International Journal for Pharmaceutical Research Scholars (IJPRS)

V-5, I-3, 2016 ISSN No: 2277 - 7873

REVIEW ARTICLE

State of the Art and Clinical Perspective of Alpha Glucosidase Inhibitors: A Review

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Manuscript No: IJPRS/V5/I3/00137, Received On: 24/09/2016, Accepted On: 02/10/2016

ABSTRACT

Diabetes is a chronic metabolic disorder caused by an absolute or relative lack of insulin production, and sensitivity. The total number of people with diabetes for all group of age is is about 171 million in 2000. Tipe 1 DM was projected with weight loss, polyurea, polydipsia, polyphagia, constipation fatigue, cramps, blurred vision and Long lasting type 1 DM patients may susceptible to microvascular complications; and macrovascular disease (coronary artery, heart, and peripheral vascular diseases). In tipe 2 DM, there are a high risk of large vessel atherosclerosis commonly associated with hypertension, hyperlipidemia and obesity. Most patients with type 2 diabetes die from cardiovascular complications and end stage renal disease. In this review, an attempt was made to present a current scenario of the bioactive compounds from plant origin that have been investigated for their alpha glucosidase inhibition. Alpha glucosidase is an enzyme which involved on the carbohydrate metabolism and absorption that influence postprandial blood glucose which was the target in the diabetes treatment. Compounds belonging to various classes of natural products such as flavonoids, steroids, and triterpen are well studied be the most active compound against the alpha glucosidase enzyme. Eventhough research on the finding of potential alpha glucosidase inhibitor has been done, there is still few compounds which entered the clinical studies and just a few molecule has been marketed after acarbose and miglitol. By HTS based screening, structure-activity relationship investigation on semi-synthetic and synthetic derivatives might also provide a direction for the development of alpha glucosidase leads component in order to treat and/or prevent diabetes.

KEYWORDS

Alpha Glucosidase, Acarbose, Obesity, Natural Products, Clinical Perspective

INTRODUCTION

Recent study meet diabetes as the most common non-communicable diseases worldwide.[1] It is the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence that it is epidemic in many low- and middle-income countries. Complications from diabetes, such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness are resulting in increasing disability, reduced life expectancy and enormous health costs for virtually every society. Diabetes is certain to be one of the most challenging health problems in the 21st century[2].

Worldwide, the prevalence of diabetes is moving rapidly and the World Health Organization (2003) has predicted that by 2030 the number of adults with diabetes would have almost doubled worldwide, from 177 million in 2000 to 370 million. There are two main types of diabetes mellitus: type 1 diabetes, also called insulin dependent diabetes mellitus (IDDM), is a

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chronic autoimmune disease resulting the selective destruction of insulin producing β-cells of the pancreas and type 2 diabetes, also called non-insulin dependent diabetes mellitus (NIDDM), is caused by decreased sensitivity of target tissues to insulin. Based on the report of American Diabetes Association (2001), type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people globally, while Type 2 diabetes is the most common form of diabetes and accounts for at least 90% of all cases of diabetes mellitus. Type 2 diabetes is a heterogenous disorder caused by a combination of genetic factors related to decrease insulin secretion, insulin resistance and environmental factors such as obesity, over eating, lack of exercise, aging and stress[3].

Diagnosis of both types of diabetes can be done using random plasma test. It is the simplest test and doesn't require fasting before taking the test. If the value 200 or more than 200 mg/dl of blood glucose it probably indicates diabetes but has to be reconfirmed. Beside that diagnose also being conduted based on fasting plasma glucose test. In this test,one should be eight hours fasting before taking this test. Blood glucose more than 126 mg/dl on two or more tests conducted on different days confirms a diabetes diagnosis[2].

The goal of diabetes therapy are controlling normal glucose level (prevent hyperglicemia) to avoid later complication, intensive therapy for associated cardiovascular risk factors and improving quality of life. The first line therapy for type 2 diabetes treatment is diet, wieght control and physical exercise. If Blood glucose remains high despite this lifestyle treatment, drugs could be advised. There are several catagories for type 2 diabetes includes sulfonylureas, biguanides, thiazolindindiones, DPPIV inhibitors and alpha glucosidase inhibitors[4].

Currently Available Anti-Diabetic Drug

Glimepiride

Glimepirid is one of the new scretagogues sulphonylurea antidiabetic drugs. It works by attached to 65 kd protein. To be compared with glibenclamide, glimepiride has three fold faster rate of association and nine fold faster rate of dissociation and has rapid onset and prolonged duration of action, so it can be used once daily. Its initial action is stimulating insulin secretion and also has insulin mimetic effect in peripheral tissues possibly mediated by GLUT-4 recruitment. It has a lower hyperinsulinaemia stimulating effect because of its extrapancreatic effect. Glimepirid prevents post-exercise release of insulin, so that it decrease the hypoglycaemia risk. Compared to the other sulfonilurea, it has low risk of coronary vasoconstriction and adverse cardiovascular events[5].

