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A CRITICAL STUDY ON STRUCTURE ANALYSIS OF TAKA-AMYLASE A (TAA)

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ABSTRACT
α-Amylase act as a best target to treat the type-2 diabetes mellitus. Therefore, in search of new therapeutic agents as α-amylase inhibitors, study presented in this dissertation is focused on the synthesis using molecular hybridization approach and α-amylase inhibition study of nitrogen and sulphur containing heterocyclic compounds having different moieties such as thiazolidin-4-one, 2,4-thiazolidinediones, 1,3-thiazoles and benzothiazoles clubbed pyrazole or oxadiazole. All the molecular hybrids were screened against Aspergillus oryzae α-amylase at various concentration. The present information, gained through the literature describing the structure, mechanism of action of α-amylase. This chapter presents a brief account of the biological application of nitrogen and sulphur containing heterocycles and their role as α-amylase inhibitors. the synthesis of twenty-one molecular hybrids based on thiazolidin4-one and pyrazolyl pharmacophore i.e., 5-((3-(aryl)-1-phenyl-1H-pyrazol-4-yl) methylene)-2-(p-arylimino)thiazolidin-4-one (2.59a-2.59u).
Keywords: - Target, Diabetes, Synthesis, Biological.

I. INTRODUCTION

For centuries together Man has used the vast resources of nature not only for their nutritional value but also for cure of dreadfull diseases. In the earlier centuries, man ignored the toxic effect of the drugs on the human body from the natural resources, though the majority of the drugs used from yore to the 19* century came from natural sources. Since ancient times mankind has used natural sources for various purposes. One of the fields where natural sources have been successfully and widely used is medicine. For example, in ancient Egypt, Cleopatra used atropine extracts from the Egyptian henbane to dilate her pupils, in the hope that she would appear more alluring. In the Renaissance, women used the juice ofthe berries from Atropa belladonna to enlarge the pupils of the eyes, for cosmetic reasons. Even though atropine is poisonous in large doses, it has a broad field of application in medicine.

Today, atropine is used by ophthalmologists to temporarily paralyze the accommodation reflex (cycloplegic) and also to dilate the pupils (mydriatic). It is also used in treatment of bradycardia (an extremely low heart rate) and cardiac arrest. Actually, still more than half ofthe world's population relies entirely on plants for medicines, and plants supply the active ingredients of most traditional medicine product. The Shen Nong's Herbal classic, a 2000-year old medicinal Chinese book, considered to be the oldest publication on oriental herbal

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medicine, classifies 365 species ofroots, grass, woods, furs, animals and mineral stones into different categories of herbal medicine.

Plants have also served as the starting point for countless drugs on the market today. Researchers generally agree that natural products from plants and other organisms have been the most consistently successful source for ideas for new drugs, since Nature is the Master Chemist. Pharmaceutical chemists seek ideas for new drugs not only in plants, but in any part of nature where they may find valuable clues. It is estimated that there is at least 250,000 different species of plants up and up to 30 million species ofinsects. Despite these vast numbers, only a few ofthese organisms have been tested for biological activity. From the past century a new era started wherein the diseases were treated with synthetic drugs. In the process also evolved, the modification of natural products through various synthetic processes producing semi synthetic drugs.

The course of civilization has immensely benefited with the advances in synthesis of drugs. Since the treatment of diseases started with synthetic and semi synthetic drugs the death rate reduced, and the life expectancy ofmankind nearly doubled within this last half century. The field ofmedicinal chemistry has evolved from an emphasis on the synthesis, isolation and characterization of drugs and an increased awareness of the biochemistry has been a great deal of success in understanding the relationship between chemical structure and its biological activity in a number of areas.

II. DIABETES MELLITUS

Diabetes mellitus is one of the most common non-communicable metabolic disorders characterized by chronic hyperglycemia or increased blood glucose levels with disturbances in carbohydrate, fat and protein metabolism resulting from the absolute or relative lack of insulin secretion. Insulin is a peptide hormone synthesized from β-cells of islets of Langerhans in the pancreas and its prime role is to control the blood glucose levels, which usually rise after dietary intake. Therefore, in diabetic patients, anomalies in the production of insulin and its utilization cause hyperglycemia. Insulin is also vital to metabolize carbohydrates and lipids because it lowers blood glucose levels by enhancing glucose uptake by cells and by stimulating glycogenesis as well as inhibiting glycogenolysis. It also retards the breakdown of fats to free fatty acids and ketone bodies. Diabetes Mellitus is classified as insulin-dependent diabetes/ juvenile diabetes/ diabetes mellitus type-1, non-insulin dependent diabetes mellitus (NIDDM)/ diabetes mellitus type-2, prediabetes and gestational diabetes mellitus (GDM)/ diabetes of pregnancy. Amongst these, type-2 diabetes is pandemic and has affected almost 200 million persons globally and this figure is likely to rise gradually to 642 million by 2040.

