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Review Article

METAL COMPLEXES IN THE MANAGEMENT OF DIABETES MELLITUS: A NEW THERAPEUTIC STRATEGY

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ABSTRACT

The medicinal uses and applications of metals and metal complexes are of increasing clinical and commercial importance.More than 2 - 8% of world's population is suffering from diabetes. The correlation of diabetes and an imbalance in metal makes metal -based therapy as an attractive proposition. The development of anti-diabetic metal complexes replacing insulin injection to regulate sugar levels appears to be interesting. It has been understood that control of the glucose level in the blood plasma has been achieved by administration of vanadium and zinc in form of inorganic salts. Number of vanadium and other metal complexes has been developed and all of which have shown insulin-mimetic properties. This paper mainly focus extensive role of metal and its complexes in biological systems and its therapeutic applications.

Keyword: Diabetes, Metals, Insulin-mimetic activity, Pancreatic Beta-Cell.

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].

Diabetes is a condition primarily defined by the level of hyperglycemia giving rise to risk of microvascular damage like retinopathy, nephropathy and neuropathy. It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications like ischemic heart disease, stroke and peripheral vascular disease and diminished quality of life[3]. Numerous factors, such as genetics, environment, eating habits, physiological state, hormones and stress are considered to be associated with the development of DM [4].

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, spiritual stress, 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].

Metallotherapy is a new therapeutic strategy being used for the treatment of a variety of ailments viz. diabetes, rheumatoid arthritis, inflammatory and cardiovascular diseases as well as diagnostic agents. Some of the examples of the role of metal ions in biological systems are iron porphyrin complex of hemoglobin in red blood cells (RBCs) for oxygen transportation and storage, the magnesium porphyrin complex of chlorophyll in green plants for photosynthesis, and cobalt in the coenzyme B12 for the transfer of alkyl groups from one molecule to another molecule. The amount of metals present in the human body is approximately 0.03% of the body weight [3,7]. The following table (Table 1) illustrates the therapeutic activity of various metal complexes approved for clinical applications.

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. The ligands not only control the reactivity of the metal, but also play critical roles in determining the nature of interactions involved in the recognition of biological target sites such as DNA, enzymes and protein receptors.

These variables provide enormous potential diversity for the design of metallodrugs [9].The oxidation state of the metal ion can be decisive in regulating the immediate *in vivo* response to metal-based pharmaceutical agents, often making the difference between a beneficial and a toxic response at the same administered dose of a metal ion, and also directing towards the metabolic pathways by which the compound will be integrated [10].

Metal based drugs to treat diabetes with metal complexes are first studied by Coulson and Dandona in the year 1980 and reported that $ZnCl_2$ 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. The orally active metal complexes containing vanadyl (oxidovanadium(IV) ion and cysteine or other ligands were first proposed in 1990 [6]. 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 DM. So far chromium, manganese, molybdenum, copper, cobalt, zinc and vanadium ions have been reported to exhibit insulin-mimetic or enhancing insulin like properties under *invitro* and *in vivo* condition[7].

Of great interest, hypoglycemiainduced bymetal compounds works by variety of mechanisms. Probable mechanisms of antidiabetic being insulin-like effects (chromium, magnesium), antioxidant effect (cobalt, manganese, tungstate, zinc),inhibition of enzyme 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) [7,8]. Table 2 depicts the metal and the complexes to induce hypoglycemia in diabetic patients [4].

Table 1 Metal Complexesas Therapeutic Agents.

