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Therapeutic Application of Zinc and Vanadium Complexes against Diabetes Mellitus a Coronary Disease: A review

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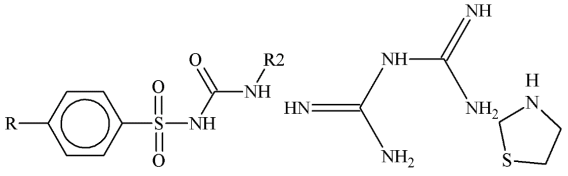
Abstract: During the last two decades, number of peoples suffering from diabetes has increased from 30-230 million globally. Today, seven out of the ten top countries are suffering from diabetes, are emergent countries. Due to alarming situations of diabetes, chemists and pharmacist are continuously searching and synthesizing new potent therapeutics to treat this disease. Now a days, considerable attention is being paid to the chemistry of the metal-drug interactions. Metals and their organic based complexes are being used clinically for various ailments. In this review, a comprehensive discussion about synthesis and diabetic evaluation of zinc and vanadium complex is summarized.

Keywords: Vanadium and Zinc Metal Complexes, Diabetes, Coronary Disease, Flavonoids.

1 Introduction

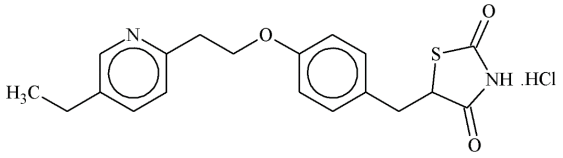
1.1 Diabetes Mellitus

Diabetes mellitus (DM), complex, multi-valued endocrine ailment in which the body does not deliver (type 1) or notice the insulin (hormone required for theentry of glucose from plasma to cells) in right way (type 2) [1]. Oral therapeutics can often be used to control the insulin for the treatment of type 1 diabetes. Now a days sulphonylureas **(1)**, biguanides **(2)** and thiazolidenemoieties **(3)** are being used as the hypoglycemic drugs for the cure of diabetes [2]. Due to aftereffects of diabetes mellitus i.e. population aging, lifestyle manner and urbanization, it is becoming the global health problem [3]. In all countries, one of the central public health question is diabetes mellitus as due to increased number of people suffering it [4] and predictable to boost to 439 million in 2030 [5]. Tentative and clinical studies proposed that chronic hyperglycemia which evoked oxidative stress is one of the main cause of growthand evolution of diabetes [6].



Sulphonylureas **(1)** Biguanides **(2)** Thiazolidenes **(3)**

Now a days, a strong antidiabetic drug, Sulphonylurea **(1)** is going to stop due to its adverse effects on the bone marrow. An oral antidiabetic agent i.e. Pioglitazone hydrochloride **(4)** is used for curing of type 2 diabetes. It clearances the insulin dependent glucose by lowering insulin resistance in the periphery and liver by reducing the hepatic glucose output [7].



Pioglitazone **(4)**

1.2 Diabetes Mellitus and Metal Complexes

Metal ions are necessary for many important operationin humans and some diseases are caused due to deficiency of metal ions [8] iron deficiency mightresult in pernicious anemia. Zinc deficiency causes growth retardation, copper deficiency leads to heart disease in infants. A fundamental aspect of medicinal bioinorganic chemistry is to notice and interpret at the level of molecular of the diseases, initiated by unsatisfactory in function metal-ion [9]. In 1980 Coulson and Dandona primitively examined

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that similar to the action of insulin, $ZnCl_2$ also activate lipogenesis in rat adipocytes. In last thirty years, large number of scientists reported insulin-mimetic activity along inhibition of sugar related enzymes with metal complexes [10].

Number of selective transition metal ions i.e. V(IV) [11-13], Zn (II) [14-18] and Cr (III) [19-21] are known to reduce the glucose in blood both *in-vivocally* as well as *in-vitrocally*. Metal based insulin derivatives have developed the pharmaceutical interest. Anderson summarized different effects of chromium additives on animals and humans, and considered that active form of chromium increases insulin signaling by pushing the activity of insulin receptor tyrosine kinase which direct the glucose uptake [20-24].

1.2.1 Zinc Complex as Antidiabetic Agents

Peculiarly, Zinc containing compounds have got fewer notice for the advancement of potential antidiabetic molecules. However, advance studies conducted by models (animal) and clinical reports sustain the idea that Zinc additives will regulate the diabetes while its deficiency causes the diabetes [25,26]. Zinc enhances the insulin activity as well contributes structural roles in case of many proteins and enzymes [27]. Among the Zn compounds which were prepared, mononuclear Zn coordination compounds exhibited remarkable antidiabetic activity [28-30]. Salil et al. studied and synthesized the complex of zinc containing sulpha drugs [31]. Iqbal and co-workers [32,33] claimed that the antidiabetic activity of zinc complex is greater than the parent drug [7]. Coulston and Dandona stated that almost the action of insulin was similar to zinc ions which activate *in-vitro* rat adipocyte lipogenesis [27] and was recognized that in the synthesis, storage and discharge of insulin, Zn imparts a greatrole [34]. Increase loss of Zinc by urinary and reduced level of Zinc in the body is due to chronic hyperglycemia [35,36]. Vijay and coworker prepared a novel Zn complex of flavanol and checked thier anti-diabetic potential in rats [37]. Zinc mixed ligand (metformin-3-hydroxyflavone) was prepared by Koothappan et al. in their laboratory and their structure were characterized through latest techniques. The synthesized molecules were evaluated against rat for antidiabetic properties [38].

