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AN OVERVIEW ON DIABETES MELLITUS AND ADVANCES IN THE SYNTHESIS OF ANTIDIABETIC DRUGS

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ABSTRACT

The present review article offers a detailed account on the antidiabetic drugs and recent advances going on in the synthesis of antidiabetic drugs. Also, the synthesis of the novel drugs for the treatment of diabetes mellitus like chitosan-stabilized selenium nanoparticles, benzothiazole clubbed oxadiazole-Mannich bases, Bio-extract-mediated ZnO nanoparticles, alkyl carbazole compounds, etc. have been discussed in detail.

KEYWORDS: Antidiabetic drugs, diabetes mellitus, treatment.

1. INTRODUCTION

Diabetes mellitus or metabolic syndrome is characterized by increased blood sugar level. Despite various advances in molecular pharmacology and drug development diabetes mellitus affects around 6% of adults in western society, which is expected to be 300 million.[1,2] by 2010. Diabetes mellitus is a chronic multifactorial metabolic disease resulting from insulin deficiency or insulin resistance. Diabetes is actually a collection of many diseases which produce the phenotype of hyperglycemia. Diabetes mellitus is considered to be one of the main threats to human health in 21st century.[3] Diabetes is threatening on account of the development of many severe secondary complications which includes atherosclerosis, microangiopathy, renal dysfunction and failure, cardiac abnormalities, diabetic retinopathy and ocular disorders.[4]

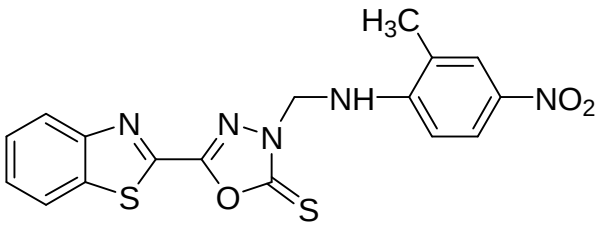
2. REVIEW

1) Synthesis of chitosan-stabilized selenium nanoparticles

By maintaining the optimal conditions (temperature of 25◦C, reaction time of 2 h, Vc concentration of 0.04 M and the CTS concentration of 1.0 mg/mL) by orthogonal experiments and reduction of selenite with ascorbic acid, the synthesis of Chitosan-stabilized selenium nanoparticles (CTS-SeNPs) were performed. The size, morphology and stability were characterized by transmission electron microscopy (TEM), scanning electron microscope (SEM) and dynamic light scattering (DLS). The antidiabetic potency of the synthesized CTS-SeNPs were investigated in streptozotocin (STZ)-induced diabetic mice. It showed that CTS-SeNPs (2.0 mg Se/kg·bw) had greater antidiabetic activity than CTS-SeNPs and other selenium compounds at different doses.[5]

2) Design and Synthesis of benzothiazole clubbed oxadiazole-Mannich bases

A novel series of benzothiazole clubbed oxadiazole-Mannich bases were designed, synthesized, characterized and assessed for binding and interactions at the binding site of receptor Peroxisome proliferator-activated receptor, PPAR-c or PPARG (PDB 1FM9). Some compounds were selected based on their D-score and further evaluated using Oral Glucose Tolerance Test (OGTT) in normal rats and by Streptozotocin (STZ) – induced diabetic rats. The results of reduction of blood glucose level of synthesized derivatives were further compared with the glibenclamide (140.29 ± 1.24) in STZ model. The compound 1 (161.39 ± 4.38) showed highest antidiabetic activity, whereas other compounds exhibited moderate activity. The online software Molinspiration was used to study the ADME of the compounds, that supported the oral activity of all the compounds (except one).[6]



