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Alpha Amylase As A Biological Scaffold For Design of Novel Antidiabetic Drugs- A Review

Nikhila Jose[1]*, K Krishnakumar[1], G Elias[1]
1.Dept. of Pharmaceutical Chemistry, St James College of Pharmaceutical Sciences, Chalakudy, Kerala

ABSTRACT

Diabetes Mellitus is a metabolic disorder characterized by high blood glucose level caused by deficiency of insulin secretion or insulin action. Postprandial blood glucose level in patients with type II diabetes may be controlled by inhibition of alpha amylase, which is one of the carbohydrate hydrolysing enzymes. Alpha amylase is an enzyme which breaks down starch to maltose by hydrolysing alpha bonds of large, alpha-linked polysaccharides, such as starch and glycogen. Alpha amylase inhibitors may be useful as adjuvant drugs in type II diabetes. The objective of this review is to gather information regarding the identification and evaluation of alpha amylase inhibitors from natural and synthetic sources.

Keywords: Alpha amylase, antidiabetic.

*Corresponding Author Email: stjamespharmacyproject@gmail.com
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INTRODUCTION

Diabetes mellitus is an endocrine disorder characterized by hyperglycemia[1]. It is associated with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion[2] and insulin sensitivity[3]. Delayed insulin secretion immediately after meal can result in persistently high postprandial blood glucose in the range of 140-190 mg/dl, and in some extreme cases even up to 400 mg/dl[4, 5]. The first two hours of post-prandial phase of diabetes is significant, as the elevated glycated haemoglobin can lead to several macro-and micro-vascular complications such as increased risk of cardiovascular diseases (CVD), neuropathy and retinopathy[6]. Hence diabetes may be treated by decreasing postprandial hyperglycaemia. This can be achieved by the use of inhibitors of alpha glucosidase and alpha amylase enzymes, which are drug-design targets in the development of compounds for the treatment of diabetes [7].

Plant derived drugs have been used for the treatment of diabetes in several developing countries. The inhibitors of carbohydrate hydrolysing enzymes have significance in plant physiology and animal and human nutrition. Ethno botanical information indicates that more than 800 plants are used for the treatment of diabetes throughout the world[8]. Plants contain different chemical constituents having potential for inhibition of alpha amylase that may be used as therapeutic agents. However there is no conclusive evidence of their antidiabetic activity[9]**.** Alpha amylase is an endoglucanase enzyme widely present in plants, animals, bacteria, and fungi[10]. In animals, alpha amylase inhibitors can slow down the conversion of starch to simple sugars immediately after a meal, thus reducing the postprandial spike in blood glucose level. This is of particular importance in patients with diabetes, where low insulin levels prevent rapid clearance of extracellular glucose from blood. Plants use alpha amylase inhibitors as a defence strategy. These inhibitors prevent the digestive action of alpha amylases and proteinases in the insect gut, thereby acting as insect antifeedants. As a result, alpha amylase inhibitors have potential in various fields, including the treatment of diabetes and crop protection.

There are very few reports of synthetic drugs that have been tested for invitro alpha amylase inhibitory activity. It has been reported by Zhen Xie et al that salicylic acid has shown inhibition of gibberellin-induced alpha-amylase expression[11]. Synthetic compounds such as citric acid, oxalic acid, salicylic acid have been reported to show significant inhibition of alpha amylase from the insect pest *Rhyzopertha dominica*[12]. Hence the inhibition of alpha amylase activity has tremendous scope to be explored further for the design of novel antidiabetic drugs.

ALPHA AMYLASE INHIBITORS

Herbal Drugs

Chakrabarti et al. have screened the plants *Artocarpus altilis, Aconitum heterophyllum, Acorus calamus, Berberis aristata, Cassia auriculata, Cyprus rotundus, Mesua ferrea, Plumbago zeylanicum,* and *Terminalia arjuna* for alpha amylase inhibition. The plants that have shown effective alpha amylase inhibition are *T. arjuna, P. zeylanicum, C. auriculata* and *C. rotundus*. *A. altilis* did not show inhibition of alpha amylase. Methanolic extracts of *Artocarpus heterophyllus* was demonstrated to have significant alpha amylase and alpha glucosidase inhibitory activity by Sindhu. S. Nair *et al* [13]. Bompard Gilles et.al, reported that the alpha amylase inhibitor from the bean *Phaseolus vulgaris* is also a potent inhibitor of mammalian alpha amylases. Nahoum et al observed that *Phaseolus vulgaris* beans has a bifunctional alpha amylase inhibitor (BASI), an endosperm storage protein in abundance. The BASI protein has been identified to play a regulatory role in the action of alpha amylase by binding to the active sites of the enzyme. Dinesh et al have evaluated *Acalypha indica*, *Allium sativum*, *Allium cepa*, *Azadirachta indica*, *Musa sapientum*, *Mangifera indica*, *Murraya koenigii*, *Ocimum sanctum*, *Phyllanthus amarus* and *Tinospora cordifolia* for their respective alpha amylase inhibitory activity. The results showed that ethanol extracts of *Mangifera indica* and *Azadirachta indica* as well as the petroleum ether extract of *Murraya koenigii* showed more inhibition on alpha amylase activity than others.

