Chapter 1

The Role of Metal Complexes in the Treatment of Diabetes Mellitus - An Overview

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Introduction

Diabetes is characterized by hyperglycemia, altered lipids, carbohydrates, and proteins metabolism which affect the patient quality of life in terms of social, psychological well-being as well as physical ill health [1,2]. Two forms of diabetes (Types 1 and 2) differ in their pathogenesis, but both have hyperglycemia as a common hallmark. In type 2 diabetes, hyperglycemia caused due to impairment in insulin secretion combined with or without impairment of insulin action [3]. The World Health Organization reported that worldwide global population is in the midst of a diabetes epidemic. The people in Southeast Asia and Western Pacific are being under greater risk, and the majority of patients have type 2 diabetes. Insulin resistance typically precedes the onset of type 2 diabetes and is commonly accompanied by other cardiovascular risk factors such as dyslipidemia, hypertension, and prothrombotic factors [4]. Diabetes mellitus (DM), a leading non communicable disease with multiple etiologies, is considered as one of the five leading causes of death in the world. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [5]. DM is a clinically and genetically heterogeneous group of disorders, characterized by abnormally high blood glucose concentration. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Deficient supply of insulin
cause abnormalities in carbohydrate, fat, and protein metabolism. These metabolic disturbances result in acute and long-term diabetic complications, which are responsible for premature death and disability [6].

Knowledge about Diabetes mellitus (DM) existed in ancient Egypt and Greece. The word “diabetes” is derived from the Greek word “Diab” (meaning to pass through, referring to the cycle of heavy thirst and frequent urination); “mellitus” is the Latin word for “sweetened with honey” (refers to the presence of sugar in the urine)[7]. According to ancient Hindu physicians, “Madhumeha” is a disease in which a patient passes sweet urine and exhibits sweetness all over the body, such as in sweat, mucus, breath, and blood. It was recommended that the low carbohydrate diet and almost total withdrawal of animal fats should be taken by the patients suffering from Madhumeha, whereas obese adults should live on low calorie diet. There are two types of Diabetes mellitus: Type 1, “Juvenile diabetes mellitus” (Insulin dependent diabetes mellitus), which is hereditary and is treated by insulin, and Type 2, “Adult type” (Non-insulin dependent diabetes mellitus), which occurs in elderly people[7]. In order to prevent or delay the onset of such complications, tight control of fasting and postprandial blood glucose levels is a central aspect of diabetes treatment. It has been suggested that medicinal plants may provide valuable therapeutics agents in modern medicine and in traditional system, especially in areas where the modern drugs are unavailable [8]. Though there are numerous medicinal plants traditionally reported to have hypoglycemic property. Many of them proved to be not effective in lowering glucose levels in severe diabetes and reported to have side effects including hematological disorders, metabolic coma and disturbances of liver and kidney. Therefore there is a need to search for more effective and safe drugs for diabetes [9].

Implementing new therapies that can manage glucose level are of great importance in recent trends. Metallo-therapy is an increasing field of interest in the treatment of diabetes mellitus. Metal compounds proposed to have the capacity to elicit beneficial effect in the pathogenesis and complication of the disease. The idea of using metal ions for the treatment of diabetes originates from the report in 1899. A number of transitional and other metal compounds like chromium, manganese, molybdenum, copper, cobalt, zinc, tungsten and vanadium have been proposed as possible adjuncts in the treatment of diabetes mellitus in vitro and in vivo [10,11]. Metal compounds induce hypoglycemia by a wide variety of mechanisms. Possible mechanisms of their antidiabetic insulin-like effects are activation of insulin receptor signaling (chromium, mangesium), antioxidant properties (cobalt, manganese, tungstate, zinc), inhibition of phosphatases (vanadium), stimulation of glucose uptake, glycogen and lipid synthesis in muscle, adipose and hepatic tissues and inhibition
of gluconeogenesis (chromium, cobalt) or stimulation of the activities of the gluconeogenic enzymes: phosphoenol pyruvate carboxykinase and glucose-6 phosphatase (manganese) [12,13]. Vanadium, chromium, copper, cobalt, tungsten and zinc were found to be effective for treating diabetes in experimental animals [14]. But still a long time use of the metal compounds as hypoglycemic drugs has to be assessed in order to have a safety and beneficial effect. The present paper gives a review on the promising effect on the metallic compounds in the management of diabetes.