1.2.2 Vanadium Complex as Antidiabetic Agents

Vanadiumis an important trace element found in animals, humans and also in plant cells. Insulin-mimetic and antidiabetic activities were showed by vanadium derivatives in animal as well as in human [39-42]. Vanadium has vast utility due to its coordination chemistry and used for alteration of medical characteristics [43]. Antidiabetic activities of mostly complexes of vanadium was examined which showed that complexes were weakly effected in in-organic and needed higher quantity which ultimately results in undesirable side effects. Different organo-complex of vanadium have been prepared and checked their antidiabetic activities to avoid the toxicity [44].

2 Literature Review

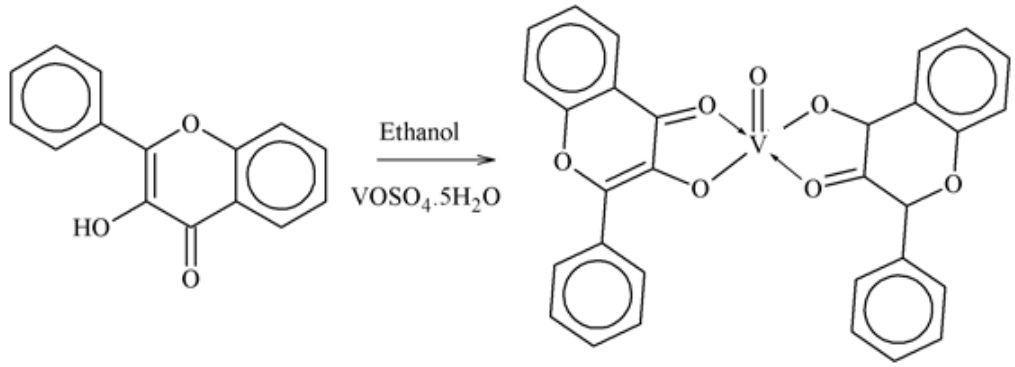
2.1 Synthesis of Vanadium Complex

A novel vanadium complex of 3-hydroxy flavones was prepared and spectrally characterized by Pillai et al. They also measured its stability constant and antidiabetic activities in streptozotocin (STZ) induced diabetic rats and observed that high glucose and glycosylated hemoglobin in diabetic rats was remarkably decreased. The lower level of plasma insulin was remarkably increased by treating the diabetic rats with thiscomplex [2].

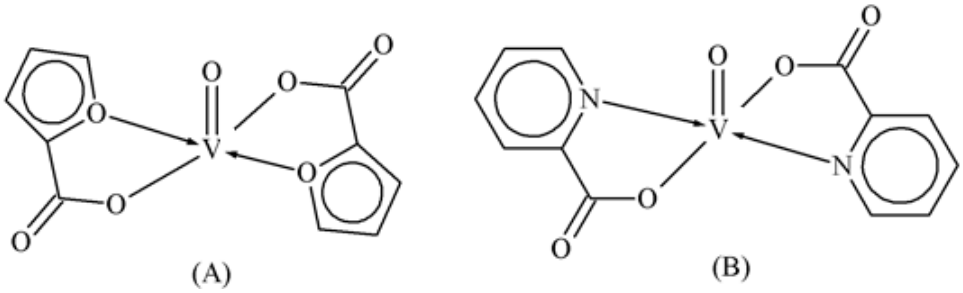
Vanadate and oxovanadium (IV) complexes are the key genus, survive in physiological situation. The physiological belongings are in a lot of gear a result of the superior performance of the complex of VO^{2+} ion with ligand, allow to rivet in a complex and after that unconstrained in the bloodstream to be stopped by biological ligands [45] such as transfer in to cells. Vanadium has been concerned in doing numerous working of insulin such as retardation of gluconeogenesis and lipolysis along motivating lipogenesis/cellular glucose uptake. Thus, such agents are subjected to as insulin mimetics [46-51].

Scientists have paid attention to the biological activation of complexes of V(V) and V(IV) with main blood serum proteins (albumin, immunoglobulins, and transferring) [52-61] and the attachment of V complexes with blood [62-65], or RBC only [66-73]. The potential roles of Vas carriers to peripheral organs have recently noted [74]. Dixithas measured the insulin mimetic activity of vanadium complexes such as bis(α-furancarboxylato) oxovanadium (IV), bis(pyridine-2-carboxylato), oxovanadium (IV) [VO(pic)2], bis(α-furancarboxylato) oxovanadium (IV), vanadyl complexes with maltol(3-hydroxy-2-methyl-4-pyrone) and kojic acid and used for clinical purpose in humans due to less toxicity [75-77].

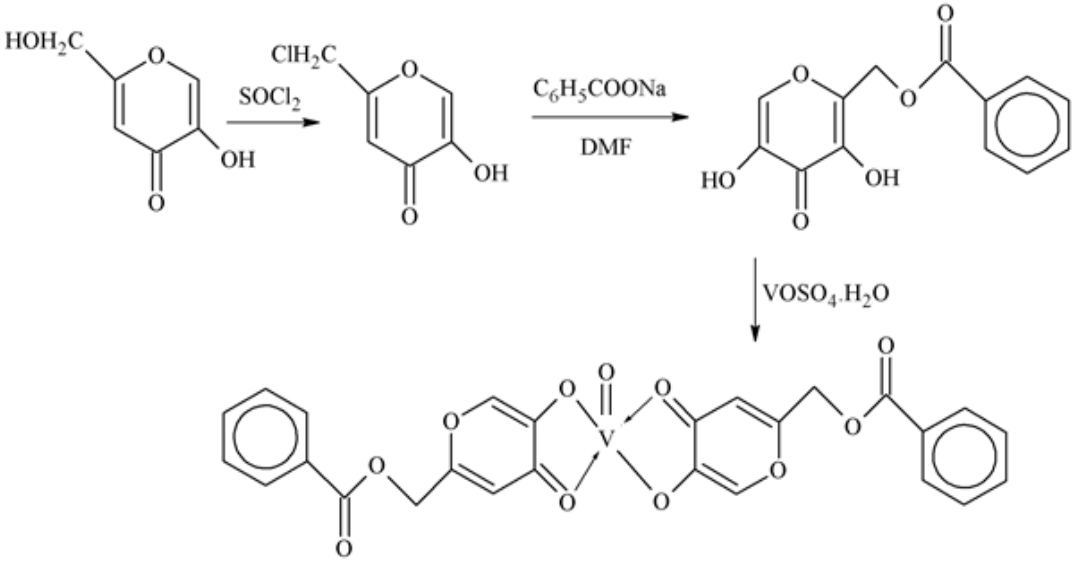
Authors worked on the metal complexes of kojato and benzoic acid moieties together by adjusting the



