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ATTENUATION AND IMPROVEMENT, TOXICITY AND EFFICACY OF VANADIUM DERIVATIVES

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ABSTRACTS

Oral administration of inorganic vanadium salts have shown anti-diabetic activity. However, the toxicity associated with vanadium limits its role as a therapeutic agent for diabetic treatment. The objective of this article is briefly to review studies on chemical approaches to reduce vanadium-associated toxicity and maintain its anti-diabetic effects meanwhile. We also provide some insights into the potential therapeutic measures of the anti-diabetic vanadium actions.

KEYWORDS: vanadium; hypoglycemic activity; diabetic; toxicity

INTRODUCTION

The prevalence of diabetes mellitus (DM) is considered to be one of the biggest health catastrophes in the world causing significant health and economic burdens on patients and communities.[1] The number of diabetic patients is estimated to rise to 300 million by 2025 according to the World Health Organization.[2] The emergence of diabetes will be accompanied by occurring of many other diseases, which make the condition complicated. In the developed world, diabetes is the leading cause of adult blindness in the non-elderly and the most common cause of non-traumatic amputation in adults.[1] Moreover, diabetes is one of the main causes of cardiovascular disease including heart attacks and strokes. Diabetic nephropathy is the main driver of renal dialysis.[3] Most of the oral hypoglycemic drugs currently used for the treatment of diabetes such as sulphonylureas, biguanides, α-glycosidase inhibitors and

thiazolidenes are often associated with undesirable side effects or diminution in response after prolonged use.[4] Hence, new therapeutic approaches are needed to treat diabetes more efficiently.[5,6] Many transition elements have been studied and found effective in controlling the altered glucose homeostasis in diabetes.[7] In this regard, studies have demonstrated that compounds of the trace element vanadium exert various insulino-mimetic and anti-diabetic effects in vitro and in vivo.[8,9]

Vanadium was first discovered in 1971 as a trace element which is essential for normal growth.[1] It exists in oxidation states of −I, 0, +II, +III, +IV, and +V; the latter two (vanadate and vanadyl) have glucose-lowering properties and improve pancreatic insulin store and secretory function in streptozotocin (STZ) diabetic rats.[6,9-12] However studies have also shown its adverse effects like diarrhea, vomiting, abdominal cramps, green tongue, bronchospasm, and irreversible renal excretion damage in experimental diabetic rats.[13] Therefore, the toxicity associated with vanadium limits its role as a therapeutic agent for diabetic treatment.[14] Because of the better therapeutic effect of diabetes, several chemical approaches have been designed to reduce vanadium-associated toxicity.[15] Research is still underway to keep the balance between therapeutic potential and associated toxicity of the metal. The objective of this article is briefly to review studies on the ways to reduce vanadium-associated toxicity and maintain its anti-diabetic effects meanwhile.

1. Inorganic vanadium compounds

The chemistry of vanadium is extremely complex due to its multiple oxidation states, hydrolysis, and polymerization. Hence vanadate is a very labile system that can interact with potential ligands, such as -OH groups and nitrogen bases, to reduce its related toxicity[17]. Yue Zhang et al. selected vanadium (III, IV, V)-dipicolinate complexes with different redox properties (Figure 1) to investigate the structure- property relationship of insulin-mimetic vanadium complexes for membrane permeability and gastrointestinal stress-related toxicity using Caco-2 cell monolayer model[18]. The results suggested that the vanadium (III) complexes were less toxic than the other two, probably due to the $[V(dipic)_2OH]_2$ and $[V(dipic)_2OH]_3$ species containing 2 equivalents of ligand thus inhibiting the interaction of the coordinating anion with the target F-actins.[18]

