Review Article

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Antidiabetic, Antioxidant, Antibacterial, and Antifungal Activities of Vanadyl Schiff Base Complexes

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Abstract

This review comprises some biological activities of vanadyl Schiff base complexes in terms of antidiabetic, antioxidant, antibacterial and anti-fungal activity. The structure activity relationship for the potential biological activities of these compounds is also discussed.

Keywords: Antidiabetic, Antioxidant, Antibacterial, Antifungal, Oxovanadium (IV) Complexes.

1. Introduction

Vanadium, a dietary micronutrient, is yet to be established as an essential part of the human diet. Over the past century, several biological effects of vanadium, such as insulin-mimetic action as well as amelioration of hyperlipidemia and hypertension, have been discovered. This transition element is known to influence various enzymatic systems, namely phosphatases, ATPases, peroxidases, ribonucleases, protein kinases and oxidoreductases (1).

Six oxidation states exist for the transition metal vanadium, along with a variety of synthesized forms. The two most biologically important and physiologically stable states are vanadyl (IV) and vanadate (V) (2). Vanadate and vanadyl ions both exist in the blood, although the later predominates. Vanadate to vanadyl transformation in plasma is a result of reducing agents, such as glutathione. These ions are conjugated with transferrin and albumin proteins, and rapidly incorporated into tissues (3).

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Oral and intraperitoneal supplementation in animal models has shown accumulation of vanadium in the brain, pancreas, lung, testes, heart, spleen, liver, kidney, and bone.

The discovery of several pharmacological properties, such as the insulin-mimetic action, antihyperlipidemia, antihypertension, antiobesity, enhancement of oxygen affinity of hemoglobin and myoglobin, and diuretic action, opens up a number of therapeutic avenues for this trace element (4).

While the vanadium requirement of lower organisms has been established, its essential value in humans remains to be proven. Daily vanadium intake has been estimated to be 10-160 µg, mainly from black pepper, dill seeds, mushrooms, parsley, shellfish and spinach, which contain between 0.05 and 1.8 µg vanadium per gram (5). The analysis of body fluids, organs and tissues has estimated that the total body pool of vanadium in humans is between 100 and 200 µg (6) and ranges from 0.014 to 7.2 µM in mammalian cells (5).

Fluconazole and itraconazole belong to triazole-derived class of known antifungal agents (7), potentially used against various fungal spe-

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cies. 1,2,4-Triazoles compounds also possess a variety of interesting biological activities such as antibacterial (8), antitumor (9), antitubercular (10), anticonvulsant (11), anticancer (12), analgesic (13), cytotoxic (14), antiproliferative (15) and plant growth regulatory functions.

This review summarizes the current *in vivo* and *in vitro* preclinical data on pharmacological properties of vanadyl Schiff base complexes, such as the insulin-mimetic action, and a broad range of other biological activities including antidiabetic, antioxidant, antibacterial and antifungal functions.

2. Antidiabetic activities

Diabetes is a presently major degenerative disease in the world today, affecting at least 15 million people with complications which include hypertension, atherosclerosis and microcirculatory disorders (Edem, 2009). Diabetes mellitus is a syndrome characterized by chronic hyperglycaemia, due to absolute or relative deficiency or diminished effectiveness of circulating insulin. It is considered as one of the five leading causes of death globaly.

There are two main types of diabetes: type 1 and type 2. Both types of diabetes are chronic diseases that affect the way the body regulates blood sugar, or glucose. Glucose is the fuel that feeds the body's cells, but to enter the cells it needs a key. Insulin is that key. People with type 1 diabetes don't produce insulin. People with type 2 diabetes don't respond to insulin as well as they should and later in the disease often don't make enough insulin. Both types of diabetes can lead to chronically high blood sugar levels. That increases the risk of diabetes complications.

