-8.2	Glibenclamide	-8.0
2.	Metformin	-5.5	Metformin	-4.9

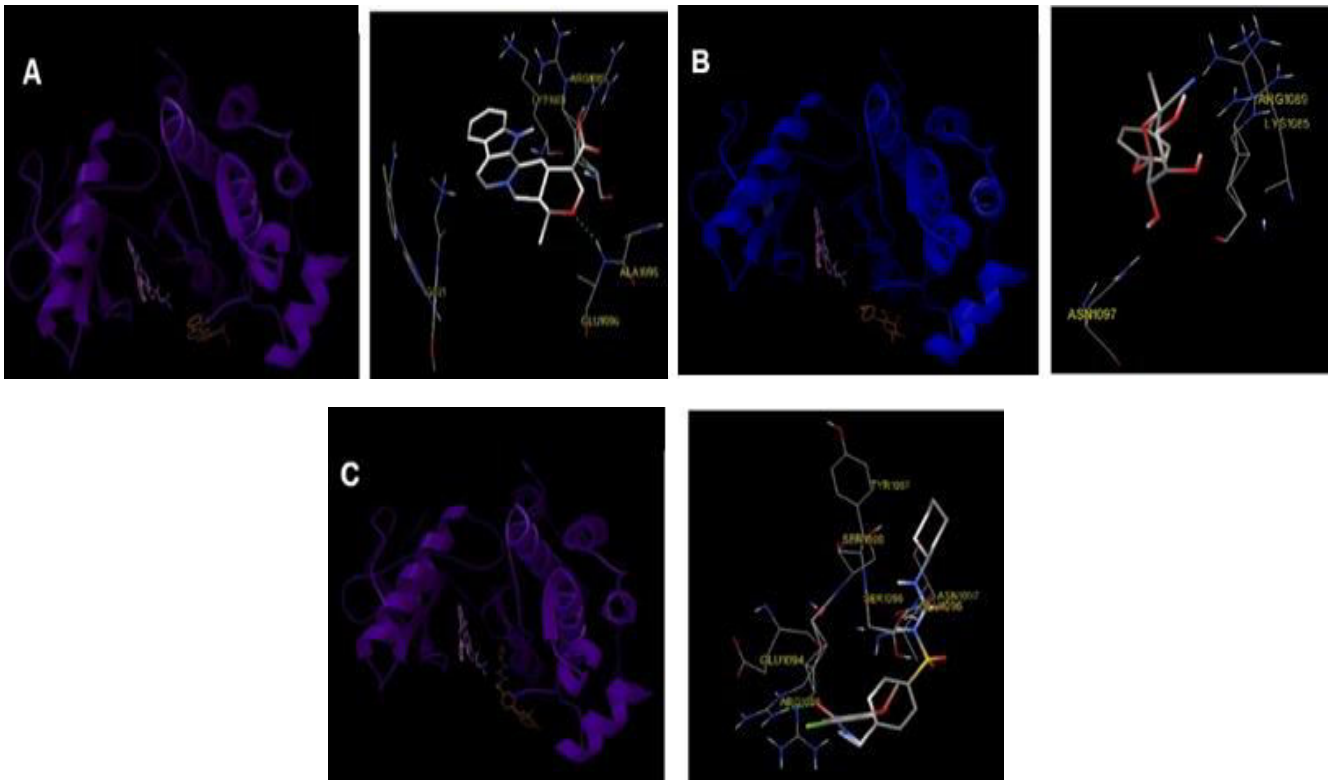


Fig. 5: Binding pose and interaction study of ligands (A=Serpentine, B=Niazirin and C=Glibenclamide) on IR tyrosine kinase A (PDB: 3ekk)

In case of the receptor-ligand binding pose and interaction study on IR tyrosine kinase B, the contact residues such as ASN1097, PRO1099 and SER1090 with a hydrogen bonding with residue TYR1087 were obtained for Anthraquinone. In comparison with Glibenclamide, the contact residues such as ARG1026, ARG1061, HIS1057, THR1055, and SER1279 with a hydrogen bonding with LYS1117 were obtained. The pose and interaction for each ligand is depicted in Fig 6A-B.

