EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 9
211-217
Year: 2016

METAL COMPLEXES: EFFECTIVE APPROACH FOR THE MANAGEMENT OF DIABETES MELLITUS

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Article Received on 12/07/2016 **Article Revised on 02/08/2016** **Article Accepted on 23/08/2016**

ABSTRACT
Inorganic medicinal chemistry is a rapidly developing field with enormous potential for applications, which offers new possibilities to the pharmaceutical industry. For example, the titanocene dichloride is already in clinical use, and antimetastatic activity of a range of Ru (III) complexes is also well established. Ligand design allows paramagnetic ions to be targeted to specific organs. Such designed ligands also enable the targeting of radiodiagnostic and radiotherapeutic isotopes. There is a significant progress in understanding the coordination chemistry and biochemistry of metal ion(s) containing complexes such as antibacterial, antifungal, antiarthritic, antiinflamatory and antiulcer drugs. Progress in coordination chemistry is strongly dependent on understanding not only the thermodynamics of reactions, but also the kinetics of metal complexes under biologically relevant conditions. The expanding knowledge of the role of metals in biochemistry is expected to provide scope for the design of new drugs in many other areas such as neuropharmaceutical and hyperglycemic agents. Therefore this review is design to focus on the importance of metal complexes in managing one of the global public health problem in the twenty-first century called diabetes mellitus.

KEY WORDS: Metal complexes, Diabetes mellitus, Pharmaceutical.

INTRODUCTION
Diabetes mellitus (DM), a metabolic dysfunction which develops many secondary complications and making it the 5th leading causes of death of human. Globally, in 2000, the total number of people suffering with diabetes is estimated nearly about 171 million and is expected to increase 366 million by 2030 if successful strategies are not implemented for prevention and control[1-3] DM is classified as either insulin-dependent type 1 DM (caused by destruction of insulin producing pancreatic β cells) or noninsulin-dependent type 2 DM (caused by aging, obesity, or other environmental factors) which are treated by daily injections of insulin or several types of synthetic therapeutic substances respectively. Unfortunately, these methods of treatment have some defects. Injecting insulin several times in a day is painful and elevates the level of patient stress, especially in young people and moreover administration of synthetic therapeutic substances often exhibits some serious side effects.[4] Chronic hyperglycemia may cause alterations in the status of trace elements in the body and thus the essential trace elements such as zinc, chromium and manganese are deficient in DM. Therefore, trace elements may play important functions for glucose and lipid metabolisms, particularly insulin function in DM.[5] Implementing new therapies that can manage glucose level are of great importance in recent trends. Metallotherapy 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.[6-7] 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).[8] Vanadium, chromium, copper, cobalt, tungsten and zinc were found to be effective for treating diabetes in experimental animals.[2] 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.

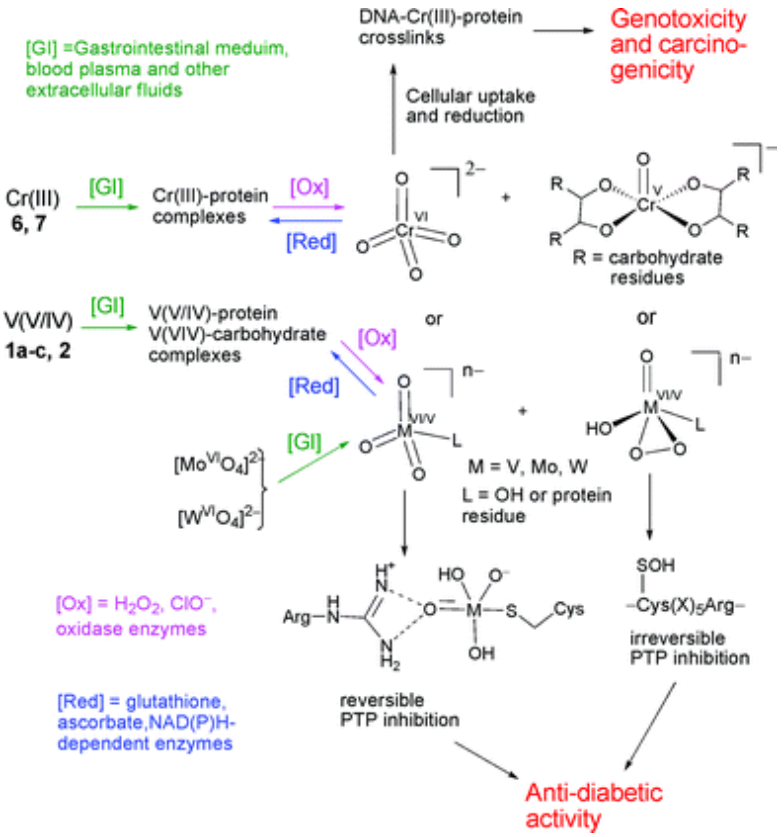

Fig.1 Proposed mechanism of protein tyrosine phosphatase inhibition in the anti-diabetic activities of Cr(III), V(IV), Mo(VI), and W(VI)complexes[9-10]