**Vanadium**

Vanadium is a trace element that is believed to have a biological significance. The role that vanadium plays in biological systems is still being investigated. The element was first discovered in 1813 by mineralogist Del Rio. Del Rio was convinced that it was an isotope of chromium [15]. The element was then rediscovered in 1831 by Sefström. The name vanadium comes from vanadis, a nickname for the Germanic goddess of beauty [15,16].

Vanadium is present in the Earth’s crust with the average concentration being 35 ppm, and 2 ppm in sea water [16]. The element is found naturally in more than 65 minerals.

![Vanadium metal](image)

**Figure 1:** Vanadium metal.

It is most commonly found in the +4 and +5 oxidation state in the form of vanadyl (VO$_2^+$) and vanadate (VO$_3^{-}$), respectively. Various oxyanions and cations act as oxidizing agents (17). Initially Sodium vanadate was tried on three diabetes patients by Lyonnet, et al. It had lowered the blood glucose level to a small extent but with no side effect. Vanadyl sulfate (VOSO$_4$) soon replaced by sodium vanadate in animal testing due to the decreased toxicity of vanadyl compared to vanadate (6-10 times less toxic [15]). Also, much of the vanadate administered is found in the vanadyl form [18].

A thorough study was carried out to know whether or not vanadium complexes would prevent the onset of diabetes. Two groups of rats one set injected with vanadyl sulfate and streptozotocin (STZ) to induce diabetes and another set injected only with STZ. The result was that the STZ rats receiving vanadyl sulfate had a delayed onset of
diabetes. The mechanism is hypothesized due to the production of NO free radicals by macrophages. Macrophages (Mø) are cells that are part of the immune defense system. They are responsible for phagocytosis, or engulfing of cellular debris and pathogens. They produce NO free radicals which are made by nitric oxide synthetase (iNOS) to be used against pathogens. A high concentration of NO is thought to cause the production of OH free radicals which causes damage to beta cells (responsible for insulin production). Vanadyl inhibits the production of NO, therefore delaying the onset of type 1 diabetes [18].

The mechanism of vanadyl complexes in the treatment of Diabetes mellitus is not clear but it could have occurred at three possible sites as it has similar effect on phosphate. It inhibits the secretion of protein tyrosine phosphatases (PTPase). This enzyme is responsible for dephosphorylating tyrosine residues in proteins [18-20]. This causes protein tyrosine kinases to be activated and phosphorylate insulin receptor substrates (IRS).

The phosphorylated IRS then attracts various signaling proteins. Signals are sent through the cell initiating two cascades that lead to glucose transport and glycogen synthesis. A second target of vanadium is PTEN, which acts as a phosphatase. This prevents dephosphorylation and allows for cell signaling to occur by a similar pathway [19]. Since 1990, a wide class of vanadyl (oxidovanadium(IV)) complexes involving bis(methylcysteinato) [VO(cysm)2]-, bis(L-tartrato) [(V2O4)(L-tart)2]-, bis(maltolato) [VO(ma)2]-,bis(pyrrrolidine-N-dithiocarbamato) [VO(pdc)2]-, bis(picolinato) [VO(pa)2] and bis(1-oxy-2-pyridinethiolato) [VO(opt)2] [22-26] have been found to improve the hyperglycemic state in streptozotocin-induced type 1-like diabetes in rats (STZ-rats). In particular, studies on VO(pa)2 with a VO(N2O2) coordination environment [26,27-29] and bis(3-hydroxy-4-pyronato) [VO(3hp)2]-,[28-30] bis(1,4-dihydro-2-methyl-4-oxo-3-pyridinolato)- and bis(1,2-dihydro-2-oxo-1-pyrimidinolato)oxidovanadium(IV) complexes [31] with a VO(O4) coordination environment have been intensively performed to find more potent analogues than the parent complexes, leading to the discovery of the linear relationship between in vitro insulin-mimetic activity and the partition coefficient of these complexes. In a clinical study by Jacques-Camarena et al. [32] revealed that administration of vanadyl sulfate (50 mg p.o. twice daily for 4 weeks) in diabetic patients increased triglyceride concentrations without changes in insulin sensitivity.