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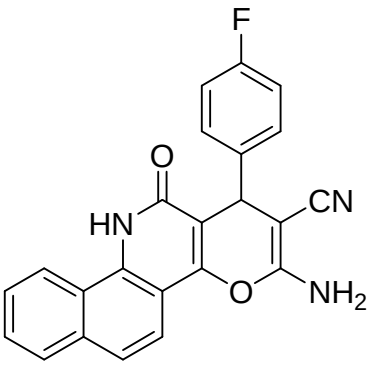
3) Microwave-assisted synthesis, characterization and antidiabetic activity evaluation of Bio-extract-mediated ZnO nanoparticles

The microwave assisted synthesis of the nanoparticles of ZnO were performed in the presence of fruit extracts of *Vaccinium arctostaphylos L*. A decrease in the size of chemically

synthesized nanoparticles was evaluated by biologically synthesized ones. The characterization can be easily done by XRD, SEM, TEM, EDX, FT-IR, UV-vis DRS and TGA analysis. The *in-vivo* evaluation was performed on the alloxan-induced diabetic rats and observations of fasting blood glucose (FBS), high-density lipoprotein (HDL), total triglyceride (TG), total cholesterol (TC) and insulin were collected. There was the significant decrese in fasting blood glucose and increase in high-density lipoprotein levels. However, there was only significant reduction of cholesterol in case of biologically synthesized ZnO. Also, the results were not significant in case of triglyceride and insulin levels. The bio-mediated ZnO nanoparticles were found to be most active.[7]

4) Design and synthesis of novel dihydropyrano[3,2-c]quinoline derivatives

The synthesis of dihydropyrano[3,2-c]quinoline derivatives were performed and their evaluation was done for *in vito* α-glucosidase inhibitory activities. The α-glucosidase inhibitory activities with the standard drug acarbose (IC50 = 750.0 ± 1.5 mM) against α-glucosidase enzyme, when compared provided potent activity of the synthesized drugs in the range of 10.3 ± 0.3 mM–172.5 ± 0.8 mM. The compounds **2** and **3** showed maximum antidiabetic potency (IC50 = 10.3 ± 0.3 and 15.7 ± 0.5 mM, respectively). Their kinetic analysis displayed that 6d was an non-competitive inhibitor, whereas 6e was an competitive inhibitor of the enzyme. The cytoxicity results revealed no toxicity by any compound.[8]



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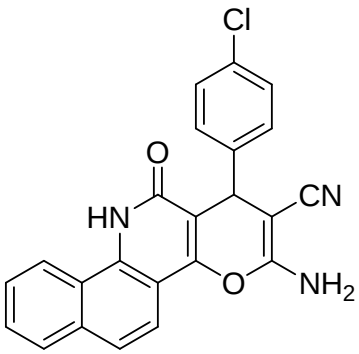

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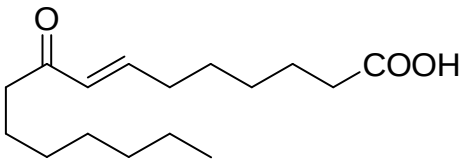
5) Synthesis of Marine Oxohexadecenoic Acids

The isolation and identification of (7*E*)-9-oxohexadec-7-enoic acid and (10*E*)-9-oxohexadec-10- enoic acid from the marine algae *Chaetoceros karianus* was performed. Also, the synthesis, characterization and biological evaluation of these natural oxyfatty acids (oFAs) were done. Both the compounds provided good dose-dependent activation of PPARα and –γ. They showed ability to regulate PPAR target genes in hepatocytes and adipocytes. They both

derived adipogenesis on evaluation in the Simpson-Golabi-Behmel syndrome (SGBS) pre-adipocyte cell model. But, they had reduced lipid accumulation and lowered expression of adipocyte markers than standard drug rosiglitazone. The transcriptome analysis showed that both **4** and **5** induced antidiabetic gene programs in adipocytes by repressing pro-inflammatory cytokines and upregulating insulin-sensitizing adipokines.[9]



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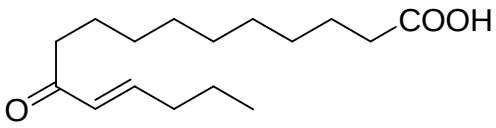

