MiniReview

Diabetes Management through α-Glucosidase Inhibitors Challenges and Current Perspectives

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Abstract
Type 2 diabetes mellitus (T2DM) known as non-insulin dependent diabetes mellitus, is a chronic metabolic disorder caused by insulin deficiency or insulin resistance. The incidence of T2DM is increasing day by day. According to data from World Health Organization (WHO), the number of diabetic patients is expected to rise up to 642 million by 2040. This alarming situation needs proper treatment to control diabetes. Physicians mostly prescribe insulin based medications, but in this new medical era, α-glucosidase inhibitors (AGIs) based drug therapy possess tremendous preventive and potential inhibitory effect upon the over expression of the enzyme which digests the carbohydrate macromolecules and breaks down into single chain monomeric α-glucose units. As a result, carbohydrate breaks down gradually decreases, which slowing down the absorption of post prandial glucose PPG, regulating the blood glucose level. This review article addresses about the management of T2DM through AGIs along with new potential leads from natural products in the pipeline of new AGI drugs development from synthetic and natural origin.

Keywords: type 2 diabetes mellitus, α-glucosidase inhibitors, post prandial glucose, acarbose, metformin, voglibose, miglitol

1 INTRODUCTION
Diabetes is a common metabolic disease characterized by abnormally elevated plasma glucose levels, leading to major complications such as diabetic neuropathy, retinopathy, and cardiovascular diseases. The best treatment is to use non-insulin based drugs, such as α-glucosidase inhibitors (AGIs) which have been widely using in clinical practices since more than 117 countries of the world and
possess a better preventive effect than other insulin based therapies\cite{1}. There are several drug therapies available for the management of diabetes. The specific medications prescribed depend on the type of diabetes, individual needs, and other factors determined by a healthcare professional. Here are some commonly used drug therapies for diabetes management:

(1) Insulin: Insulin is a hormone administered through injections or insulin pumps, helping to regulate blood sugar levels. It is commonly used in the treatment of type 1 diabetes and may also be prescribed for type 2 diabetes when other medications are not sufficient.

(2) Oral Medications: There are various classes of oral medications used to manage type 2 diabetes. These medications work in different ways to control the blood sugar levels. Including AGIs (acarbose, voglibose & miglitol) metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists.

(3) Combination Therapy: In some cases, multiple medications may be prescribed in combination to achieve better blood sugar control. For example, a healthcare professional may prescribe a combination of oral medications or oral medications and insulin, along with lifestyle modification through diabetes nutrition plan and proper physical activity for instance, 30-45min daily walk plan at least 5 days in a week.

2 α-Glucosidase ENZYME
2.1 Location and Mechanism of Action of the Enzyme

α-glucosidase is a calcium containing microvilli intestinal enzyme located in the brush border like cells of intestine. It is responsible for metabolizing complex carbohydrate into simpler forms (monosaccharides), which are then absorbed in small intestine and increase glucose level in the blood (Figure 1). However, once this enzyme over expressed, a decrease in the conversion is required of complex carbohydrate into monosaccharide by using AGIs\cite{4-7}.

2.2 α-Glucosidase Inhibitors

The AGIs are generally recommended as oral antidiabetic drugs for treating type 2 diabetes mellitus (T2DM) patients, predominantly in Asian population. This review article focuses on the management of diabetes patients by using AGIs. AGIs have preventive effects on the absorption of carbohydrates through gut, therefore decreasing the concentration of glucose level in the blood stream. Recently AGIs have been identified to significantly treating coronary microvascular disease, one of T2DM associated complication. AGIs have protective effects on pancreatic beta cells, which release insulin into the blood\cite{12-15}.

3 DIABETES MANAGEMENT THROUGH AGI DRUGS

3.1 History of AGI Drugs Discovery

Drug acarbose was first developed in Germany and was isolated from Actinoplanes. Voglibose was first developed in Japan, it was isolated from validamycin A, which is a product of Streptomyces hygroscopicusvar while miglitol is an American based invention it is a semisynthetic derivative of 1-deoxynojirimycin, obtained from Streptomyces and Bacillus spores\cite{8} (Figure 2).