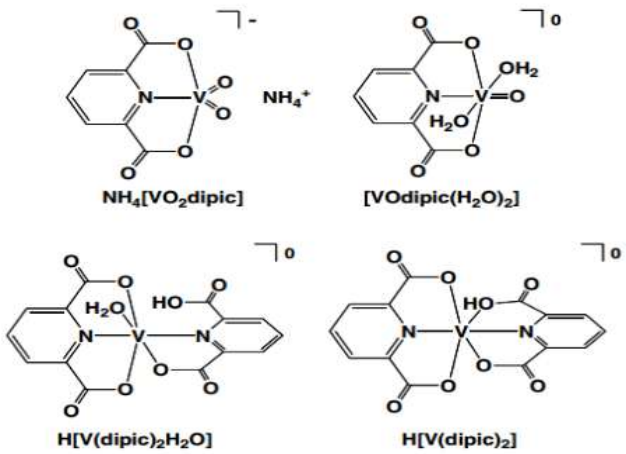


Fig. 1. Structures of vanadium (III, IV, V)-dipicolinate complexes

13 peroxidovanadium (V) complexes (pVs) were evaluated bound to a variety of ligand by Hironori Sugiyama et al.[19] The cytotoxicities of these pVs could be classified into three groups according to experiment in vitro: significantly toxic, moderated toxic, and non toxic. $Cs_2[VO(O_2)(Hedds)]$ and $Na[VO(O_2)(edda)]$(Figure 2), which are comprised of pVs with a linear tetradentate ligand showed little to no cytotoxicity. The finding provided a guide for synthesis of new pVs that may be used as candidate therapeutic agents.[19]

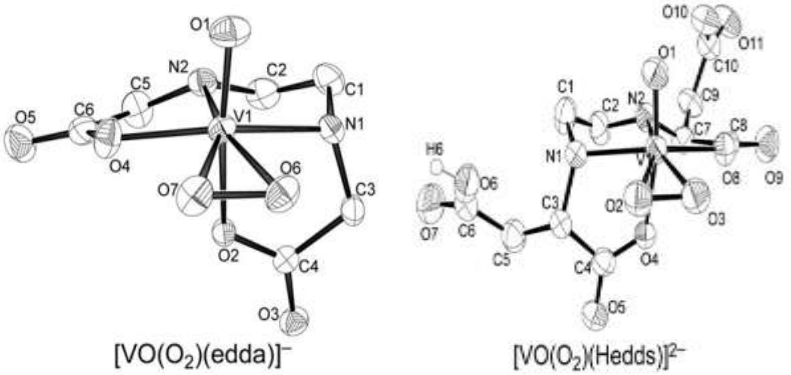


Fig: 2 Structures of $[VO(O2)(edda)]^-$ and $[VO(O2)(edda)]^-$

Several studies on the acute toxicity of vanadium compounds revealed that both vanadate and vanadyl were moderately toxic[20-22], with the severity of the toxic effects increasing as the valency increases.[23] The present study is designed to screen the possible effects of sodium orthovanadate therapy in alloxan-induced diabetic rats. 300 mg/kg sodium orthovanadate orally could protected against direct action of lipid peroxidation on brain AChE in diabetic rats reported by Doaa A. Ghareeb et al., which is one of the major complications in diabetes.[24]

The use of various chelating agents to reduce vanadium toxicity and improve insulin potency are the earliest and effective goals of vanadium research.

2. Organic vanadium compounds

In addition to inorganic vanadium salts, researchers have modified metal ion reactivity with organic ligands[25], for example, maltol ligand (3-hydroxy-2-methyl-4-pyrone) and its derivatives[26,27], picolinic acid (2-pyridinecarboxylic acid)[28], dipicolinic acid, and acetylacetonate[29]. These ligands have increased efficacy and decreased toxicity of vanadium compounds.[30] These complexes had no significant gastrointestinal side-effects and appeared to be more potent. Hence it appears that these compounds have an advantage over the inorganic salts as promising therapeutic anti-diabetic agents.[31]

2.1 Vanadium-Flavonoid complex

Flavonoids have a basic structure of 2-phenyl-benzo-γ-pyrones, mostly polyphenolic in nature.[32] Compounds between oxovanadium (IV) cation and flavonoid derivatives were developed recently in order to increase the intestinal absorption and to reduce the toxicity.