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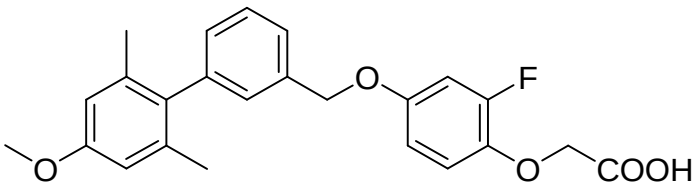
6) Design and synthesis of Nitric oxide donor-based FFA1 agonists

Due to highly prevalent cardiovascular complications in type 2 diabetes mellitus (T2DM) there was a urgent need for new hybrids for intervention of cardiovascular complications. Thus, a series of compounds of FFA1 agonist and NO donor were designed for both antidiabeties and antithrombosis. The compound **6** showed induced-fit docking study. These compounds exhibited average FFA1 agonistic activities and anti-platelet aggregation activities. However, the compound **7** showed significant hypoglycemic effect than TAK-875 in an oral glucose tolerance test in mice. The compound 7 is also expected to be a potent with additional cardiovascular benefits with T2DM.[10]



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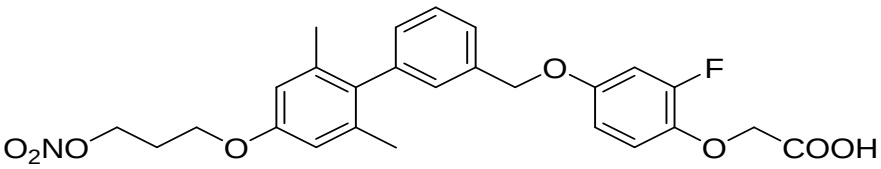

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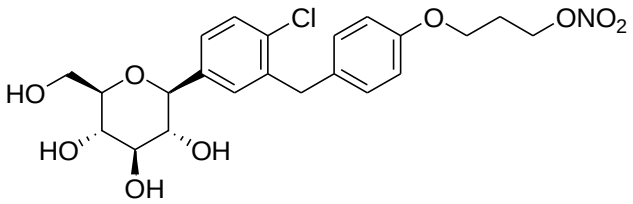
7) Design and synthesis of nitric oxide releasing derivatives of dapagliflozin

At the early stage of type 2 diabetes mellitus (T2DM), cardiovascular complications are very prevalent. This enhanced the need for the intervention of cardiovascular complications in

T2DM. The designing of new analogues of NO donor and SGLT2 inhibitor were done to achieve antidiabetic as well as anti-thrombosis effect. The compound **8** exhibited moderate SGLT2 inhibitory effect, anti-platelet aggregation and significant antidiabetic effect. There was the excreation of urinary glucose during an oral glucose tolerance test in mice. It is thus believed to be a potent compound for intervention of cardiovascular complications in type 2 Diabetes.[11]



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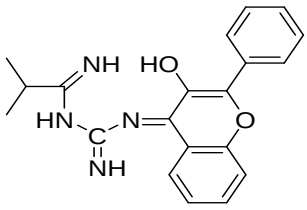
8) Synthesis of some alkyl carbazole compounds

Some alkyl derivatives of carbazole were synthesized and evaluated for their *in vitro* inhibitory effect on alpha amylase and alpha glucosidase. The acid-catalysed alkylation method was used for the synthesis of methylcarbazole, ethylcarbazole, propylcarbazole and butylcarbazole having the IC50 values of alpha amylase inhibitory assay were 87.47, 50.23, 47.20, 42.36 and 42.11 µg/mL respectively. The IC50 values of ethylcarbazole, propylcarbazole and butylcarbazole for alpha glucosidase inhibitory assay were found to be 205.30, 153.93 and 152.90 µg/mL, respectively. The reference drug showed much better inhibitory effect toward both the enzymes than synthesized compounds. The alkylation of carbazole thus increased the alpha amylase inhibitory effect of carbazole. But, inhibitory effect was found to be directly proportional to the chain length of the alkyl group.[12]

