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Evaluation of Anti-Diabetic Nature of some Boswellic Acid Derivatives by Molecular Docking Method

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Abstract

Diabetes mellitus is a metabolic disorder and the rising trend in the globe has created great concern in recent times. Since the synthetic drugs used to treat diabetes causes a large number of side effects, so the discovery of a novel plant-based drug molecule is necessary. The gum resin of *Boswellia serrata* contains a large number of molecule used to treat many numbers of diseases including the diabetes mellitus. The present work is an *in silico* approach to identify the boswellic acid derivative that can be suitably used for diabetes treatment. The ligand boswellic acid derivatives for the present study were obtained from searching the PubChem database followed by filtration and energy minimization of the molecules were performed. The receptor molecular structure of human alpha-amylase and alpha-glucosidase were retrieved from the Protein Data bank (PDB). Molecular docking was performed by using the Autodock Vina tool. The alpha boswellic acid (PubChem ID 637234) showsthe highest affinity towards the selected two enzymes. Then the amino acid binding residues, as well as the pharmacokinetic properties of these derivatives, were predicted and analyzed. After overall analysis, the alpha boswellic acid showed an excellent pharmacokinetic profile, except for solubility. Hence it was predicted to be the best inhibitor among the selected boswellic acid derivatives and can be used to treat diabetes mellitus.

Keywords: Boswellic acid, molecular docking, diabetes mellitus, pharmacokinetic property, alpha-amylase, alpha-glucosidase.

Introduction:

Diabetes mellitus is a common metabolic disorder in human and creates hyperglycaemia in the body due to the defect in the secretion insulin hormone from the pancreatic gland. If the patient is left untreated in the early stage it may lead to the cause of other diseases well as multiple organ failure. There is a global concern about the rapid increase in the numbers of diabetes in recent times. As per the recent report given by World health organization (WHO), recently the number of diabetes patient is about 177 million of the global population the number is more likely to be increased by coming 10 years (1-2-3).

One of the basic mechanism is used to reduce the blood carbohydrate of the body is to enhance carbohydrate absorption after taking of food. The only monosaccharide, such as glucose and fructose, are only transported from the intestinal lumen into the bloodstream after digestion of complex carbohydrates such as oligosaccharides and polysaccharides. This complex polysaccharide is digested to monosaccharide is assisted by two main enteric enzymes, such as alpha-amylase and alpha-glycosidase. The current therapeutic strategies that are practised are synthetic drugs and other

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oral hypoglycemic agents include insulin but associated with many limitations and continuous use may cause side effects (4-5). Therefore, the discovery of novel plant-based drugs molecules are preferred that is having little or no side effect (7-8-9).

In this context, the *Boswellia Serrata* plant product is used as treatment of many of the diseases throughout the globe.The gum resin obtained from the *Boswellia serrata* plant has been used as the therapeutic compound. The gum resin of the plant contains several forms of the chemical such as boswellic acid, AKBA (3-O-acety l-11 keto- alpha -boswellic acid) and so on, are widely in ayurvedic medicines. This is also used to treat the disease like inflammatory conditions of the body, respiratory disorders such as asthma, bronchitis. Now the medical practitioners also use boswellic acid to treat arthritis, pain as it blocks the synthesis of proinflammatory leukotrienes by inhibiting 5-lipoxygenase (10-11). In-vitro assays of these compounds having anti-diabetic property are essential for its development of an anti-diabetic drug. Mostly, the enteric enzyme inhibition assays of alpha-amylase inhibition and alpha-glucosidase are popularly used as a primary screening method to evaluate the anti-diabetic potential (12-13). Computer-based molecular docking method is an important tool to evaluate the binding affinity of the ligand towards the receptor. In this process, the ligand-binding affinity, as well as the binding conformation of the ligand on the receptor, can be evaluated, hence widely used for the *in silico* screening of ligands (14). Little is known about the effect of the specific boswellic acid compounds towards inhibition of the enteric enzymes like alpha-amylase and alpha-glucosidase.

Therefore, the objective of the present work is to discover and predict about some of the effective boswellic derivatives as the inhibitor for alpha -amylase and alpha-glucosidase enzymes by using molecular docking method followed by considering the drug property.

Material and Methods

System configuration : The configuration of the PC used from performing computation studies is as follows; OS Windows 10, 64bit operating system, RAM 4 GB, 500 GB HD, 2.16 GHz processor speed.

