Inhibitory Activities of α-Glucosidase and α-Amylase and their Hypoglycaemic Capability in the Treatment of Diabetes

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Abstract

Carbohydrate metabolizing enzyme inhibitors such as α-glucosidase (αG) and α-amylase (αA) have been reported in various research articles. They were originated from both natural and synthetic sources. Both αG and αA inhibitors need to be explored for the benefit of postprandial hyperglycemia in diabetic patients. In late years, many efforts were made for the identification and discovery of αG and αA inhibitors from different sources in order to combat postprandial hyperglycemia. Various αG inhibitors that were phytoconstituents, such as alkaloids, flavonoids, anthocyanins, terpenoids, phenolic compounds, glycosides, and so on, sequestrated from plants. In the present review, we focused on the compounds isolated from different plants having αG inhibitory potency along with αA inhibitory activity. In this review article, we appraised the naturally occurring αG and αA inhibitors reported during the past decade.

Keywords: α-glucosidase; α-amylase; Carbohydrate Metabolizing Enzyme Inhibitors; Postprandial Hyperglycemia

Introduction

Polyphenols (PPs) were derived from plant sources as a bioactive secondary metabolite. PPs have gained more attention among the medical, pharmaceutical and life scientists due to their contribution in human health [1-6]. Several PPs that contained more than two phenolic hydroxyl groups were natural antioxidants and having proposed to possess various health benefits to humans. According to the literature, PPs were assorted into four main groups, including phenolic acids, flavonoids, tannins, and stilbenes. Postprandial blood glucose levels were modulated by PPs [7-10]. Type I DM (T1DM) worth about 5 - 10% of total patients and estimated that about 346 million people (90 - 95% of total patients) worldwide suffer from Type II DM (T2DM). Pancreatic β-cell dysfunction and/or increased resistance to insulin with impaired glucose tolerance caused T2DM [11]. The importance of the gastrointestinal tract in glucose homeostasis is being increasingly recognized; and is underscored by the beneficial glycemic effects of some forms of metabolic surgery and the advent of incretin-based therapies for patients with T2DM. In addition, prevailing blood glucose concentrations influence gastric emptying (Figure 1).

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Figure 1: Bidirectional kinship between gastric emptying and glycaemia. The rate of gastric emptying is a critical causal factor of postprandial glycaemia. Glucose entry into the small intestine induces a feedback loop via CCK, PYY and GLP 1, which were secreted from the intestine in reaction to nutrient exposure. GLP 1 and GIP stimulate the release of insulin and GLP 1 inhibits glucagon secretion, which attenuates postprandial glycaemic excursions. Amylin, which is co-secreted with insulin, also slows gastric emptying. At the same time, the blood glucose concentration modulates gastric emptying, such that acute elevations of blood glucose levels slow gastric emptying (effects were evident even within the physiological range) and emptying is accelerated during hypoglycaemia. Abbreviations: CCK, cholecystokinin; GIP, gastric inhibitory polypeptide; GLP 1, glucagon-like peptide 1; PYY, peptide YY. This figure was adapted with permission [12].

Recently, the inhibition of the αA and αG enzymes has attracted attention as an important strategy in the treatment of diabetes and/or obese patients, since inhibitors of these enzymes can retard the uptake of dietary carbohydrates and reduce postprandial hyperglycemia. Chemical investigation led to the identification of six new compounds, including three coumarins [13], two iridoids [14], together with 17 known secondary metabolites constituted by five coumarins [15-19], three flavonols [20-22], seven iridoids [23] and two quinic acid derivatives [24]. Several investigations reported in the literature on plant constituents such as coumarins [13], flavonoids [25], iridoids [26] and quinic acid derivatives [18] as potential leads for the development of inhibitors. A number of lead compounds obtained from natural sources, of which some were of clinical importance [27].