Vanadium complexes of Allixin (a non sulphur compound present in garlic) was prepared and administered on the adipose cells are prepared from epididymal fat tissue and treated with adrenaline (epinephrine). In fact, vanadyl ions, in place of insulin, induce insulin-mimetic effects with regard to both incorporation of glucose in the rat adipocytes and inhibition of free fatty acids (FFA) re-
lease from the adipocytes [18,27,33,34]. The vanadyl ions are found to simultaneously act on multiple sites in the adipocytes, we thus named it as “the ensemble mechanism” [29]. The insulin-mimetic effect of vanadyl-3-hydroxy-4-pyronate (VO(3hp)2) and the related complexes were examined[35] . Among 5 complexes, VO(alx)2 exhibited the strongest effect in terms of FFA release inhibition (IC50 (50% inhibitory concentration of FAA release from the cells) = 553 μmol/L. and glucose uptake (EC50 (50% enhancing concentration of glucose uptake) = 24 μmol/L. An increase in the cell membrane penetration of the complexes will enhance the insulin-mimetic effect [30].

Cam et al. [36] administered vanadyl sulphate in drinking water (0.75 mg/ml) from 3, 10 and 17 days after the streptozotocin injection for 5 months. Glucose tolerance and adipose tissue function was normalized in vanadyl treated diabetic rats, supporting the concept that vanadyl sulphate acts as an insulin-mimetic.

Tolman et al. [37] showed that several inorganic vanadium compounds, similar to insulin, stimulated glucose transport and oxidation in adipocytes, increased glycogen synthesis in the rat diaphragm and hepatocytes, and inhibited gluconeogenesis in liver cells.

Meyerovitch et al. [38] demonstrated that chronic sodium metavanadate administration also lowered plasma glucose levels and enhanced basal hexose transport in both liver and muscle.

Further new orally active β- diketonato complexes such as VO (acac)2 and bis (α- furancarboxylato) oxovanadium (IV) have shown glucose lowering ability comparable to Bis(maltolato)oxovanadium (IV) (BMOV) and possess high water solubility and less toxicity when orally administered in diabetic rats. Vanadium complex, bis(pyridine-2-carboxylato) oxovanadium (IV) [VO(pic)2] has shown higher insulin-mimetic activity than VOSO4. Recently, the first human Phase I clinical trial was carried out by Medeval Ltd. in Manchester, UK, was to assess the safety and tolerability of Vanadium (IV)
(BEOV), the ethylmaltol analogue of BMOV. It proved that there is adverse effect on the malfunctioning of liver, kidney and blood parameters remained to be normal[10].

**Zinc**

Zinc (Zn) plays an important role in the synthesis, storage, and secretion of insulin as well as conformational integrity of insulin in the hexameric form. Zinc was considered as a component of insulin crystals as earliest since 1934 [39]. Zinc presence would facilitate the uptake of glucose by adipose tissue. A deficiency of zinc results in reduced uptake of glucose by adipose tissue. Of interest is the fact that the zinc content of secretory vesicles is, at best, barely adequate to complex stored insulin as the 2-Zinc insulin hexamer. Surprisingly, zinc was found to have important physiological and pharmacological functions involving an insulin-mimetic activity. Hyperzincuria and impaired intestinal absorption of zinc results in diabetes. Higher zinc intake has also been associated with a slightly lower risk of type 2 diabetes in women [11]. More clinical data would be needed to prove zinc has an insulin-mimetic effect and protects against oxidative damage associated with the disease for the treatment of DM with an increased deficiency of Zinc [40]. Upon oral administration of Zinc(II) complexes containing bis(6- methylpicolinato) [Zn(6mpa)$_2$], bis (maltolato) [Zn(ma)$_2$], bis (1-oxy- 2-pyridonato) [Zn(opd)$_2$] and bis(1-oxy-2-pyridinethiolato) [Zn(opt)$_2$], it has found to exhibit anti-diabetic activity and upgrade hyper-insulinemia and massive hereditary obesity in experimental studies on mice. In addition, structure–activity relationships on zinc complexes with dithiocarbamates and pyridine-2-sulfonates made to create new potential zinc complexes such as bis(pyrrolidine-N-dithiocarbamato) Zn and bis(3- methylpyridine-2-sulfonato) Zn respectively, under in-vitro insulin mimetic activity.