Scheme 1: Vanadium-3-hydroxy flavone (V3HF) Complex



Scheme 2: Bis-(α-furancarboxylato)oxovanadium (IV).

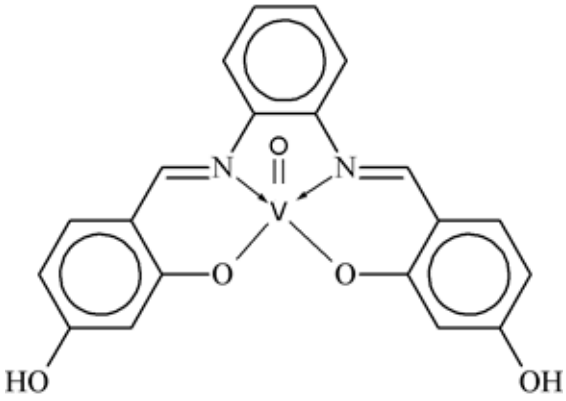


Scheme 3: Bis((5-hydroxy-4-oxo-4H-pyran-2-yl)methylbenzoatato)oxovanadium(IV)(BBOV).

lipo/hydrophilicity and finally synthesized BBOV (bis(5-hydroxy-4-oxo-4-hpyran-2-yl) methylbenzoatato). Antidiabetic activity of this compound demonstrated that it reduced hyperglycemia and impaired glucose tolerance activity is improved and giving BBOV and BMOV shifted blood glucose level to near normal level [78].

Pharmacologists and chemists showed interest in the diabetic activity of vanadium (IV) complexes of oxygen,

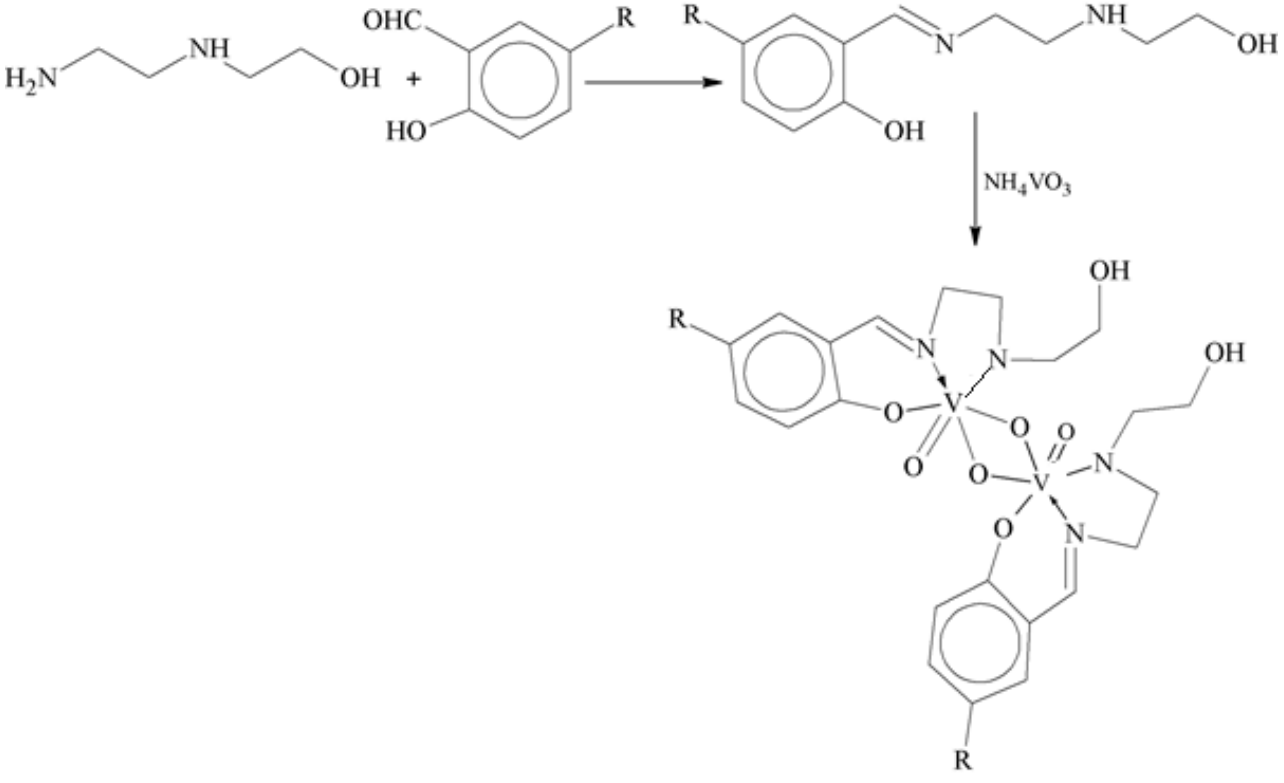
nitrogen and oxygen, oxygen donor ligands and their complexes which was characterized. Among them bis-maltolatooxidovanadium (IV) complex and maltol which is monoprotic bidentate O,O chelating ligand showed best activity. Recent research involves the synthesis of few oxovanadium (IV) complexes of the type $[M_2(H_2O)_n]$ $[VO(mal)_2(H_2O)]$ with malonic acid and their structural characterization, spectroscopic studiesand antidiabetic activities were also checked. Insulin mimetic activity of the complexes, blood sugar level and lipid profile of streptozotocin induced diabetic rats were checked. Results showed that drug $[Na_2(H_2O)][VO(mal)_2(H_2O)]$ protected the damage of liver and other organs by diabetes and contributes highest hypoglycemic effect. It was concluded that the synthesized complexes are best antidiabetic agents [79].