Control of postprandial hyperglycemia

The pancreas secretes a measured quantity of insulin at dissimilar intervals in the body. Increase in insulin release from the pancreas as blood glucose levels were elevated follow Masshe meals; however, in type 2 diabetics this functioning was deficient. This dysfunction
leads to cause hyperglycemia, which was an important and early defect in type 2 diabetics and was due to poor suppression of endogenous glucose formation due to no early-phase insulin response [28]. The pathophysiology of postprandial hyperglycemia is represented in figure 2. The determinants of postprandial blood glucose levels were the presence of insulin and the entry of glucose from the gut. However, disposing glucose in peripheral tissues as well as decreased down regulation of hepatic glucose output were the significant contributors [29] shown in figure 2. Importantly, the mealtime hyperglycemia might be a more accurate predictor for glycated hemoglobin A1c (HbA1c) level analysis and of cardiovascular mortality than fasting hyperglycemia. Postprandial hyperglycemia has been connected to cardiovascular complications, even though HbA1c values were within non-diabetic range, whereas increased fasting plasma glucose levels were not independently linked to increased cardiovascular disease risk [30]. To overcome microvascular and macrovascular complications good glycemic control was one of the cornerstones [31]. This finding concentrated for more attention on control of postprandial hyperglycemia and should think of having an oral antidiabetic drug to control postprandial hyperglycemia so as to achieve an early phase insulin release without causing late hyperinsulinemia or an increased risk of hypoglycemia [28]. However, available oral antidiabetic drugs have limitations of either being contraindicated or with dose reduction in patients with compromised renal function especially diabetes associated with nephropathy. αG inhibitors were reported to contribute in reducing HbA1c in individuals by targeting postprandial hyperglycemia and without dose alteration for those with renal impairment could prove to be a new armamentarium of treating diabetes in the majority population [32]. To overcome postprandial hyperglycemia in type 2 diabetics, αG inhibitor drugs like acarbose and miglitol could block the action of an enzyme αG in the small intestine that normally broke down carbohydrate into glucose. Therefore, glucose entered the bloodstream more slowly, giving the pancreas additional time to secrete enough insulin to handle it. Moreover, αG inhibitors were reported to be useful in elderly patients and in those with mild to moderate renal function impairments when other anti-diabetic agents were contraindicated. It potentially provided another therapeutic option for patients with T2DM in which glycemic control is inadequate, despite diet alone or with pharmacological therapy with sulfonylurea and biguanide. αG inhibitors reported to improve post-prandial hyperglycemia and fasting blood sugar in type 2 diabetics who were uncontrolled, despite on diet control and taking other oral antidiabetic agents [33].

**Figure 2:** Depicts that pathophysiology of postprandial hyperglycaemia. Increased glucose influx from gut, glucose production from liver, altered insulin release pattern from pancreas and decreased glucose uptake from liver, and from muscle adipose tissue were contributing in PPHG.
Biochemistry of α-glucosidase and α-amylases

α-glucosidase, associated with glycoside hydrolase family and tangled in the lysosomal breakdown of glycogen to glucose [34]. αG has been purified from many different tissues such as bovine testis, rat liver, pig liver, human liver, rabbit muscle, human heart, human urine, and human placenta. Proteolytic dispersion appears to be obligatory for optimal activity toward the natural substrate glycogen [35]. There was a 7-10-fold upsurge in the affinity of the 76/70-kDa species for glycogen related with the 110-kDa precursor. In addition, proteolytic development of the αG peptide backbone, there was extensive processing of the carbohydrate chains [36]. Lysosomal αG was targeted to the lysosomes by the mannose 6-phosphate specific subtype of receptor, but analysis of carbohydrate chains from purified 76/70-kDa αG from human placenta revealed the absence of mannose 6-phosphate and additional carbohydrate processing. Functional shortage of αG consequences in lysosomal accumulation of glycogen and cellular damage in all tissues, predominantly cardiac and skeletal muscle. αG which was embattled to the lysosome via the mannose 6-phosphate receptor and undergoes in the late endosomal/lysosomal section a series of proteolytic and N-glycan processing events to yield a mature active form composed of four tightly associated peptides [37].

Figure 3: Shows high-resolution crystal structures of recombinant human α-glucosidase (GAA), schematic representation of the sequence of GAA. Here, corresponding domains to the rhGAA construction were colored with α-chymotrypsin colored in white. Cartoon representation of the structure of rhGAA consisting of the trefoil type-P domain (salmon), the N-terminal β-sheet domain (slate), the catalytic GH31 (β/α) barrel domain (green) with insert I (gold) and insert II (pink), and the proximal (orange) and distal (teal) β-sheet domains.