Retrieval of ligands and receptors : The ligand molecules were retrieved from the PubChem database (https://pubchem. ncbi. nlm. nih.gov/). The PubChem database is a free repository of small molecules along with their available physicochemical properties and structure and improved methods for retrieval of query data (15). In the database searching the keyword “Boswellic acid” indicates 51 related molecules. Then the drug-like property was used to filter the data and the exact similar molecules were removed [16]. The high-resolution molecular structure of the human alpha -amylase and alpha-glucosidase enzymes were obtained from Protein Data Bank (PDB) (https://www.rcsb.org/).

Docking simulation and further analysis : For the molecular docking simulation, Autodock Vina tool was used. Autodock Vina is a user friendly and freely available docking software and during its development, several stochastic approaches such as genetic algorithms, particle swarm optimization (GA), simulated annealing (SA) has been implemented to facilitate the searching and scoring process (17). While processing of the receptor molecule, the co-crystalized ligands and water molecules were also removed from the crystal structure by using the Pymol tool (www.pymol.org) and then polarhydrogen atoms were added. Then, a suitable grid box was created around the receptor molecules by choosing the maximum dimension to provide a better binding option for the ligands. Also, the exhaustiveness for the docking simulation was set as 8. Similarly, the Gasteiger charge was added to the ligand molecule. After the completion of the docking process, the docking score and ligand binding conformation was analysed. Further, the drug-like properties were calculated by Swissadme (http://www.swissadme.ch/) and then analysed.

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Results

Retrieval of the ligand molecules: As mentioned in the materials and methods section, the ligand molecules were searched from the PubChem Database by the keyword "*Boswellic Acid*" resulted in the 51 molecules.The retrieved molecule was screened for the drug-like property by considering the parameters such as no more than five hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms); no more than ten hydrogen bond acceptors (nitrogen or oxygen atoms); a molecular mass less than 500 Da. Finally, after using the above filtration criteria 8 boswellic acid molecules were obtained as shown

Table 1: Showing the Receptor molecule details obtained from PDB

S.N	PDB ID	Name of the protein	Amino acid Length	Resolution (Angstrom)	Reference
1	3BAW	Human pancreatic alpha-amylase complexed with azide	496	2	18
2	5NN4	Crystal structure of human lysosomal acid-alpha-glucosidase, GAA, in complex with N-acetyl-cysteine	847	1.83	19

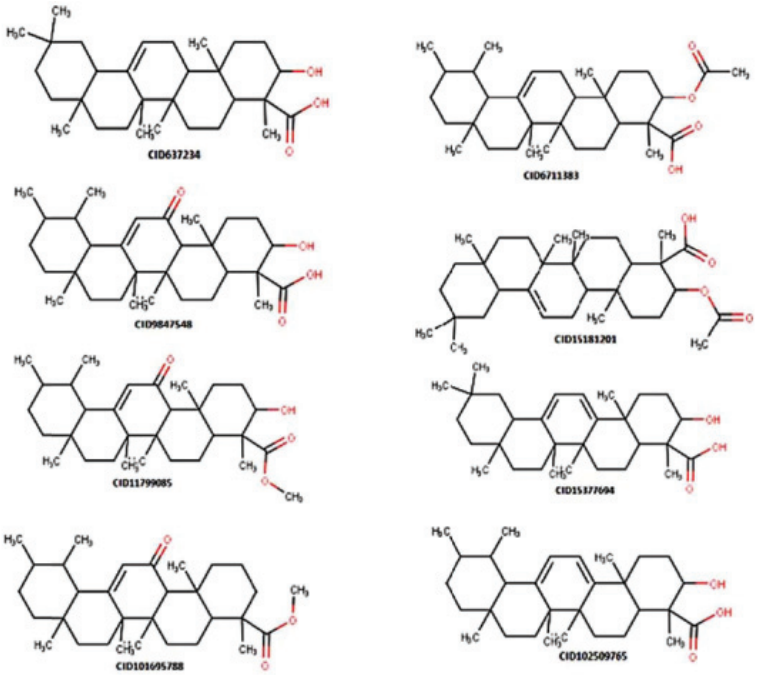

Fig. 1: Structure of Boswellic acid molecules as ligands with the PubChem ID

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in Figure 1 and Table 2. The receptor molecules were obtained from the Protein Databank (PDB) by searching for human alpha-amylase and alpha-glucosidase enzymes. The low-resolution structures were selected as the receptors for the present study shown in Table 1.