Transition metal complexes in diabetes therapy

Many metal compounds play a vital role in living systems and found to elicit potential effect in the pathogenesis and complication of the disease. The metal, its oxidation state, the number and types of coordinated ligands, and the coordination geometry of the complexes can provide a variety of properties. A characteristic of metals is that they easily lose electrons to form positively charged ions, which tend to be soluble in biological fluids. It is in this cationic form metals play their role in biology. Metal ions are electron deficient, whereas, most biological molecules such as proteins and deoxyribonucleic acid are electron rich. The attraction of these opposing charges leads to a general tendency for metal ions to bind to and interact with biological molecules and elicit pharmacological activity. These variables provide enormous potential diversity for the design of metallo-drugs.[11] The transition metal ions are responsible for proper functioning of different enzymes.[12] Chronic hyperglycemia may cause alterations in the status of trace elements in the body and thus the essential trace elements such as zinc, chromium and manganese are deficient in diabetes mellitus. Therefore, trace elements may play an important functions for glucose and lipid metabolisms, particularly insulin function in Diabetes mellitus.[4] The amount of metals present in the human body is approximately 0.03% of the body weight.[13]

Metal based drugs to treat diabetes with metal complexes are first studied by Coulson and Dandona in the year 1980 and reported that Zinc chloride (ZnCl2) stimulate lipogenesis in rat adipocytes similarly to the action of insulin.[1] The idea of using metal ions for the treatment of diabetes originates from the report in 1899. Vanadium, chromium, copper, cobalt, tungsten and zinc were found to be effective for treating diabetes in experimental animals. The orally active metal complexes containing vanadyl oxidovanadium (IV) ion and cysteine or other ligands were first proposed in 1990.[14] Many metal complexes have been synthesized and evaluated to overcome the problems of painful insulin injection and the side effects for type 1 or type 2 diabetes mellitus. So far chromium, manganese, molybdenum, copper, cobalt, zinc and vanadium ions have been reported to exhibit insulin-mimetic or enhancing insulin like properties under *in vitro* and *in vivo* condition.[13] Metal compounds induce hypoglycemia by a wide variety of mechanisms. Possible mechanisms of antidiabetic insulin-like effects are due to the activation of insulin receptor signaling (chromium, magnesium), 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).[8;13]

COPPER

Copper (Cu) is an essential metallo element that is required for a variety of molecules to maintain the normal structures and functions and for cells to live, grow and proliferate. Copper is found in the liver, gallbladder, lungs and heart and is needed for synthesis of hemoglobin, proper iron metabolism and maintenance of blood vessels.[15] Copper plays an important role in electron transfer reactions.[2] Copper complexes have different pharmacological actions such as antiulcer, anticonvulsant, anticancer, and antidiabetic activity[16,17] proposed that copper (II)-picolinate [Cu (Pic) 2] may be a potent alternative antidiabetic agent and Cu (Pic)2 complexes by single intraperitoneal injection, exhibited a higher hypoglycemic effect on treatment with STZ induced diabetic mice.

Copper ions are also involved in the pathogenesis of type II diabetes and copper chelating agent exerts a beneficial 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 mice.[18] Treatment with copper sulfate can exert beneficial effects in diabetes with preservation of cell function by reducing free radicals or through reduction in glucose levels.[19]

MOLYBDENUM

Molybdenum (Mo), an important trace element plays a key role for participation in the active sites of metallo-enzymes. It is capable of forming complexes with many compounds of biological importance and excreted in the form of simple molybdate ion, [MoO4]2-. Molybdenum is essential for life and is much less toxic than many other metals of industrial importance. Most organisms including human beings require molybdenum for their existence. Various forms of molybdenum have shown insulin mimetic properties and being used as anti-diabetic agent. Sodium molybdate (Na2MoO4) and its complex compounds such as cis- MoO2L2 (L ¼ maltol (3-hydroxy-2-methyl-4 pyrone)) were found to reduce the levels of blood glucose significantly and also free fatty acids [20]. Molybdenum/ascorbic acid complex showed some significant insulin-mimic and cardio protective effects.[21]