Synthetic Drugs

Insect pests cause extensive damage to stored grains and grain products. Carbohydrates are essential energy producing nutrients, required for both optimal growth and for the maintenance of adult longevity for the majority of insects[14]. The secretion of carbohydrate digestive enzymes by the insect pests is critical to their survival by breakdown and assimilation of the grains. The presence of alpha amylase has been demonstrated in many insects of Orthoptera, Hymenoptera, Diptera, Lepidoptera and Coleoptera orders[15]. Insect pest like *Rhyzopertha dominica*, *Tenebrio molitor*, cowpea weevil (*Callasobruchus maculates*) and mexican bean weevil (*Zabrotus subfaciatus*) are extensively starch dependent insects and utilize alpha amylase for their survival[16-20]. *Rhyzopertha dominica* is an insect pest which causes extensive damage to stored wheat grains. The inhibitors of alpha amylase, the major insect digestive enzyme may effectively prevent these insect pests from damaging the grains. S Priya et al have reported salicylic acid to produce 58% inhibition of alpha amylase of *Rhyzopertha dominica* at 10mM concentration.

Alpha amylase could be a potential target for the development of novel drugs for the treatment of diabetes and obesity. Alpha amylase is an enzyme which increases the bio availability of glucose

in the blood. So inhibitors of alpha amylase can effectively retard the digestion and assimilation of starch at the early stages of digestion. Thus they provide a beneficial effect on insulin resistance.

DIFFERENT SOURCES OF ALPHA AMYLASE

Pancreatic Alpha Amylase

Pancreatic alpha amylase (E.C. 3.2.1.1) is a key enzyme in the digestive system that catalyzes the initial hydrolysis of starch into a mixture of smaller oligosaccharides consisting of maltose, maltotriose and a number of other oligoglucans. These are further degraded by alpha glucosidases to glucose leading to elevated postprandial hyperglycemia. It has been shown that activity of human pancreatic alpha amylase in the small intestine correlates positively with postprandial glucose levels, the control of which is therefore an important aspect in treatment of type II diabetes[21]. Delayed starch digestion by inhibition of alpha amylase could be crucial in the control of diabetes. Inhibitors of pancreatic alpha amylase could cause a considerable reduction in the rate of glucose absorption and thus lower the postprandial blood glucose levels[22]. Some inhibitors currently in clinical use are acarbose and miglitol which inhibit glycosidases such as alpha glucosidase and alpha amylase, while others such as voglibose inhibit alpha glucosidase.

Human Salivary Amylase

Human salivary alpha amylase is an important carbohydrate digestive enzyme in the oral cavity. Humans produce two kinds of alpha amylase - salivary and pancreatic amylase. Balz Frei et al have demonstrated that the extracts of grape seed and green tea can be used as alternatives to pharmaceutical inhibitors of the glycoside hydrolase enzymes, alpha amylase and alpha glucosidase. Singh, A. and Marar, T have studied the inhibitory effect of extracts of *Syzygium cumini* and *Psidium guajava* on human salivary amylase[23].

Estimation of In-vitro Alpha Amylase Activity

Various methods have been applied for alpha amylase inhibitory assay. Dineshkumar et al have carried out the in-vitro alpha amylase inhibition by using starch azure method[24]. A modified dinitrosalicylic acid (DNSA) method of Bernfeld[25] was followed by Marar T to estimate the maltose equivalent. Chakrabarti et al have described the alpha amylase inhibition by using iodine reagent.

CONCLUSION

Alpha amylase enzyme is a promising drug target for the development of antidiabetic drugs. Alpha amylase inhibitors can limit the spike in postprandial blood glucose levels and may prove useful in the treatment of type II diabetes. Several methods have been employed for assessing the inhibitory

activity on alpha amylase. Numerous herbs have been found to have alpha amylase inhibitory action. However there are very few reports of synthetic drugs that have been tested for this activity. As salicylic acid, a synthetic drug has shown inhibition of alpha amylase from *Rhyzopertha dominica*, derivatives of salicylic acid may be tested for the same activity. Hence alpha amylase is a potential biological scaffold for further research in the development of novel synthetic antidiabetic drugs.

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