Domain prediction of receptor molecules *:* To identify functional domain , Simple modular architecture research tool (SMART) was used, that is available freely at http://smart.embl-heidelberg.de/.In case of alpha-amylase protein 2 different functional domains were observed, shown in Table 3

Docking simulation: Autodock Vina tool was used for the docking purpose and the binding energy and conformations were obtained for the best ligand alpha-Boswellic acid out of 8 selected ligands and shown in Table 4 and shown in Figure 2 (A) and 3 (A). Also, the amino acid binding residues with the ligand alpha Boswellic acid with the alpha-amylase and alpha-glucosidase enzyme were calculated by Accelrys DS Visualizer tool (www. acclyrys.com) and shown in Figure 2 (B) and 3 (B) respectively. The alpha Boswellic acid showed interacted with major amino acid residues, namely, GLY 9, PRO 34, LYS 35, GLY 36, ARG

Table 2: Selected Boswellic derivatives details

S.N	PubChem Compound ID	Name of the compound	SMILE	Molecular weight (g/mol)
1	637234	α-Boswellic acid	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C(=O)O)O)C)C)C2C1)C)C)C	456.7
2	6711383	beta-Boswellic acid acetate	CC1CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C(=O)O)OC(=O)C)C)C)C2C1C)C)C	498.7
3	9847548	11-Keto-beta-boswellic acid	CC1CCC2(CCC3(C(=CC(=O)C4C3(CCC5C4(CCC(C5(C)C(=O)O)O)C)C)C2C1C)C)C	470.7
4	15181201	3-α-O-acetyl-α-boswellic acid	CC(=O)OC1CCC2(C(C1(C)C(=O)O)CCC3(C2CC=C4C3(CCC5(C4CC(CC5)(C)C)C)C)C)C	498.7
5	11799085	3α-Hydroxy-11-oxours-12-ene-24-oic acid methyl ester	CC1CCC2(CCC3(C(=CC(=O)C4C3(CCC5C4(CCC(C5(C)C(=O)OC)O)C)C)C2C1C)C)C	484.7
6	15377694	9,11-Dehydro-α-boswellic acid	CC1(CCC2(CCC3(C(=CC=C4C3(CCC5C4(CCC(C5(C)C(=O)O)O)C)C)C2C1)C)C)C	454.7
7	101695788	11-Keto-beta-boswellic acid methyl ester	CC1CCC2(CCC3(C(=CC(=O)C4C3(CCC5C4(CCCC5(C)C(=O)OC)C)C)C2C1C)C)C	468.7
8	102509765	9,11-Dehydro-beta-boswellic acid	CC1CCC2(CCC3(C(=CC=C4C3(CCC5C4(CCC(C5(C)C(=O)O)O)C)C)C2C1C)C)C	454.7

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Table 3: Predicted domains of the Receptor molecule

S.N	Name of the Domain Enzyme		Amino acid residue positions	Function
1	α-amylase	**Aamy** (Á-amylase domain)	11 to 398	Probable catalytically inactive region
		Aamy_C domain	407 to 495	Catalytically active region
2	α-glucosidase	**PD** domain	1 to 54	cysteine-rich domain
		NtCtMGAM _N domain	67 to 173	Beta-barrel-like structure just N-terminal to the catalytic domain of maltase-glucoamylase in eukaryotes. It contributes to the architecture of the substrate-binding site by donating a loop.
		Gal_mutarotas _2 domain	174 to 240	Domain is found in proteins that belong to the glycoside hydrolase family 31. The domain appears to be similar to the galactose mutarotase superfamily.
		Glyco_hydro _31 domain	260 to 744	O-Glycosyl hydrolases are a widespread group of enzymes that hydrolyse the glycosidic bond between two or more carbohydrates, or between a carbohydrate and a non-carbohydrate moiety.

Table 4: Docking score obtained by Autodock Vina tool

S.N	Ligand PubChem Compound ID	Docking score (Kcal/mole) with α-amylase receptor (PDB ID: 3BAW)	Docking score (Kcal/mole) with α-amylase receptor(PDB ID:5NN4)
1	CID637234	-9.0	-9.4
2	CID6711383	-8.6	-8.9
3	CID9847548	-9.0	-8.3
4	CID15181201	-6.9	-7.7
5	CID15377694	-8.4	-8.4
6	CID44558899	-8.7	-8.6
7	CID101695788	-8.1	-8.2
8	CID102509765	-8.1	-8.2