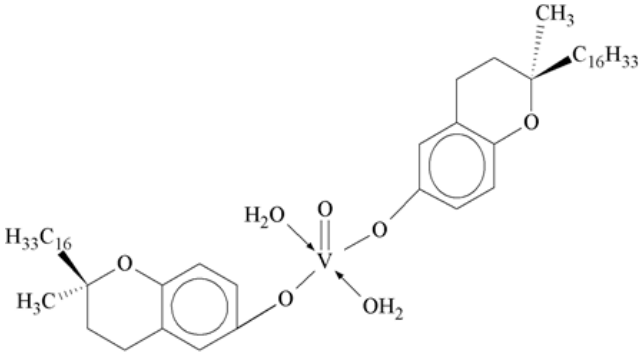
Scheme 4: Synthesis of BPOV.

Xie et al. synthesized complex (BPOV) which showed insulin-enhancing and antidiabetic activity. Their structures were confirmed with latest techniques.V(IV) atom has five-coordinated atomsand surrounded by distorted square-pyramidal. *In-vivo* study, by giving BPOV to STZ-diabetic rats for four weeks andblood glucose levels were decreased [80].

Xie along his team synthesized the two novel vanadium complexes by using Schiff bases of substituted salicylaldehyde and 2-hydroxyethylenediamine. IR were described paramountcally as a dinuclear complexes of six centers coordinated vanadium bridged by O-O atoms of the homocitrate with a V_2O_2 diamondcore. *In-vivo* tests showed that complex has no antidiabetic activity, while other complex showed remarkable antidiabetic activity



Scheme 5: Vanadium complexes by usingsalicylaldehyde2-hydroxyethylenediamine.



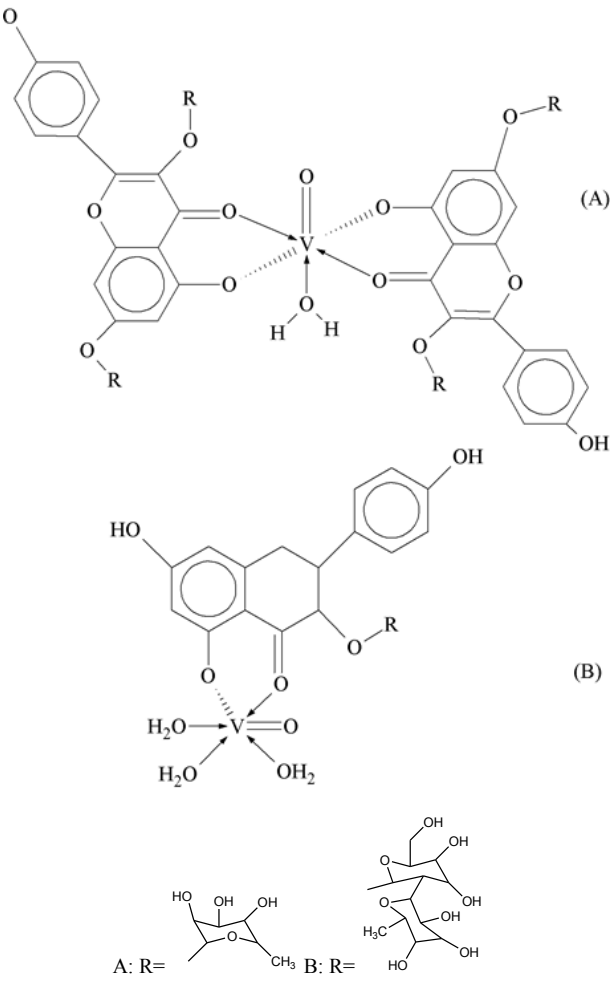
Scheme 6: Structure of $[VO(Vit\text{-}E)_2(H_2O)_2]2H_2O$ complex.

by lowering the glucose level in blood and also improved impaired glucose patience in diabetic rats. This result demonstrated that the ligand with a halogenatom was initiate to boost antidiabetic characteristics of vanadium complexes with Schiff base [81].

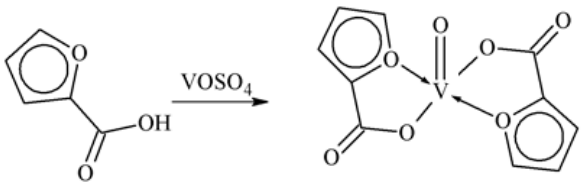
A number of vanadyl complexes with vitamin E were synthesized and characterized. The antimicrobial activity of vanadyl (II) complex was considerable as compared to the ligands. Results showed that the blood glucose level remarkably reduced from 442.87 to 294.87 mg/dl with vanadyl (II) sulfate at a dose100mg. Hence indicated that synthesized vanadyl complex $[VO(Vit\text{-}E)_2(H_2O)_2]2H_2O$ complex is good enough to treat a type I diabetic experimental animal [82].

