Studies on α-Glucosidase Inhibitors Development: Magic Molecules for the Treatment of Carbohydrate Mediated Diseases

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Abstract: α-Glucosidase (EC 3.2.1.20) enzyme belongs to the glycosidase family enzymes, cleave the glycosidic bond of the oligosaccharides that liberate glucose and its inhibition retards the carbohydrate digestion. In the present review, we have discussed the structural features of different α-glucosidase inhibitors (small molecules) responsible for the inhibitory activities. The reported computational studies including, QSAR, pharmacophore modelling, homology models, docking (with analogs enzymes), etc revealed that the topological, electronic and hydrophobicity properties determine the interactions of those molecules. The aromatic substituents connected with flexible bonds in the molecules have significant effect on the interactions, which may due to the presence of aromatic amino acid residues in the active site. The reported homology modelled and other analogs enzymes (enzymes of other species) also confirmed the existence of aromatic residue (amino acids) especially, histidine, phenylalanine and tyrosine in their active site along with the polar (glutamic and aspartic acids) residues. Multiple sequence alignments of the α-glucosidase enzymes (from different species) described that the abovementioned amino acid residues are present in the active site of all the studied enzymes. Recently, Celgosivir (MIGENIX Inc) is an oral prodrug of the natural product castanospermine used for the treatment of HCV infection by inhibiting α-glucosidase I. BMN-701 is an α-glucosidase inhibitors in the phase I pipeline (BioMarine) for the treatment of Pompe diseases. CKD-711 and CKD-711a are aminooligosaccharide α-glucosidase inhibitors and the *in vitro* study of CKD-711 showed similar effects to acarbose on porcine intestinal maltase and sucrase (IC_{50}s of 2.5 and 0.5 μg/ml). This review also concluded that many α-glucosidases inhibitors obtained from natural products are used for the treatment of various carbohydrate mediated diseases. The structural analysis of these synthetic and natural derivatives guide for the development of novel semisynthetic/synthetic α-glucosidase inhibitors with free of toxicities.

Keywords: α-Glucosidases, HIV, QSAR, hydrophobicity, vdW surface area.

INTRODUCTION

The glycosidase family enzymes such as glucosidases (α and β), glucotransferases, mannosidases, galactosidases, etc cleave the glycosidic bonds of the oligosaccharides and liberate glucose, which are important for the carbohydrate digestion. Glucosidases are responsible for the catalytic cleavage of a glycosidic bond with specificity, which depends upon the number of monosaccharide units on the substrate, the position of the cleavage site and the configuration of the hydroxyl groups in the substrate [1-3]. The bond cleaving activity of the glucosidases is important to several biochemical process such as (i) degradation of diet polysaccharides to furnish monosaccharide units (to get absorbed and used by the organism), (ii) lysosomal glycoconjugate catabolism and glycoprotein processing and (iii) biosynthesis of glycoprotein of glycolipids from its precursors [4,5]. Due to its catalytic role in digesting carbohydrate substrates, α-glucosidase has drawn a special interest by the pharmaceutical research community for the development of inhibitors used for the treatment of carbohydrate mediated diseases such as cancer, viral infections, diabetics, hepatitis, etc [6-8]. Inhibition of these glucosidases, especially α-glucosidase (EC 3.2.1.20), has a profound effect on the glycon structure. The inhibitors of α-glucosidase are known to possess a large number of therapeutic effects, such as antitumor, antidiabetics, antiviral, immunoregulatory activities, etc [1-3,9-13]. α-Glucosidase inhibitors such as DNJ, NB-DNJ and castanospermine are potent inhibitors of the HIV replication and HIV mediated syncytium formation *in vitro*. NB-DNJ is known to impair the processing of gp120 associated N-linked oligosaccharides, resulting in predominantly neutral glucosylated precursor N-glycon [3,14].