Oral administration of Zn(3hp)$_2$-related complexes with a Zn(O$_4$) coordination environment helped to induce high quality anti-diabetic properties and also a few complexes exhibited not only anti-diabetic activity but also anti-metabolic syndrome activity with respect to hypoglycemic effects on STZ- rat [10]. In evaluation of in vitro insulin-mimetic effect of a series of zinc-3-hydroxy-4-pyronate (Zn(3hp)$_2$) complexes, the Zn(alx)$_2$ complex exhibited the highest insulin-mimetic effect (reciprocal IC50), where it correlated linearly with the partition coefficient (log P) of the ligand (r = 0.99), indicating that the effect of Zn(3hp)$_2$-related complexes is dependent on the membrane permeability of the ligand[41]. A novel zinc complex with thioxoallixin-N-methyl (Zn(tanm)$_2$) with a Zn(S$_2$O$_2$) coordination environment was found[41]. The Zn(tanm)$_2$ exhibited an extremely high in-vitro insulin mimetic effect (IC$_{50}$ = 11±1 μmol/L) compared with others (IC$_{50}$ = 31–220 μmol/L)[41,42].

Daily oral administrations of Zn(tanm)$_2$ to KK-Ay
mice at the dose of 15 mg for 4 weeks significantly improved hyperglycemia, OGTT, insulin resistance, hyperleptinemia, obesity and hypertension. Interestingly, this complex increased the depressed plasma adiponectin levels in the mice [43]. On the basis of these results, Zn(tanim)$_2$ is proposed to be an active therapeutic for treating obesity-linked type 2 diabetes and metabolic syndrome. Adiponectin is an adipocytokine, which is synthesized and released by adipocytes, abundantly present in plasma and leads to enhanced insulin action, indicating that this adipocytokine maintains insulin sensitivity and glucose homeostasis. However, adiponectin levels are reduced in patients with increased insulin resistance due to conditions such as obesity, type 2 diabetes and hypertension. Thus, adipocytokine is considered as a good biomarker to assess efficacy for developing therapeutics for type 2 diabetes [44–47]. It is already known that thiazolidinedione derivatives (TZDs) increase the adiponectin level as potential insulin-sensitizing therapeutics [48]. However, TZDs are associated with edema, body weight gain, congestive heart failure, osteoporosis and liver dysfunction in type 2 diabetic patients [48]. In contrast, Zn(tanim)$_2$ neither induces such symptoms nor exerts appreciable toxic effects in the liver of animals [43]. Zn (tanim)$_2$ is thus the first example which improves not only type 2 diabetes but also metabolic syndrome with respect to the adipocytokine level.

Copper

Copper in food (organic copper) is processed by the liver and is transported and sequestered in a safe manner. Inorganic copper, such as that in drinking water and copper supplements, largely bypasses the liver and enters the free copper pool of the blood directly. This copper is potentially toxic because it may penetrate the blood/brain barrier [49]. The complexes of copper play an important role as potential drugs for therapeutic intervention in various diseases.

Copper exhibits its biochemical action as trace element as it is bound to ceruloplasmin, albumin, and other proteins, while as exogenously administered compounds in humans it is bound to ligands of various types forming complexes that interact with biomolecules, mainly proteins and nucleic acids. The multifaceted role of copper in human diseases has been described from a medicinal-chemical [50] and a biochemical view [51] focusing on the molecular physiology of Cu transport [52]. Much of the current research effort is cited on copper homeostasis [53] and its relation to iron metabolism [54] as well as the role of copper in biological processes related to human physiology and pathology [55,56]. While a lot of the functions that have been proposed to account for the homeostasis of inorganic non-complexed copper in humans have been described [52-54], only a limited number of review studies have focused on the multiple biochemical events which
could be directly implicated in the use of copper complexes in medicine. Numerous Cu(II) complexes of NSAIDs showing enhanced anti-inflammatory and antiulcerogenic activity, as well as reduced gastrointestinal toxicity compared to the uncomplexed drug, have been prepared and structurally characterized [57].

Abdul et al have worked on copper(II) complexes such as bis(acetato)tetrakis(imidazole) copper (II), [Cu(OAc)_{2}(Im)_{4}], bis(acetato)bis(2-methylimidazole) copper(II), [Cu(OAc)_{2}(1,2dmIm)_{2}], and bis(acetato)bis(μ-acetato)tetrakis(N-methylimidazole) copper(II) hexaaquo, [Cu_{2}(OAc)_{4}(NmIm)_{4}•6H_{2}O]. Intramuscular administration of various doses of Cu(OAc)_{2}(Im)_{4} ranging from 10 to 100 mg/kg body mass to overnight fasted rats decreased blood glucose levels in a dose-dependent manner. Intramuscular administration of Cu(OAc)_{2}(Im)_{4} to diabetic rats caused a reduction in blood glucose levels and improved their tolerance for glucose[57].