Researchers tested hypoglycemic effect of 'glycosylated flavonoids' (free) and complex of V (IV) and VO (IV) with flavonoid on rats. Antidiabetic activities of complexes) were checked by different routes on wistar rats. Potentiometric study was used to measure the equilibrium constants and two group of complex were projected at working pH, VOH_2L_2 (kaempferitrin) and VOHL (kaempferol-3-neohesperidoside). The second one showed diabetic potential throughout starting from 50-100 mg/kg while first one decreased from 0 to 6 hour and serum glucose level is lowered by the administration of the VO (IV) complexes (0.0146 mmol/kg). Results indicated that kaempferol-3-neohesperidoside-VO(IV) (56.0%) was 2.5 times more helpful than VO(IV) (16.8%), double effective as compare to free compound and thrice than kaempferitrin VO (IV) (17.8%) [83].

In 2005, Xie along his co-workers synthesized a potent oral active bis-(α-furancarboxylato)oxovanadium (IV) complex used for treatment of diabetes mellitus in experimental animals. The complex showed antidiabetic activity by normalizing the glucose and lipids values without any effect on insulin level after 4-week treatment. The results indicated that complex has an antidiabetic



Scheme 7: Glycosylated flavonoids complexes (A) = M: L (1:2) & (B) = M: L (1:1).

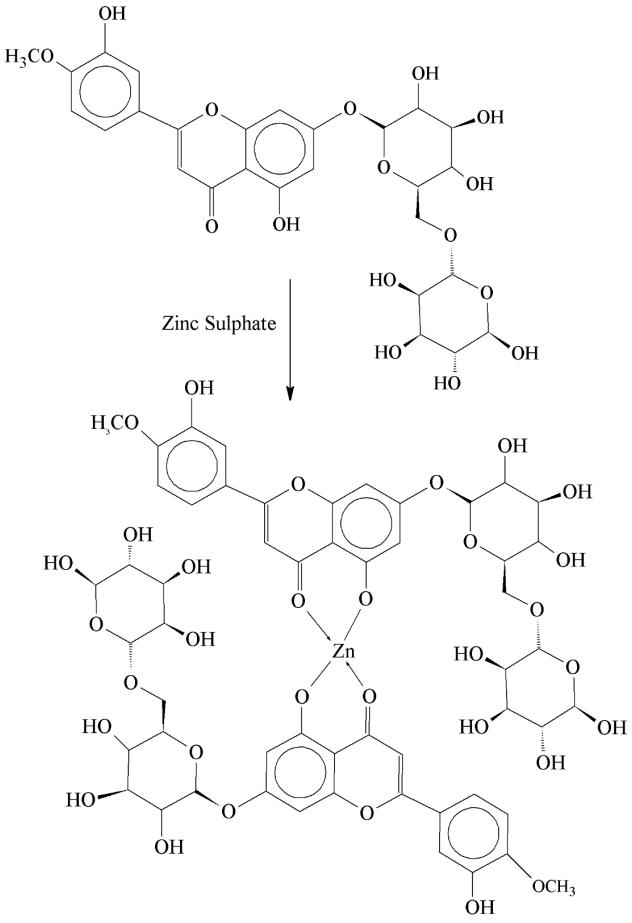


Scheme 8: Bis-(α-furancarboxylato)oxovanadium (IV) complex.

activity by increasing the sensitivity of insulin-receptor inperiphery and biological efficacy of insulin [84].

2.2 Synthesis of Zinc Complexes

Zinc-diosmin complex were evaluated in rats by inducing experimental type 2 diabetes. Zn- diosmin complex was prepared and characterization was done by various

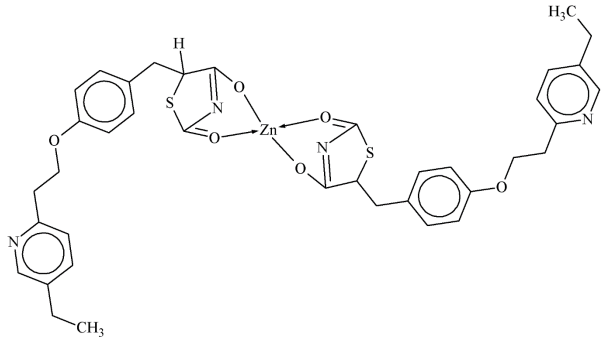


Scheme 9: Zinc-diosmin complex.

spectral studies. Rats were treated orally with complex at 20 mg/kg for 30 days. Treatment notably enhanced the glucose homeostasis and insulin sensitivity in diabetic rats. The findings suggested that this compound is nontoxic and has praising prospective to extend as an anti-hyperglycemic molecule for the cure of mellitus [35].

Solutions of PLZ and metallic salt were stirred, refluxed for 3-4h at 70°C and solid product was yielded on cooling. Fe (II) and Zn (II) complexes were evaluated as hypoglycemic agents. The geometry of the complexes were octahedral and tetrahedral on the basis of elemental and structural data. Hypoglycemic effect of pioglitazone zinc complexes on alloxan induced diabetic rats ranges from 27 to 33% from 0 to 8 hours [7].

Rakesh and Vaidya synthesized metal complex by mixing to butamide equal molar solution of metal chloride and ligand were refluxed for one hour in EtOH which resulted solid product. Zn complex was given to albino rats. It was confirmed that this complex may be used as antidiabetic agent by decreasing blood glucose from 220-82 after 14 hours [85].



