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REVIEW ARTICLE

A review of α-amylase inhibitors on weight loss and glycemic control in pathological state such as obesity and diabetes

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Abstract Overweight, obesity, and diabetes are the most common disorders in the world. In most diets, carbohydrates are the greatest source of calories. Inhibition of carbohydrate digestion or absorption can decrease calorie intake to promote weight loss and combat obesity. It is also a mechanism for reducing hyperglycemia in diabetic subjects. Before being absorbed by the body, carbohydrates must be broken down into monosaccharides. α-Amylase catalyzes the hydrolysis of α-(1,4)-D-glycosidic linkages of starch and other glucose polymers. Inhibitors of this enzyme can be used in treatment of obesity and diabetes. In diabetic patients, inhibition of α-amylase leads to prohibition starch breaking and results in lower levels of blood glucose. The effects of pseudosaccharides, proteinaceous, and polyphenolic inhibitors have been previously reported. Polyphenolic compounds are widely distributed in plants and fruits and are present in normal diets. These compounds have been shown to possess beneficial effects in diabetes, cardiovascular diseases, atherosclerosis, allergy, inflammation, and osteoporosis. Among polyphenolic compounds, flavonoids are of particular significance: They have been shown to reduce cholesterol synthesis via direct action on HMG-CoA reductase and hydrolyze lipids via inhibition of phosphodiesterase (PDE) and diminution of cAMP breakdown. In recent years, many lines of research have been done on those plants which are being used traditionally as drug plants, and their effects have been surveyed on weight loss and control of blood glucose levels in diabetic patients. In this review, we want to investigate α-amylase inhibitors especially human pancreatic α-amylase (HPA)

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Introduction

The most common nutritional disorders in the world are overweight and obesity. Being obese increases the risk of arthritis, dyslipidemia, hypertension, diabetes, and coronary artery disease (Rosak and Mertes 2009; Yamagishi et al. 2005).

Compounding these health risks, obese individuals have a lower quality of life than those who are not obese (Goutham et al. 2011). In 2005, the World Health Organization (WHO) estimated that approximately 1.6 billion adults worldwide are overweight and at least 400 million are obese. Further, the WHO reported that at least 20 million children under the age of 5 years are overweight. The projected numbers for 2015 are larger, with 2.3 billion adults expected to be overweight and 700 million to be obese (Marsh and Brand 2008). The Centers for Disease Control in a 2006 survey reported that an average of 37 % of Americans are overweight (Kilmer et al. 2008). According to the International Diabetes Federation (IDF) (http://www.diabetesatlas.org), the global prevalence of diabetes is predicted to grow from 6.6 in 2010 to 7.8 % in 2030. Translation of these percentages to numbers would give 439 million people suffering from diabetes in 2030. Diabetes is cited in the IDF report as being the fourth or fifth leading cause of death in most high-income countries and an epidemic disease in economically developing and newly industrialized nations (Najafian et al. 2010). In most diets, carbohydrates are the greatest source of calories. Inhibition of carbohydrate metabolism or absorption can decrease calorie intake to promote weight loss and combat obesity. It is also a mechanism for reducing hyperglycemia in diabetic subjects. Before being absorbed by the body, carbohydrates must be broken down

into monosaccharides. This breakdown occurs due to two major enzymes: amylase and glucosidase. α-Amylase (α-1,4-glucan 4-glucanohydrolase, EC 3.2.1.1) is an enzyme that plays a major role in the digestion of dietary starch and glycogen. Amylase hydrolyzes α-1,4-glycosidic bonds in large polymers such as starch, amylose, amylopectin, glycogen, and various maltooligosaccharides. The mechanism of this hydrolysis is called "multiple attack" in which the encounter of the α-amylase with a starch chain occurs with several α(1–4) glycosidic linkages being hydrolyzed to immediately give the formation of low molecular weight maltodextrins, such as maltose, maltotriose, and maltotetraose (Moran et al. 2011; Yoon et al. 2007). In fact amylase performs the first step of an important process by which cells are provided with glucose, their principal energy and carbon source. Digestion of carbohydrates begins in the mouth, with amylase secreted by salivary glands. This action accounts for only about 5 % of the breakdown of carbohydrates. The process is halted in the stomach due to the high-acid environment destroying the amylase activity. When the food enters the intestine, the acidic pH is neutralized by the release of bicarbonate secreted by the pancreas and by the mucous that lines the walls of the intestine. Amylase is secreted into the small intestines by the pancreas. α-Glucosidase enzymes are located in the brush border of the small intestines. Amylase breaks down the carbohydrates into oligosaccharides. The glucosidase enzymes (including lactase, maltase, and sucrase) complete the breakdown to monosaccharide units. It is only the monosaccharide units that are absorbed into the body (Obiro 2008).

Dietary carbohydrates that are composed mostly of monosaccharide units are absorbed quickly and are said to have a "high glycemic index." Carbohydrates in polymeric form are absorbed more slowly and are said to have a "low glycemic index." The glycemic index (GI) is defined as the incremental area under the blood glucose curve following ingestion of a test food, expressed as a percentage of the corresponding area following an equivalent load of a reference carbohydrate, either glucose or white (wheat) bread (Radulian et al. 2009). Low-GI foods are (<55) such as vegetables, unsweetened yogurt, and protein-enriched spaghetti. Some examples for high-GI foods (>70) are white bread, baked potato, and dates. After consumption of high-GI foods, there is a large, rapid increase in blood sugar levels, and in response, a rapid increase in insulin levels is seen. Insulin promotes the uptake of glucose from the blood into cells in the liver and skeletal muscle tissue, storing it as glycogen. Insulin also increases fatty acid synthesis and can result in the accumulation of lipids. Accumulation of lipids in skeletal muscle and the liver is associated with a decrease in insulin sensitivity. Insulin resistance increases the chance of developing type 2 diabetes and heart disease. Postprandial hyperglycemia and insulin resistance are thought to play a central role in the development and progression of cardiovascular disease in subjects with impaired glucose tolerance (Barclay et al. 2008; Brand-Miller et al. 2009; Thomas et al. 2007). Three large-scale epidemiological studies on women report a correlation between a high-GI diet and the incidence of type 2 diabetes (Krishnan et al. 2007; Schulze et al. 2004; Villegas et al. 2007). As previously indicated for GI, the choice of the type of carbohydrate foods in the diet, with their varying glycemic properties, can determine the rate of absorption of sugars into the body. One method of reduction for the GI in a meal is the inclusion of resistant starches. Resistant starches are those that resist digestion in the small intestine, thereby passing into the large intestine; they act like dietary fiber (Englyst and Englyst 2005).