α-Amylases were enzymes that catalyses the hydrolysis of internal α-1,4-glycosidic linkages in starch in low molecular weight downstream products, such as glucose, maltose and maltotriose units. They were attained from several sources, such as plants, animals and microorganisms. αA has been derived from several fungi, yeast and bacteria. However, enzymes from fungal and bacterial sources dominated applications in industrial sectors [38,39]. αA have potential application in a wide number of industrial processes such as food, fermentation, textile, paper, detergent, and pharmaceutical industries. Fungal and bacterial amylases could be potentially useful in the pharmaceutical and fine-chemical industries. The end products of αA action were oligosaccharides with varying length with an α-configuration and α-limit dextrins, which constituted a mixture of maltose, maltotriose, and branched oligosaccharides of 6-8 glucose units that contain both α-1,4 and α-1,6 linkages [40]. Others amylolytic enzymes participate in the process of starch breakdown, but the contribution of αA was the most important for the initiation of this process. The salivary αA (SAA) enzyme was produced by the salivary glands and its main function was to initiate the digestion of macromolecules such as carbohydrates. Its release was regulated by the sympathetic autonomic
nervous system (ANS), whose action was of paramount importance in the psychobiology of stress. Studies showed that the SAA levels in humans increased under physical and psychological stress. For this reason, SAA had become a marker of stress and anxiety, being a fast, painless, and noninvasive tool for assessment of the ANS pathological dysregulation in specific clinical and subclinical conditions [41].

Figure 4: Shows that diagram of the porcine pancreatic αA (PPA) structure. The three domains were shown: domain A is colored red; domain B, yellow; domain C, purple. The calcium ion (blue sphere) and the chloride ion (yellow sphere) were also shown in the immediate vicinity of the catalytic center. The acarbose ligand (ball-and-stick representation in green) is bound at the active site cleft. Monosaccharide and disaccharide ligands (in ball-and-stick representation) were shown bound to the surface binding sites.

Intestinal absorption and digestion of carbohydrates

Carbohydrates were the most abundant biological molecules in nature. They delivered a broad range of uses, including supplying a substantial fraction of the dietary calories for most beings, representing as a storage form of form of energy in the liver, muscle and dishing out as cell membrane components that mediated some forms of intercellular communication. Carbohydrates could be classified as monosaccharides, disaccharides, oligosaccharides and polysaccharides based on the number of carbon atoms they contain or monosaccharide units attached to their structure [42].

Digestion of dietary carbohydrates

The main sites of dietary carbohydrate digestion were the mouth and intestinal lumen. This phenomenon of digestion was catalyzed by enzymes known as glycoside hydrolases (glycosidases) that hydrolyze glycosidic bonds. Glycosidases were typically precise to the
structure and conformation of the glycosyl residue to be detached, as well as for the type of bond to be wrecked. The terminal products of carbohydrate digestion were the monosaccharides, glucose, galactose and fructose, which were primarily absorbed by segment of the small intestine [43].

The major dietary polysaccharides were of plant (starch, composed of amylose and amylopectin) and animal (glycogen) origin, because there was little monosaccharide present in the diets of mixed animal and plant origin. During chewing, ptyalin or SAA acts briefly on dietary starch and glycogen, hydrolyzing random α (1-4) bonds. The carbohydrate digestion resulting from enzymatic action comprised a mixture of short, and unbranched oligosaccharides known as dextrins, since split amylopectin and glycogen also contain α-(1-6) bonds, which αA cannot hydrolyze. Carbohydrate digestion standstills provisionally in the stomach, because the strong acidity inactivates SAA enzyme activity. When the acidic stomach chime, digestion initiated in saliva reaches the small intestine, they were neutralized by bicarbonate secreted by the pancreas, and pancreatic αA continues the process of starch digestion [44].