Insulin Sensitisers

The insulin sensitiser increase the peripheral tissues sensitivity to insulin without stimulate the release of insulin from pancrease. This mechanisme is important in the management of Tipe 2 diabetes that experiencing metabolic 'syndrome' of associated obesity, hypertension, and dyslipidaemia[5].

Biguanides

Found in 1958, biguanides are known to be suitable for tipe 2 management because it significantly counteract insulin resistance. One of the examples is metformin, which has a significant glycaemic control capacity, lipid profile, and with no notable increase in plasma lactate, serum insulin, weight gain, and frequency of hypoglycaemia have been observed with this group of drugs . Its major modes of action include (a) inhibition of gluconeogensis, (2) reduction of hepatic glucose output, (3) They reduce bodyweight thereby improve the sensitivity of insulin[5].

Thiazolidinediones

The PPAR(γ) agonists (ciglitazone, pioglitazone, englitazone, troglitazone, and rosiglitazone) are working by decrease the formation of glucose in the liver and increase the utilisation of peripheral glucose by improving insulin sensitivity at hepatic and muscle sites. They decrease glycogenolysis to restore the sensitivity of phosphophenol pyruvate carboxy kinase

(PEPCK) to insulin and also increase peripheral triglyceride clearance and decrease the sythesis of hepatic triglyceride. At the cellular level, they increase tyrosine kinase activity and binding of insulin receptors and enhance insulin induced of GLUT-4 translocation on to the plasma membranes. All these effects are dependent on insulin[5].

Inhibitors of Intermediary Metabolism

Glucose and fatty acid cycle metabolisme in muscle has been desired for a long time. Glucose uptake and utilization decease when fatty acids oxydation reduced because of substrate competition. It can result resistence of insulin receptor. In type 2 diabetes, hepatic glucose output is responsible for fasting hyperglycaemia, drugs which are decreased level of fatty acids and it oxidation are a good relevant alternative for controlling fasting hyperglycaemia. In this class of action includes acipimox and bezafibrate (as dug decreasing fatty acids), and also Lysofillin as short acting inhibitors of long chain fatty acids oxidation[5].

Inhibitors of Gastro-Intestinal Glucose Absorption

Alpha Glucosidase Inhibitors

Acarbose is one of the examples of this class of drugs that act by competitively inhibit the glucosidases at the small intestinal brush border, which responsible for breakdown of complex polysaccharides (Starches) and sucrose into glucose so that decrease the postprandial glycaemia. The average decrease in post prandial blood glucose during acarbose treatment in diet treated type 2 diabetic patients was 3 mmol/1 and maximal decrease in HbA1C was 1%. Acarbose is recommended thrice daily in doses of 50-200 mg with the first bite of each major meal. Side effects, which include flatulence, cramp, and diarrhoea. The newer-glucosidase inhibitor is Miglitol derived from 1-deoxy nojirimycin and has similar structure to glucose. It is almost completely absorbed from GI tract, is short acting and hence is expected to have less GI side effects than acarbose with usual dose is 50-100 mg daily[5].

Vanadium salts (vanadyle orthovandate, metavandate and peroxovandate)

Vanadium (insulinomimetic drugs) is an ultra trace element. It has an insulinomimetic actiion on adipocytes, hepatocytes, and the skeletal muscles as well as in hyperinsulinaemic and hypoinsulinaemic animal models of the diabetes. The most common side effects are gastrointestinal and possibly has mitogenic risk, as it stimulates tyrosine kinase[5].

α-Glucosidase in Carbohydrate Digestion and Absorption

In the carbohydrate homeostasis (absorption, metabolism, transfer, storage, deposition, and oxydation), there was a variety tipe of enzyme being the target in treating some desease. Dietary carbohydrates are build up with some saccarides structure which undergo a complex series of biochemical reactions before being absorbed in the gastrointestinal tract. Oligosaccaride in starch is being attached to α-glucosidase enzyme at the surface of microvillus of the intestine wall **(1)**, then it catalyzes the hydrolysis of 1,4-α-glucosidic bonds within carbohydrates with release of α-glucose , glucoses are then delivered by blood to targeted cells throughout the body and promotes the increase of blood glucose levels after meal.[6]