3.2 Mechanism of Action of AGIs Drugs

AGIs, including Acarbose, Miglitol, and Voglibose, have been extensive studied in Japan and Europe, with acarbose and miglitol are widely used and prescribed orally in United States. They are responsible for inhibiting α-glucosidase enzyme in dose dependent manner by reducing the post prandial absorption of glucose. In old age group patients with type 2 diabetes, acarbose has the potency of increasing the insulin sensitivity and has also been shown to reverse impaired glucose tolerance towards normal glucose tolerance\cite{16}.

Acarbose is considered as one of the most popular inhibitor of α-glucosidase enzyme it can decrease the blood glucose level, along with the curable effect on cancer, metastasis and Human immunodeficiency virus, this property differentiates the acarbose from other inhibitor members of AGIs. Published survey has also been shown that microvascular complications during the consumption of AGIs are minimum. Acarbose is widely used during medical practices around the world. Beside that it has several side effects such as reduction of body weight as well as hypoglycaemia. Acarbose regulates lipid metabolism and reduce the risk of complications in cardiovascular diseases. Published survey has also been shown that the most effective medicines of non-insulin origin are metformin, miglitol, acarbose and voglibose. However Acarbose prescribe medical practices for diabetes patients in more than 117 countries while miglitol is approved in 10 countries and voglibose is approved in 3 countries. Acarbose and voglibose should be used with caution in patients with hepatic disorder. Miglitol decreases the postprandial glucose level better than acarbose and voglibose. Additionally miglitol resulted in weight loss during treatment within 4 weeks. These results show that miglitol is a preferable agent for regulation glycemic control with involving body weight loss\cite{10,11}. Safety and efficacy studies of AGIs are still under process to established in children and pregnant women (acarbose during pregnancy and in nursing woman is not recommended) while in another study Zaung et al.\cite{12} considered acarbose as a new treatment option of ulcerative colitis by increasing H2 gas production in the gastrointestinal tract. Interestingly, voglibose and miglitol did not show these effects. Mechanisms of action of AGIs, insulin, and other anti diabetic drugs can make excellent result in curing and management of diabetes\cite{13-15}.

3.3 AGIs in Combinational Therapy

AGIs can be used as the first-line drug therapy in newly diagnosed T2DM patients along with proper diet plan, exercise, and lifestyle modification, these AGIs, are...
Figure 1. The function of AGIs. A: α-Glucosidase enzyme converts carbohydrates into their simpler form of monomeric units which finally absorb in brush-like borders of small intestine and enhance the postprandial hyperglycaemic level; B: α-Glucosidase Inhibitor (AGI) inhibits the activity of α-glucosidase enzyme present in the brush-like borders of small intestine which reduces the absorption of carbohydrates and postprandial hyperglycaemic level.

Figure 2. α-Glucosidase Inhibitor Drugs. Particularly useful in newly diagnosed type 2 diabetes with excessive PPG, because of the unique mode of action to control the release of glucose from complex carbohydrates and disaccharides in a slow process. AGIs may also be used in combination with sulfonylurea drugs, insulin, metformin, GLP1RA, SGLT-2i, DPP4i for diabetes management [16].

4 ADVERSE EFFECTS ASSOCIATED WITH AGI DRUGS

Reported adverse effects of AGIs include it prevents the digestion of complex carbohydrates into simple sugars namely glucose in the intestinal region and then moves into colon. When it reaches the colon the gut
bacteria degrades the complex carbohydrates which results in flatulence in 78% of patients and diarrhoea in 14%. Generally, the side effects are mostly dose related, therefore it is recommended to start with a low dose and then gradually increase the dose to the desired amount. Few cases of hepatitis have also been reported associated with the use of acarbose, which replaced when the medicine was stopped, therefore, liver enzymes profiling should be performed before and during use. AGIs should be started at a low dose to identify the minimum dose required for patients glycemic control. If the prescribed diet is not followed, the intestinal side effects may worsen[17].