The same pattern of hypoglycemia, although less pronounced, was observed for Cu_{2}(OAc)_{4}(NmIm)•6H_{2}O and Cu(OAc)_{2}(1,2dmIm)_{2}. Binary copper(II) acetate complex, the ligand imidazole, and the inorganic form of copper, such as copper(II) chloride, had no significant effect on blood glucose level. These results indicate that the hypoglycemic activity of these complexes varies with the imidazole ligand and structure of the complex.

Copper (II) (3,5-diisopropylsalicylate)_{2} is lipophilic and possesses superoxide dismutase bioactivity. Prior administration of this compound to male rats appeared to attenuate the severity of streptozotocin-induced diabetes as assessed by glycosuria and glucose tolerance. Diisopropylsalicylate, which has no superoxide dismutase activity, did not alter the severity of streptozotocin-induced diabetes. Rats treated with the copper complex, with Streptozotocin or with a combination of the two agents gained 50% less weight than untreated controls, or rats treated with diisopropylsalicylate [58].

Tripathi I.P et al has synthesized, characterized three Cu (II) metal complexes such as [Cu(en)_{3}] SO_{4}, [Cu (en)_{3}] 2Cl, [Cu (en)_{3}] 2NO_{3} and evaluated % of α- glucosidase inhibition. All three complexes possess α-glucosidase inhibition activity, among them [Cu (en) 3] 2NO_{3} have the highest α-glucosidase inhibition of 67.33% at 1mg/ml, having IC_{50} value 0.4755 mg/ml I comparison with standard Acarbose. In this complex the % inhibition of α-glucosidase may be due to the presence of NO_{3}^{2-} species [59].

Copper chelating agent exhibits hypoglycemic effect in the treatment of type II diabetes. The treatment with copper chelating agent tetrathiomolybdate decreased both serum copper ion and ROS levels and consequently ameliorate glucose and lipid metabolism in diabetic db/db mice [60].
Cobalt

Cobalt is considered to be an essential trace element which has wider application as therapeutic agents in pharmacological fields. Cobalt chloride (CoCl₂) decreases the glycemia of diabetic rats by augmentation of GLUT-1 gene expression [61].

Vaidya and Choure [62] observed that Co complex with glimepiride found to be more effective in bringing down the blood glucose level. Glimepiride is a sulphonylurea drug that is used as an anti-hyperglycaemic agent for the oral therapy of type 2 diabetes mellitus. Streptozotocin induces diabetic rats were given 0.035gm/kg of drug and complexes orally in canulla separately. The glimepiride drug and Co complexes show a decrease in the blood glucose in 9 hours. Glucosaminic acid-cobalt chelate has been reported to be effective as an antidiabetic agent.

The glycemic lowering effect of glucosaminic acid-cobalt chelate has been reported to be effective agent for diabetes [63]. Cobalt therapy may prove effective in improving the impaired antioxidant status during the early stage of diabetes [64, 65].

Chromium

Chromium is the most important micronutrient for humans according to the biologists. The two most common forms of chromium are trivalent chromium (III) and hexavalent chromium (VI). Chromium (III) is the principal form in foods as well as the form utilized by the body [66]. It is an essential element required for normal carbohydrate and lipid metabolism [67].

Y Yinan Hua et al in their review examined emerging reports on the effect of chromium, as well as molecular and cellular mechanisms by which chromium may provide beneficial effects in alleviating insulin resistance. Chromium has been shown to improve insulin sensitivity and alleviate cardiovascular functions, in a number of animal models of type-2 diabetes, thereby giving credence to the argument that chromium may possess beneficial effects in countering these conditions. These beneficial effects of chromium, together with its wide safety profile, may justify its use as an adjunct therapy in the management of insulin resistance and type-2 diabetes [68].