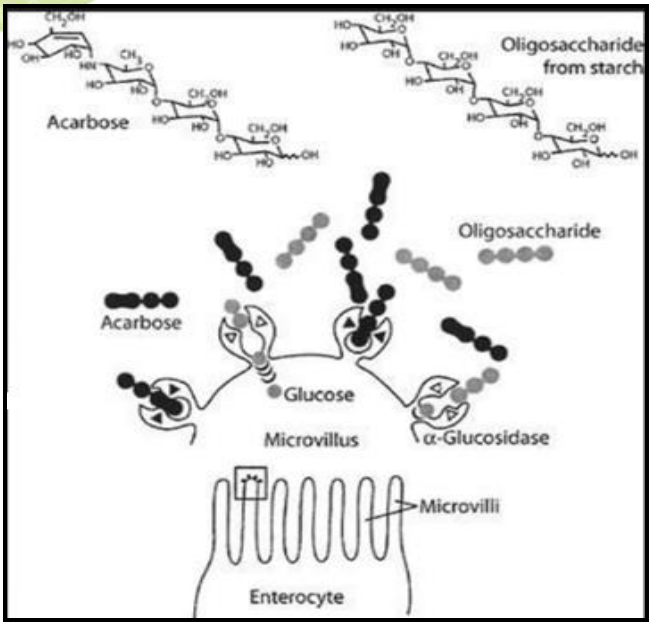


Figure 1: Pathway of Alpha Glucosidase

Approaches Towards Alpha-Glucosidase Inhibition

Glucosidases are the enzymes located in the intestinal brush-border surface of small intestinal cells that catalyze the cleavage of glycosidic bonds in oligosaccharides. Alpha Glucosidase leads to high production in the body. Hence, by targeting this enzyme and identifying its inhibitors, excess glucose production can be controlled by retard carbohydrate digestion and absorption so that slowing the sharp rise in blood sugar levels that diabetic patients typically experience after meals. These can lead to the better control of blood glucose that was the goal of diabetes treatment specially for tipe 2 diabetes[6].

For solving that problems, α-glucosidase inhibitors, such as acarbose and voglibose, are clinically used as oral antihyperglycemic agents. They are tetrasaccharide synthesized by Actinomyces that has been reported to blunt postprandial rise in plasma glucose. However, they often cause severe gastrointestinal side effects such as flatulence and diarrhea. Therefore, research for new α-glucosidase inhibitors from natural resources has become an attractive approach for the treatment of postprandial hyperglycemia. Research has been developed to gain the α-glucosidase inhibitors with molecular weights below 250, which can be absorbed appreciably from the gut into the bloodstream and arousing great interest as antidiabetic agents. Therefore, present study was targeted towards the identification of low molecular weight α-glucosidase inhibitor from medicinal plants and their hypoglycemic activity[7].

Phytochemicals as Source of Alpha Glucosidase Inhibiitors

Various extracs and their phytochemical content have been searched out for their alpha glucosidase inhibitory activity in the term to get new potential antidiabetic agents from natural resources. These are some phytochemical classes as follows :

Flavonoids

Two pure flavonoids compound isolated from Azuki beans (*Vigna angularis)*, they are vitexin (**2**) and isovitexin (**3**) showed high inhibitory activities against alpha glucosidase enzyme with the IC_{50} values of 0.4 mg/ml and 4.8 mg/ml respectively[8]. Beside that, three flavonoid glycosides from the methanol extract of Microctis Folium have been investigated to thier α-glucosidase inhibitory effects and found to have satisfied result. They are vitexin (**2**), isovitexin (**3**), and isorhamnetin 3-O-β-D-rutinoside (**4**) with IC_{50} values of 244.0 µM, 266.2 µM and 275.4 µM, respectively[9].

Experiments have been also carried out to evaluate the bioactive antidiabetic compounds from red sweet pepper (*Capsicum annuum*) and resulted about 4 bioactive compound. They are capsaicinoids, quercetin (**5**), myricetin (**6**), and luteolin (**7**). Beside that compound, capsiate has been found to has a greater antidiabetic action than capsaicin. Capsiate could enhance insulin sensitivity during euglycemic hiperinsulinemia clamp, reduce release of glucose from hepar, and increase the storage of glycogen. The IC_{50} values of quercetin, myricetin, and luteolin were 1.59, 2.12, and 6 µg/mL, respectively. Compare with acarbose 36 µg/mL[10].