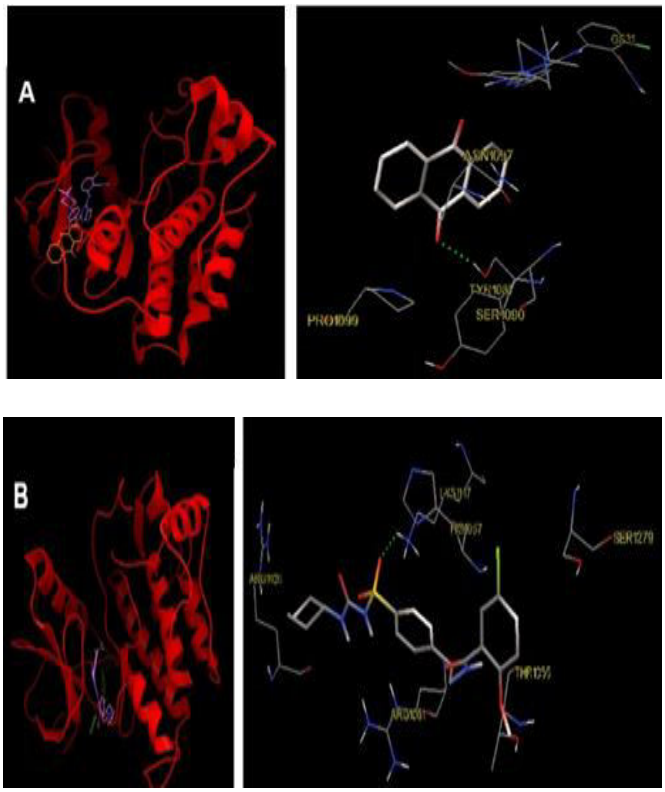


Fig. 6: Binding pose and interaction study of ligands (A=Anthraquinone and B= Glibenclamide) on IR tyrosine kinase B (PDB: 3ekn)

4. DISCUSSION

The present predictive toxicity results indicated that all phytoligands of *M. Oleifera* and synthetic antidiabetic medicines were observed toxic class of V except the phytoligand Serpentine as class III while others two ligands viz. Laurifoline and Metformin as class IV predicted through the online webserver (ProTox-II). According to Awodele et al [37]. the aqueous extract of leaves was found safe after oral intake by the rats. Moreover, Heymans Institute of Pharmacology [38] determined LD_{50} value of Serpentine was 42 mg/Kg in rats and overdoses may cause toxicity but in the present predictive data of the LD_{50} value was 250 mg/Kg.

Besides predictive toxicity, the prediction of pharmacokinetics (ADME), bioavailability, drug-likeness and medicinal chemistry especially lead-likeness of these ligands are the present research interest in case of new antidiabetic drug design, which supported the earlier studies performed by using Swiss ADME online tool [30-32,39]. It was well-known that the physicochemical properties such as solubility and lipophilicity prediction were also detected the phytoligand(s) may develop a successful drug candidate [30-32, 39]. In overall predictive results, Serpentine and Niazirin can be suitable drug candidate after isolation from the leaves of *Moringa* sp. as per bioavailability radar and BOILED-Egg representation.

In recent research, it was reported that anti-diabetic activity can be possibly known as per receptor-ligand binding results by molecular docking. In the case of the receptor A, Serpentine and Niazirin obtained favourable binding energy and interaction found near the mouth of active site in which excess glucose control in the intestine can be possible after inhibiting the activities of α-amylase and α-glucosidase [19] while for the receptor B, Anthraquinone obtained favourble binding energy and interaction found near the catalytic pocket as per earlier study [19] and potential for same inhibitory action. It has been well established that the crude extract of leaves is potential for blood glucose level in rat [12-16] but the present *in silico* approach helps to identify lead molecule for new drug design in relation to DM prevention. Furthermore, these predictive results of toxicity, pharmacokinetics and molecular docking should be validated by *in vitro* and *in vivo* toxicological and pharmacological assay for the new drug development to prevent DM.

5. CONCLUSION

In *in silico* approach, the docking helps to know exact lead small molecule(s) against specific receptor through favourable binding energy value and interaction with amino acid residues as per inhibitory action. Besides docking, the prediction of toxicity along with pharmacokinetics (ADME), bioavailability, drug-likeness, and medicinal chemistry to identify the data-driven drug design. In the present predictive study, the small molecules, Serpentine and Niazirin can be suitable for mutated protein A and Anthraquinone can also be a lead compound for mutated protein B for antidiabetic phytomedicine. Moreover, pharmacokinetics revealed that suitable lead-likeness was only Niazirin as without violation. However, it is suggested further *in vitro* and *in*

vivo assay for toxicology and pharmacology study for antidiabetic drug to validate the present predictions.

6. ACKNOWLEDGEMENT

The authors convey thanks to all developers of software /tools used in the predictive study, data bank for protein and phytochemicals.

Conflict of interest

Authors do not have any conflict of interest.