These starches are naturally found in seeds, legumes, and unprocessed whole grains. The amount of resistant starch in food is influenced by processing, which can either increase or decrease the amounts found in the raw substance. Resistant starch can be added to foods such as bread, biscuits, sweet goods, pasta, nutritional bars, and cereal, in order to their lower-GI index, without affecting taste or texture (Grabitske and Slavin 2008; Higgins 2004).

An alternative to a low-GI diet is some products that have slow absorption for carbohydrates through the inhibition of enzymes responsible for their digestion. These products include α-amylase and glucosidase inhibitors. A beneficial method for the treatment of diabetes and obesity is inhibiting sugar uptake in the small intestine. α-Amylase catalyzes the hydrolysis of α-(1,4)-D-glycosidic linkages of starch and other glucose polymers. Inhibitors of this enzyme can be used in the treatment of diabetes and obesity. With inhibition of α-amylase, lower levels of blood glucose in diabetic patients can be seen (Ceriello 2005; Preuss 2009; Rebolledo and Dato 2005). Acarbose is a prescription drug, which inhibits α-glucosidase enzymes in the brush border of the small intestines and pancreatic α-amylase. Other drugs that belong to this class are miglitol and voglibose. Acarbose reduces postprandial hyperglycemia and is used to treat type 2 diabetes. Clinical studies with subjects about impaired glucose tolerance have demonstrated not only an improvement in postprandial hyperglycemia but also cardiovascular benefits (Yamagishi et al. 2009). α-Amylase inhibitors with activity against mammalian forms of the enzyme are present in plants, and it is suggested that they are developed by plants in order to strengthen their defense against predators. Plant constituents with enzymatic inhibitory activity include polyphenolic compounds and glycoproteins (McDougall and Stewart 2005; Tundis et al. 2010). In addition, theaflavins and catechins present in green and black teas have been reported to inhibit α-amylase and α-glucosidase activity as well as retarding starch digestion in an in vitro model (Lee et al. 2010).

Carbohydrates that are resistant to digestion in the intestine enter the colon, where they are fermented by colonic bacteria

to produce short-chain fatty acids, carbon dioxide, and methane. The most common side effects are including flatulence 24 %, meteorism 21 %, diarrhea 2 %, and abdominal pain 4 %. The gastrointestinal effects of acarbose are mostly due to the fermentation of undigested carbohydrates in the intestine. These effects tend to subside with time, because of the enzyme activity adaptation. It has been reported that these events are markedly reduced after 8–10 weeks (Baotic et al. 2000).

Structure of α-amylase and the role of calcium in structure and activity

α-Amylases are endoglycosidases that hydrolyze (1–4) glucosidic linkages. From their primary structures, these enzymes have been classified into glycosyl hydrolase family 13 (1–3), a family that also includes α-glucosidases and cyclodextrin glucanotransferases. Analysis of tertiary structures reveals that the catalytic domain of family 13 enzymes, especially the active site, is very well conserved. Indeed, a number of studies have shown that members of this family of glycosidases utilize a common double-displacement catalytic mechanism, in which a glycosyl-enzyme intermediate is formed and hydrolyzed with acid/base catalysis.

In human, the major tissues that produce amylase are the pancreas and salivary glands. The ease of detection of salivary and pancreatic amylases in serum contributed to an extensive clinical literature, relating the levels of amylase isozymes to various disease states.

In human, human pancreatic α-amylase (HPA) and human salivary α-amylase (HSA) are responsible for cleaving large maltooligosaccharides to smaller oligosaccharides (Numao et al. 2004; Schwarz et al. 2007).

By X-ray crystallographic methods, it has been recognized that these enzymes are found to be composed of three structural domains. Figure 1 shows the conformational structure of HPA. In HPA, the largest domain is domain A (residues 1–99, 169–404), which forms a central eight-stranded parallel β-barrel. The active site residues are located in domain A and include Asp 197, Glu 233, and Asp 300. Also in the vicinity, a bound chloride ion is found that forms ligand interactions to Arg 195, Asn 298, and Arg 337. Domain B is the smallest one (residues 100–168) and serves to form calcium binding site against the wall of the β-barrel of domain A. Protein groups making ligand interactions to this calcium include Asn 100, Arg 158, Asp 167, and His 201. Domain C (residues 405–496) is made up of anti-parallel β-structure (Brayer et al. 1995). It is notable that the N-terminal glutamine residue of HPA undergoes a posttranslational modification to form a stable pyrrolidone derivative that may provide protection against other digestive enzymes (Brayer et al. 1995). HSA consists of 496 amino acids and is found in two forms in human saliva: a glycosylated isoform (apparent molecular weight 62 kDa) and a nonglycosylated form of 56 kDa (Fisher et al. 2006). The HSA structure consists of three domains (A, B, and C): Domain A (residues 1–99 and 169–404) contains $(\beta/\alpha)_8$-barrel motif, domain B (residues 100–168) consists of an open loop that contains several helices and β-strands and domain C (residues 405–496) is composed of ten β-strands of which the eighth forms a Greek key motif. HSA binds a chloride ion near the active site in domain A and is coordinated by the side chains of Arg 195, Asn 298, and Arg 337 and a calcium ion that is coordinated by His 201 from domain A and Asn 100, Arg 158, and Asp 167 from domain B (Mac Gregor et al. 2001). Binding of various substrate analogs to the enzyme suggests that the amino acid residues involved in the catalytic reaction are glutamic and aspartic acids. A number of other residues surround the substrate and seem to participate in its binding via hydrogen bonds and hydrophobic interactions. The basic calcium ion is located near the active site region between two domains, each of them providing two calcium ligands. On the basis of sequence comparisons, this calcium binding site is suggested to be a common structural feature of all α-amylases. The calcium ion is required for the tertiary structure and optimal enzymatic activity (Boel et al. 1990; Buisson et al. 1987).