A putative mechanism by which chromium augments cellular glucose uptake is summarized in the pathways described in the figure 3, highlighting only those molecules that have been shown to be affected by chromium both in-vivo and in-vitro. Chromium has been shown to enhance the kinase activity of insulin receptor β, to increase the activity of downstream effectors of insulin signaling pI3-kinase and Akt and to enhance Glut4 translocation to the cell surface. Chromium also down-regulates PTP-1B, the negative regulator of insulin signaling and alleviates ER-stress within the cells, rescuing IRS from JNK-mediated serine phosphorylation and subsequent ubiquitination.
Transient up regulation of AMPK by chromium leads to increased glucose uptake. Chromium mediates cholesterol efflux from the membranes causing glut4 translocation and glucose uptake [69].

Leigh et al., in their studies used Chromium (Cr) picolinate (CrPic) and brought about a relationship among Cr status, diabetes, and associated pathologies has been established. Virtually all trials using CrPic supplementation for subjects with diabetes have demonstrated beneficial effects. Thirteen of 15 clinical studies (including 11 randomized, controlled studies) involving a total of 1,690 subjects (1,505 in CrPic group) reported significant improvement in at least one outcome of glycemic control. All 15 studies showed salutary effects in at least one parameter of diabetes management, including dyslipidemia. Positive outcomes from CrPic supplementation included reduced blood glucose, insulin, cholesterol, and triglyceride levels and reduced requirements for hypoglycemic medication. The greater bioavailability of CrPic compared with other forms of Cr (e.g., niacin-bound Cr or CrCl3) may explain its comparatively superior efficacy in glycemic and lipidemic control [70].

Yang et al. [71] evaluated the effects of a novel synthetic chromium (D-phenylalanine)3 complex on insulin-sensitivity, plasma lipid profile and oxidant stress in a mouse model of type II diabetes. Plasma glucose levels and total serum cholesterol to high-density lipoprotein ra-

tio following intra-peritoneal insulin-challenge (1 U/kg) to obese ob/ob (+/++) mice treated with Cr (D-Phe)₃ (150 µg/kg/day for 6 weeks) were significantly lower compared to vehicle-control. The complex also inhibited lipid-peroxidation in vitro, in a concentration dependent manner.

Figure 3: Mechanism of Cr augmenting the cellular glucose uptake.

Sahin et al. [72] evaluated the metabolic effects of chromium picolinate (CrPic) in a rat model of type II diabetes mellitus. The addition of CrPic in the treatment lowered glucose by an average of 63%, total cholesterol by 9.7% and triglycerides by 6.6%. CrPic treatment also lowered free fatty acid levels by 24%, blood urea by 33%, and creatinine level by 25%, and reduced the severity of glomerular sclerosis.
Tungsten

Tungsten, also known as wolfram when orally administered as Sodium tungstate preserves the pancreatic beta cell function in diabetic rats. Gomez et al [73] in their work with Sodium tungstate on healthy and streptozotocin-induced diabetic rats were treated for one, three or six weeks, after which the species of Tungsten (W) in serum were analyzed. An increase in serum W with treatment time was observed. After six weeks, the serum W concentration in diabetic rats (70 mg L(-1)) was about 4.6 times higher than in healthy specimens. The results revealed that the stability of the complexes between W and proteins is not too high enough to remain unaltered during protein separation by SDS-PAGE in denaturing and reducing conditions. Further the procedures for in-solution tryptic digestion and for ESI-MS analysis in MeOH/H2O/with 0.1% formic acid could be used for protein identification without large loss of binding between W and proteins.

Cirera et al. [74] in their work highlighted the use of tungsten (VI) compound for the preparation of an oral medicament for lowering blood sugar in a human suffering from Type 1 (IDDM) or Type 2 (NIDDM) diabetes mellitus. Compared with the known insulin-mimicker vanadium compositions, the pharmaceutical compositions of the invention have the advantage of providing a much lower oral toxicity, both short- and long-term. Compared with insulin, the pharmaceutical compositions of the invention do not present the adverse effect of inducing hypoglycemia when administered in excess. The present invention solved the above-mentioned problem of having an appropriate insulin-mimicker drug for the oral treatment of diabetes mellitus, by providing a composition comprising an effective amount of a compound of tungsten (VI) with a pharmaceutically acceptable chemical moiety, or a hydrate of said compound, in combination with a pharmaceutically acceptable carrier, for use as a medicament.

Barbera et al. [75] observed that oral administration of tungstate (2 mg/ml sodium tungstate in 0.9% NaCl) for 16 days normalize glycemia and glucose hepatic metabolism in streptozotocin-induced diabetic rats.