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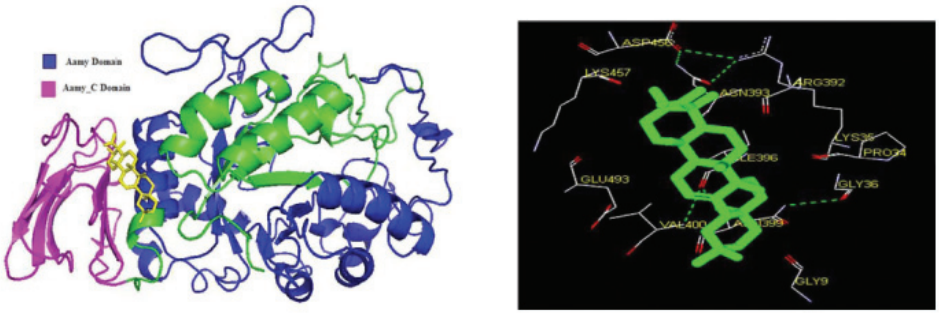
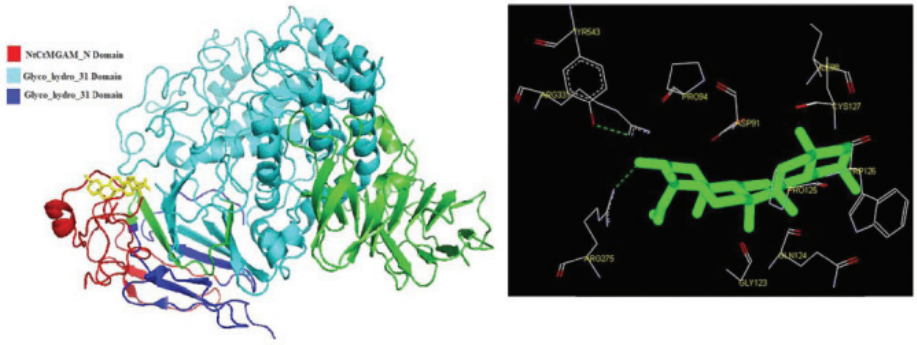


(A) (B)

Fig. 2: (A) 3D structure of the á-amylase enzyme, the domains are shown in colour codes (PDB ID: 3BAW) along with the docked ligand á boswellic acid (Yellow colour) (B) Predicted ligand-binding residues after docking



(A) (B)

Fig. 3: (A) 3D structure of the alpha-glucosidase enzymedomains are shown in colour codes (PDB ID: 5NN4) along with the docked ligand á boswellic acid (Yellow colour) (B) Predicted ligand-binding residues after docking

392, ASN 393, ILE 396, ASN 399, VAL 400, ASP 456, LYS 457, GLU 493, out of which four are present on the catalytic binding domain.

Similarly, in case of alpha-glucosidase enzyme the alpha Boswellic acid was also showed an interaction amino acids, namely ASP 91,PRO 94,ILE 98 , GLY 123,GLN 124,PRO 125, TRP 126,CYS127, ARG 275, ARG 331, TYR 543 out of which eight were observed to be on catalytic domain of maltase-glucoamylase and remaining four were on the Glycosyl hydrolases domain.

Drug like property calculation from Swiss adme server: SwissAdme server was used to compute the drug-like properties of the selected Boswellic acid derivatives (Table 5) and analysed further for applicability of thedrug molecule for the treatment of diabetes mellitus.

The various properties are described in the below section. The topological polar surface area (TPSA) is an important feature and defined fora molecule as the summation of the surface of all the polar atoms. The TPSA is commonly used as a metric for the ability of the (drug) molecule to permeate cell membrane. As a rule of thumb, the molecules with a polar surface area <140 (Å²) is considered as good at permeating through the cell membranes (20-21). Similarly,

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the lipophilicity (measured as Log P) is a valuable parameter of the drug molecule that affects the permeability of the drugs to reach the target in the body. The desirable lipophilicity of a compound according to Lipinski's rule, remains in the range of log P < 5. However, as per recent literature suggested that the optimum range of lipophilicity of the drug molecules lies within the range between 1 and 3 (22). Solubility is considered as one of the most important properties in drug discovery. Because the lower solubility in water is directly linked to poor absorption as well as oral bioavailability.The solubility propertyis expressed as log S and thevaluefor a drug molecule > 4 is considered as the acceptable range (23-24). The drug molecules that are administered by oral route usually show a low rate of absorption and may cause the gastric irritation. In addition to this, the GI (gastrointestinal) absorption also affects the solubility and stability of the drug molecule (25-26). The dermal absorption of acompound related to health hazard is evaluated by a parameter known as skin permeation coefficient (Kp) measured as log Kp. It is defined as the rate of permeation of the drug compound through the outermost layer of the skin and having unit is measured in cm/sec. The more negative value of the log Kp of a compound, the less is the skin permeability of the compound (27-28). Another important parameter is the synthetic accessibility score (SAscore) is computed by considering the fragment contributions. The fragment contribution towards computation of synthetic accessibility score is calculated based on the fragments available in the PubChem database and knowledge-based synthetic approaches of fragments and easy of their synthesis. Finally, the score is normalized between 1 (easy synthesis) and 10 (very difficult synthesis) (28-29).