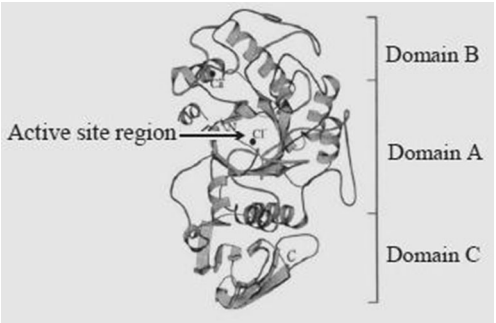

Fig. 1 A stereo drawing showing the structure of human pancreatic α-amylase, which is folded into three domains (domains A–C). Domain A (residues 1–99, 169–404), domain B (residues 100–168), and domain C (residues 405–496), along with locations of the calcium and chloride binding sites. N-terminal end of the polypeptide chain has been located in domain A, and C-terminal end of the polypeptide chain has been located in domain C. A central feature of this structure is the eight-stranded parallel and barrel that forms the bulk of domain A and is believed to contain the active site region

The effect of temperature, pH, and salt on HPA

The effect of temperature on enzyme activity is measured at pH 6.0 over a temperature range of 5–80 °C. The optimum temperature of the enzyme is 30 °C. Fifty percent of hydrolyzing activity occurs between 10 and 55 °C. At 70 °C, activity is 15 %, and at 80 °C, activity is zero. Also, the enzyme retained 100 and 70 % active for 120 min when it is being heated to 30 and 40 °C, respectively. At 50 °C, 50 % of its activity is retained for up to 85 min. The rate of thermal

inactivation is faster at higher temperatures. At 60 and 70 °C, the enzyme loses its activity after heating for 120 and 60 min, respectively (Areekijseree et al. 2004; Dutta et al. 2006; Yamaguchi et al. 2011). The optimum pH of the enzyme is 6.0. The amylase keeps more than 50 % of its original activity between pH 4.6 and 6.8. The enzyme is stable over a wide pH range. More than 50 % residual activity is obtained between pH 4.7 and 9.0. The enzyme is not stable below pH 3.5 or above pH 10.0 (Dutta et al. 2006). The amylase is stable in NaCl solution and maintains 80 and 50 % of its original activity in 2 and 5 M concentrations, respectively, after 2 h of incubation at 4 °C. Only 60 and less than 10 % of its original activity are retained in 2 and 5 M NaCl, respectively, after 24 h of incubation at the same temperature. Below 0.5 M NaCl concentration, the enzyme retains full activity for up to 24 h of incubation under the same conditions. Metal ions like Hg^{2+} and Li^{2+} completely inhibit amylase activity, while Cu^{2+}, Mg^{2+}, and Pb^{2+} reduce activity to as little as 5 % of the original activity. In contrast to these, most of the metal ions enhance activity. Fe^{2+}, Ba^{2+}, Co^{2+}, Ag^{2+}, and Mn^{2+} can enhance original activity by up to 130–200 %, while K^{+} and Sn^{2+} cause a negligible increase in activity (Dutta et al. 2006; Yamaguchi et al. 2011).

Inhibitors of HPA

In recent years, an increasing number of investigations have evaluated the possible efficiency of α-amylase inhibitors in the treatment of diabetes and obesity. The first commercialized inhibitor of α-glucosidase and α-amylase was acarbose. Acarbose in micromolar concentrations is inhibitor of glucosidase and amylase. In addition, it is safe and can maintain its effect in the long-term. The acarbose effect in the control of postprandial hyperglycemia suggests it as a potential preventive aid in metabolic syndrome complications (Yamagishi et al. 2005; Godbout and Chiasson 2007).

Acarbose and its derivatives

Acarbose is a well-known, natural product produced by several species of *Actinoplanes* and is a potent inhibitor of α-amylase (Yoon and Robyt 2003; Kim et al. 1999).

Acarbose is a pseudotetrasaccharide that has a pseudosugar ring, [4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl] at the nonreducing end, linked to the nitrogen of 4-amino-4,6-dideoxy-D-glucopyranose (4-amino-4-deoxy-D-quinovopyranose), which is linked α-1→4 to maltose (Fig. 2). The mechanism of inhibition for α-amylase has been postulated to be the unsaturated cyclohexene ring and the glycosidic nitrogen, which is usually protonated to give a positively charged nitrogen atom. The structure is thought to mimic the transition state for the cleavage of glycosidic

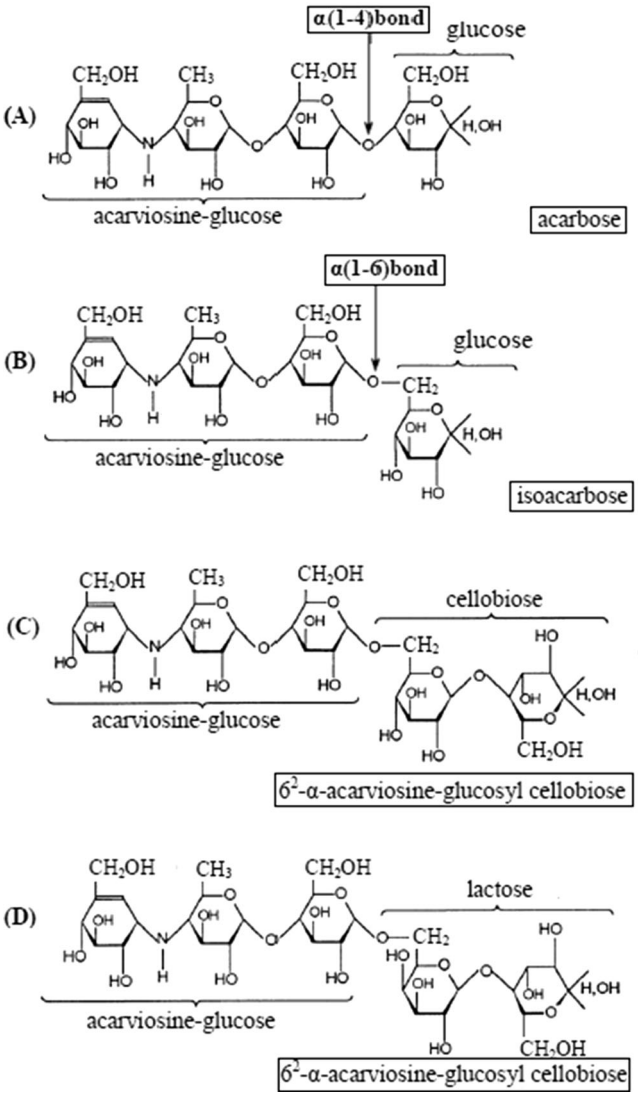

Fig. 2 Structure of acarbose and the reaction of *Bacillus stearothermophilus* maltogenic amylase with acarbose