MECHANISM OF GLUCOSIDASE ENZYME

The α-glucosidase (yeast) belongs to glycoside hydrolase (GH13) family, whereas the targets of antiviral drugs are processed on α-glucosidases I and II enzymes. Various forms of α-glucosidases can hydrolyze α-1,1-; α-1,2-; α-1,3-; α-1,4-; and α-1,6-linked Glc from the glycoproteins or from the non-reducing ends of carbohydrates ranging in size from disaccharides to polysaccharides (starch) (Fig. (**1**)) [15,16]. The protein components of all glycoproteins are synthesized from the polyribosomes that are bound to the endoplasmic reticulum (ER). The processing of sugar groups occur co-translationally in the lumen of the ER and continue in the Golgi apparatus for *N*-linked glycoproteins [1,17].

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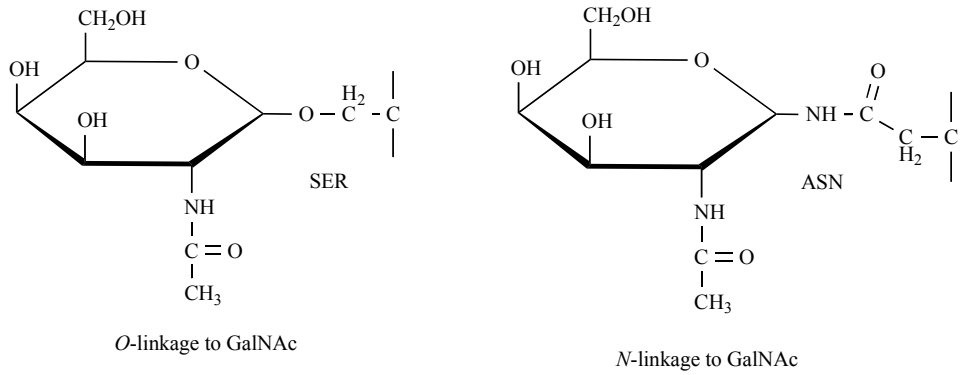

Fig. (1). Structure of O and N-linkage to GalNAc.

Inhibition of these α-glucosidase enzymes (I and II) can prevent the biosynthesis (inhibit the cleavage of glycosidic bonds) of the N-linked oligosaccharides on the HIV envelope glycoproteins (gp120 and gp41) from their precursor (gp160). The HIV viral envelope is composed of a bilipidic layer and a complex protein known as Env that consists of glycoprotein gp41 (transmembrane) and gp120, the later being displayed on the viral surface and anchored to gp41. The glycosylation pathway (including the transfer of the glycon precursor onto the nascent protein and the subsequent glucose trimming) is required for the processing, the folding and the routing of the precursor gene (Env) [1,17-21].

Glycan processing starts immediately after its transfer from a dolichol-P-P-derivative to an Asn residue in nascent polypeptide chain, entering lumen of the ER. The formation of the N-linked oligosaccharide chains in the ER starts with the attachment of $Glc_3Man_9GlcNAc_2$ to a nascent protein and removal of the glucose residues by processing α -glucosidases I and II, expose the $Glc_1Man_9GlcNAc_2$ epitope. This epitope then passes through the calnexin/calreticulin cycle for folding of protein and the unfolded proteins undergo degradation by the action of ER-mannosidases (Fig. (**2**)) [5,22,23].

α-GLUCOSIDASE INHIBITORS

A variety of inhibitors of α-glucosidases are being studied as potential therapeutic drugs to treat diabetics, human immune deficiency virus (HIV) infection, metastatic cancer, lysosome storage diseases, etc. Up until now, approximately 160 compounds have been reported to be inhibitors of α - and/or β -glucosidases [24-26]. Three important drugs such as acarbose (Precose), miglitol (Glyset) and N-butyl-1-deoxynojirimycin (Zavasca) are used therapeutically as α-glucosidase inhibitors for HIV and diabetics [5]. Scientists have described the structure and the activity relationship of structurally different α-glucosidase inhibitors and they reported the following characteristics: (1) sugar (substrate)-mimic structures, (2) the ability to form ionic bonds with nucleophilically catalyzing residues, (3) transition-state-like structures, (4) the ability to form hydrogen bonds with catalytic acid residues, (5) the ability to make ionic and hydrophobic interactions at sites other than the active site, and (6) the ability to form covalent bond with enzymes through an epoxy or aziridine group [24,27].