5 ACARBOSE FOR TREATING PREDIABETES CONDITIONS

Studies shows that acarbose can reduce body weight, blood glucose levels, and blood pressure as well. It also has the tendency to reduce the incidence rate of cardiovascular disease as well as diminish fasting and post prandial hypertriglyceridemia. Due to its multiple benefits, acarbose is used to manage and treat metabolic disorders and prediabetes conditions too[18-21].

6 GRAPHICAL DEPICTION OF GLOBAL PREDICTING TRENDS OF T2DM

Following graphical figures are the predicting global trends of T2DM in top 10 countries of the world, from 2010 to 2045 (Figure 3).

7 METFORMIN AS A POTENTIAL ANTI-DIABETIC AND WEIGHT REDUCING AGENT

Metformin (biguanide) is a potent anti-diabetic drug that is potentially effective to treat prediabetes, insulin resistance, polycystic ovary syndrome, and diabetes. Metformin acts directly or indirectly on the liver to decrease glucose production. It also acts on the intestine to increase glucose utilization, thus helping to reduce post prandial glucose level like AGIs. At the molecular level, metformin also increases insulin sensitivity, which increasing fat metabolism, therefore helping in weight management to achieve the desired results based on body mass index with few adverse effects. Metformin is considered as a first line medicine to treat DM, and works better than insulin by lowering down the blood glucose level in type 2 diabetes.
Metformin is alone or in combination with sulphonylurea class anti-diabetic agent along with diet and exercise is one of the best ways to keep control and managing the diabetes mellitus. Some other antihyperglycemic drugs which belongs to different classes of compounds and follow different mechanism of action, such as: (1) Biguanide (metformin), (2) Sulphonylurea (tolbutamide), (3) Glinidines (repaglinide), (4) Thiazolidinediones (pioglitazone), (5) Dipeptidyl peptidase 4 inhibitors (sitagliptin), and (6) α-glucosidase inhibitor (acarbose) [22,23].

8 AGI FROM PLANT, VEGETABLES AND DIFFERENT NATURAL ORIGINS

Potent bioactive compounds are identified from various classes of vegetables and plants, with inhibitory activities against AG enzyme. These AGIs are mostly secondary metabolites which are shown in Tables 1-3, along with their potent bioactive compounds and their Half-maximal inhibitory concentration (IC\textsubscript{50}) values respectively [23-57].

9 CONCLUSION

There are three ways to treat DM: (1) Through regular physical activities and exercise; (2) Through proper nutrition based on diet control; (3) Insulin based and non-insulin based medicinal therapy. Treatment of type 2 diabetes with the therapeutic intervention targeting α-glucosidase enzyme is an established approach that has been used for decades to treat and manage the disease. The only commercially
Table 3. Classes of Natural AGI Compounds and Their IC\textsubscript{50} Values