Element	Compound	Uses	Trade names/Comments
Approved Agents (mostly US or worldwide)			
Li	Li_2CO_3	Manic depression	Camcolit; Cibalith-S; Lithane (of many)
Fe	$[Fe(NO)(CN)_5]^{2-}$	Vasodilation	Nipride. For acute shock. NO release
Ga	$Ga(NO_3)_3$	Hypercalcemia of malignancy	Ganite. Possible anticancer agent. In clinical trials for use in lymphomas
As	As_2O_3	Anticancer agent	Trisenox. Use in acute promyelocytic leukemia
Ag	$AgNO_3$	Disinfectant	Neonatal conjunctivitis
	Ag(sulfadiazene)	Antibacterial	Flamazine; Silvadene; 1% cream is used in the treatment of burns.
Sb	Sb^{III}(tartarate)	Antiparasitic, leishmaniasis	Tartar Emetic Stibophen; Astiban
Pt	cis-$[Pt(amine)_2X_2]$	Anticancer agents	Platinol; Paraplatin; Eloxatine Testicular, ovarian, colon cancers
Au	$Au(PEt_3)$(acetylthioglucose)	Rheumatoid arthritis	Ridaura. Orally active
Bi	Bi(sugar)polymers	Antiulcer; antacid	Pepto-Bismol; Ranitidine Bismutrex; De-Nol
Hg	Hg-organic compounds	Antibacterial Antifungal	Thiomersal; mercurochrome (amongst many) Slow release of Hg^{+2}
Agents in Clinical Trials			
Pt	Polynuclear PtIV species	Anticancer agents	BBR3464, Satraplatin, AMD-473
Mn	Mn chelates	Anticancer agents	SOD mimics
Ru	trans-$[RuCl_4(Me_2SO)(Im)]^-$	Anticancer agent	NAMI-A; antiangiogenic
V	$VO(maltate)_2$	Type II diabetes	BMOV; insulin mimetic
Ln	$Ln(CO_3)_3$	Hyperphosphatemia	Fosrenol; phosphate binder

Table 2: Reports of Metal Ions and the Complexes with Antidiabetic Activity in Experimental Animals and the Subjects with DM.

Metal	Ionic form	Complex form
V	Vanadyl sulfate (VOSO4)	Bis(methylcysteinato) oxovanadium(IV) Bis(maltolato)oxovanadium(IV)
	Sodium vanadate ($NaVO_3$)	Bis(picolinato)oxovanadium(IV)
Cr		Bis(picolinato)chromium(III) Chromium polynicotinate
Mn	Manganese chloride ($MnCl_2$)	
Co	Cobalt chloride ($CoCl_2$)	
Zn	Zinc chloride ($ZnCl_2$)	Bis(picolinato)zinc(II) Bis(maltolato)zinc(II)
Se	Sodium selenite (Na_2SeO_3)	
Mo	Sodium molybdate (Na_2MoO_4)	
W	Sodium tungstate (Na_2WO_4)	

Vanadium

Humans usually consume 10-60 µg of vanadium through foods daily. The human body is estimated to contain 50-200 µg of vanadium. In each organ, vanadium is present at very low concentrations, 0.01-1 µg, and is thought to play a role in a wide variety of physiological processes. In tissues, approximately 90% of vanadium is bound with proteins and 10% is present in the ionic form. The importance of vanadium pertaining to the growth of rats and chicks has been determined, but this has not been established in humans [12].

Vanadium complexes with organic ligands have proved to be less toxic, with improved solubility and lipophilicity. Designing new vanadium complexes requires stereochemical considerations for binding the complexes with receptors such as glucose transporter and other enzymes, as well as consideration of the redox properties of vanadium [9]. So far number of vanadium complexes has been developed; most of them have insulin-mimetic properties [13].

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 [10]. It is a d-block metal which known to exist in a variety of oxidation states (-1, 0, +2, +3, +4 and +5) among which +3, +4 and +5 are accessible under physiological conditions in the form of $V^{+3,}$ vanadyl (VO^{2+}) and vanadate (VO^{3-}) respectively [11,12]. Vanadium exhibits a rich redox chemistry but in the medical context the oxidation states V(+4) and V(+5) appear to be of primary importance, both being found to participate in extra- and intra-cellular equilibria [12].