The mechanistic, catalytic and the pharmacological studies of the α -glucosidase enzyme and its inhibitors are lacking due to the availability of limited structural information on the α-glucosidases enzymes (no proper X-ray crystallography structures are available). Hence, it is a difficult task to discover good lead compounds based on the structure based inhibitors design (receptor based). Literatures showed that some homology modelled α -glucosidase enzymes were used to study the binding mode analysis of the inhibitors on the way to design novel molecules [13,28,29]. In this section, we have reported the *in silico* studies on the existing inhibitors for structural optimization and active site characterization (can be used for the ligand based drug design).

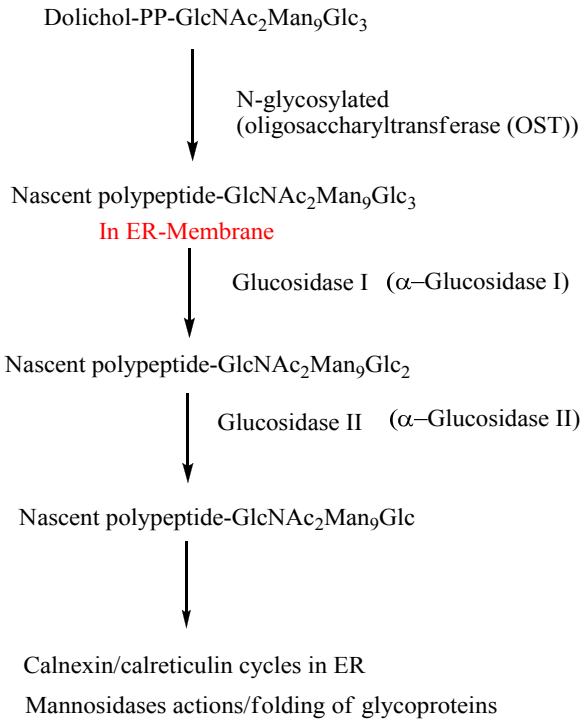

Fig. (2). Schematic representation of the mechanism of α -glucosidase enzyme action.

COMPUTATIONAL INSIGHTS OF α-GLUCOSIDASE INHIBITORS

Computational based drug design is a rapidly growing field and an important component to characterize the interactions between small molecules and their targets using structural features of the molecules (inhibitors) [30-33]. In this present review, we reported the structural features of the small molecular α-glucosidase inhibitors responsible for the interaction on the target and the activity prediction using quantitative structure activity relationship (QSAR) analysis. The literatures showed that only some QSAR studies have been performed on this target, using simple 2D and 3D descriptors.

Xu *et al* was studied QSAR analysis on andrographolide derivatives using 2D and 3D physicochemical (structural) descriptors. Those 2D and 3D QSAR models suggested that the atomic connection in the molecules and the molecular properties belonging to steric, hydrophobic and H-acceptor fields, respectively are important for the α-glucosidase inhibitory activity of these andrographolide derivatives [34]. Moorthy *et al* have also performed studies on the andrographolide derivatives alone (set I) and in combination with other derivatives (andrographolides, chromenone and triazole derivatives) (set II), which revealed that the van der Waals (vdW) surface area properties of the molecules were significantly contributed for the interactions. The descriptors such as E_str, vsurf_Wp4 and VSA_SMR0 of set I compounds and the descriptors such as inclusion of subdivided surface area descriptor (SlogP_VSA2), polar surface volume and shape descriptor (vsurf_wp7), Petitjean and PM3-LUMO of the set II compound were contributed in the models. These results illustrated that the polarizable properties on the vdW surface area, the balanced hydrophobic and hydrophilic properties and the presence of flexible bonds in the substituents/side chains are favorable for the α-glucosidase inhibitory activity [35,36].

QSAR analysis on a series of isosteviol derivatives, which are structural analogs of andrographolides was studied. These compounds contain the isosteviol parent structure with substituents in different positions, additional rings and many chiral carbons in the parent nucleus. The physicochemical descriptors present in the significant models suggested that the presence of nitrogen atoms along with the hydrophobic-hydrophilic distance in the molecules had effect on the favourable α-glucosidase inhibitory activity. Also, the triple bonded atoms connected with other triple bonded atom by four and seven bond distances along with the hydrophobic property had profound effect on the inhibitory activity [13].