Heidari et al. [76] suggested that sodium tungstate protects pancreatic beta cells from STZ-induced cell damage. Islets volume density, mean islets volume, and mass of beta cells, islets, and pancreas were significantly higher in sodium tungstate treated STZ-induced diabetic rats.

Kawasaki et al. [77] indicated that tungstate regenerated pancreatic beta-cells population in neonatal STZ rats, a type II diabetes model. Tungstate administration enhances the insulin activity rather than increased insulin levels. Tungstate-treated STZ-diabetic rats showed a significant reduction in fluid and food intake, plasma glu-
cose, triglycerides, and free fatty acid levels, and improved tolerance to glucose [78].

Fernandez-Alvarez et al. [79] indicated that tungstate treatment redeveloped a stable, functional pancreatic beta cell population which maintains glucose level. Tungstate treatment increases extra-islet \(\beta\)-cell replication without any change in intra-islet \(\beta\)-cell replication rates. PDX-1 gene expression studies revealed that the treatment stimulates an increase in insulin-positive cells located close to ducts, as well as PDX-1 positive cells scattered in the exocrine tissue, suggesting active neogenesis.

Tungstate improves pancreatic function through a combination of hyperglycemia-independent pathways and through its own direct and indirect effects, whereas the MAPK pathway has a key role in the tungstate-induced increase of beta cell proliferation [80].

**Managanese**

Manganese (Mn) plays a key role in a number of physiologic processes and is considered to be essential for the carbohydrate, amino acid and cholesterol metabolism. The human body does not require much of this element, but it acts as activator of various enzymes responsible for carbohydrate, lipid and amino acid metabolism. Additional enzymes make use of manganese to build up strong and healthy bones [66].

Gluck et al. [81] observed that \(d\)-chiro-inositol (DCI) and manganese sulfate reduced hyperglycemia even more effectively (40%) as compared to control animals. They suggested that DCI and manganese are combined in vivo in the cell in the form of chelated insulin mediator glycans such as INS-2. In addition, both phosphoprotein phosphatases PP2C and PDHP, which activate glycogen synthesis and pyruvate oxidation, require manganese and/or magnesium for bioactivity.

Coppey et al. [82] in their work studied on M40403 which is a manganese(II) complex with a bis(cyclohexylpyridine)-substituted macrocyclic ligand that was designed to be a selective functional mimetic of superoxide dismutase. Treatment with M40403 significantly improved diabetes-induced decrease in endoneurial blood flow, acetylcholine-mediated vascular relaxation in arterioles that provide circulation to the region of the sciatic nerve, and motor nerve conduction velocity (\(P<0.05\)). M40403 treatment also reduced the appearance of superoxide in the aorta and epineurial vessels and peroxynitrite in epineurial vessels. Treating diabetic rats with M40403 reduced the diabetes-induced increase in thiobarbituric acid reactive substances in serum but did not prevent the decrease in lens glutathione level. Thus, M40403 provides a useful tool to evaluate the roles of superoxide in disease states and also provide additional evidence that diabetes-induced oxidative stress and the generation of superoxide and perhaps peroxynitrite may be partially responsible for
the development of diabetic vascular and neural complications.

EUK-8 is a member of a new class of synthetic salen-manganese compounds with low toxicity that possess catalytic superoxide dismutase, peroxidase, and catalase activity that can inactivate superoxide and nitrogen oxides (e.g., peroxynitrite and nitrogen dioxide). The observations was that the EUK-8 administration inhibited the adoptive transfer of type 1 diabetes to NOD mice. In addition, administration of EUK-8 to NOD mice with established autoimmunity completely prevented the development of type 1 diabetes for up to 1 year in age, even though the treatment was discontinued after 35 weeks of age [83].

Conclusion

Recent advancement in medicinal chemistry the metal complexes play a significant role in treating DM. In this review, the metal complexes being a platform in designing novel therapeutic drugs has found to be effective in treating this chronic disorder, which cannot be fulfilled by pure organic compounds. Metallo–allixinate complexes are now evolving in a new Metallomics world, and the fruitful outcome may offer a novel medicine with high quality of anti-diabetic and anti-metabolic syndrome activity for humans in the future. Further for their therapeutic applications, it is necessary to know their mechanism of action, cellular target and toxicological studies and that can be done with the aid of molecular docking studies.

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