However, vanadyl is less toxic than the vanadate ion. 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 inhumans. Oxovanadium(IV) with maltol/ethylmaltol has shown enhancing insulin mimetic activity in experimental diabetic animals in recent years [7]. Since 1990, a wide class of vanadyl (oxidovanadium(IV) complexes involving bis(methylcysteinato) $[VO(cysm)_2]$- (1990), bis(L-tartrato) $[(V_2O_4)(L\text{-}tart)_2]$- (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 $VO(N_2O_2)$ 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 $VO(O_4)$ 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 [6].

The discovery that modification of the vanadium core by chelation could improve biodistribution and tolerability was found to be a crucial step in development of vanadium compounds for treatment of diabetes. Bis(maltolato) oxovanadium(IV) or BMOV is the first vanadium complexes shown superior activity over other inorganic vanadium sources (*e.g.* $VOSO_4$ or $NaVO_3$) both *in vivo* and/or *in vitro* studies [7,10] (Fig 1).

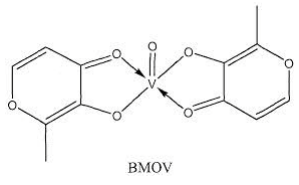

Fig. 1: Bis(maltolato)oxovanadium(IV), BMOV, the First Purpose Designed Vanadium-Based Insulin Enhancing Pharmaceutical Agent

Earlier reports haveshown that VV-dipicolinato complex has more insulin enhancing effect compared to BMOV. New orally active β-diketonato complexes such as $VO(acac)_2$ and bis(α-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 $VOSO_4$ [7].

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-based antidiabeticprodrug, bis(ethylmaltolato) oxovanadium(IV) (BEOV), the ethylmaltol analogue of BMOV. The overall objectives of this study were to assess the health effects of single, escalating doses of orally administered BEOV; determination of the pharmacokinetics parameters of BEOV from measured plasma, urinary, fecal and total biological fluids[V] and compare the bioavailability of a well-tolerated dose of oral BEOV and an equivalent molar dose of oral in bothfasted and fed state. The outcome of this initial clinical trial suggested that no observed adverse health effectsin any of the human volunteers including non-diabetic, gastrointestinal disturbances, liver and kidney function and blood parameters all remained within normal levels throughout the study. Pharmacokinetic analysis showed a clear, non-proportional, dose-dependence in vanadium uptake from BEOV, along with a more rapid and efficient uptake compared to that from $VOSO_4$.Fasted subjects absorbed more vanadium from BEOV than did fed subjects. Lastly, the relative bioavailability of vanadium from BEOV was estimated to be three times that of an equivalent dose of vanadium from $VOSO_4$, corroborating earlier results in experimental animals [10] (Fig 2).

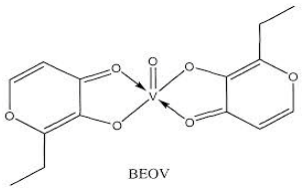

Fig. 2: Bis(ethylmaltolato) Oxovanadium (IV), BEOV, VanadiumBased AntidiabeticProdrug

In addition to the therapeutic effect of vanadium ion (Va+)and vanadium complexes, these vanadium compounds have a preventive effect on the onset of streptozocin STZ-induced diabetes in terms of nitric oxide released from the macrophages [11].

Zinc

Zinc is a natural component of insulin, a substance crucial to the regulation of sugar metabolism in all living and plays a major role in hundreds of zinc enzymes and in thousands of protein domains. In addition to vanadium complexes, zinc complexes have been proposed to be the new candidates in treating type 2 DM. In fact, zinc and diabetes interact at several points during metabolism in a cell. Zinc seems to have a similar action to insulin, in stimulating 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 [13]. 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 diabetes mellitus with an increased risk of zinc deficiency [14].