2.1.1 Vanadium-3-hydroxyflavone (V3HF)

Pillai et al. have synthesize a novel vanadium complex named vanadium-3-hydroxyflavone (V3HF) using 3-hydroxyflavone as an organic ligand (Figure 3). Antidiabetic activity and chronic toxicity of the complex were studied in streptozotocin-induced experimental diabetes in rat. The results indicated that the complex possessed anti-diabetic activity and had no toxicity.[33] Furthermore, the group then evidenced that the V3HF protected the beta cells from hyperglycemia-induced oxidative stress.[34]

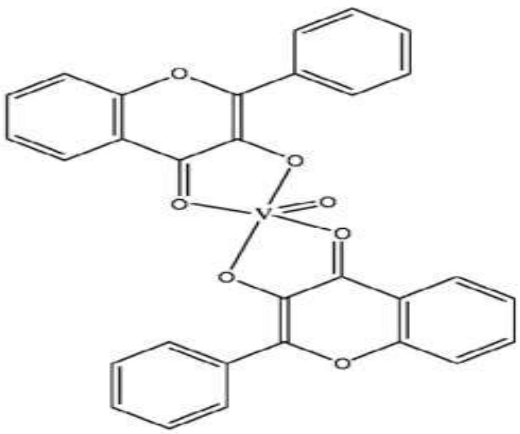


Fig. 3. Structure of vanadium-flavonol complex

2.1.2 Flavonoid rutin (Rut) and vanadyl cation

Two novel complexes [VO (Rut)$(H_2O)_2$]$(SO_4)_{0.5}\cdot 2H_2O$ and [$VO(Rut)_2$]$\cdot 4H_2O$ have been obtained in solid state and characterized using elemental and thermal analyses and several spectroscopic techniques (Figure 4). The results indicated that the two complexes had a moderate stability.[35] No observed toxic level of vanadium-rutin complex at 20 ppm dose level, which could be good for further study.[36]

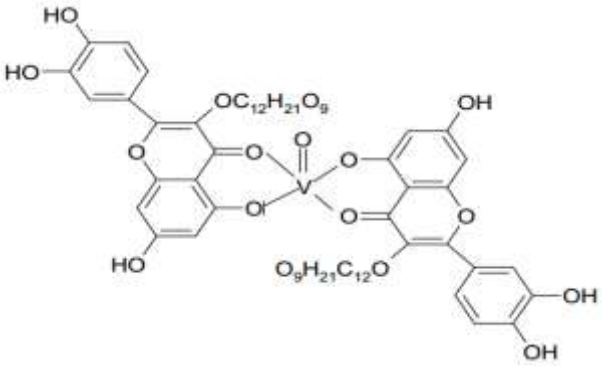


Fig. 4. Structure of vanadium-rutin complex

2.1.3 Bis(quercetinato) oxovanadium(IV) (BQOV)

In vitro cytotoxicity of $VOSO_4$ and bis(quercetinato) oxovanadium (IV) (BQOV) was examined and contracted in CHO cells by Shukla et al.. Meanwhile, Hypoglycemic potential of $VOSO_4$ and BQOV was tested in streptozotocin-induced diabetic Balb/c mice (Figure 5). An obvious difference was that the hypoglycemic effect lasted only for about 6 h in $VOSO_4$-treated mice as against 24 h in BQOV-treated. Comparison of acute toxicity of the compounds revealed negligible nephrotoxicity of BQOV.[37] All of these clearly demonstrated immense hypoglycemic activity and lower toxicity of BQOV, making the conjugate a suitable candidate for therapeutic utility.