linkages. *Bacillus stearothermophilus* maltogenic amylase (BSMA) can hydrolyze acarbose at the first glycosidic linkage from the reducing end to give D-glucose and acarviosine-glucose. In addition, BSMA catalyzes a transglycosylation reaction between acarviosine-glucose and D-glucose to give a new pseudotetrasaccharide with acarviosine-glucose linked α-1→6 to D-glucose, which is isoacarbose. Isoacarbose is an effective inhibitor of α-amylase, inhibiting 15.2 times more than acarbose. BSMA was also capable of transferring acarviosine–glucose from acarbose to the C-6-OH group of the nonreducing-end moiety of a variety of disaccharides, including cellobiose and lactose. These products also, the same as isoacarbose, have inhibitory effect (Robyt 2005; Lee and Robyt 2001; Lee et al. 2001).

One kind of acarbose analog inhibitors is glycosylated acarbose. This compound was synthesized by the reaction of acarbose with cyclomaltohexaose and cyclomaltodextrin

glucanyltransferase (CGTase). In this reaction, six, 12, and 18 glucose units are attached to the nonreducing ends of acarbose. These compounds are shown as G6-Aca, G12-Aca, and G18-Aca, respectively (Lee and Robyt 2001; Lee et al. 2001; Yoon and Robyt 2002).

The inhibitory effects of maltohexosyl acarbose (G6-Aca) and maltododecaosyl acarbose (G12-Aca) were examined for four α-amylases from different origins: fungal α-amylase from *Aspergillus oryzae* (AOA), bacterial α-amylase from Bacillus *amyloliquefaciens* (BAA), human α-amylase from saliva (HSA), and mammalian α-amylase from porcine pancreas (PPA). Acarbose, G6-Aca, and G12-Aca showed mixed, noncompetitive inhibition for all four of the α-amylases. Their K_i values were determined and compared with the K_i values of acarbose for each of the enzymes.

The acarbose inhibition constants, K_i, for the four α-amylases were 270, 13, 1.27, and 0.80 μM, respectively; the K_i values for G6-Aca were 33, 37, 14, and 7 nM, respectively; and the G12-Aca Ki constants were 59, 81, 18, and 11 nM, respectively. The G6-Aca and G12-Aca analogs have more α-amylase inhibitory effect than acarbose. The inhibitory effect of G6-Aca on AOA, BAA, HSA, and PPA is 8,182; 351; 90; and 114 times more than acarbose, respectively. In terms of G12-Aca, the respective figures are 4,576; 160; 70; and 72 times (Yoon and Robyt 2003; Lee and Robyt 2001; Lee et al. 2001). Subsite-mapping studies indicate that active site cleft of PPA, HAS, AOA, and BAA have a different number of D-glucose-binding subsites (Yoon and Robyt 2003; Kandra et al. 2002).

By energy of binding glucose at the glucose-binding subsites and X-ray crystallographic and kinetic studies, it is determined that the numbers of D-glucose-binding subsites of BAA, AOA, HAS, and PPA are 9, 7, 6, and 5, respectively (Fig. 3) (Desseaux et al. 2002; Saboury 2002; Svensson et al. 2002).

The X-ray crystallographic analysis of PPA, HAS, AOA, and BAA α-amylases in the presence of acarbose (G6-Aca) shows that the two units of acarviosine at the nonreducing end of acarbose are bound at subsites +1 and −1, where the catalytic groups are located. These are the two units of acarbose that act as the transition-state mimics for the cleavage of the α-1→4 glycosidic linkage of starch and thereby produce inhibition. On the basis of the structural features of the active site of α-amylases and related enzymes, it can be postulated that the acarviosine unit of acarbose inhibits the α-amylases by binding with the two D-glucose-binding subsites, +1 and −1, on either side of the catalytic groups (Fig. 3) (Robyt 2005; Svensson et al. 2002; Kandra et al. 2003). These studies show that the attachment of maltodextrins to the nonreducing end of acarbose such as G6-Aca and G12-Aca greatly enhances the affinity of the acarbose unit for the active sites of the amylases, making the analogs much more potent active site-directed inhibitors than acarbose. Because G6-Aca and G12-Aca have relatively long maltodextrin chains, it can be expected that the α-amylases may hydrolyze the chains (Yoon and Robyt 2003; Ramasubbu et al. 2005).

Polyphenolic compounds as α-amylase inhibitors

Polyphenolic compounds are widely distributed in plants and fruits and are present in normal diets. These compounds have been shown to possess beneficial effects in diabetes, obesity, cardiovascular diseases, atherosclerosis, allergy, inflammation, and osteoporosis (Nijveldt et al. 2001; Tadera et al. 2006). The plants that have polyphenolic compounds act as anti-hyperglycemia and anti-hyperlipidemia in animals (Aslan et al. 2007; Li et al. 2007; Sharma et al. 2008).

Among polyphenolic compounds, flavonoids are of particular significance: These have been shown to reduce cholesterol synthesis via direct action on HMG-CoA reductase and hydrolyze lipids via inhibition of phosphodiesterase (PDE) and diminution of cAMP breakdown (Peluso 2006). There are more than 6,400 known flavonoid compounds. Flavonoids contribute to the flavor and pigmentation of the fruits and vegetables in the human diet (Kay 2010).