CHROMIUM

Chromium is an essential element required for normal carbohydrate and lipid metabolism. Chromium, Cr (III) the most stable oxidation state, is considered as an essential micronutrient for humans by many nutritionists. In 1950s, Schwarz and Mertz conducted experiments on nutrient-deficient rats and suggested that a biological Cr (III) compound could act as a nutritional enhancement to glucose metabolism. The Cr (III) complexes with propionate, L-histidinate, Dphenylalaninato and nicotinato (niacinato or 3- pyridinecarboxylato) ligands as well as Cr (III) - enriched yeast have been proposed as safer antidiabetics.[2] Chromium supplementation significantly improves glycemia among patients with diabetes, but do not show any significant effect on glucose metabolism in healthy subjects.[22] Chromium picolinate (CrPic) may have a possible antidiabetic effect in insulin-resistant 3T3-L1 adipocytes through the involvement of p38 Mitogen-activated protein kinase (MAPK). Treatment with Chromium picolinate (CrPic) could partially reduce hyperglycemia and insulin induced insulin resistance.[23]

TIN

Tin is an ultra-trace element in humans and generates a wide variety of biological activities deriving from its chemical character. It has been suggested that the amount of tin found in a healthy diet should be the value used to describe appropriate intake. Vanga bhasma, an Ayurvedic preparation of tin is used traditionally for treatment of diabetes. Vanga bhasma is purified and calcinated form of tin with additional herbs.[24]

COBALT

Cobalt is one of the most important trace elements and has therapeutic value in pharmacological doses. In the form of vitamin B12 (Cobalamin), this metal plays a number of crucial roles in many biological functions. Vitamin B12 is the only metal-containing water-soluble vitamin that is stored in the liver and must come from the diet. Cobalamin is necessary for deoxyribonucleic acid (DNA) synthesis, formation of red blood cells, maintenance of the nervous system, growth and development of children. Cobalt was found to boost the effects of insulin and its action. Cobalt chloride (CoCl2) works by augmentation of GLUT-1 gene expression and found to decreases the glycemia of diabetic rats. Treatment of STZ diabetic rats with cobalt chloride showed significant decline in blood glucose, no effect on plasma insulin and significant increase in liver glycogen showing no effect on muscle glycogen. Since cobalt is toxic to patients in its single and pure form various cobalt complexes has been suggested, which could reduce the potential toxicity of cobalt without impacting on its effectiveness.[2] Glucosaminic acid-cobalt chelate has been reported to be effective as an antidiabetic agent.[25] Cobalt therapy may prove effective in improving the impaired antioxidant status during the early state of diabetes and ascorbic acid supplementation at this dose potentiates the effectiveness of cobalt action.[26-27]

VANADIUM

The human body is estimated to contain 50-200 g of vanadium. In each organ, vanadium is present at very low concentrations, 0.01-1 g, and is thought to play a role in a wide variety of physiological processes. So far number of vanadium complexes have been developed; most of them have insulin-mimetic properties.[7] In 1985, it was discovered that a simple vanadium salt, sodium orthovanadate, when added to drinking water, could reverse most of the diabetic symptomatology of experimentally-diabetic rats, was exceptionally enticing.

Vanadyl complexes with maltol (3-hydroxy-2-methyl-4-pyrone) and kojic acid (3- hydroxy-2-hydroxymethyl-4-pyrone) which possess insulin mimetic activity and low toxicity profile, have been proposed for clinical use in humans. Oxovanadium(IV) with maltol/ethylmaltol has shown enhancing insulin mimetic activity in experimental diabetic animals in recent years.[13] Since 1990, a wide class of vanadyl oxidovanadium (IV) complexes involving bis(methylcysteinato) [VO(cysm) 2]- (1990), bis(L-tartrato) [(V2O4)(L-tart)2]- (1990), bis(maltolato) [VO(ma)2]- (1992), bis(pyrrolidine-N-dithiocarbamato) [VO(pdc)2]- (1994), bis(picolinato) [VO(pa)2]- (1995), and bis(1-oxy-2- pyridinethiolato) [VO(opt)2]- (1999) have been found to improve the hyperglycemic state in streptozotocin induced diabetes in rats (STZ-rats). In particular, studies on VO(pa)2 with a VO(N2O2) coordination environment and bis(3-hydroxy-4-pyronato) [VO(3hp)2]-, bis(1,4-dihydro-2-methyl-4-oxo-3-pyridinolato)- and bis(1,2-dihydro- 2-oxo-1 pyrimidinolato) oxidovanadium (IV) complexes 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.[14] The discovery that modification of the vanadium core by chelation could improve bio distribution and tolerability was found to be a crucial step in development of vanadium compounds for treatment of diabetes. Bis oxovanadium(IV) is the first vanadium complexes shown superior activity over other inorganic vanadium sources (e.g. VOSO4 or NaVO3) both *in vivo* and/or *in vitro* studies.[13-28] Earlier reports have shown that VV-dipicolinato complex has more insulin enhancing effect compared to BMOV. New orally active diketonato complexes such as VO (acac)2 and bis(furancarboxylato) oxovanadium (IV) have shown glucose lowering ability comparable to 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.[13]