The earliest documented evidence of the insulin-like effects of the inorganic vanadium salt, sodium orthovanadate (Na_3VO_4), was published by Lyonnet *et al*. (16) in 1899, 22 years before the discovery of insulin. They observed that oral Na_3VO_4 administration decreased glucosuria in two out of three diabetic patients (16). Their study went unnoticed for a long time, but the demonstration of an in vitro insulin-mimetic effect of vanadium salts by Tolman *et al*. (17) in 1979 sparked further interest. This group showed that several inorganic vanadium compounds, similar to insulin, stimulated glucose transport and oxidation in adipocytes, increased glycogen synthesis in the rat diaphragm and hepatocytes, and inhibited gluconeogenesis in liver cells.

Among the *in vivo* actions of vanadium, the seminal work of Heyliger *et al*. (18) attracted the attention of diabetologists and endocrinologists which showed that Na_3VO_4 normalized hyperglycaemia in an animal model of diabetes mellitus. Meyerovitch *et al*. (19) confirmed this observation, and it was suggested that vanadium compounds could have potential in the treatment of diabetes mellitus.

A potential insulin-enhancing role of vanadium has also been suggested based on the studies in which mildly diabetic rat models exhibited significant glucose-lowering effects with suboptimal doses of vanadium and insulin (20). Moreover, a decrease in insulin requirement, observed in vanadium-treated subjects with Type 1 diabetes, would also support an insulin-sensitizing action of vanadium. It has been speculated that vanadium exerts a protective influence on pancreatic β cells and enhances the effect of the residual insulin (21). Its insulin-sensitizing effect may be particularly important in the context of Type 2 diabetes. It should be noted that thiazoldinediones (TZD), which function as insulin sensitizers, are already being used clinically to treat Type 2 diabetes (22). This therapy in some cases is associated with increased adipocyte mass and weight gain.

The precise mechanism by which vanadium compounds improve hyperglycaemia and glucose homeostasis in diabetes remains unclear. Vanadium therapy in a Type 1 model of diabetes mellitus slightly but insignificantly increased plasma insulin level (18), whereas a significant, up to 50% decrease of plasma insulin was observed in Type 2 models.

Clearly, this alteration in insulin levels cannot be attributed to the anti-diabetic effects of vanadium compounds in Type 1 diabetes, but may be beneficial in Type 2 diabetes. Vanadium therapy of animal models is generally associated with a reduced rate of body weight gain and hypophagia (23).

Furthermore, both *in vitro* and *in vivo*,

vanadium compounds modified glucose and lipid metabolism in adipose tissue, muscle, liver and several cultured cell lines (reviewed in (24)), which may contribute to the glucose-regulating effects of vanadium.

Another physiological response modulated by vanadium is its action on glycogen synthesis. NaOV and VS stimulate glycogen synthesis in vitro systems, including the mouse diaphragm (25), rat hepatocytes and diaphragm, rat adipocytes, and Chinese hamster ovary cells over-expressing insulin receptor (CHO-HIR) and 3T3-L1 adipocytes (26).

In addition to the stimulatory action on glucose uptake and utilization, vanadium-induced suppression of hepatic glucose output will also improve glucose homeostasis. Decreased hepatic glucose production has been noted in diabetic animals and humans after vanadium therapy in some, but not all studies. Consistent with these data on gluconeogenesis, vanadium treatment decreased the heightened expression of the gluconeogenic enzymes PEPCK and G6Pase (27). In addition to their action on glucose metabolism, vanadium compounds can modulate lipid metabolism both in vivo and in vitro. NaOV treatment of insulin-resistant, sucrose-fed diabetic rats and fa/fa Zucker rats significantly lowered plasma triglycerols (28).

Vanadate has also been shown to reduce total and free cholesterol levels in normal subjects, which may be due to inhibition of the steps involved in cholesterol biosynthesis.

The demonstration of a beneficial effect of vanadium compounds in both Type 1 and Type 2 animal models of diabetes mellitus has encouraged several investigators to determine clinical benefits of vanadium therapy in human subjects with diabetes.