Flavonoids based on differences in molecular backbone structure may be divided into eight different classes (flavonols, flavones, flavanones, catechins, anthocyanidins, isoflavones, dihydroflavonols, and chalcones) (Fig. 4) (Peluso 2006).

Among these classes, flavonols, dihydroflavonols, catechins, and anthocyanidins are hydroxylated at the 3-position of the C-ring. For all of the shown flavonoids, the B-ring is attached to the C-ring at the 2-position of the C-ring, except the isoflavones for which the B-ring is attached to the C-ring at the 3-position of the C-ring. Chalcones have a five-membered open C-ring structure (Peluso 2006).

The flavonol quercetin and the flavone apigenin are found in many fruits and vegetables, including onions, apples, broccoli, and berries. Naringenin is a citrus flavanone. Naringin was transglycosylated by BSMA reaction with maltotriose to give a series of monoglycosylnaringin, diglycosylnaringin, and triglycosylnaringin. The major transglycosylation product was maltosylnaringin, in which the maltose unit was attached by an α(1–6) glycosidic linkage to the D-glucose moiety of naringin (Lee et al. 1999). Catechin and other catechins are abundant in green tea. Cyanidin and other anthocyanidins are largely responsible for the deep colors of berries and grapes. Genistein is an isoflavone found predominantly in legumes (Beecher 2003). Plants derived polyphenols such as quercetagetin, fisetin, and quercetin, which belong to the flavonoid family, have been shown to be effective inhibitors of mammalian α-amylase with half maximal inhibitory concentrations (IC_{50}s) in the order of micromolar (Lo et al. 2008). Chalcone (1,3-diphenyl-2-propen-1-one) is a precursor of flavonoids in plants (Ferrer et al. 2008; Verhoeyen et al. 2002).

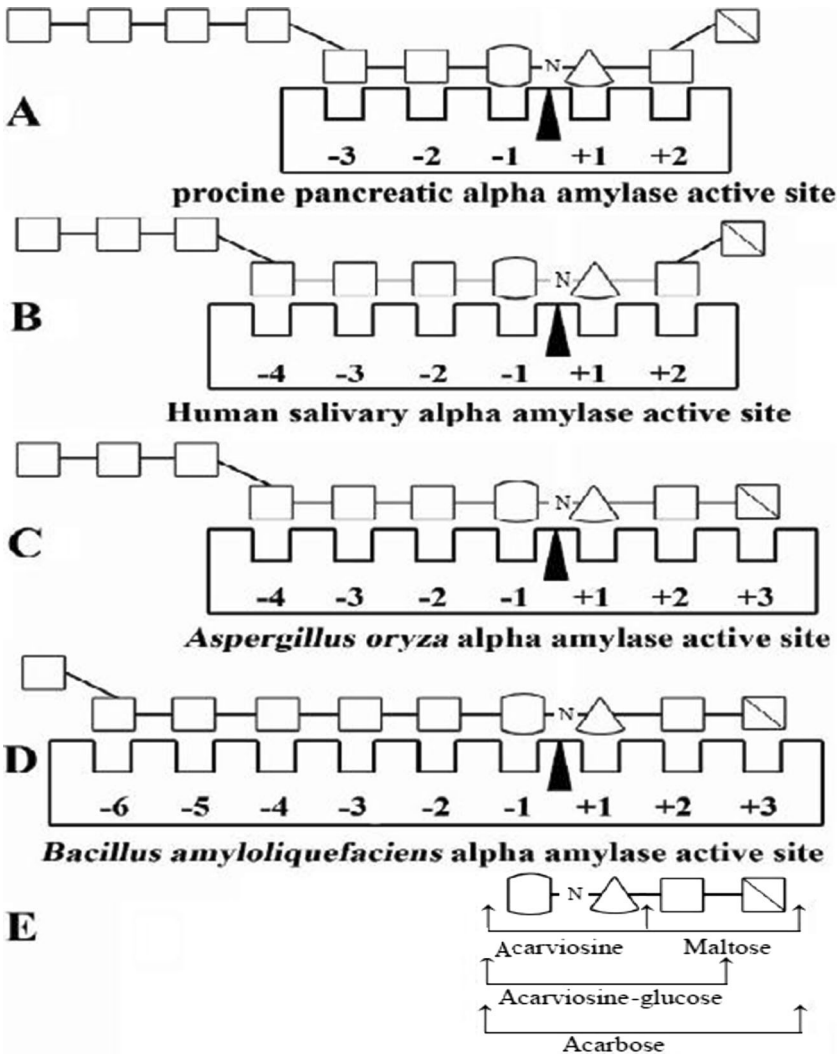

Fig. 3 D-Glucose-binding subsites of PPA, HAS, AOA, and BAA α-amylases (**a**, **b**, **c**, and **d**, respectively) and their inhibited complexes with G6-Aca. The nitrogen atom of acarviosine unit of acarbose is specifically bound at the catalytic sites that are bound to the +1 and −1 subsites. E is the structure of acarbose and part of acarviosine

This compound is found to be effective in the micromolar range. A reversible partial inhibitory effect toward PPA is observed for transchalcone, with an IC_{50} of96.44 μM. To determine the type of inhibition, plot 1/V against 1/[S] shows that chalcone is a competitive inhibitor for PPA. It is distincted with Dixon plot that K_i of chalcone for PPA is 48.0 μM (Najafian et al. 2011a, b).

This compound is also effective in vivo. Rats with streptozotocin-induced diabetes (Tormo et al. 2004), considered usually as a model of type 1 diabetes mellitus, and normal rats are treated with four doses of this compound (2, 8, 16, and 32 mg/kg body weight). Orally for 24 days, this experiment is done which show actual benefit in lowering serum glucose, lipid levels, and α-amylase activity in serum (Najafian et al. 2010).

As a known consequence of both type 1 and type 2 diabetic patients (Lawrence et al. 2008), the body weight in the diabetic control group is significantly reduced in comparison with the nondiabetic control group (206.3±13.1 vs. 245.1± 15.8, $P<0.01$). Treated with chalcone, a dose-dependent body weight loss is observed in both diabetic and nondiabetic rats. In this regard, the therapeutic potential of a compound that is able to lower glucose levels while also inducing weight loss would be interesting. This effect of chalcone can be related to its α-amylase inhibitory property (Najafian et al. 2010).