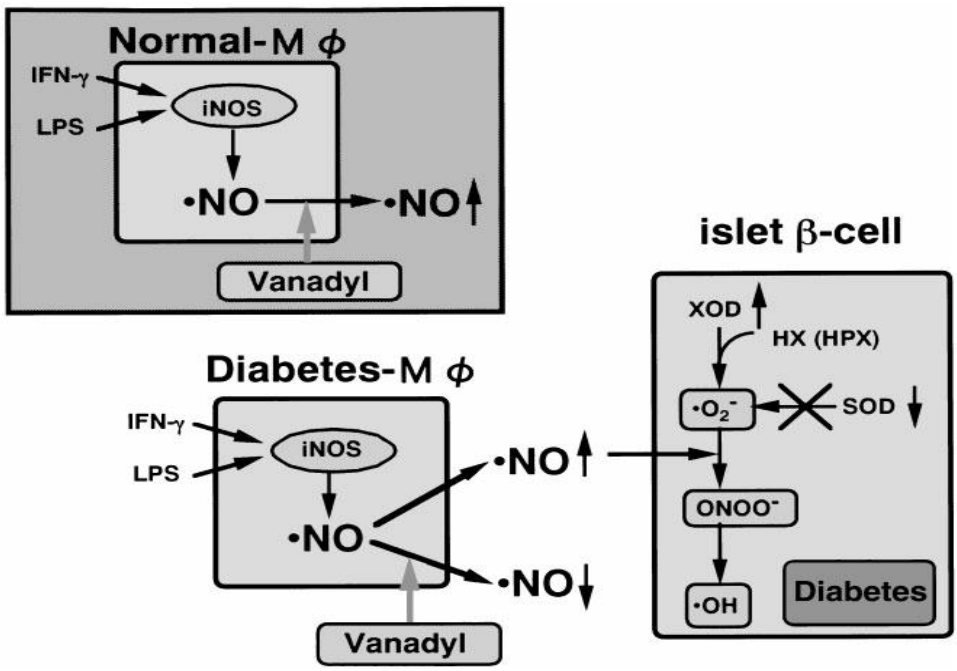

Fig.2 A possible mechanism for vanadium-dependent prevention of the onset of diabetes mellitus in rats as related to NO release from macrophages.[29-30]

ZINC

Zinc, an essential trace element is an activator for more than three hundred enzymes in the body[31] and plays a major role in various metabolic pathways including glucose metabolism. The antidiabetic activity of zinc is currently thought to be its important role. In fact, zinc and diabetes interact at several points during metabolism in a cell. In the relevance of zinc to diabetes mellitus, zinc is known to be present in insulin, coordinated by three nitrogen atoms from histidines and three water molecules in an irregular octahedral environment, which is also believed to have a functional structure. Zinc is also known to keep the structure of insulin[32], and has a role in insulin biosynthesis, storage and secretion.[33] There are several zinc transporters in pancreatic cells[34] like zinc transporter which has a potent role in insulin secretion.[35] Zinc promotes hepatic glycogenesis through its actions on the insulin pathways and thus improves glucose utilization. Surprisingly, zinc was found to have important physiological and pharmacological functions involving an insulin-mimetic activity. Diabetes is usually accompanied by zincuria. Higher zinc intake has also been associated with a slightly lower risk of type 2 diabetes in women.[7] For

diabetes mellitus with an increased risk of zinc deficiency, more important clinical data would be needed because zinc has an insulin-mimetic effect and protects against oxidative damage associated with the disease.[36] 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 been found to exhibit anti-diabetic activity and ameliorate 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-Ndithiocarbamato) Zn [Zn(pdc)2] 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(O4) coordination environment helped to induce high quality anti-diabetic properties and also a few complexes exhibited not only antidiabetic activity, but also anti-metabolic syndrome activity in respect to hypoglycemic effect and adiponectin secretion enhancing effect, when it was given to Streptozotocin induced rats by daily intraperitoneal injections.[13] Zinc supplementation produced a significant improvement in glucose disposal.[2]