Discussion

In the previous study, the Herbal formulation containing *B. serrata* oleo-gum-resin has been reported to produce significant anti-diabetic activity by affecting hepatic gluconeogenesis, pyruvate carboxylase and phosphoenolpyruvate carboxykinase (30). Also, the hypoglycaemic properties of the gum extract of*Boswellia serrata* plantcontaining 11-Keto-alpha-boswellic acids compounds has been studied in *vitro* modelby Shehata et al. in 2011 and in 2015 (31-32). Azemi, M. E et al., in 2012 demonstrated about the beneficial effect of the *Boswellic* gum resin as an anti-diabetic agent that prevents the complications in liver and kidney due to hyperglycaemia (33). Ammon et al., in 2019 reviewed the therapeutic evidence of *Boswellic* extracts such as 11-keto-ß-boswellic acids in the prevention/treatment of diabetes mellitus by discussing the molecular mechanisms (34). Similarly, the isolated alpha keto Boswellic acid

Table 5: Molecular pharmacokinetic properties of the selected compounds computed by SwissAdme server

Pub Chem Compound ID	TPSA Å²	Consensus Log P	ESOL Log S	GI Absorption	log Kp (cm/s)	Synthetic Accessibility
637234	**57.53**	**6.18**	**-7.9**	**Low**	**-3.11**	**6.04**
6711383	63.6	6.41	-7.96	Low	-3.46	6.36
9847548	**74.6**	**5.39**	**-7.23**	**High**	**-4.06**	**6.24**
15181201	63.6	6.57	-8.05	Low	-3.36	6.24
11799085	63.6	5.82	-7.46	High	-3.91	6.32
15377694	57.53	6.12	-7.71	Low	-3.31	6.61
1.02E+08	43.37	6.58	-7.86	Low	-3.25	6.1
1.03E+08	57.53	6	-7.62	Low	-3.41	6.74

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(AKBA) has been reported to be an important compound to treat many chronic diseases including diabetes mellitus has been reported by Roy et al., in 2019 (35). Many researchers have also considered the molecular docking procedure to predict the therapeuticpotential of Boswellic acid. Kendall et al., in 2018 used a reverse docking approach to 16034 different targetproteins responsible for many metabolic disorders including the diabetes mellitus (36). Also, the molecular docking studies of Boswellic derivatives have shown its potential against the anti-inflammatory and anticancer agents (37).

Overall pharmacokinetic factors (Table 5) as well as the docking scores (Table 4) taken together in indicates the PubChem compound ID CID 637234 the alpha-Boswellic acid may be important for inhibitation both alpha-amylase and alpha-glucosidase enzymes. Further, the compound ID, CID 9847548, beta boswellic acid is also shown comparatively good result in docking towards alpha-amylase enzyme. Also, another advantage in case of beta boswellic acid molecule is the GI absorption is high, that was predicted low in case of alpha-Boswellic acid. Although boswellic acid has shown it's potential to inhibit the alpha-amylase and alpha-glucosidase enzyme, they are predicted to be poor in the solubility property. This could be the major obstacle for using these molecules as the drug candidate. Hence further research strategies are necessary towards effective formulations to enhance the solubility of these molecules. So that, the compound can be used as an effective drug molecule to treat the diabetes mellitus.

Conclusion

Considering the severity of the diabetes mellitus disease, it is considered as one of the five leading causes of death in the world. In addition to this, it also affects the carbohydrate, fat, and protein metabolism and ultimately causes the disorder. In this work, based on the binding affinity of the selected boswellic acids were computationally evaluated by Autodock Vina tool by taking alpha-amylase (PDB ID 3BAW) and alpha-glucosidase (PDB ID 5NN4) as the receptor. The docking study of the boswellic derivatives resulted that, the alpha boswellic acid (PubChem ID CID637234) having the lowest docking energy for both the receptors in comparison to the other selected derivatives of boswellic acid. Further, the molecular and pharmacokinetic properties were evaluated for the boswellic acid derivatives. It was observed that derivative beta boswellic acid (PubChem ID9847548) also show comparatively less docking score as that of alpha boswellic acid, but having high gastrointestinal (GI) absorption property. Above all, all the selected derivatives might face the common obstacle for its use as a drug candidate as they are less soluble in water. Therefore, methods should be implemented to make them more soluble to enhance their effectiveness to treat diabetes mellitus. However, the present work is a computational approach, therefore further experimental validation is necessary.

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