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In silico analysis of compounds with hypoglycaemic potential

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Abstract

Objective: To find digestive enzyme inhibitors as the therapeutic approach to deal with the management of diabetes mellitus.
Methods: In this study, we had *in silico*, analysed the anti-diabetic activity of the commercially available drugs used for diabetes treatment and few compounds which may have a potential to treat the disease. The main studied compounds are miglitol, voglibose, metformin, acetohexamide, squalene, stearic acid, heptacosanol, stigmasterol. The compounds were predicted for their biological properties based on their chemical structures as well as drug like activities. The compounds were docked with the digestive enzyme α- amylase and hydrogen bondings were revealed to study the relative stability of the complexes, which may result in the enzyme inhibition.
Findings: It may be concluded that if we succeed in achieving enzyme inhibition by a compound, then the compound may prevent the breakdown of carbohydrates into glucose in the body, thus maintaining the appropriate blood glucose levels.
Application: Compounds acting as digestive enzyme inhibitors could help in control of diabetes mellitus by delaying the release of post-prandial glucose level in the blood.
Keywords: Diabetes mellitus, Drugs, PASS.

1. Introduction

Diabetes mellitus is primarily characterized by post-prandial hyperglycaemia. It is an abnormal condition in which carbohydrate metabolism is disturbed due to insulin deficiency and/ or insulin resistance resulting in high blood glucose levels. Nearly 5% of the global population is affected by the disease [1]. Medical market is largely occupied by chemically synthesized anti-diabetic drugs that are effective but possess inevitable side effects. Hence enormous amount of research is being done globally to explore such compounds which may suppress the disease with lesser side effects. Development of extensive bioinformatics tools had provided an effective platform for preliminary *in silico* studies for screening of various compounds that may contribute to settle an abnormal health condition.

In 1972, thenational registration system of new chemical compounds organized in the USSR introduced the computer program PASS [2,3]. Bioactive compounds possess various biological activities and have a relative specificity of action. The biological potential of compounds can be studied under specific experimental conditions which constitute the biological activity spectrum that can be predicted on the basis of structure-activity relationships of compounds in large chemical-pharmacological space by using PASS [4,5]. The activity list comprises of names of pharmaco-therapeutic effects as well as names of mechanism of action. Papers and electronic sources are referred to attain new information about the biologically active compounds and evaluated by experts before adding to the training sets containing more than 35,000 compounds which are further SAR analysed. The SAR base is a complex knowledge base comprising of MNA descriptors vocabularies and activity names, substance structure database presented by MNA descriptors and the types of biological activity. The mean accuracy of prediction is about 85% in leave-one-out cross-validation (LOOCV).

Marvin Sketch is a user-friendly editor that helps in powerful and fast sketching of structures of molecules and reactions employing basic functions of the graphical-user interface and advanced functions like customisable short-cuts sprout drawing, default and user-defined templates and context-sensitive popup menu.

It enables robust inter-conversion of chemical file types and accurate visualization of 2D and 3D structures of molecules. To study molecular interactions based on chemistry of protein and ligand, molecular docking is an ideal approach for their virtual screening that could be achieved with an open-source program Auto Dock Vina [6]. The tool attempts to compute the non-covalent binding of the macromolecule receptor and the ligand by calculating their binding affinity. The accuracy of the binding mode prediction of this tool is 78% and it uses the PDBQT molecular structure file format. This prediction is of practical importance because it provides leads for drug developments by allowing screening of drug like molecules from virtual libraries. Ligplot^{+} is a graphical-user interface software tool that enables to generate schematic 2D- representative diagrams of receptor-ligand interactions from standard Protein Data Bank input file and facilitates drug discovery.

The interactions are shown by hydrogen bonds that are revealed by green dashed lines between the involved atoms and hydrophobic contacts indicated by an arc with spokes radiating towards the ligand atoms they contact. It allows automatic superposition of related plots. Chemicalize.org^{beta} software tool is a free web search engine public resource for identification of compounds chemical names and structure based predictions of compound's molecular properties.

The *in silico studies* of the following compounds were done.

1. Miglitol

It is a second generation digestive enzyme inhibitor derived from 1-deoxynojirimycin which is another digestive enzyme inhibitor extracted from *Bacillus* and *Streptomyces* strains or plants such as mulberry tree [7]. *Glucanobacter oxydans* is responsible for the formation of miglitol from D-glucose.

It is approved as an additional therapy to diet alone therapy or diet plus sulphonylurea therapy in type II diabetic patients. It is also an effective therapy for weight gain, or lactic acidosis [8].

2. Voglibose

It belongs to the class of digestive enzyme inhibitor and synthesized from valiolamine isolated from *Streptomyces hydroscopicus* subspecies *limoneus* [9]. It is approved for type II diabetes treatment.

3. Metformin

It belongs to the biguanides class of digestive enzyme inhibitor obtained from plant like *Galega officinalis*. It is approved for treatment of type II diabetes, modest weight reduction, lowering of cholesterol and improving cardiovascular profile of patients.

4. Acetohexamide

It is a first-generation sulfonylurea medication used to treat type II diabetes mellitus. It is also known as cyclamide and belongs to the drug class of pancreatic stimulants. It is synthesized chemically.