Substitution on A-ring of chalcones derived from 3,4-methylenedioxybenzaldehyde and the substituted acetophenone gives derivatives with anti-hyperglycemic activity. It is showed that substitution of both electron donor groups such as methoxy and electron acceptor groups such as nitro group in A-ring of chalcone increases the anti-hyperglycemic effects of chalcone (Alberton et al. 2008; Satyanarayana et al. 2004).

Tannin is a potent inhibitor for HSA. Kinetic analysis shows that tannin is a mixed noncompetitive inhibitor for HSA and one molecule of tannin binds to the active site of enzyme. Kinetic constants such as K_{EI} and K_{ESI} show that tannin is as an effective inhibitor of HSA as acarbose and indicates a higher stability of the enzyme-inhibitor complex (EI) (K_{EI}=9.03 μg L^{-1}) than enzyme-substrate-inhibitor

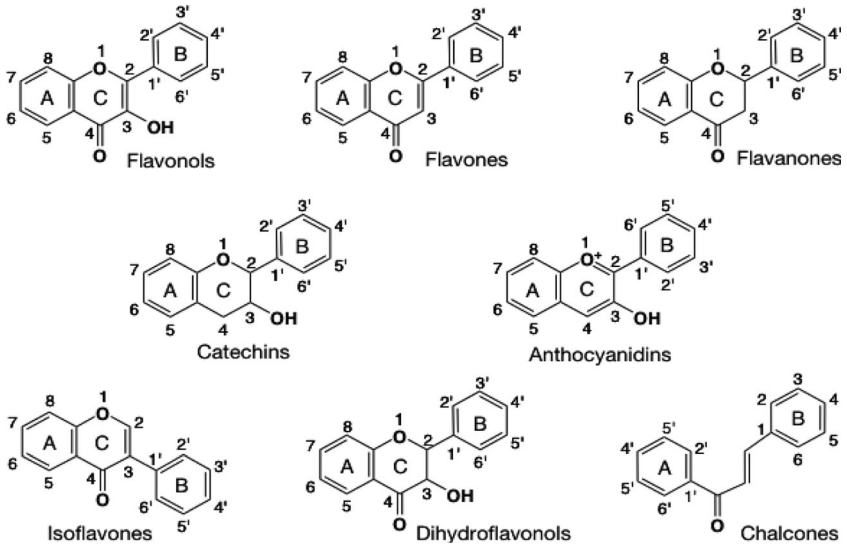

Fig. 4 Eight backbone structures of the different classes of flavonoids. All of the major classes of flavonoids are comprised of three six-membered rings: an aromatic A-ring fused to a heterocyclic C-ring that is attached through a single carbon-carbon bond to an aromatic B-ring. Backbone structural differences occur primarily at the C-ring

complex (ESI) (K_{EI}=47.84 μg L^{-1}) (Kandra et al. 2004). Many flavonoids are tested for inhibitory activities against α-amylase. Luteolin, amentoflavone, luteolin 7-*O*-glucoside, and daidzein are the strongest inhibitors among the compounds tested. These compounds may be used effectively to control postprandial hyperglycemia in patients with type 2 diabetes (Paloma et al. 2012). In a recent report on HPA, myricetin has been found to be a competitive inhibitor for the enzyme (Tarling et al. 2008).

Plant α-amylase inhibitors

Synthetic hypoglycemic agents can produce serious side effects and are not suitable to be used during pregnancy. It is estimated that more than 200 species of plants exhibit hypoglycemic properties, including many common plants, such as pumpkin, wheat, celery, wax gourd, lotus root, and bitter melon (Jia et al. 2003). Polyphenolic compounds are widely distributed in plants. Polyphenol-rich extracts are effective inhibitors of α-amylase with the ability to lower postprandial blood glucose level and can be used in the supplementary treatment of diabetes. Important constituents for the inhibitory activity against α-amylase are mainly polyphenolic compounds. These compounds are extracted from leaves of blueberry, tamarind, lemon balm, rosemary, green tea, the hulls from white kidney beans, and many other plants (Kusano et al. 2008; Melzig and Funke 2007). Plant extracts such as cinnamon and *Angelica keiskei* have chalcone derivatives which are used as medicine for glycemic control in diabetes. Chalcone derivatives with inhibition of α-amylase reduce serum glucose levels (Alberton et al. 2008; Sirichai et al. 2011; Ogawa et al. 2005; Ogawa et al. 2007).

There are two types of cinnamon, *Cinnamomum verum* and *Cinnamomum cassia. Cinnamomum cassia* contains biological active substances that have demonstrated insulin mimetic properties. Chalcone derivatives exert their hypoglycemic effect by increasing glucose uptake in adipocytes, promoting glycogen synthesis, and inhibiting α-amylase (Anderson et al. 2004; Jarvill-Taylor et al. 2001; Tackett and Jones 2009).

In a study, the effects of many plants were examined on diabetes. The aim of this study was the screening for α-amylase inhibition of plants that traditionally are being used in anti-diabetic treatment in Europe or Africa. The anti-diabetic potency of these plants is defined by the inhibition of α-amylase activity (Funke and Melzig 2006). This study demonstrates that several plants are able to influence α-amylase activity. The inhibition rates of the tested plants are different. Plant materials were obtained from leaves, barks, roots, and seeds. Plants are usually prepared as decoction. Extraction of plant materials was obtained with boiling water or buffer solution. These plant materials have polyphenolic compounds. A blood-sugar-lowering effect of some of the tested plants has been shown in animal tests (Funke and Melzig 2006; Funke and Melzig 2005; Neuwinger 2004). The extract of the leaves of *Tamarindus indica* and *Vaccinium myrtillus* leads to a 90 % inhibition of α-amylase. The extract of *Balanites aegyptiaca* (bark), *Camellia sinensis* (leaves), *Khaya senegalensis* (bark), *Mitragyna inermis* (leaves), and *Rosmarinus officinalis* (leaves) induced an inhibition of 75 %. The extract of the root of *Securidaca longepedunculata* induced an inhibition of 45 %. The extract of *Salvia officinalis* (leaves) and *Trigonella foenum-graecum* (seeds) induced an inhibition less than 20 % (Funke and Melzig 2006; Yeh et al. 2003).

