

Gastrointestinal Enzymes Inhibitors from Medicinal Herbs and Food Plants as Therapeutic Pharmacophores for the Management of Diabetes

Mahomoodally Mohamad Fawzi

Department of Health Sciences, Faculty of Science, University of Mauritius, Réduit, Mauritius

Corresponding Author: Mahomoodally Mohamad Fawzi, Department of Health Sciences, Faculty of Science, University of Mauritius, Réduit, Mauritius, Tel: +230 403-7578; Fax: +230 465-6928; E-mail: f.mahomoodally@uom.ac.mu

It is a known fact that carbohydrates are the core constituents of the human diet which consist mainly of complex sugars (starch ~60%), and disaccharides (sucrose ~30%). These complex carbohydrates cannot be absorbed unless they are first broken down by gastrointestinal enzymes (amylases, glycosidase and lipases) before they can be transported through the mucosa of the gastrointestinal tract into the circulatory system. α -Amylase is present in both salivary and pancreatic intestinal secretions for hydrolyzing starch and large malto-oligosaccharides to maltose, which is further broken down by α -glucosidase to glucose prior to absorption in the small intestine. A couple of minutes after the ingestion of starch a marked hyperglycemia leading to hyperinsulinemia is observed [1]. It has also been shown that activity of α -amylase in the small intestine correlates to an increase in post-prandial glucose levels, the control of which is therefore an important aspect in the management of diabetes. Hence it is argued that a retardation of starch digestion by inhibition of digestive enzymes such as amylases

and glucosidases would play a key role in the control of diabetes. Indeed, it is a known fact that postprandial hyperglycemia strongly depends on the amount of absorbed monosaccharides and the velocity of absorption in the small intestine.

A plethora of research is acknowledging that the inhibition of carbohydrate-digesting enzymes such as α -amylase and α -glucosidase in the alimentary canal should help to reduce the unfavorable high postprandial blood glucose peaks observed in diabetes; thereby acting as 'starch blockers'. Additionally, reports tend to suggest that reduction of amylase activity has the effects of reducing post meal blood sugar peaks and of slowing gastric emptying [2,3]. Drugs, which reduce postprandial hyperglycemia by suppressing the hydrolysis of carbohydrates mainly starch, have been shown to be effective for the prevention and treatment of non-insulin diabetes mellitus by decreasing postprandial hyperglycemia and improve insulin sensitivity, as well as protecting the β -cells of the pancreas [4, 5].

Endoglucanases, such as α -amylase that catalyze hydrolysis of the internal α -1,4-glucosidic linkage in starch and other related polysaccharides, have also been targets of medicinal food plants investigations as potential candidates for the suppression of postprandial hyperglycemia [6-10]. On the other hand, α -glucosidase is a membrane-bound enzyme,

located at the epithelium of the small intestine, which catalyses the cleavage of glucose from disaccharides and oligosaccharides. Indeed, α -glucosidase inhibitors were the first drug developed to meet the needs of better postprandial glucose control when sulfonylureas and biguanides were the only available oral anti-diabetics [5]. Hence, α -glucosidase inhibition has been postulated as one of the effective management of diabetes mellitus. Additionally, α -glucosidase inhibitors that retard digestion of both sucrose and starch are regarded as superior to α -amylase inhibitors. Although α -glucosidase inhibitors such as acarbose and miglitol are sold by prescription, there are also herbal supplements and functional foods that are thought to act by same mechanism. For instance, several plants from the *Salacia* genus (e.g., *S. prinoidea*, *S. reticulata*, and *S. oblonga*) have been used for many years as part of the Ayurvedic system of traditional Indian medicine to treat diabetic conditions [11]. To this effect, α -glucosidase inhibitors together with α -amylase have received considerable attention in the past two decades as they are potential therapeutic agents for the treatment of diabetes [12-15].

Several reports tend to suggest this inhibition of α -glucosidase and α -amylase can significantly decrease the postprandial increase of blood glucose after a mixed carbohydrate diet and therefore can be an important strategy in the management of postprandial blood glucose level in type 2 diabetic patients and borderline patients. Studies have been performed yielding potential α -glucosidase inhibitors from various food components and plants like cranberry extracts [16], *Cuscuta reflexa* [17], pepper [18], soy bean extracts, [19], oregano [20], Fenugreek and Balanite [21], amongst others. Matsuda et al. [22], have studied in detail the structure activity relationship among saponins isolated from various sources and their hypoglycemic activity and showed that the 3-O-glucuronic acid moiety of oleanolic acid possesses strong hypoglycemic activity. Regarding mechanism of action, they proposed that these compounds act as hypoglycemic by