5. Squalene

It is a hydrocarbon and a triterpene. It is obtained commercially from shark liver oil as well as plants. It is reported to play a role in reducing oxidative stress [10].

6. Heptacosanol

It is a fatty alcohol and occurs in plants. It is being studied to play a role in cholesterol reduction.

7. Stigmasterol

It is an unsaturated phytosterol and is found in plants [11]. It is reported to possess hypoglycaemic and anti-oxidant properties [12].

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2. Methodology

PASS analysis of the compounds was done by extracting their structures from Pubchem database. Chemical structures of compounds were drawn using Marvin Sketch v5.10.0. Affinities of the ligand compounds with the α-amylase were studied using Autodock Tools 1.5.7 package. Appropriate charges are added to the ligands while computing. Ligplot^{+} v.1.4.4 software was used to study the presence of hydrogen bonding in the protein-ligand complexes. The drug like activities of the compounds was examined using Chemicalize.org^{beta} software tool by Chem Axon.

3. Results and discussion

The predicted biological activity spectrum of the compounds by PASS which may contribute to their anti-hyperglycaemic potential is shown in Table 1. Pa represents % activity whereas Pi represents % inactivity of the compounds for the respective biological pathways that may contribute in the management of hyperglycaemia. Molecular interactions of chemical structures of receptor protein (α-amylase) and ligands (compounds) along with their molecular affinities in the complex are shown in Table 2.

Drug parameters of the studied compounds are shown in Table 3. All the compounds studied exhibited comparable molecular affinities with respect to each other as well as with the commercially available drugs. Although there was no hydrogen bonding observed in the protein-ligand complex in case of squalene. Rest all the complexes showed the presence of hydrogen bonds.

Ideally for a compound to possess drug like property, it should obey Lipinski's rule of 5 but in our study only miglitol, metformin and acetohexamide followed the rule. Molecular masses of all the studied compounds were found to be in range i.e., <500 Da, according to the rule. Log P values of squalene and heptacosanol were out of range i.e., > 5.6. Polar surface areas of all the compounds were found in range except that of voglibose, which was greater than 140 $Å^2$and squalene with 0.0 polar surface areas. Molar refractivity for all the compounds other than metformin was in range i.e., 40-130.

Table 1. Biological activity spectrum of the anti-diabetic compounds

Compound	Pa	Pi	Biological activity
Miglitol	0,896	0,001	β- galactosidase inhibitor
	0,893	0,001	Oligo-1,6-glucosidase inhibitor
	0,802	0,001	α- glucosidase inhibitor
	0,796	0,003	Fructan β-fructosidase inhibitor
	0,753	0,001	β-glucosidase inhibitor
	0,540	0,004	4- α-glucanotransferase inhibitor
	0,498	0,000	α- glucosidase I inhibitor
	0,486	0,000	α-amylase inhibitor
	0,467	0,014	Galactose oxidase inhibitor
	0,446	0,007	α- glucosidase II inhibitor
	0,440	0,001	α-L-fucosidase inhibitor
	0,394	0,005	β-D-fucosidase inhibitor
Voglibose	0,938	0,001	Oligo-1,6-glucosidase inhibitor
	0,822	0,001	α- glucosidase inhibitor
	0,598	0,001	β- galactosidase inhibitor
	0,604	0,012	Antidiabetic
	0,572	0,011	Fructan β-fructosidase inhibitor
	0,511	0,011	Galactose oxidase inhibitor
	0,489	0,006	α-amylase inhibitor
	0,472	0,001	β- glucosidase inhibitor
	0,449	0,006	4- α-glucanotransferase inhibitor
	0,304	0,002	α-L-fucosidase inhibitor
	0,331	0,103	β- glucuronidase inhibitor