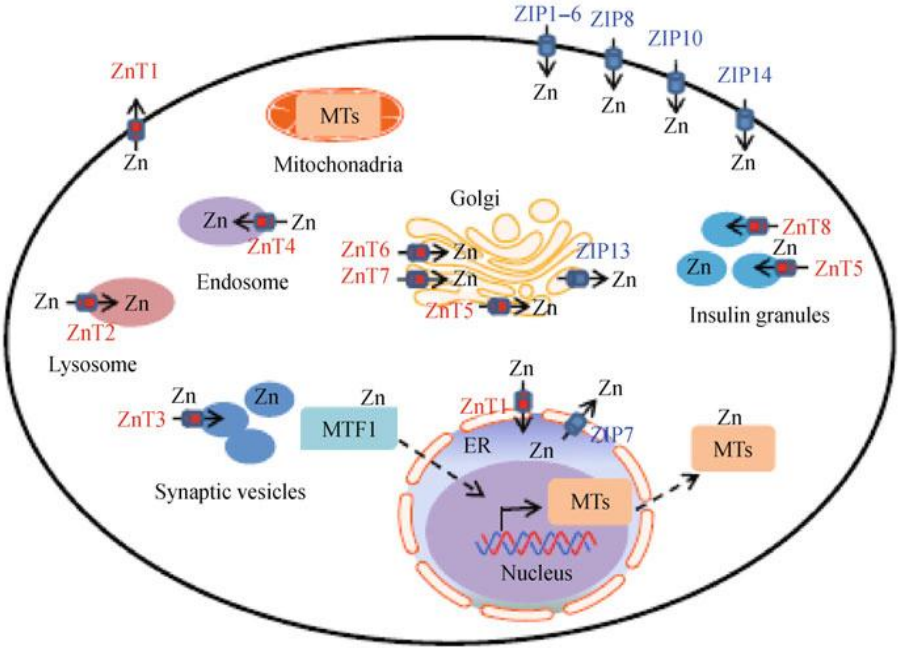

Fig.3 Subcellular localization of Zn transporters and MTs. Localization and potential functions of Zn transporters from the Slc39/ZIP (blue) and Slc30/ZnT (red) families, MT, and metal response element (MRE)-binding transcription factor 1 (MTF1) within the cell. Arrows show the predicted direction of Zn mobilization. ER, endoplasmic reticulum.[37]

TUNGSTEN

The antidiabetic properties of sodium tungstate have been widely reported. Sodium tungstate has shown a remarkable normoglycemic effect in several animal models of diabetes and found to be low toxic in diabetic and healthy animals.[38-39] Administration of this metal enhances the insulin activity rather than increased insulin levels[40] and also treatment with this metal found to increases extra-islet –cell replication without modifying intra islet -cell replication rates.[41] 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.[42-44]

MANGANESE

Manganese (Mn) seems to be particularly important for the proper functioning of enzymes and it plays an important role in a number of physiological processes as a constituent or activator of some enzymes needed for metabolism process. The human body does not require much of this element, but several biological uses of manganese for the proper functioning of the body, and it is often included in small doses in mineral supplements. These enzymes have a variety of different functions. Some aid in repairing damage to the body. Others are antioxidants. Additional enzymes make use of manganese to aid in the development of strong and healthy bones. It is an essential component of metalloenzymes such as Se–cys containing glutathione peroxidase, Cu/Fe cytochrome C oxidase or different types of superoxide dismutase, all of them important in intra- and extra-cellular antioxidant defense.[45] Synthetic manganese porphyrins can be used as potent therapeutic agent in diabetes. 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). EUK-8 administration inhibited the adoptive transfer of type II diabetes and completely inhibited spontaneous disease progression in pre-diabetic NOD mice with established cell autoimmunity.[46]

CONCLUSIONS

In this review, an overview of the various metallic compounds which have shown promising results in the treatment of diabetes has been presented. The metal compounds offer new properties that cannot be found amongst purely organic agents. Although various metals like chromium, manganese, molybdenum, tungsten, copper, cobalt, zinc and vanadium were reported to exhibit insulin mimetic activity out of these a wide class of vanadium, copper and zinc complexes was found to be effective for treating diabetes in experimental animals. Since metallotherapy overcome the problems of painful insulin injection and side effects for type 1 or type 2 DM, It seems that good opportunities exist to exploit metal and metal based drugs in the discovery and development of alternative tool for the prevention of diabetes. Further, understanding of the mechanism of action, cellular target and toxicological studies are required for their therapeutic applications. This area should be essentially explored in adequate clinical trials so that diabetes related problems can be resolved.

Conflict of interest

The author declare no conflict of interest

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