Ultimate digestive processes occurred mainly in the mucosal lining of the proximal jejunum, where sucrase and isomaltase were exact enzyme activities of a single protein which was cleaved into binary functional subunits that endure associated in the cell membrane, forming the sucrase-isomaltase complex. Maltase formed a comparable complex with an exoglucosidase (glucoamylase) that cleaves α (1-4) glycosidic bonds in dextrins. These enzymes were secreted through, and remain associated with, the luminal side of the brush border membranes of the intestinal mucosal cells. For instance, isomaltase hewed the α (1-6) bond in isomaltose and maltase cleaves maltose and maltotriose, each producing glucose, sucrase cleaves sucrose constructing glucose and fructose, and lactase (β-galactosidase) cleaves lactose producing galactose and glucose [45].

**Figure 5:** Shows SAA enzyme begins carbohydrate digestion in the oral cavity and its activity continues till the stomach until acid penetrates the bolus. Further, hydrolysis of starch by pancreatic α-amylase occurs in the brush border of duodenum which were scavenges by brush border enzymes-e.g., lactase, sucrase and maltase. Resulting monosaccharide end products- glucose, fructose and galactose were readily absorb from small intestine.
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Synthetic α-glucosidase and α-amylase inhibitors

Inhibitors of αG and αA enzymes scale down the absorption of starch, dextrin, and disaccharides from the intestines by inhibiting the action of αG in the intestinal brush border. Acarbose, miglitol, and voglibose were the example of drugs which were used in this class [46]. αG inhibitors were used as a single or in a combined form with other oral antidiabetic drugs like metformin and the thiazolidinediones and were taken just before a meal [47]. Acarbose and miglitol were potent inhibitors of glucoamylase, αA, and sucrase but have less effect on isomaltase and hardly any on trehalase and lactase. Acarbose had the molecular mass and structural features of a tetrasaccharide and very little was absorbed. In contrast, miglitol had structural similarity to glucose and was absorbed [48]. Treatment with αG inhibitors showed reduction in postprandial glucose concentrations (2.2 - 2.8 mmol/L), however, these inhibitors lack an effect on fasting blood sugar [49]. Malabsorption, flatulence, diarrhea, and abdominal bloating were the prominent adverse effects reported with this class of drugs. Moreover, mild-to-moderate increase of hepatic transaminases documented with the use of acarbose, however symptomatic liver disease was very less, also cutaneous hypersensitivity reported but is rare. When αG and αA inhibitors combined with insulin, insulin secretagogue, hypoglycemia reported to take place [46]. That’s why, patients were taking an αG inhibitor who experienced hypoglycemia should be treated with oral glucose (dextrose) and not sucrose, because the absorption of sucrose will be delayed [47]. αG inhibitor could interact with the other drug absorption if given concurrently, since acarbose decreased the absorption of digoxin; whereas miglitol of propranolol and ranitidine, thereby limited their use of medications. Moreover, these inhibitors were not metabolized and cleared by the kidney [48]. So, these inhibitors were contraindicated in patients with stage 4 renal failure [46]. αG inhibitors modestly reduced HbA1c levels, which showed to be related with the risk of microvascular complications. Both Acarbose and miglitol should be taken with the first bite of the meal so that the drug may be present to inhibit enzyme activity. Only patients consuming a diet high in complex carbohydrates will have significant reductions in glucose levels. αG and αA inhibitors contraindicated in patients with short-bowel syndrome or inflammatory bowel disease, and neither should be administered in patients with serum creatinine > 2 mg/dL (> 177 μmol/L), as this population has not been studied [49].

Natural α-glucosidase and α-amylase inhibitors

The multifactorial pathogenicity of diabetes postulated a multimodal therapeutic approach. The nutraceuticals owned a variety of biochemical and pharmacological properties that might be efficacious to combat diabetes and its linked complications. Novel drug spark advances distinguished from natural sources forms the basis of divine counsels for the synthesis and testing of synthetic or semisynthetic molecules. The following phytochemicals were investigated for their αG and/or αA inhibitory effect.