delaying the transfer of glucose from the stomach to the small intestine, the main site of glucose absorption and by inhibiting the glucose transport at the site of intestinal brush border membranes. A similar study was carried out on seven exotic/indigenous antidiabetic medicinal plants of Mauritius; interestingly one food plant *Artocarpus heterophyllus* (also known as bread fruit), was found to possess significant inhibitory effects on starch breakdown *in vitro*. Further kinetic studies using the Michaelis-Menten and Lineweaver-Burk equations showed that the bioactive inhibitor phytochemical (s) present in *A. heterophyllus* leaf extract was acting as a competitive inhibitor of this enzyme [12]. Recently, Nickavar and Yousefian [14], have demonstrated appreciable α -amylase inhibitory activity of some *Allium* species (Onion) and proposed that *A. akaka*, *A. cepa*, *A. porrum* and *A. sativum* could be good candidates as potential carbohydrate hydrolyzing enzyme inhibitors. The inhibition of α -amylase activity by medicinal plants might be attributed to several possible factors such as fiber concentration, the presence of inhibitors on fibers encapsulation of starch and enzyme by the fibers present in the sample, thereby reducing accessibility of starch to the enzyme, and direct adsorption of the enzyme on fibers, leading to decreased amylase activity [13]. Interestingly, some investigators have extended these enzyme-inhibition assays in mouse plasma [23,12] and reported the direct inhibitory activities of crude plant extracts on the amylase activity in mouse plasma and postulated that some of these crude drugs could be further investigated as potential modulator of postprandial insulin peak in humans.

It is to be noted that important constituents for the inhibitory activity against α -amylase are mainly plant secondary metabolites particularly polyphenolic compounds. Food compounds with such properties include tannins (ellagitannins and proanthocyanidins), anthocyanins, chlorogenic acid in coffee and many other polyphenols [2,10]. Common secondary metabolites studied in light of the above assay are triterpenoids such as oleanolic acid and ursolic acid

isolated from *Phyllanthus amarus* [17]. Which was reported to possess α -amylase inhibitory activity? Triterpene glycosides from *Sarmatia grosvenori* have been observed to inhibit intestinal maltase and thereby suppress the rise in the blood glucose level in maltose administered rats [24]. Recently, pancreatic α -amylase inhibitory activities of reported from *Ficus bengalensis* bark, *Syzygium cumini* seeds, isopropanol extracts of *Cinnamomum verum* leaves and *Curcuma longa* rhizome were mainly due the presence of alkaloids, proteins, tannins, cardiac glycosides, flavonoids, saponins and steroids as probable inhibitory compounds. *Phlomis armeniaca*, *Salvia limbata* and *Plantago lanceolata* teas exhibited weak alpha-amylase inhibitory activities and pronounced α -glucosidase inhibitory activities [9]. Gastrointestinal lipase inhibitors hinder fat digestion and absorption. Phenolic lipase inhibitors such as epigallocatechin-3-gallate, grape seed, kaempferol, quercetin [25]. Ellagitannin, tannins and proanthocyanidins are present in green and black tea, berries (lingonberry, bearberry, arctic bramble, cloudberry, strawberry, raspberry and blueberry); garden pea (*Pisum sativum*), Norway spruce (*Picea abies*), large leaved lime (*Tilia platyphyllos*) [26] and *Plantago lanceolata* [9]. Herbal teas may have comparable or superior phenolic and antioxidant levels to black tea and many suppressed the activity of enzymes involved in metabolic syndrome, namely alpha amylase, alpha-glucosidase and pancreatic lipase [10].

Over the last decades, the quest for new lead molecules from natural products as potential inhibitors of carbohydrate digestion with a high specific affinity has experienced a bloom. Common drugs such as acarbose, miglitol and voglibose which are currently in use as α -amylase and α -glucosidase inhibitors are not without side effects. However, since many such lead compounds from natural products lack specificity in their action, they are associated with some severe side effects (flatulence, bloating and diarrhea) creating the need to look for more specific, hence safer and more effective anti-hyperglycaemic agents. To this

effect, medicinal herbs and food plants have attracted much interest as potential inhibitors as such therapeutic use of high-affinity plant derived enzyme inhibitors would be of considerable clinical relevance in the management of diabetes. Nonetheless, there is still need for further clinical studies to establish a rational amylase, glucosidase and lipase inhibition therapy with traditional herbal preparations, especially for the leaves from the blueberry, tamarind, lemon balm and rosemary, the hulls from white kidney beans or green tea extract as structure-related activity are rarely described in the literature.

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