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 ameliorate hyperinsulinemia 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 $[Zn(pdc)_2]$ and bis(3-methylpyridine-2-sulfonato)Zn, respectively under *invitro* 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 in respect to hypoglycemic effect and adiponectin secretion enhancing effect, when it was given to STZ-rats by daily intraperitoneal injections[7].There is evidence that zinc is utilized in the beta cells of the pancreas to both store and release insulin as required. Release of insulin from the beta cells is accompanied by a loss of zinc. Sosupplementation ofzinc may produce a significant improvement in glucose level.

Copper

Copper (Cu) is an essential transition metals that is required for a variety of molecules to maintain their 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 seems to play a crucial role especially in electron transfer reactions[2]. Copper insufficiency results in several abnormalities of the immune system, abnormal metabolism of glucose and cholesterol, more oxidative damage [17]. Copper complexes have different pharmacological actions such as antiulcer, anticonvulsant, anticancer, and antidiabetic activity[16]. Yasumatsu et al.[18] reported that by single intraperitoneal injection copper (II)-picolinate $[Cu\ (Pic)\ _2]$ complexes have shown a higher hypoglycemic effect in animal models.

Copper (Cu(II)) chelator that prevents or reverses diabetic copper overload, thereby suppressing oxidative stress. Treatment with copper chelating agent like tetrathiomolybdatereduces both serum copper ion and ROS levels and consequently rises glucose and lipid metabolism in diabetic mice [19]. Copper sulfate treatment in diabetes showed beneficial effects with preservation of β-cell function by reducing free radicals or through reduction in glucose levels [20].

Chromium

Chromium is an essential element required for normal carbohydrate and lipid metabolism. 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. 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 particularly essential for glucose metabolism. The Cr (III) complexes had better bioavailability and more beneficial influences on the improvement of controlling blood glucose and proposed to act as safer antidiabetics [2]. Supplementation of chromium significantly improves glucose level among patients with diabetes but fails to show any significant effect on glucose metabolism in healthy volunteers [21]. Treatment with Chromium picolinate (CrPic) improves glycemic control in diabetic patients [22]. Chromium picolinate is more bioavailable than other supplemental forms of chromium and therefore may be more efficacious.

Cobalt

Cobalt is one of the most important trace elements in the world of animals and humans and finds therapeutic application in pharmacological fields. 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 DNA synthesis, formation of red blood cells and maintenance of the nervous system, growth and development of children. Cobalt is used to treat anaemia with pregnant women, because it stimulates the production of red blood cells.Cobalt was found to boost the effects of insulin and its action. Treartment with cobalt chloride ($CoCl_2$) decreases the glycemia of diabetic rats which may be mediated by gene expression of GLUT-1 mRNA. Treatment with cobalt chloride showed significant decline in blood glucose in STZ induced diabetic rats but no observed change in plasma/serum insulin levels of normal or diabetic rats. Cobalt is the most important contributor to metal ion toxicityin patients both in single and pure form. Different forms of cobalt complexes have been reported to reduce the potential toxicity of cobalt without modifying its therapeutic effect[2]. The glycemic lowering effect of glucosaminic acid-cobalt chelate has been reported to be effectiveagent for diabetes [23]. 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 [24,25].

Tungsten

Tungstate counteracts diabetes in the form of sodium tungstate. Studies in several animal models of diabetes have shown sodium tungstate to be an effective anti-diabetic agent and found to be less toxic both in diabetic and healthy animals [26, 27]. Administration of this metal enhances the insulin activity rather than increased insulin levels [28] and also treatment with this metal found to rise extra-islet β-cell replication without modifying intra islet β-cell replication rates [29]. 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 [30].