9) Synthesis of a new metformin-3- hydroxyflavone complex

Metformin is a clinically important drug for the treatment of both T1DM and T2DM due to its safety and efficacy. But, athigh dose, it cause lactic acidosis in addition to complications in gastrointestinal tract. There are manny researchers trying to minimize the dosage of metformin to avoid these complications. It can be done by synthesizing a new complexes of metformin. Hence, the synthesis of Metformin-3-hydroxyflavone complex (**9**) was performed and evaluated in high fat diet fed-low dose STZ induced experimental type 2 diabetes in Wistar rats. The results showed that the oral administration of complex (20mg/kg.b.w./rat/day) for 30 days provided significant antioxidant as well as, antidiabetic effect in diabetic rats than metformin (50mg/kg.b.w).[13]



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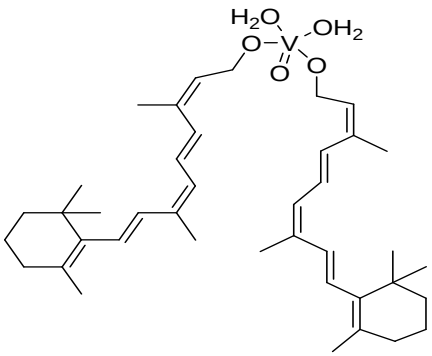
10) Synthesis of Silver Nanoparticles Synthesized with Argyreia nervosa Leaf Extract

The economic green synthesis of silver nanoparticles (AgNPs) using Argyreia nervosa leaves extract (ANE) provided potent reducing and capping agent. There was the inhibition activity against carboohydrate digestive enzymes a-amylase and a-glucosidase. Also, antioxidant activity was evaluated in terms of DPPH (1,1-diphenyl-2-picrylhydrazyl) and ABTS (2,20-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) free radicals having IC50 value of 55.9 and 44.3 g/mL, respectively. All these activities can be used in various bio-applications such as cosmetics, food, and biomedical industry **(14)**.

11) Synthesis of a new insulin-mimetic antidiabetic drug containing vitamin A and vanadium(IV) salt

Due to abnormalities in insulin excreation, the diabetic patients suffer from chronic disorders in the metabolism due to high blood glucose. Vanadium compounds are recently synthesized to decrease the level of glucose. The beta cell activity of Vitamin A is needed by the type 2 diabetic patients. The synthesis of a complex **10** formed by combination of vanadium(IV) salt with vitamin A in a binary solvent system having MeOH/H2O (1:1 ratio) in alkaline media at pH = 8. The synthesized compounds were evaluated against streptozotocin (STZ)-induced diabetic mice ans showed improvement in lipid profile, antioxidant activity, malondialdehyde (MDA), glutathione, methionine synthase, and kidney and liver functions.[15]



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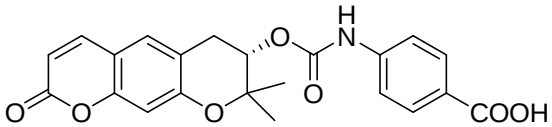
12) Synthesis of Decursinol Derivatives

No antidiabetic drugs are available that can reduce the blood glucose level without any secondary side effects. A molecule Decursinol, was isolated from *Angelica gigas* ans was proved safe. The synthesis of various analogues from Decursinol were performed. The compound **11** showed the blood glucose reduction equivalent to glimepiride (standard drug) in rat and mouse models of diabetes. It is of a non-sulfonyl urea class compound with high efficacy and few side effects. Thus, making it a potent drug for treatment of diabetes.[16]



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CONCLUSION

Many antidiabetic drugs have been developed for the reduction of blood glucose with less side effects. But, due to many secondary complications of these antidiabetic drugs, there is a dire need for the new antidiabetic drugs. The newer analogues are designed and synthesized keeping in view the least adverse effects and better antidiabetic activity. This review article focusses on the synthesis of some compounds for the decrease in the side effects and increase in the diabetic potency.

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