7. REFERENCES

1. De Vegt F, Dekker JM, Stehouwer CDA, Nijpels G, et al. *Diabetes Care*, 1998; **21:**1686-1690.
2. Bastaki S. *International Journal of Diabetes Metabolism*, 2005; **13:**111-134.
3. Cade WT. *Physical Therapy*, 2008; **88:** 1322-1335.
4. Grewal AS, Sekhon BS, Lather V. *Mini Reviews in Medicinal Chemistry*, 2014; **14(7):**585-602.
5. Grewal AS, Bhardwaj S, Pandita D, Lather V, Sekhon BS. *Mini Reviews in Medicinal Chemistry*, 2016; **16:**120-162.
6. Escribano O, Beneit N, Rubio-Longás C, López-Pastor AR, Gómez-Hernández A. *Journal of Diabetes Research*, 2017; 2017.
7. Grewal AS, Sharma N, Singh S, Arora S. *Journal of Pharmaceutical Technology, Research and Management*, 2018; **6(2):**125-133.
8. Taylor SI, Accili D, Imai Y. *Diabetes,* 1994; **43:**735-40.
9. Foti D, Chiefari E, Fedele M, Luliano R, et al. *Nature Medicine*, 2005; **11:**765-773.
10. Whitehead JP, Humphreys P, Krook A, Jackson R, et al. *Diabetes*, 1998; **47:**837-839.
11. Morino K, Petersen KF, Dufour S, Befroy D, et al.*The Journal of Clinical Investigation*, 2005; **115:**3587-3593.
12. Ndong M, Uehara M, Katsumata SI, Suzuki K. *J Clin BiochemNutr.*, 2007; **40(3):**229-233.
13. Jaiswal D, Rai PK, Kumar A, Mehta S, Watal G. *J Ethnopharmacol.*, 2009; **123:**392-396.
14. Manohar VS, Jayasree T, Kiran Kishore K, Mohana Rupa L, et al. *Journal of Chemical and Pharmaceutical Research*, 2012; **4(1):**249-253.
15. Soliman GZA. *Indian J Appl Res.*, 2013; **3(23):**18-23.
16. Omodanisi EI, 1, Aboua GY, and Oguntibeju OO. *Tropical Journal of Pharmaceutical Research*, 2017; **16(7):**1737-1746.
17. Mali AA, Kanade MB. *Annals of Biological Research*, 2014; **5(3):**89-92.
18. Mondal MF, Asaduzzaman M, Asao T. *American Journal of Plant Sciences*, 2015; **06(06):**804-810.
19. Zainab B, Ayaz Z, Alwahibi M, Khan S, Rizwana H, et al. *Saudi Journal of Biological Sciences*, 2020; **27:**2999-2307.
20. Yang Y, Shi CY, Xie J, Dai JH, et al. *Molecules*, 2020; **25:**189.
21. Bösenberg LH, van Zyl DG. *Journal of Endocrinology, Metabolism and Diabetes of South Africa*, 2008; **13(3):**80-88.
22. Pandarekandy ST, Sreejesh PG, Harikumaran Thampi BS, Sreekumaran E. *Indian J Pharm Sci.*, 2017; **79(5):**768-777.
23. Drwal MN, Banerjee P, Dunkel M, Wettig MR, Preissner R.*Nucleic Acids Research*, 2014; **42:**W53-W58.
24. Banerjee P, Eckert AO, Schrey AK, Preissner R.*Nucleic Acids Research*, 2018; **46:**W257-W263.
25. Ghosh S, Tripathi P, Talukdar P, Talapatra SN. *World Scientific News*, 2019; **132:**35-51.
26. Biswas S, Talapatra SN. *Journal of Advanced Scientific Research*, 2019; **10(3) Suppl 1:**186-195.
27. Morris GM, Lim-Wilby M. *Methods in Molecular Biology*, 2008; **443:**365-382.
28. Abd Rani NZ, Husain K,Kumolosasi E. *Front Pharmacol,* 2018; **9:**108.
29. Ghosh P, Talukdar P, and Talapatra SN. *Journal of Advanced Scientific Research*, 2019; **10(4):**186-191.
30. Daina A, Michielin O, Zoete V. *Sci Rep.*, 2017a; **7:**42717.
31. Daina A, Blatter M-C, Gerritsen VB, Palagi PM, et al. *J Chem Educ.*, 2017b; **94:**335-344.
32. Karmakar B, Talukdar P, Talapatra SN. *Research Journal of Life Sciences Bioinformatics Pharmaceuticals and Chemical Sciences*, 2019; **5(1):**582-596.
33. Chamberlain SD, Wilson JW, Deanda F, Patnaik S, et al. *Bioorg Med Chem Lett.*, 2009a; **19(2):**469-473.
34. Chamberlain SD, Redman AM, Wilson JW, Deanda F, et al. *Bioorg Med Chem Lett.*, 2009b; **19(2):**360-364.
35. Morris GM, Goodsell DS, Halliday R, Huey R, et al. *Journal of Computational Chemistry*, 1998; **19:**1639-1662.
36. Trott O, Olson AJ. *Journal of Computational Chemistry*, 2010; **31:**455-461.
37. Awodele O, Oreagba IA, Odoma S, da Silva JA, Osunkalu VO. *J Ethnopharmacol.*, 2012; **139(2):** 330-336.
38. Heymans Institute of Pharmacology. *Archives Internationales De Pharmacodynamie Et De Therapie*, 1989; 123(168).
39. Mondal B, Manna AK, Talukdar P, Ghosh I, Talapatra SN. *Research Journal of Life Sciences, Bioinformatics, Pharmaceuticals and Chemical Sciences*, 2019; **5(1):**853-868.