Prenylated flavonoids

Prenylated flavonoids were a sub-category of flavonoids, which had a supernumerary lipophilic prenyl side-string along with its flavonoid skeleton. They were widely circulated among the plant kingdom and possess a broad range of pharmacological activities. The outcome of various flavonoids on αG inhibition was well described, but, studies on prenylated flavonoids were circumscribed. In recent decades, prenylated flavonoids in plants, accounted for their αG inhibitory activity. Xanthohumol was a natural prenylated flavonoid derived from hops (Humulus lupulus L.) and beer and it dissembles as a αG inhibitor [50]. A prenylated flavanone isolated and characterized from the aerial parts of Arcytophyllum thymifolium exhibited high αG inhibitory activity [51]. A prenylated flavanone isolated and characterized from the roots of Sophora flavescens had greater αG inhibitory activity than Acarbose [52]. Prenylation of flavonoids might result in meliorated bioactivities compared with unprenylated flavonoids. Nevertheless, the low abundance in nature and complex chemical synthesis determined the application of prenylated flavonoids in medicines and dietary supplements [53].

Phlorotannins

Brown seaweed was ample in PPs and were bringing in importance as nutritional diets referable to their protective effect on glucose homeostasis [54]. Phlorotannins belongs to the polyphenols class that was mainly produced by the brown seaweed [55] and their antdia-
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Betic mechanisms was mediated through αG and αA inhibition [56,57]. Two phlorotannins from Eisenia bicyclis namely fucofuroeckol-A and dioxidodehydroeckol expressed non-competitive inhibitory activity against Ag [58]. Three phlorotannins (phlorofurolueckol-A, dieckol, and 7-phloroeckol) isolated from two edible brown algae, Ecklonia stolonifera and Eisenia bicyclis demonstrated potent αG inhibition [59].

Sulfonium-ion and its derivatives

In recent decades, naturally occurring cyclic sulfonium or salacinol like compounds was realizing importance as a novel class of αG inhibitors. Principal sulfonium constituents of Salacia chinensis namely salacinol, neosalacinol, kotalanol, and neokotalanol inhibited human αG enzyme and were highly stable in an artificial gastric juice [60]. The nitrogen and selenium analogues of kotalanol and de-O-sulfonated kotalanol synthesized and found to have greater αG inhibitory activities than Acarbose [61]. The sulfonium ion was an indispensable structure for the αG inhibitory activity of cyclic sulfonium compounds. Various derivatives of salacinol synthesized and tested for its ability to suppress αG. Replacement of the sulfur atom in salacinol with a nitrogen reduced the αG inhibitory activity considerably [62]. Ponkoranol, a sulfonium constituent of Salacia reticulata was accounted for its αG inhibitory effect [63] and substitution of the sulfur atom in de-O-sulfonated ponkoranol and its 50 epimer salacinol with selenium resulted in a 13-fold and 23-fold improvement in the αG inhibitory activity [64].

Coumarins and its derivatives

Coumarins, a plant secondary metabolites, have been used as anticoagulants and antithrombotic agents for cardiovascular diseases. In recent decades, there was an increasing scientific evidence on coumarins and its αG inhibitory effects. Novel αG inhibitors based on coumarins cores were constantly searching and expanded either from natural resources or through chemical synthesis. Several simple coumarins [65], furanocoumarins [66], dihydrofurocoumarin [67], bicoumarins [68], terpenylated coumarins [69], deduced from natural resources and reported to inhibit αG [70]. Similarly, a series of novel hetaryl [71], isatin [72], 3-Thiazolyl [73] thiazole [74], hydroxyl [75] derivatives of coumarins were synthesized and measured from αG inhibitory activity. Both naturally occurring and chemically synthesized derivatives of coumarins indicated promising αG inhibitory effect.

Conclusion

Despite the availability of modern medicines in the market to manage type-2 diabetes mellitus, plant derived medicines have accumulated significant knowledge in treating various diseases including diabetes mellitus. The natural α-glucosidase and α-amylase inhibitors discussed in this review have not been well studied or characterized for its clinical use in modern medicine. The researchers should pay more attention in providing substantial preclinical and clinical evidences on their safety and mechanism to control postprandial hyperglycemia. The findings of such research could lead to development of novel carbohydrate hydrolyzing enzyme inhibitors to treat diabetes.

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