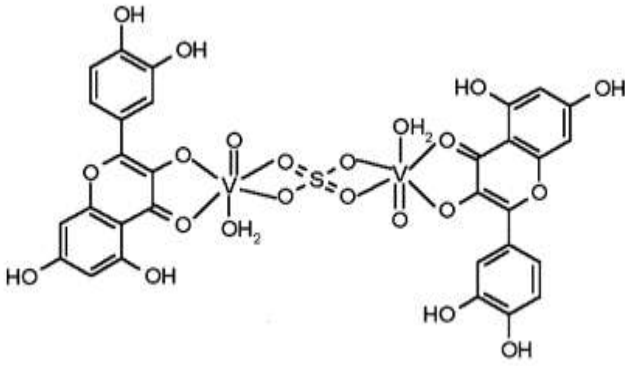


Fig: 5 Structure of BQOV

2.2 Bis (maltolato) oxovanadium (BMOV)

A new organic vanadium complex, Bis(maltolato)oxovanadium (BMOV), was developed to improve the absorption of vanadium from gastrointestinal tract and reduce the dose of vanadium to produce glucose-lowering effects. According to the comparison between BMOV and $VOSO_4$, we clearly discovered that BMOV had a more rapid onset of action and was approximately 1.5 times more potent than $VOSO_4$ at producing glucose-lowering effects[38], without any overt signs of toxicity.

2.3 Aminophenol-derivatized nitrilotriacetic acid vanadyl complexes

Wang et al. synthesized three novel aminophenol-derivatized nitrilotriacetic acid vanadyl complexes (VOohpada, VOmhpada, VOphpada) using the strategy of rational incorporation of antioxidant groups in ligand in order to balance the side effects with the therapeutic properties.[25] The results revealed that vanadyl complex of p-hydroxyl aminophenol derivative (VOphpada) exhibited better antioxidant activity and lower cytotoxicity than other analogs (Figure 6). VOphpada (0.1 mmol/kg/day) effectively reduced blood glucose level, improved glucose tolerance, and alleviated stresses in type II diabetic mice. The insulin enhancement effects of VOphpada were observed more potent than BMOV. In overall, the present results suggested VOphpada as a novel hypoglycemic agent with improved efficacy-over-toxicity index.

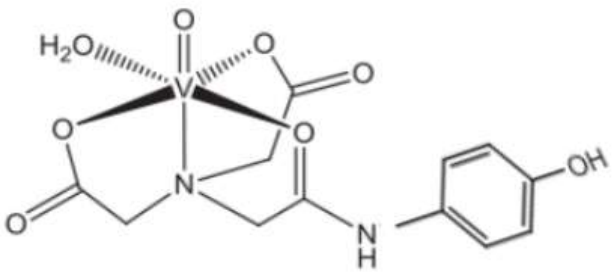


Fig: 6 Structure of VOphpada

2.4 Bis(cysteine, amide N-octyl) oxovanadium IV (naglivan)

A organic complex of vanadyl-naglivan was synthesized by Margatet et al. in order to improve the poor gastrointestinal absorption of the ion (Figure 7). They conducted a study to determine whether naglivan had beneficial effects on glycemia and cardiac dysfunction in the STZ-diabetic rats as well as test the gastrointestinal tolerance of this form of vanadyl.[39] As in the case for vanadyl sulfate, the dose of insulin required for maintaining euglycemia was

reduced, abnormal plasma lipid levels were corrected and the side effect of diarrhea was disappeared. Thus, naglivan could be a more therapeutically desirable form of vanadyl.