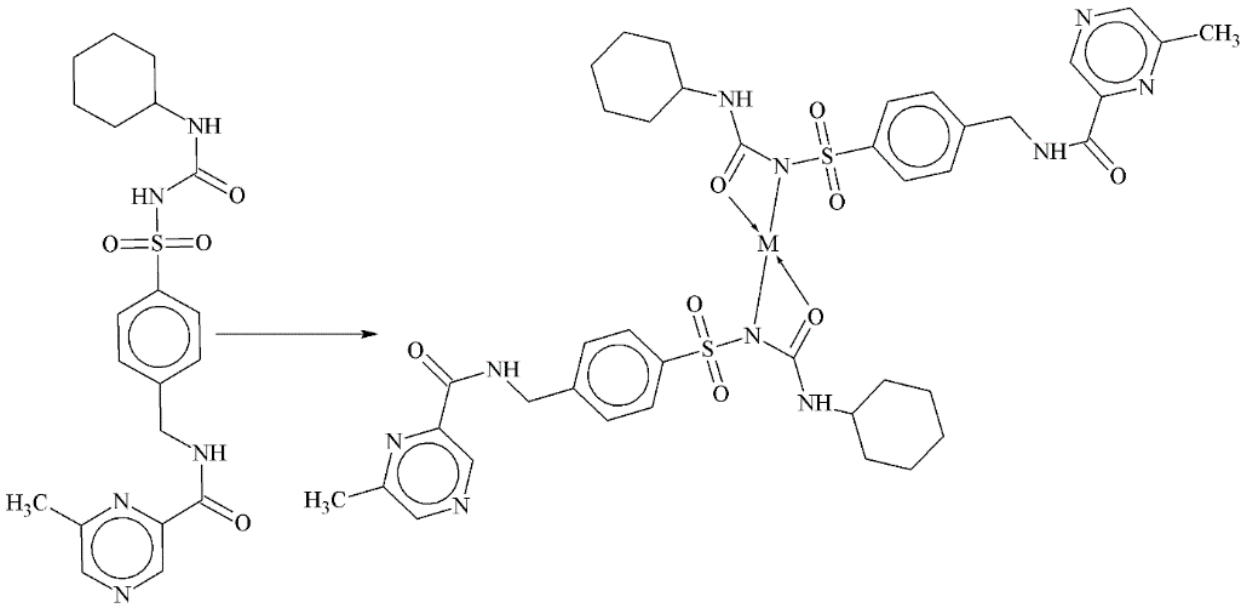
Scheme 10: PLZ-Zn Complex.

Glipizide, commonly known sulfonylurea oral hypoglycemic agent and complexed with the metals. FTIR analysis recommended the coordination of 'N' and carbonyl oxygen atom of $-SO_2NHCONH-$ moiety of glipizide with the under investigated metals. Complexes have been characterized using AAS and this technique was also useful for the indirect grit of glipizide in the form of dosage for first time [86].

2.3 Mechanism of Action of Zn and Its Complexes Against Diabetes Mellitus

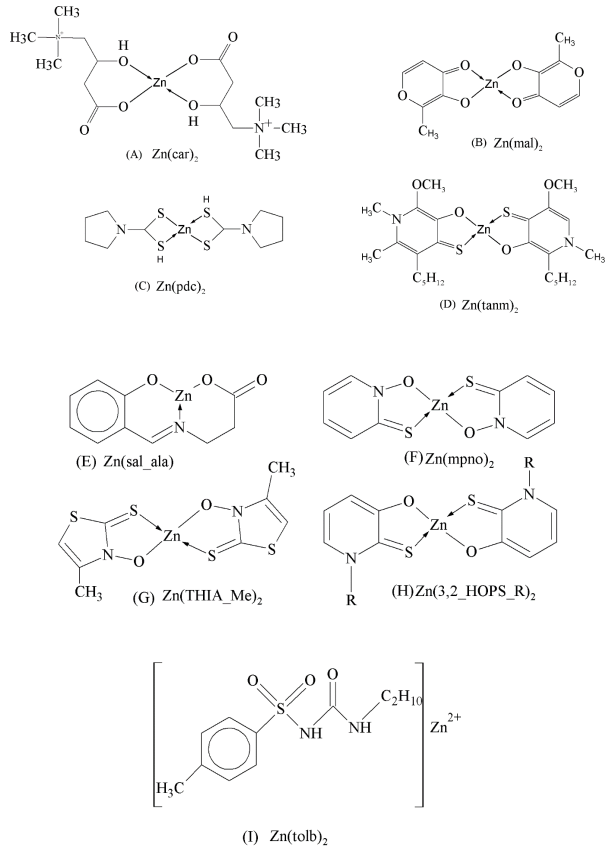
Various animal models were used to check the activity of zinc for the treatment of diabetes.

Zinc is a known antioxidant in the immune system [87]. Different tests were performed to prevent the type 1 DM by enhancing the zinc level in diet, which is due to blockage of NF-κB activity in pancreas [88]. The experiments performed on alloxan and STZ induces diabetic animal models revealed that risk factors of type 1 diabetes is significantly minimized by increasing the zinc intake. In genetic type 2 diabetes of mouse model insulin receptor tyrosine kinase activity was regulated by zinc in skeletal muscle. The β-subunit of the insulin receptor produces less tyrosine phosphorylation as compared to insulin in the presence of zinc as well as insulin receptor substrate (IRS) does not increase the glucose uptake on stimulation of zinc [89]. This model presented the activation of P13K without the participation of IRS; in epididymal cells the production of H_2O_2 may stimulated by zinc, which than stimulates focal adhesion kinase (FAK) and at the end FAK, triggers the P13K-Akt pathway. Furthermore, zinc activates Akt in preadipocytes and enhance the phosphorylation of serine residues which leads the stimulation of Akt in preadipocytes and adipocytes, thereby increasing GLUT translocation [89]. Ezaki also revealed glucose uptake



M = Cd(II), Hg(II), Fe(III), Zn(II), Co(II), Ni(II and Ca(II)

Scheme 11: Glipizidemetal complexes.