Polydipsia, renal disorder, nephropathy, blurred vision, hunger and hypertension are the major complications of diabetes. Almost 50% of the diabetic patients are affected by these complications, which can be fatal and

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thus diabetes is recognized as a serious disorder in many regions of the world. The management of blood glucose to a normal level in patients with diabetes mellitus is the most challenging task. Diet, exercise and prescribed oral hypoglycemic agents e.g., sulphonylureas, biguanides, peroxisome proliferator-activated receptors, thiazolidinediones and other drugs like acarbose are the different methods for treatment of diabetes mellitus. But somehow, the use of the oral antihyperglycemic medicines is associated with the miscellaneous adverse effect and toxicity.

For the control of this disease, there is a necessity of exploration for enzyme inhibitors as alternative targets because enzymes catalyze the biochemical reactions and show a high degree of specificity for their substrates. To avoid the condition of hyperlipidemia, dysbetalipoproteinemia, obesity, diabetes, etc. there is a need to study the kinetics of digestion of carbohydrate and absorption of monosaccharide. One of the best methods to control the postprandial glucose level is to delay the rate of glucose absorption resulting from carbohydrate digestion.

The delay in glucose absorption by using carbohydrate hydrolyzing enzyme is well accepted clinical strategy where α-amylase and α-glucosidase are used as hydrolytic enzymes. In this aspect, the inhibitors of α-amylase have attained a specific position because α-amylase initiates the hydrolysis of polysaccharides.

III. STRUCTURE ANALYSIS OF TAKA-AMYLASE A (TAA)

At the three-dimensional level, the structure of the native α-amylase has been described together with an analysis of both the structural and inhibitory calcium sites. The Aspergillus oryzae α-amylase often called as "Taka-amylase A" or 1,4-α-D-glucan glucanohydrolase having molecular weight 52.53 kDa. Taka-amylase A is a single peptide consisting of 478 amino acid residues with four disulphide bond, one free sulfhydryl group and one calcium ion per molecule. It is one of the first glycosylhydrolases to receive the extensive biochemical characterization.

Taka amylase contains two domain assignments i.e., d7taaa1 (95 residues) and d7taaa2 (381 residues). Secondary structure of α-amylase contains wide arrangements of 34% α-helices and 21% β-sheets and contains four L-cystine protein modification legend. d7 Taaa1 does not contain any binding site for calcium and acarbose. Calcium ion Ca2+, which is located at the interface between the catalytic A domain and the B domain. The Ca2+ ion is bound by eight legends: the carboxylate oxygens of Asp175 in a bidentate fashion with a bond length of 2.54 Å and 2.85 Å, respectively, the side chain carbonyl oxygen of Asn121 (2.51 Å), three water molecules (2.41, 2.46, and 2.76 Å), and the main chain carbonyls of Glu162 (2.51 Å) and His210 (2.54 Å). Acarbose also binds with d7taaa2 at Gln35(A), Asp340(A), Arg344(A), Asp206(A), Glu230(A), His210(A),

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Gly234(A), Arg204(A), Asp297(A), Lys209(A), His121(A) and Trp83(A).

One distinct polypeptide chain contains 12 β-bridges, 38 S-bends, 89 β-strands, 60 turns, 363/10 helix, 130 α-helix.

IV. CONCLUSION

The present study emphasizes the potential of Momordica charantia and Trigonella foenum graecum seed extracts to inhibit pancreatic alpha- amylase, an enzyme that is responsible for the digestion of starch. The seeds of both the plants were found to be effective in terms of antioxidant potential and are expected to act through different mechanisms. In vivo studies demonstrated the blood glucose- lowering effect by the plant extracts. Presence of phytochemicals namely flavonoids, phenols, tannins, terpenoids, steroids and saponins might be responsible for antidiabetic and antioxidant activities. In silico docking studies of bioactive compounds identified from the seeds of Momordica charantia and Trigonella foenum graecum with human pancreatic alpha amylase and porcine pancreatic alpha-amylase enzymes as target proteins showed good binding affinity and might act as potential inhibitors. Hence, inhibition of pancreatic alphaamylase inhibitor compounds obtained from Momordica charantia and Trigonella foenum graecum seeds might be a promising strategy in the management and prevention of Diabetes.

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