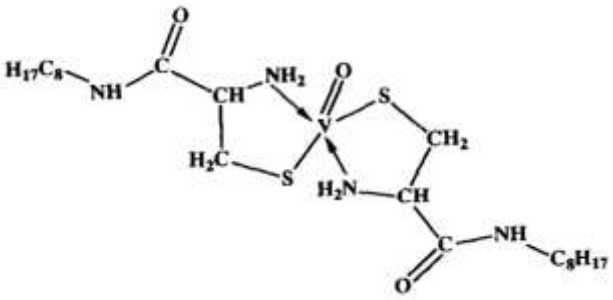
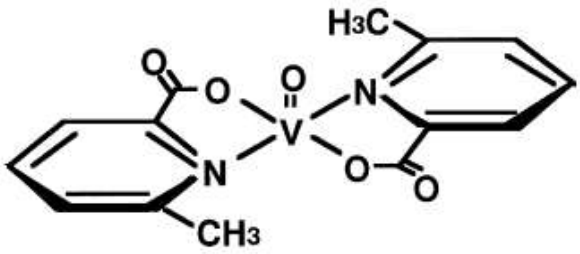


Fig: 7 Structure of naglivan

2.5 Vanadyl-methylpicolinate-colinate complex (VO-MPA)

Blood circulation monitoring-electron spin resonance (BCM-ESR) method was applied to elucidate the relationship between the blood glucose normalizing effect of VO-MPA and the global disposition of paramagnetic vanadyl species (Figure 8). As a result, the exposure amounts of VO-MPA in the blood were approximately 1.5–2 times higher than those of VS.[40] The pharmacokinetic characteristics of VO-MPA are dependent on its physicochemical properties and structure, being closely related to its high antidiabetic activity and lesser toxicity.



Bis(6-methylpicolinato)oxovanadium(IV)

Fig: 8 Structure of VO-MPA

2.6 [$V^{V}O_2$ (OH)(picolinamide)](TSAG0101)

TSAG0101, [$V^{V}O_2$(OH)(picolinamide)], is a new vanadium coordination compound designed by Thomas Scior et al. to inhibit the enzyme protein tyrosine phosphatase 1B (PTP1B), which acts as a negative regulator of insulin signaling by blocking the active site where phosphate hydrolysis of the insulin receptor takes place[41]. The lethal dose (LD_{50}) of TSAG0101 was determined in Wistar mice yielding a value of 412 mg/kg. It is also less toxic than caffeine

(LD_{50} 192 mg/kg) and BMOV (LD_{50} 220mg/kg). The value classifies it as a mild toxicity agent when compared with literature data.

3. Vanadium-enriched microorganism

Edible fungi have a widespread use in tradition Chinese medicine.[42] Many species of wide-growing mushroom possess the ability to take up and accumulate trace metals such as cadmium, lead, arsenic, copper, nickel and vanadium in the body or mycelium of the mushroom.[43-45] Thus, combining trace metals with edible fungi which were ascribed to have anti-diabetic properties will be a more therapeutically desirable method to diabetic desease.

The hypoglycemic action of fermented mushroom of Coprinus comatus rich in vanadium was researched by Han et al.,[46] The group concluded that vanadium(V) in combination with C. comatus caused significant decreases of the blood glucose and HbA1c levels in hyperglycemic mice. Based on the great discovery, Ma et al. initiated deeply study of the effect and toxicity of vanadium (IV, V) absorbed by Coprinus comatus (VACC), which administrated on alloxan-induced hyperglycemic mice, respectively.[47] The blood glucose and the lipid profile of hyperglycemic mice decreased after the mice were administered with VACC, irrespective of the VACC produced by vanadium (IV) or vanadium (V). However, the organ masses of the mice were significantly different, which suggested that vanadium (IV) absorbed in C. comatus is less toxic to mice than vanadium (V). This provided an alternative medicine for the better control, management, and prevention of diabetic mellitus progression.

Inonotus obliquus is a mushroom possessing the ability to lower blood glucose, which was used as traditional Chinese medicine for a long history.[48,49] Vanadium at lower doses was absorbed by fermented mushroom of I. Obliquus studied by Zhang et al.[50] They compared the hypoglycemic activity of fermented mushroom of I. obliquus rich in vanadium and wild-growing I. obliquus. The vanadium concentration of the cultured mushroom was 3.0 mg/g while in the wild variety is 1/100 of that amount. The toxicity of vanadium at the 3.0 mg/g level is negligible, but its anti-diabetic effects are significantly different to those of the wild variety ($p<0.05$). From these observations, it followed that vanadium-enriched I. obliquus could be used as a means of vanadium supplementation, with expectation of obtaining higher bioavailability and lower toxicity in animals.