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Metformin	0,633	0,030	Insulysin inhibitor
	0,414	0,019	Diabetic neuropathy treatment
Acetohexamide	0,795	0,001	Sulfonylureas
	0,673	0,012	Insulysin inhibitor
	0,414	0,040	Antidiabetic
	0,346	0,033	γ-glutamyltransferase inhibitor
	0,323	0,115	Insulin promoter
Squalene	0,656	0,004	Antioxidant
	0,588	0,014	Antihypercholesterolemic
	0,576	0,007	Sorbitol-6-phosphate 2-dehydrogenase inhibitor
	0,578	0,009	Gluconolactonase inhibitor
	0,548	0,018	Dextranase inhibitor
	0,544	0,029	Cholesterol antagonist
	0,492	0,001	Nitric oxide scavenger
	0,456	0,013	Free radical scavenger
	0,447	0,005	α-glucuronidase inhibitor
	0,445	0,006	Cholesterol synthesis inhibitor
	0,453	0,023	Fructan β-fructosidase inhibitor
	0,367	0,024	Galactose oxidase inhibitor
	0,371	0,038	Glycerol-3-phosphate dehydrogenase inhibitor
	0,318	0,027	α-amylase inhibitor
	0,369	0,078	Diabetic neuropathy treatment
Heptacosanol	0,943	0,002	Dextranase inhibitor
	0,776	0,001	α-glucuronidase inhibitor
	0,768	0,003	Sorbitol-6-phosphate 2-dehydrogenase inhibitor
	0,732	0,004	Fructan β-fructosidase inhibitor
	0,658	0,004	Galactose oxidase inhibitor
	0,654	0,013	Cholesterol antagonist
	0,633	0,011	Insulin promoter
	0,555	0,004	α-amylase inhibitor
	0,542	0,002	Oligo-1,6-glucosidase inhibitor
	0,529	0,002	Isoamylase inhibitor
	0,494	0,002	Dextransucrase inhibitor
	0,474	0,008	Diabetic neuropathy treatment
	0,452	0,028	Antihypercholesterolemic
	0,422	0,004	β-glucosidase inhibitor
	0,470	0,060	Insulysin inhibitor
	0,376	0,016	Antidiabetic symptomatic
	0,335	0,003	β- galactosidase inhibitor
	0,326	0,004	Diabetic nephropathy treatment
	0,335	0,017	Cholesterol synthesis inhibitor
	0,311	0,009	β-amylase inhibitor
Stigmasterol	0,982	0,001	Antihypercholesterolemic
	0,965	0,001	Cholesterol antagonist
	0,670	0,001	Cholesterol synthesis inhibitor
	0,632	0,013	Dextranase inhibitor
	0,303	0,007	Nitric oxide scavenger
	0,347	0,095	Insulin promoter

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Table 2. Computational analysis of compounds revealing their molecular interactions

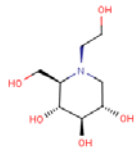
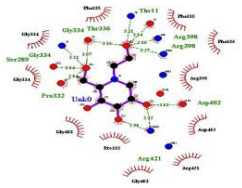
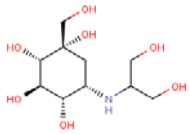
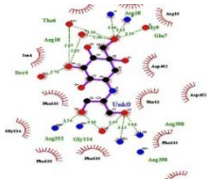
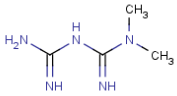
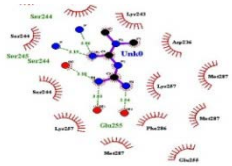
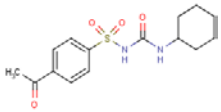
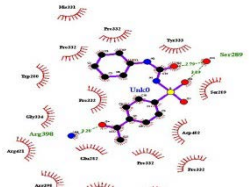
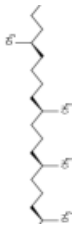
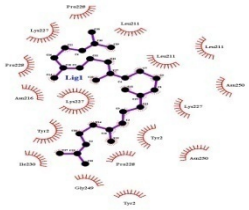
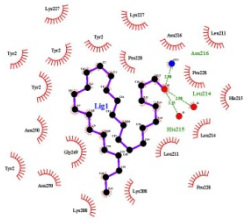
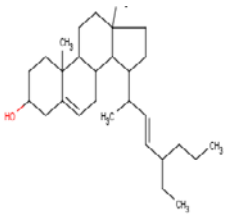
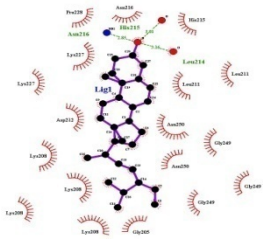
S.No.	Compound name	Chemical structure drawn using Marvin Sketch v5.10.0	Affinity calculation with enzyme α amylase (kcal/mol) using Auto Dock Vina	Hydrogen bonding visualization with enzyme α-amylase using Ligplot+v.1.4.4
1.	Miglitol		-5.8	
2.	Voglibose		-5.7	
3.	Metformin		-5.3	
4.	Acetohexamide		-6.9	
5.	Squalene		-5.3	
6.	Heptacosanol		-4.0	
7.	Stigmasterol		-7.2	

Table 3. Evaluation of drug parameters of compounds to study their drug like activities

Compound	Mass (Dalton)	Formula	Log P	Polar Surface Area ($Å^2$)	Molar Refractivity ($m^3\ mol^{-1}$)	Lipinski's rule of 5
Miglitol	207.2243	$C_8H_{17}NO_5$	-4.67	104.39	46.676689	Yes
Voglibose	267.2762	$C_{10}H_{21}NO_7$	-5.51	153.64	58.345989	No
Metformin	129.1636	$C_4H_{11}N_5$	-2.13	91.49	38.691193	Yes
Acetohexamide	324.395	$C_{15}H_{20}N_2O_4S$	3.29	92.34	82.216888	Yes
Squalene	410.718	$C_{30}H_{50}$	6.11	0.00	130.948959	No
Heptacosanol	396.7329	$C_{27}H_{56}O$	6.74	20.23	125.059982	No
Stigmasterol	412.6908	$C_{29}H_{48}O$	4.48	20.23	114.037956	No

4. Conclusion

All the above studied compounds have shown to exhibit anti-hyperglycaemic potential and therefore results need to be validated by wet lab experimental analysis. Hence, these natural compounds could be exploited in future to establish their potency to be used as anti-diabetic drug.

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