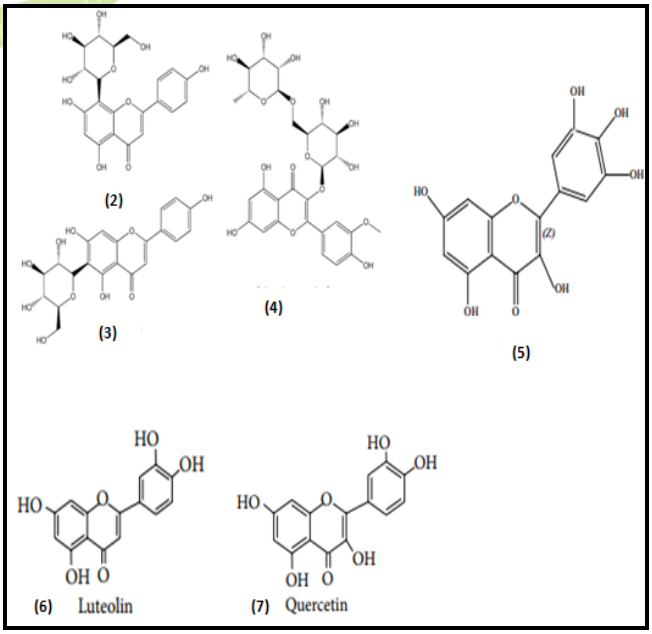
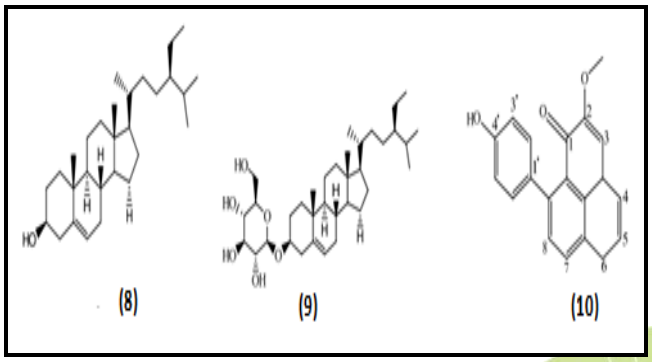


Figure 2: Chemical Structure of flavonoid glycosides

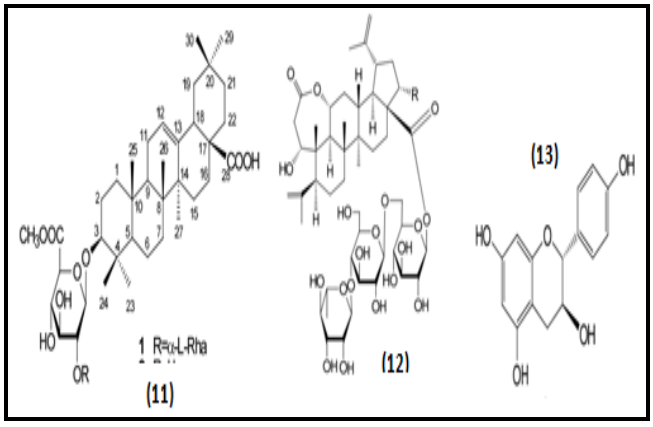
Steroids

Three compounds were isolated from banana flowers projected potential α-glucosidase Inhibitory activity. They are β-sitosterol **(8)**, ducosterol **(9)** and 9-(4-hydroxyphenyl)-2-methoxyphenalen-1-one **(10)** which have excelent activity to inhibit α-glucosidase with the IC_{50} values of 283.67, 247.35 and 3.86 mg/L, respectively[11].



Triterpenoids

Studies have been done to Acanthopanax senticosus (Rupr. Maxim) Harms. In vivo study to the 30% EtOH fraction of A. Senticosus leaves showed inhibition of plasma glucose levels of the alloxan-induced rats and show significant α-glucosidase inhibition activity. Three active compounds have been isolated and showed inhibitory activities against α-glucosidase, they are 3-O-[(α-L-Rhamnopyranosyl)(1→2)]-[β-D-glucuronopyranosyl-6-O-methyl ester]-olean-12-ene-28-olic acid **(11)**, 22α-hydroxychiisanoside **(12)** and (+)-afzelechin **(13)** with IC_{50}values of 186.0 µM, 908.5 µM and 819.7 µM, respectively[12].



CONCLUSION

Materials from plant has become resources for the development of novel types of medicine. However, no compound was being use clinically yet. Thus, It is a big challange for newer chemical compound from the natural resources to be developed as new anti-diabetic drugs. Natural compounds and phytomolecules used in daily life have an advantage of biological friendliness and safety. Some natural product report, particularly flavonoids, terpenoids, glycosides and steroids have already shown alpha glucosidase inhibitory activity. Although, research is continually going on in the development of alpha glucosidase inhibitors from nature, but has not reached the clinical use. To raise up the number of substances from the natural product libraries for alpha glucosidase inhibition, there is a need to develop a high throughput screening (HTS) protocol. Application of more current and recent approach such as structure-activity relationship, in silico studies, metabolomics, and system biology should be performed and highly desirable. Beside that, improvement in the bioavailability of natural products is also needed for better drug development. Thus, natural product inspired molecules might provide a potential substance or pharmacophore for further development.

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