A pharmacophore model AADR1 for flavonoids acting as α- glucosidase inhibitors was reported by the researcher [37] revealed that two hydrogen bond acceptor, one hydrogen bond donor and one aromatic ring features are relevant pharmacophore contours for the inhibitory activity. These pharmacophore models were able to predict accurately the α-glucosidase inhibitory activity and the validation results also provided additional confidence in the proposed pharmacophore models [37].

There are number of QSAR reports published on the xanthone derivatives. Kraim *et al*. performed QSAR analysis on a set of 57 xanthone and curcuminoid derivatives by multiple linear regression (MLR) analysis, using genetic algorithms as variable selection method. The vdW volumes and electronegativity of atoms have a clear mechanistic meaning for the inhibitory activity of the compounds [38]. CoMFA and CoMSIA analysis revealed that the CoMSIA models provided additional information over CoMFA in terms of hydrogen bonding and hydrophobic interactions with the receptor. Alignment of the molecules over the homology modelled enzyme suggested that Asp, His and Asn residues are responsible for the polar interactions and Phe, Ile, Trp and Met are caused for the hydrophobic interactions [39]. Gupta *et al* reported the MLR models with three descriptors such as Henry's law constant, standard Gibbs free energy and total valence connectivity. These three descriptors described that the thermodynamic and steric properties of compounds play an important role for the activity prediction [40]. The study performed in our laboratory revealed that the presence of heteroatoms (number of oxygen atoms connected with carbon atoms) in the molecules and the carbon atoms connected with three aromatic bonds and hydrogen or other atoms are favourable for the α-glucosidase inhibitory activity. The hydrophobicity descriptors contributed in the models also suggested that the optimum hydrophobicity on the vdW surface area of the molecule is favourable for the inhibitory activity [41].

A set of chromenone derivatives provided the models with the log of aqueous solubility (LogS) and the molar refractivity on the vdW surface area (SMR_VSA4) descriptors. The distance between the hydrophobic and the hydrophilic regions and the electronegativity of the molecules (presence of electronegative groups) are important for the α-glucosidase inhibitory activity. It was also supported by the result of the pharmacophore analysis performed on the same set of molecules. The pharmacophore contours of the molecule also explained the need of the polar surface property on the molecules for significant interactions [42].

A study on chlorogenic acid derivatives possessed α-glucosidase inhibitory activity against the enzyme of two species (*B. stearothermophilus* and *S. cerevisiae*) showed that the integy moment of hydrophobicity descriptors (vsurf_ID4 and vsurf_ID7) are contributed for the α-glucosidase inhibitory activity in both the species. The pharmacophore analysis results confirmed the requirement of the hydrophilic properties on the vdW surface of the molecules by properly aligned polar and aromatic/hydrophobic regions for all highly active and less active compounds [43].

An analysis on structurally different inhibitors such as aminated chalcone (sulfonamide analogues), *trans*-cinnamic acid, 8-amino methylated oroxylin A and tetrachloro-phthalimide derivatives were reported by our laboratory. The molecular connectivity descriptors in the model revealed that the molecules with less number of branches on carbon or heteroatoms along with the presence of electronegative atoms (double bonded oxygen) and aromatic rings are important for the inhibitory activity [44]. These studies