Extracts of many Malaysian plants used in diabetes treatment are examined for α-amylase inhibitory effect using an in vitro model. The studies show that hexane and dichloromethane extracts of *Anacardium occidentale*, *Lagerstroemia speciosa*, *Averrhoa bilimbi*, *Pithecellobium jiringa*, *Parkia speciosa*, and *Phyllanthus amarus* have α-amylase inhibitory

effect. Extraction and fractionation of *Phyllanthus amarus* hexane extract lead to isolation of dotriacontanyl docosanoate, triacontanol, and a mixture of oleanolic acid and ursolic acid. All compounds are tested and show that mixture of oleanolic acid and ursolic acid (2:1) is a potent α-amylase inhibitor with IC_{50}=4.41 μM. Furthermore, the studies show that pure pentacyclic triterpenoids, oleanolic acid, ursolic acid, and lupeol have inhibitory effect on α-amylase (Ali et al. 2006).

α-Amylase treated with ginger extract can react with cooked rice, and the percentage of glucose content is measured. The α-amylase activities on the rice inhibited by addition of ginger cause significant reduction in glucose percentage (49.04±0.65 to 35.35±2.22, P<0.05). This study shows that ginger is a potent inhibitor for α-amylase (Abeysekara et al. 2007). Amaranth is an annual plant with about 100-cm height. The *Amaranthus* plants are able to produce grains and leafy edible vegetables. Nutritionally, amaranth grain has higher levels of protein than common cereal grains and has potential beneficial use as a therapeutic adjunct in diets for hypercholesterolemic susceptible individuals (Plate and Areas 2002).

The grain amaranth is used as an anti-hyperglycemia agent. In a study, we investigated the biological properties, antioxidant and anti-diabetic, of two varieties of *Amaranthus caudatus* seeds, Oscar blanco and Victor red, and oil, squalene, and phenolic contents were also determined. Seeds of both investigated varieties were found to possess very different levels of squalene (2.2 % in Oscar blanco variety and 7.5 % in Victor red variety). Methanolic extracts of Oscar blanco and Victor red in 25 mg/mL via inhibition of α-amylase (50.5 and 28.0 %, respectively) reduced the high postprandial blood glucose peaks in diabetic patients. In this study, an α-amylase inhibition in vitro model was used to screen the extracts of both *Amaranthus caudatus* varieties to evaluate their potential hypoglycemic effects. This study showed that the same as in vivo test (diabetic patient), these extracts were inhibited the α-amylase activity (Conforti et al. 2005).

White kidney bean extract for α-amylase inhibitory effect has been examined. It was found to be a potent in vitro amylase inhibitor. This extract in normoglycemic subjects and diabetic patients reduced plasma glucose level. An in vitro test showed that the extract significantly decreased weight gain and food intake in normal animals after 3 weeks and significantly decreased food intake, water intake, and body weight gain in the diabetic animals (Vinson et al. 2009). α-Amylase inhibitor of the cereal family is composed of 120–160 amino acid residues forming five disulfide bonds. Extract of wheat (*Triticum aestivum* var. *zarrin*) was examined for α-amylase inhibitory effect. This study showed that the extract was isolated from *zarrin* wheat grains inhibited HSA and *Bacillus subtilis* α-amylase 97.07 and 89.97 %, respectively. High inhibitory activities of this inhibitor against HSA are a potential agent in prevention and therapy of obesity and diabetes (Heidari et al. 2005).

Rosmarinic acid (á-*o*-caffeoyl-3,4-dihydroxyphenyllactic acid; RA) is a diphenolic compound common to many species of herbs and spices, particularly in the families of *Boraginaceae* and *Lamiaceae*. RA is regarded as a potential pharmaceutical plant (Exarchou et al. 2002; Anitha et al. 2012). Herbs, many of which that contain RA as the dominant phenolic constituent, have long been used in traditional medicines (Javanmardi et al. 2002; Maroo et al. 2002). Various RA-containing extracts from the leaves of herbs and spices have been reported to possess antioxidant, anti-mutagenic, anti-tumorigenic, anti-HIV, anti-proliferative, anti-cyclooxygenase, and anti-diabetic properties (Amessis and Madani 2014; Huang et al. 2014). The effect of RA extracts from lemon balm and oregano on porcine pancreatic α-amylase compared to pure (97 %) RA was examined. This study showed that amylase inhibition by the RA extracts correlates with the concentration of RA present in the extracts. The influence of different concentrations (97, 50, and 7 %) of RA in the herbal extracts on the reaction was investigated. Pure (97 %) RA inhibited amylase activity by 85 % and lemon balm-based extract with 50 % RA inhibited amylase activity by 50 %, while oregano-based extract with 7 % RA inhibited amylase activity by 42 % (Mc Cue and Shetty 2004). In a study, a purified pancreatic α-amylase inhibitor (α-AI) from white beans (*Phaseolus vulgaris*) was administered orally (100 mg/kg body weight dissolved in 9 g NaCl/L) for 22 days to nondiabetic and diabetic rats. When treated with α-AI, body weight loss was observed in both diabetic and nondiabetic rats. This extract in diabetic and nondiabetic rats reduced plasma glucose level, water, and food intake and and serum activity of α-amylase (Tormo et al. 2006).

This study investigated the inhibitory effect of *Costus pictus* leaves extract on α-amylase from porcine pancreas. It is used for the treatment of diabetes in southern parts of India. In vitro studies in aqueous, methanol, ethyl acetate, and ethanolic extract of *Coctus pictus* revealed good inhibitory effects on α-amylase. Among the four extracts studied, aqueous extract showed maximum α-amylase inhibitory effect of about 84.16 %, whereas methanolic extract showed 82.23 %, ethanolic extract showed 80.12 %, and ethyl acetate showed 78.14 % of inhibition at a concentration of 100 mg/mL. The results obtained reveal that this plant may be considered as a potential candidate in the treatment of diabetes (Jayasri et al. 2009).