Manganese

Manganese (Mn) plays a key role in a number of physiologic processes and is considered tobe essential for the carbohydrate, amino acid and cholesterol metabolism. The human body does not require much of this element, but several biological uses of manganese are critical to the proper functioning of the body, and it is often included in small doses in mineral supplements. Manganese seems to be particularly important for the proper functioning of enzymes. 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 considered to be a key component of metalloenzymes such as Se–Cyscontaining glutathione peroxidase, Cu/Fe cytochrome C oxidase or different types of superoxide dismutase, which are in turn important for intra- and extra-cellular antioxidant defense mechanism[2]. Synthetic derivative of manganese found to be used as potent therapeutic agent in diabetes. Two newly classified antioxidants namely EUK-8 and EUK-134 reported to reduce the serum levels of glucose [31].

Molybdenum

Molybdenum (Mo), an important trace element plays a major role for participation in the active sites of metalloenzymes. Molybdenum is capable of forming complexes with many compounds of biological importance: carbohydrates, amino acids, flavins, porphyrins; but is probably taken up, transported, and excreted in animals as the simple molybdate ion, $[MoO_4]^{2-}$. 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. Molybdenum alongwith tungstate helps in the key transformations in the metabolism of nitrogen, sulphur, carbon, arsenic, selenium and chlorine compounds. This element plays a crucialrole in the structure of certain enzymes involving redox reactions [32]. Molybdenum in different forms have shown to possess insulin mimetic properties and hence it used in the treatment of diabetes. Sodium molybdate (Na_2MoO_4) and its complex compounds such as cis-MoO_2L_2 (L ¼ maltol (3-hydroxy-2-methyl-4 pyrone)) were found to reduce the levels of blood glucose significantly and also free fatty acids [33]. Combination of molybdenum and ascorbic acid exhibited significant insulin-like activites and also shown cardio protective effects [34].

Tin

Tin generates a wide variety of biological activities deriving from its chemical character. Tin is an ultra-trace element in humans. It has been suggested that the amount of tin found in a healthy diet should be the value used to describe appropriate intake. *Vangabhasma*, an Ayurvedic preparation of tin is used tradionally for treatment of diabetes. *Vangabhasma* is purified and calcinated form of tin with additional herbs[35].

Siddha System Of Medicine

Siddha system of medicine, one of the ancient medical systems has the great potential of treating many disease ailments. Siddha system of Medicine, many single and poyherbal formulations and higher medicines like *Parpam, Chendooram*and *Chunnam*have been practiced to cure or control diabetes mellitus from time immemorial. The familiar Siddha medicines prescribed for diabetes are *AvaraiKudineer* (decoction), *MadhumegaChooranam*(Fine powder), *ThetranChooranam, SeenthilChooranam, NaavalChooranam, AbragaParpam,Vangaparpam* etc. In Siddha, the management of a disease not only depends on the medicine but the modification of food, habits, and lifestyle also. In addition to this, yoga and exercise therapy also plays a key role for themanagement of diabetes.SidhhaKudineer, a polyherbal formulations equally referred to Khashayasin Ayurveda are more useful to prevent the diabetes and their associated complications.

Oral administration of Siddha formulation (*Madhumegachuranam*) ameliorated the plasma glucose and lipid levels in alloxan- induced diabetic rats reported by Vadivelanet al.Anbu et al. studied that*Aavaraiyathichurnam*is one of the herbal based Siddha anti diabetic formulation for Type II maturity onset diabetes mellitus possess significant hypoglycemic effect when compared with non-treated diabetic rats. *KovaiKizhanguChooranam* found to possess remarkable anti-diabetic action in alloxan induced diabetic rats was reported by Parthiban et al. [36-40].

CONCLUSION

Metal complexes offer a platform for the design of novel therapeutic compounds. The metal compounds offer new properties that cannot be found amongst purely organic agents. Treatment of diabetes mellitus with metal complexes is a new therapeutic strategy. Although various metals like chromium, manganese, molybdenum, tungsten, copper, cobalt, zinc andvanadium 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; the encouraging results of preclinical and clinical studies with metal compounds form the basis for further investigations towards the development of metallodrugs for better healthcare.

CONFLICT OF INTERESTS

Declared None

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