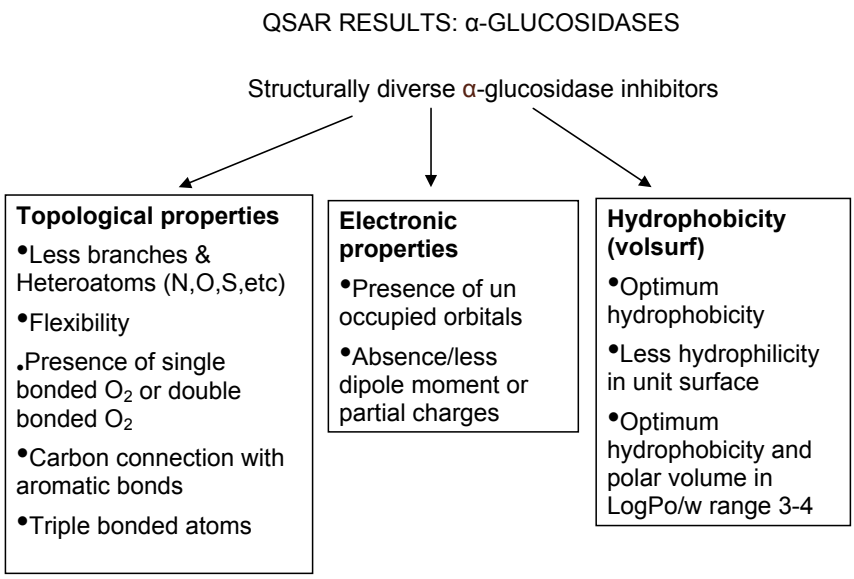

Fig. (3). Summary of the QSAR results of various α-glucosidase inhibitors.

concluded that the presence of balanced hydrophobic and hydrophilic (polar and/or electron negative) properties on the vdW surface area is responsible for hydrogen bonding and other electrostatic interaction (aromatic) of inhibitors with the enzyme and for favourable α -glucosidase inhibitory activity. The summary of the results obtained from the reported QSAR studies are graphically represented in (Fig. (**3**)).

NOVEL α-GLUCOSIDASE INHIBITORS FROM NATURAL PRODUCTS

Natural products are one of the important sources of α-glucosidase inhibitors. Number of reports were published on the α-glucosidase inhibitors, isolated from natural products such as acarbose [45,46] and voglibose [47] from microorganisms and nojirimycin [48-50] and 1-deoxynojirimycin [50] from plants, as well as α-glucosidase inhibitor from wheat kernels used for the maintenance of blood glucose levels after food uptake [51,52]. Literatures showed that huge research is undergoing in natural products for the development of novel α-glucosidase inhibitors for the treatment of carbohydrate mediated diseases (Fig. (**4**)).

The active constituents quercetin 3-*O*-β-D-xylopyranosyl (1```-2``)-β-D-galactopyranoside and (-)-lyoniresinol-3-*O*-β-D-glucopyranoside, isolated from the Devil tree (*Alstonia scholaris*) exhibited an inhibitory activity against both sucrase and maltase enzyme with IC_{50} values of 1.95 mM and 1.43 mM, respectively [53]. Novel constituents such as macatannins A (IC_{50} = 0.80 mM) and B (IC_{50} = 0.55 mM) along with other known chemicals mallotinic acid (IC_{50} >5.00 mM), corilagin (IC_{50} = 2.63 mM), chebulagic acid (IC_{50} = 1.00 mM) were isolated from the *Macaranga tanarius* leaves, which possessed α-glucosidase inhibitory activity [54]. The leaf extract of *Machilus philippinense* Merr yielded two active compounds, kaempferol-3-*O*-α-L-rhamnopyranoside 3``,4``-di-Ep-coumaroic acid ester (6.10 μM) and 3``-E, 4``-Z-di-p-coumaroic acid ester (1 μM) have inhibitory activity against α-glucosidase type IV of *Bacillus stearothermophilus*. Structurally, these compounds possessed chromane nucleus and L-rhamnopyranoside sugar moiety [55].

The potential antidiabetic activity of the active constituent (diphlorethohydroxycarmalol (DPHC)) from *Ishige okamurae* was investigated and it showed that the antidiabetic activity elicited through the inhibition of α-glucosidase (IC_{50} = 0.16 nM) and α-amylase (IC_{50} = 0.53 mM) enzymes [56]. Four pure compounds such as trans-N-p-coumaroyltyramine (IC_{50} = 0.40 mM), 1,7-bis(4-hydroxyphenyl)heptane-3,5-diol (IC_{50} = 0.38 mM), 6-hydroxy-2,4,7-trimethoxyphenanthrene (IC_{50} = 0.77 mM) and cis-N-p-coumaroyltyramine (isomer has now inhibition), were isolated from the tuberous rhizomes of Chinese Yam (*Dioscorea opposita* Thunb.) showed considerable α-glucosidase inhibitory activity [57]. A new cyclic peptide with a pyrrolidine-2,5-dione unit, gypsophin, was isolated from *Gypsophila oldhamiana* and it showed moderate α-glucosidase inhibitory activity with IC_{50} = 305 μM (acarbose, IC_{50} = 388 μM) [58]. Dieckol isolated from *Ecklonia cava*, brown algae, evidenced prominent inhibitory effect against α-glucosidase and α-amylase (IC_{50} = 0.24 mM and IC_{50} = 0.66 mM) enzymes [59].