4. Vanadium combining with herb

An effort has been made in the present study to find non-conventional methods of using transitional metal and plant products to have a better glycemic control in experimental diabetes and to visualize their effects on the development of peripheral neuropathy.

Trigonella foenum graecum seed power (TSP), has been extensively used in Ayurvedic system of medicine, known well for its hypoglycemic effects as well as vanadium.[51] Due to the reported toxicity of vanadium[14], a combination of Na_3VO_4 at a lower dose was used with Trigonella.[52] The combination including 5% TSP as an anti-diabetic drug was tried to reduce the toxicity associated with Na_3VO_4 by reducing its dose to 0.2 mg/mL from 0.6 mg/mL[53], which showed better results without causing prooxidative damages seen with higher dose (0.6 mg/mL) treatment with Na_3VO_4 alone. This study suggested the combination could be a dietary supplement for the diabetic status and further work of the vanadium combined with herb for the anti-diabetic activity should be deeply researched.

In recent years, a new attenuated method of vanadium combining with herb has been developed by Mao et al.[54] Three batches of vanadium-enriched chickpea sprout (VCS) were prepared by incubating chickpea seeds in presence of 200, 100, and 50 μg/mL of sodium orthovanadate (SOV).[55] Compared with chickpea sprout administrated alone, VCS100 food exhibited enhanced effectiveness in alleviating diabetes inducing hyperglycemia and memory loss. Moreover, vanadium-enriched chickpeas appeared to abolish the toxicity induced by vanadium during the 8-week study period. This vanadium containing food can be explored further to develop a therapy, with reduced toxicity and better therapeutic index which provides a controlled normoglycemic state over sustained diabetes.

Administration of vanadate in a black tea decoction has shown impressive hypoglycemic effects without evidence of toxicity in short-term studies.[56] Clark et al. investigated the hypoglycemic action and the toxic adverse effects of a tea/vanadate (T/V) decoction in diabetic rats over a 14-month treatment period.[57] The results showed that oral administration of a T/V decoction had safe, long acting hypoglycemic effects in type I diabetes mellitus rats, which provided a wide perspective for us to find novel hypoglycemic agents with herb and vanadate.

Table 1. List of vanadium combinations and corresponding references.

Vanadium Combinations	References
Inorganic vanadium compounds	[17-24]
V3HF	[32-34]
Flavonoid rutin (Rut) and vanadyl cation	[35-36]
BQOV	[37]
BMOV	[38]
VOphpada	[25]
Naglivan	[39]
VO-MPA	[40]
TSAG0101	[41]
Vanadium-enriched microorganism	[42-50]
Vanadium combining with herb	[14,51-57]

DISCUSSION

All human studies have utilized inorganic vanadium salts, and the efficacy of organo-vanadium compounds has not been tested in the last century. However, more and more sights were focused on organic vanadium compounds in the recently years because of lower toxicity and better effects on diabetes than inorganic vanadium complexes. These results demonstrated that ligand choice can be used to tailor vanadium complexes as therapeutic agents and provide guidelines for the synthesis of useful complexes.

An effort has been made to have a better glycemic control in experimental diabetes using vanadium and edible mushrooms or plant products. The combination exhibited remarkably enhanced effectiveness and decreased toxicity compared with vanadium alone in alleviating diabetes. This provided an alternative medicine for the better control, management, and prevention of diabetic mellitus progress.

In summary, although animal studies have provided convincing evidence for the anti-diabetic effects of vanadium compounds, a similar role of vanadium in controlling human diabetes is yet to be established.

Conflict of Interests

The authors declare that there is no conflict of interests.

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