Andrographis paniculata is a traditional medicinal plant common in southeast. *Andrographis paniculata* contains andrographolide as the major active principle and also others like 14-deoxy-11,12-didehydroandrographolide and 14-deoxyandrographolide. *Andrographis paniculata* extract has anti-cancer, anti-angiogenic, antioxidant, and anti-hyperglycemic effects (Ajaya Kumar et al. 2004; Sheeja

et al. 2007; Yu et al. 2003). In a study, the effect of *Andrographis paniculata* extract on in vitro activity of α-glucosidase and α-amylase was investigated as well as in vivo effect on plasma glucose levels in normal and streptozotocin-induced diabetic rats. The in vitro experiment showed that *Andrographis paniculata* extract showed an appreciable α-glucosidase inhibitory effect in a concentration-dependent manner (IC_{50}=17.2±0.15 mg/mL) and a weak α-amylase inhibitory activity (IC_{50}=50.9±0.17 mg/mL). Andrographolide showed a similar (IC_{50}=11.0±0.28 mg/mL) α-glucosidase and α-amylase inhibitory activity (IC_{50}=11.3±0.29 mg/mL). Part of in vivo experiment showed that *Andrographis paniculata* extract significantly (P<0.05) reduced peak of postprandial blood glucose. This results obtained reveals that *Andrographis paniculata* extract may be considered as a potential candidate for the treatment of postprandial of blood glucose (Subramanian et al. 2008).

Citral (3,7-dimethylocta-2,6-dienal) is present in a variety of plants essential oil, especially in *Backhousia citriodora* (lemon myrtle) oil. It is used as food additive and fragrance and has anti-bacterial, anti-fungal and anti-cancer properties (Mesa-Arango et al. 2009; Somolinos et al. 2010)

In a study, its inhibitory effect toward PPA was investigated. This compound was found to be effective in the micromolar range (IC_{50}=120 μM). This compound was also effective in vivo. Rats with streptozotocin-induced diabetes and normal rats were treated with four doses of this compound (2, 8, 16, and 32 mg/kg body weight) orally for 24 days, which showed actual benefit in lowering serum glucose, lipid levels, and α-amylase activity in serum. When treated with citral, a dose-dependent body weight loss was observed in both diabetic and nondiabetic rats (Najafian et al. 2011a, b).

Discussion

Diabetes and obesity are two of the most common problems among human societies (Melanie and Diana 2012; Najafian et al. 2012). One of the most current methods for prevention of these diseases is reduction of caloric intake through decreasing of the food digestion and absorption. Carbohydrates were digested with many enzymes such as amylase that breaks glucose polymer such as starch to low-molecular-weight maltodextrins, such as maltose, maltotriose, and maltotetraose, lactase that hydrolyzes lactose to glucose and galactose, and sucrase hydrolyzes sucrose to glucose and fructose (Moran et al. 2011; Yoon et al. 2007). Since carbohydrate is one of the major parts of human diet, we tried to review on α-amylase inhibitors. α-Amylase is able to hydrolyze carbohydrates such as starch. By α-amylase inhibition in diabetics, lowering blood sugar levels can cause to weight reduction in obese individuals. The studies on α-amylase inhibitors have been done on the broad range of research. In a research for reducing of the amount of digestible carbohydrates and low blood sugar, the idea has been to use carbohydrates with low GI. For this purpose, resistance starch should be used which must be prepared either synthetically or extracted and added to food (Radulian et al. 2009). We have to consider whether it is difficult or even impossible to prepare this type of food permanently. On the other hand, these foods are manipulated and maybe have some side effects in a long time. In respect to the structure of enzyme and recognizing its active site, the researchers have tried to reduce the enzyme activity or inactivate it by manipulation of amino acids in active site. One method that seems to be useful for producing inactive enzyme is genetic manipulation of the HPA-producing genes including AMY2A and AMY2 and producing of inactive enzyme. This is due to being irreversible of the enzyme and the lack of complete digestion of starch material is not impossible in human samples. So, using the amylase inhibitors can be used as an appropriate method in reducing blood sugar level.

Although the use of α-amylase inhibitors by preventing of degradation of polysaccharides and by the accumulation of undigested starch in the colon is causing symptoms such as flatulence, diarrhea, nausea, meteorism, and abdominal pain (Baotic et al. 2000), it can be a reasonable approach in reducing the rate of carbohydrate digestion and decrease of blood sugar.

Amylase inhibitors either synthetic or derived from plant are generally categorized in three groups including pseudosaccharides, proteinaceous, and polyphenolic inhibitors. Among these three categories, some symptoms including dermatitis and sensitivity have been reported (Heidari et al. 2005). For α-amylase inhibitors, pseudosaccharides like acarbose and its derivatives, G6-Aca and G12-Aca with low K_i are useful and appropriate inhibitors. Inhibitory effect of polyphenolic compounds has been studied in a wide range. These compounds are very varied and diverse in shape and molecular structure and exist in different amounts in various fruits, vegetables, and plant products.

A major group of polyphenolic compounds is flavonoids, in which many lines of research have been done about their inhibition effects. Most of them have strong inhibitory effect on enzymes and can be utilized as a base designation of inhibitory drugs. It seems that the number of OH and other functional groups has different effects on flavonoid structures. So, by adding different numbers of OH, NO_2, Cl^-, CH_3, and other functional groups to different sites of molecule, we can evaluate the inhibitory effects of new compounds and design some inhibitors with higher inhibitory power. With this approach, by application of lower dose of drugs, the blood sugar levels will be reduced. Since α-amylase synthesis inhibitors can cause serious side effects, so it is better to emphasize much greater on the use of plant inhibitors. Most plant-

derived compounds have fewer side effects than synthetic compounds. It seems that using fruits and vegetables naturally, which have polyphenolic compounds especially flavonoids, can inhibit α-amylase, which are the best and most useful substances to lower the blood sugar. In conclusion, inhibition of α-amylase is a successful manner in the prevention and therapy of obesity and diabetes. Traditional medicines, including herbal medicine, possess great potential in this regard (Hasani-Ranjbar et al. 2009; Najm and Lie 2010). A better method than alternative one to inhibit α-amylase is using amylase inhibitors in reducing blood sugar.

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