A new class of α-glucosidase inhibitors, neoponkoranol and neosalaprinol were isolated from the water extracts of the sulfonium salts family in *Salacia* genus plants. Among them, 3'-epimer of neoponkoranol was found most potent as the currently used antidiabetics (voglibose and acarbose) [60]. A chemical compound called aloresin A isolated from the Chinese aloes exhibited α-glucosidase inhibitory activities (IC_{50} = 11.94 mM and IC_{50} = 2.16 mM), against rat intestinal sucrase and maltase, respectively [61]. Pure flavonoids such as quercetin, kaempferol, guaijaverin, avicularin, myricetin, hyperin and apigenin were isolated from the n-BuOH-soluble and EtOAc-soluble fractions of

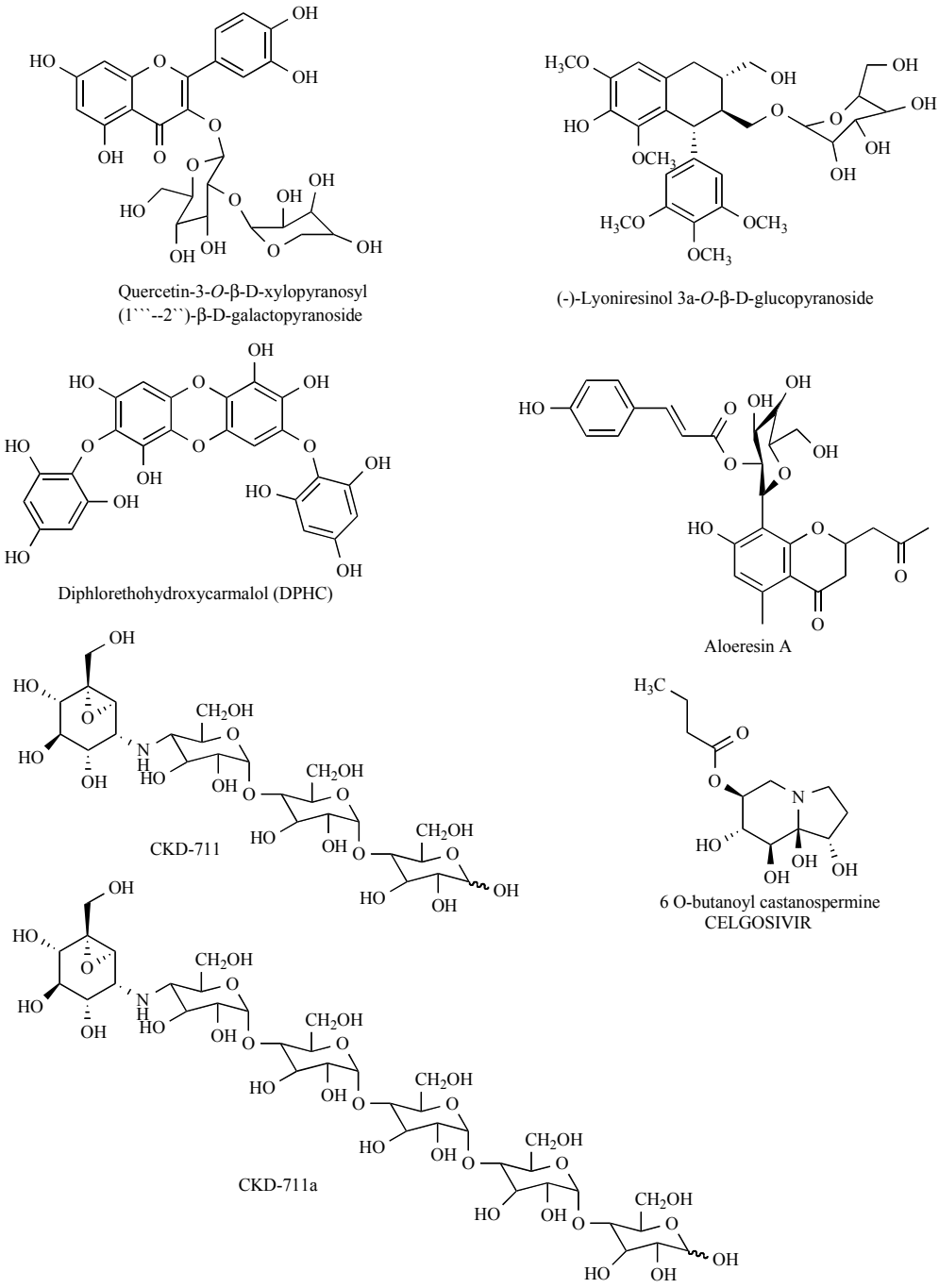

Fig. (4). Novel α-glucosidase inhibitors obtained from natural product and in clinical studies.

guava leaves which showed high inhibitory activity against α-glucosidase and α-amylase enzymes [62]. These showed that the active constituents isolated from the natural products have profound inhibitory effect on α-glucosidase enzymes and other carbohydrate digesting enzymes.

NOVEL α-GLUCOSIDASE INHIBITORS IN CLINICAL STUDY

Celgosivir (MIGENIX Inc) (6-*O*-butanoyl castanospermine) (MX-3253) (Fig. (**4**)) is an oral prodrug of the natural product castanospermine that has used for the treatment of HCV infection by inhibiting α-glucosidase I. MX3235 Celgosivir α-glucosidase I inhibitor has failed in phase II clinical trials as monotherapy in HCV, but has a synergistic effect with PEG/RBV. Celgosivir is rapidly converted to castanospermine *in vivo* and the phase II clinical study demonstrated that it has synergistic effect in combination with PEGylated IFNalpha2b plus ribavirin (patients with upto 1 year chronic HCV infection) [63-66]. The results of the plaque assay and the cytopathic effect assay on celgosivir (MX-3253) (IC_{50} = 16 μM and IC_{50} = 47 μM respectively) was shown that the celgosivir is potent than N-nonyl DNJ (IC_{50} = 105 μM and IC_{50} = 74 μM), castanospermine (IC_{50} = 110 μM and IC_{50} = 367 μM) and N-