<table>
<thead>
<tr>
<th>Class Name</th>
<th>Potent Compound/Extract</th>
<th>IC\textsubscript{50} Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloids</td>
<td>Piperumbellactam A</td>
<td>98.07±0.44µM</td>
<td>[33,36]</td>
</tr>
<tr>
<td></td>
<td>Piperumbellactam B</td>
<td>43.80±0.56µM</td>
<td>[34,36]</td>
</tr>
<tr>
<td></td>
<td>Piperumbellactam C</td>
<td>29.64±0.46µM</td>
<td>[35,36]</td>
</tr>
<tr>
<td></td>
<td>Vasicine</td>
<td>125µM (0.8µM)</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>Quercetin</td>
<td>7µM</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>Luteolin</td>
<td>21µM</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>Cyanidin</td>
<td>4µM</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>Baicalein</td>
<td>0.26µM (0.02µM)</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td>Quercitrin (quercetin-3-O-α-L-rhamnoside)</td>
<td>~0.5mM (0.90mM)</td>
<td>[40]</td>
</tr>
<tr>
<td></td>
<td>Isoquercetin</td>
<td>64.1±3.3µM (1.50±0.14µM) Mal tase</td>
<td>41]</td>
</tr>
<tr>
<td></td>
<td>Cinnamon-diglucoside</td>
<td>14.7µg/mL</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>Pelargonidin-3-rutinoside</td>
<td>64.5µg/mL</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>Epicatechin-(4β,8)-Epicatechingallate</td>
<td>0.31µM (5.3µM)</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>Epicatechingallate</td>
<td>0.71µM (5.3µM)</td>
<td>[44]</td>
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<tr>
<td>Terpenes</td>
<td>22α-hydroxychiisanoside</td>
<td>819.7µM (788.6µM)</td>
<td>[44]</td>
</tr>
<tr>
<td></td>
<td>7β-acetoxy-6β-hydroxyroyleanone</td>
<td>108.2µM (131.2µM)</td>
<td>[45]</td>
</tr>
<tr>
<td></td>
<td>Spicatanol</td>
<td>34.1µM (23.8µM)</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>Lupeol</td>
<td>7.18µg/mL (9.68µg/mL)</td>
<td>[47]</td>
</tr>
<tr>
<td>Phenols</td>
<td>p-hydroxycinnamic acid</td>
<td>90.8µg/mL (230.4µg/mL)</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>Protocatechuic acid</td>
<td>85.1µg/mL (230.4µg/mL)</td>
<td>[48]</td>
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<td></td>
<td>Trans-N-(p-Coumaroyl)tyr amine</td>
<td>4.47µM (168.95µM)</td>
<td>[49]</td>
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<tr>
<td></td>
<td>2,4-dimethoxy-6,7-dihydroxyphenanthrene</td>
<td>0.40 mM (3.52mM)</td>
<td>[50]</td>
</tr>
<tr>
<td>Phenols</td>
<td>Ferulic acid</td>
<td>4.9mM (1.7mM)</td>
<td>[51]</td>
</tr>
<tr>
<td></td>
<td>Ellagic acid</td>
<td>18.4µg/mL</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>Umbelliferone</td>
<td>7.08µg/mL (9.68µg/mL)</td>
<td>[46]</td>
</tr>
<tr>
<td>Iminosugars</td>
<td>N-(9′-methoxynonyl)-1-deoxyojirimycin</td>
<td>0.015µM</td>
<td>[52]</td>
</tr>
<tr>
<td></td>
<td>N-(6′-4″-azido-2″-nitrophenylamino) hexyl-1-deoxyojirimycin</td>
<td>0.017µM</td>
<td>[53]</td>
</tr>
<tr>
<td>Cinnamon aldehyde</td>
<td>Cinnamon bark</td>
<td>4.810µM</td>
<td>[57]</td>
</tr>
<tr>
<td>Standard drug Acarbose</td>
<td>Cinnamon bark</td>
<td>860±0.14µM</td>
<td>[57]</td>
</tr>
</tbody>
</table>

available AGIs over the past 30 years have been acarbose, miglitol and voglibose, but these commercially available drugs still have some adverse effects, for instance, stomach disturbance, flatulence etc. Therefore, the search for new effective therapeutic methods with lower toxicity requires the development of new compounds. Phytophaphic compounds are the natural resources of bioactive compounds which can be used to develop effective anti-diabetes drugs in future. This review article shared about the antidiabetic potential of various lead molecules from plant origin, such as cinnamaldehyde, jamboline, jambosine, charantia, Quercetin, ferulic acid etc., which demonstrate efficient inhibitory potential of α-glucosidase enzyme, comparative to standard drug acarbose. These molecules can be considered as promising lead candidates for future antidiabetic drug design and discovery.

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Conflicts of Interest
The authors declared no conflict of interest.

Abbreviation List
AGIs, α-Glucosidase inhibitors
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