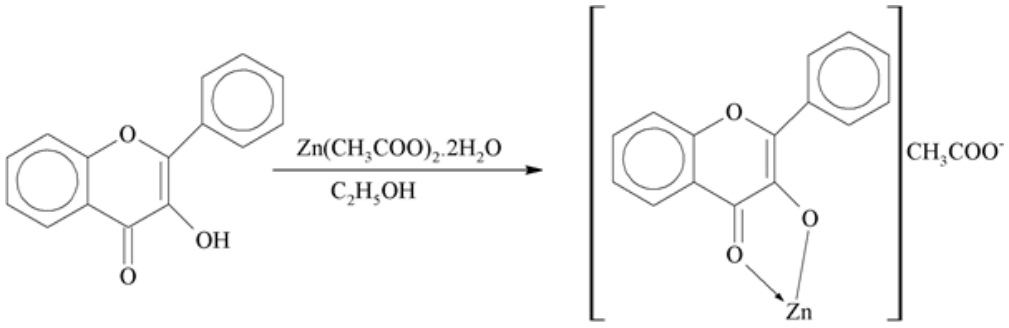


Scheme 12: Anti-diabetic active zinc complexes.

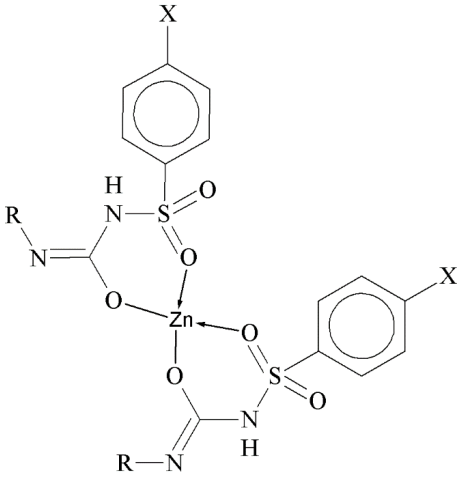
is increased by tissue cells by stimulation of zinc which transfer GLUT to the plasma membrane [90].

Since 2001, orally active anti-diabetic zinc complexes have been produced and evaluated. Various zinc complexes of different coordination compounds have recently been exposed which have impressive anti-diabetic activity. Zinc is considered as biologically active and react with several objective proteins connected to diabetes mellitus [90]. For the clinically useful metallopharmaceutics, zinc complexes are being evaluated for long-term toxicity (side effects) and clear-cut proof of marked agent for the *in-vivo* pharmacological application. The superior pharmacokinetic assets are important in the this as well as for past [91]. Kalavakunda synthesized Zn complex by reacting equal molar zinc aceteate and flavanol in ethanol at 80°C with stirring for 4 hours.

The synthesized zinc-3-hydroxy flavone and characterized with spectral techniques. It was concluded that toxicity and dosage fixation were depicted that it was non-toxic and by orally giving complex (5 mg/kg b.w. (body weight)/rat/day) for 30 days to induced diabetic rats, blood glucose level and glycosylated hemoglobin (HbA1c), uric acid, urea, and creatinine were lowered indicating the non-toxic nature of the zinc-flavonol complex while the plasma insulin and C-peptide levels were improved. Further the Zn-flavonol complex depicted noteworthy anti-hyperglycemic potential in induced diabetic rats. The antidiabetic activity (142.83mg/dl) of the complex was comparable with gliclazide, a standard antidiabetic drug (127.66mg/dl) [36]. Glimepiride zinc complex was



Scheme 13: Synthesis of zinc-flavonol complex.



Scheme 14: Structure of glimepiride zinc complex.

synthesized by mixing the metal salt solution with that of ligand in 1:2 molar ratios at pH 6.5-8 for 3 hours at 80°C [92].

Tetrahedral structure was given to complex with spectral and X-ray studies that indicating the co-ordination of sulphonyl oxygen on one face and enolic oxygen fond of from other pose with the metal ion [91]. Solutions of Zn (II) chloride and 3-carboxy-pyrazole in water (30 mL) were stirred at normal condition and white crystals obtained. Lopez and coworker synthesized new Zinc complex (mononuclear) with 3-carboxy-pyrazole (ligand) showed a probable anti-diabetic activity can be regarded insignificant. Vijayaraghavan et al. [36] following cure with Zn-3HF (5–50 mg/kg) for 30 days failed glycemic glucose less than 150 mg/dl. Moniz et al. explained different Zn complexes specially with Zn $(dmpp)_2$ at doses of 10 mg/kg intraperitoneally administered daily. They find good results of blood glucose which were comparable to standard administered orally. However, Zn $(dmpp)_2$ produces a significant hyperglycemic effect. Zn sulfate tested by Moniz et al. is less active as hypoglycemic agent. The results showed that it has similar pharmacological characteristics to Zn $(dmpp)_2$ [29].

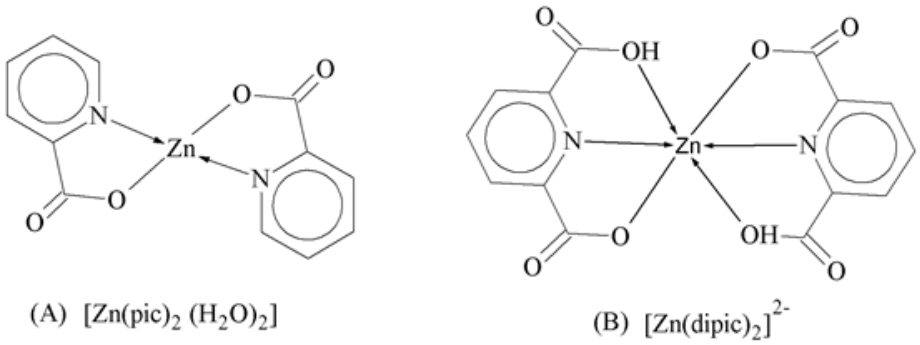
Bytzek and coworker synthesized Zn (II) complexes in situ by reacting $ZnCl_2$ solution and ligand in buffer (pH 7.4) at various ratios. When anti-diabetic Zn (II)-complexes are administered in animal DM type 2 models, the Zn (II) level was increased significantly to 100-200 mM. Zn (II) complex which are applied as insulin increasing agents in the cure of diabetes are under development. CZE-ICP-MS analysis on the interaction of Zn (II) maltolato $[Zn(mal)_2(H_2O)_2]$, 2-picolinato and $[Zn(pic)_2(H2O)_2]$ and 2,6-dipicolinato complexes $[Zn(dipic)_2]_2$ with serum (human) proteins were studied [93].