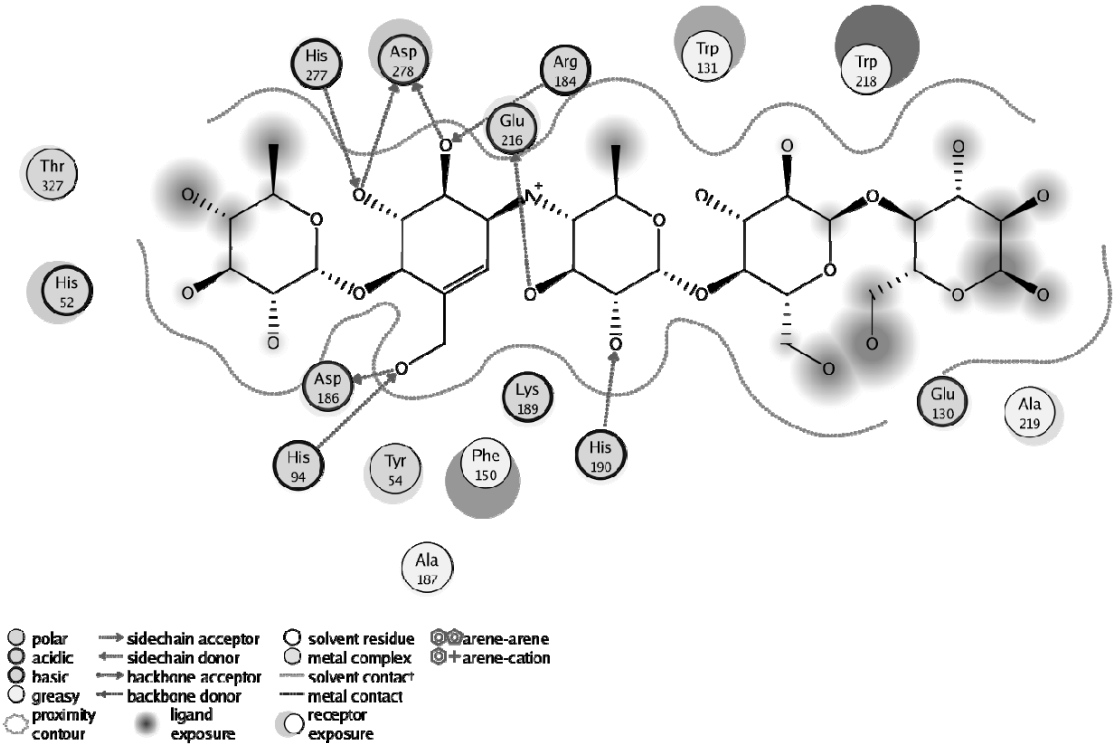

Fig. (5). Graphical representation of ligand interaction sites of *T. maritima* 4-alpha-glucanotransferase/acarbose complex (PDB: 1LWJ).

butyl DNJ (IC_{50} = > 250 μM and IC_{50} = 550 μM). Other observations revealed that the number of viral genomes released from BVDV-infected cells was inhibited by either castanospermine or celgosivir in parallel with the number of infectious [67].

The key attribute of BMN-701 is that it has ability to bind the key cell receptors which direct the enzyme to the cell's lysosome. Every molecule of BMN-701, a fusion of insulin-like growth factor 2 (IGF-2) and acid α-glucosidase (GAA), can bind the M6P receptor which taken up into cells and trafficked to the lysosome where it can degrade the glycogen that causes Pompe disease. The phase 1/2 trial is an open-label study, in which the BMN 701 administered as an intravenous infusion every two weeks at doses of 5 mg/kg, 10 mg/kg and 20 mg/kg [68].

CKD-711 and CKD-711a are aminooligosaccharide α-glucosidase inhibitors (Fig. (**4**)) and the CKD-711 showed similar effects to acarbose on porcine intestinal maltase and sucrase (IC_{50}s of 2.5 μg/ml and 0.5 μg/ml, respectively), whereas, it had about 2 fold lower α-amylase inhibitory activity (IC_{50} = 78.0 μg/ml) than acarbose (IC_{50} = 36 μg/ml). CKD-711a showed less inhibitory activity than CKD-711 against all the enzymes tested and also both molecules (CKD-711 and CKD-711a) showed antibacterial activity against *Comamonas terrigena* [69,70]. A randomized, double blind trial on the voglibose for the prevention of type 2 diabetic mellitus was carried out on Japanese individuals with 0.2 mg/three days oral dose (1780 patients). Voglibose significantly improved glucose tolerance, in terms of delayed disease progression and in the number of patients who achieved normoglycaemia [71].

CONCLUSION

The *in silico* structural analyses clearly explained that the hydrophobic and hydrophilic properties on the vdW surface area of the molecules should be balanced. It reveals that the active site of the enzyme should have polar, aromatic/ hydrophobic residues for the interactions. It is evidenced from the homology modelled enzymes and other glycosidase family enzymes, and the active site residues of the α-glucosidase enzyme of different species. This showed that the active site has aspartic acid, histidine and glutamic acid residues. Hence, it is possible that the polar, aromatic groups in the molecule can interact with the active site residues (aspartic acid, glutamic acid, tyrosine and histidine) by hydrogen bonding or other electrostatic interaction (including π-π stacking) [13,28,35]. The multiple sequence alignment of the α-glucosidase enzyme also showed that the aspartic acid, glutamic acid and histidine amino acid residues aligned with significant identity. The PDB structure (PDB: 1LWJ) of the glucotransferase acrabose complex showed the importance of these residues for the interactions (Fig. (**5**)). The active constituents isolated from the natural products also have distributed polar property, aromatic rings and flexible bonds in their structure to elicit inhibitory activity. The structural analysis of these synthetic and natural derivatives also guide for the development of novel semisynthetic/synthetic α-glucosidase inhibitors with free of toxicities.

CONFLICT OF INTEREST

The Authors do not have any conflict of interest on this manuscript.

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