Zn complexes were synthesized by added excess amounts of $ZnSO_4$ (1 M) and 10 mL of $_\gamma$-pgaD, L-poly($_\gamma$-glutamic acid) (1% w/v) solutions and stirred over night at room temperature.

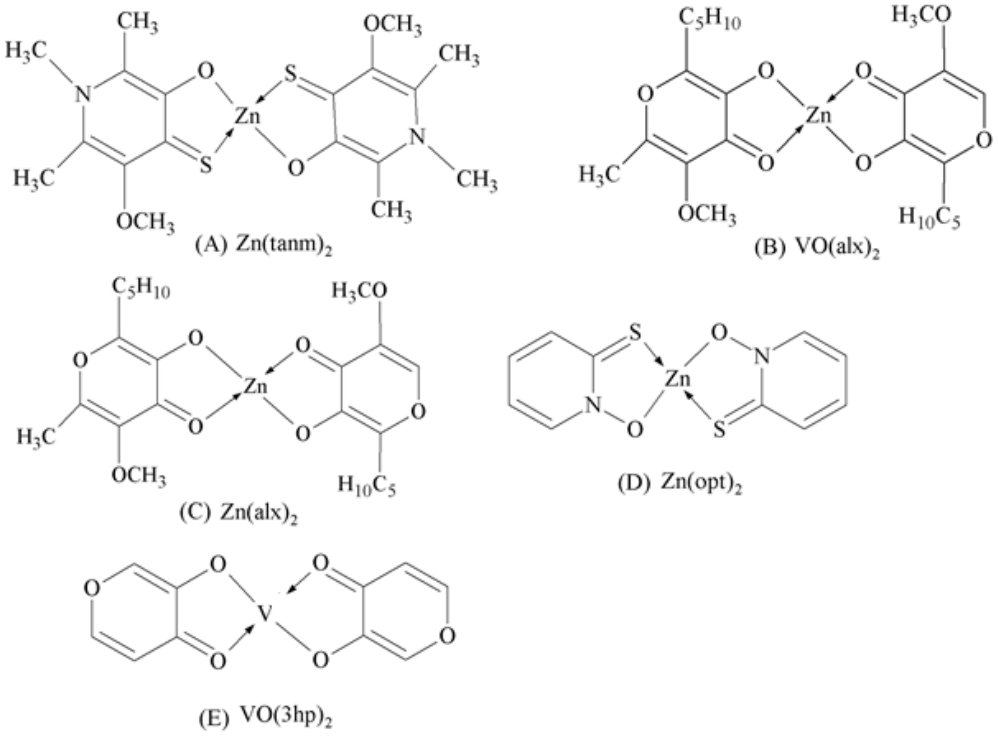
The synthesized Zinc (II) complexes were characterized and checked *in-vitro* insulin-mimetic activity which was considerable better than that of $ZnSO_4$ as well as *in vivo* antidiabetic activity in type-2 diabetic in KKAy mice. The Zn($_\gamma$-pga) complex were given orally (0.15–0.31 mmol) for 30 days and the hyperglycemia in mice was normalized within 21 days. The impaired glucose tolerance and prominent HbA1c levels along metabolic syndromes were appreciably enhanced in Zn($_\gamma$-pga)-treated mice as compared to those with saline and $ZnSO_4$ [94].

2.4 Mechanisms of Action of Vanadyl and Zinc Complexes

Recently, action mechanisms for some oxovanadium (IV) and zinc (II) complexes were purposed in isolated rat adipocytes [95-99]. Both these complexes raised glucose uptake into the adipocytes without the addition of any hormones [99,100] and inhibited epinephrine-induced free fatty acid (FFA) release [97,98]. The results showed that the



Scheme 20: [Zn(pic)$_2$(H2O)$_2$] and 2,6-dipicolinato complexes [Zn(dipic)$_2$]$_2$.



Scheme 21: Oxovanadium (IV) and zinc (II) complexes.

complexes have common insulin-mimetic activities. The inhibition of FFA release by vanadyl and zinc complexes was reversed by selective insulin receptor β-subunit (IRβ) inhibitor [HNMPA-(AM)$_3$] [101].

To measure the insulin mimetic ability 10 vanadium and zinc ion containing organic complexes were synthesized by Cheol-Min Lee and Cheong-Soo Hwang to compare their PTP-1B inhibition activities. Complexes of Zn were depicted to reduce FFA (free fatty acid) release from adipocytes of rats, and to display *in vivo* lowering of blood glucose [101].

3 Conclusion

Metal complexes as therapeutic agents playing vital role inthe field of medicinal chemistry. A large numberof metal complexes are formed by the use of different metal ions and organic ligand ofinterest. Metal complexes like *cis*-platin have confirmed to be extremely efficient chemotherapeutic agents for cure of different disorder. The inhibition of PTP1B (protein-tyrosine phosphatase 1B is a latent objective for healing of type 2 diabetes. The complexes of Vanadium and zinc metal have insulin increasing potencies, while vanadium complexes slow down the PTP1B, slight is recognized on the method of

zinc compounds. Researchers designed a robotic PTP1B inhibition method for a rapid assessment of the PTP1B inhibition. It is the need of this era to synthesize new metal complexes with lease side effect to treat diabetes.

Conflict of interest: Authors declare no conflict of interest.

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