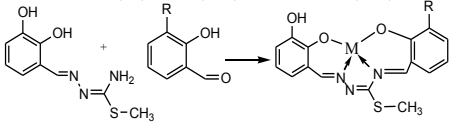
In earlier studies, small doses (50–125 mg/day) of NaMV or VS were administered orally to a limited number of Type 1 or Type 2 diabetic subjects for periods ranging from 2 to 4 weeks (29). In Type 1 diabetes, NaMV (125 mg/day) for 2 weeks had no effect on fasting plasma glucose levels, but caused a small yet significant decline in daily insulin requirements and improved glucose utilization in two out of five patients (30). In Type 2 diabetes, NaMV resulted in an increased insulin sensitivity due to enhanced nonoxidative glucose disposal (30).

Despite their impressive anti-diabetic properties, vanadium compounds have been associated with several side effects (reviewed in (31)). The most common are diarrhea, decreased fluid and food uptake, dehydration and reduced body weight gain (19, 23) which can, however, be corrected by adding NaCl to the drinking water, adjusting the pH of the solution to neutrality, and by gradually increasing the dose of vanadium (19, 25). In summary, although animal studies have provided convincing evidence for the antidiabetic effects of vanadium compounds, a similar role of vanadium in controlling human diabetes is yet to be established. The slow progress in this direction may be attributed to the gastrointestinal intolerance of the inorganic vanadium salts used in earlier work. However, the availability of organically complexed vanadium compounds with better tolerance should encourage more detailed evaluation of these compounds as potential anti-diabetic agents for humans.

3. Antioxidant activity

Antioxidant compounds may function as free radical scavengers, which play important role in food and chemical material degradation, and significantly delay or prevent the oxidation of easily oxidable substrates. Therefore, the importance of searching for antioxidants has greatly increased in the recent years (32). These facts have led to a large amount of research involving such systems.

In a study by Al Zoubi *et al.*(33), the nickel(II), iron(III) and oxovanadium(IV) complexes of 3-hydroxysalicylidene-S-methylthiosemicarbazone were obtained from 3-hydroxysalicylaldehyde-S-methylthiosemicarbazone with R1-substituted salicylaldehyde (R1: H, 3-OH) in the presence of Ni(II), Fe(III), and VO(IV) as tem-



M= $NiCl_3$, $FeCl_3$, $VOSO_4$

Figure 1. Complexes of 3-hydroxysalicylidene-S-methylthiosemicarbazone.

plate ions (Figure 1). The free ligand and its metal complexes have been tested for in vitro antioxidant capacity by using the CUPRAC (CUPric Reducing Antioxidant Capacity) method.

This method is antioxidant measurement based on the absorbance measurement of Cu(I)-neocuproine (a heterocyclic organic compound and chelating agent) chelate formed as a result of the redox reaction of chain-breaking antioxidants with the CUPRAC reagent, Cu(II)-Nc, where absorbance is recorded at the maximal light-absorption wavelength of 450 nm. The ligand exhibited more potent *in vitro* antioxidant capacity than its complexes. The obtained trolox equivalent antioxidant capacity (TEAC) value of the iron(III) complex (TEACCUPRAC=3.27) was higher than those of the other complexes. Furthermore, the antioxidant activities of the free ligand and its complexes were determined by *in vitro* methods measuring the scavenging activity of reactive oxygen species including hydroxyl radical ($^{\bullet}OH$), superoxide anion radical ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2), showing that especially VO(IV) and Fe(III) complexes had significant scavenging activity for reactive oxygen species (34).

4. Antibacterial activity

Coordination compounds have been studied for their antitumor, antiviral, and antimalarial activity which is related to the ability of metal ions to form stable complexes (35). The results have led to an understanding of the coordination sphere and the electronic properties of the metal ions and the factors such as chelate formation, ring size, number of aromatic rings, and the presence of amino groups, which modify the coordination sphere. The increase in bactericidal activity of the vanadyl complexes may be due to the effect of the vanadium ion on the normal cell process. An acceptable reason for this increase in bactericidal activity may be considered in the light of Overtone's concept (36) and Tweedy's chelation theory. According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipidsoluble materials so that liposolubility is an important factor which controls bactericidal activity.

A new series of oxovanadium (IV) complexes have been designed and synthesized from a new class of triazole Schiff bases derived from the reaction of 3, 5-diamino-1, 2, 4-triazole with 2-hydroxy-1-naphthaldehyde, pyrrole2-carbox-

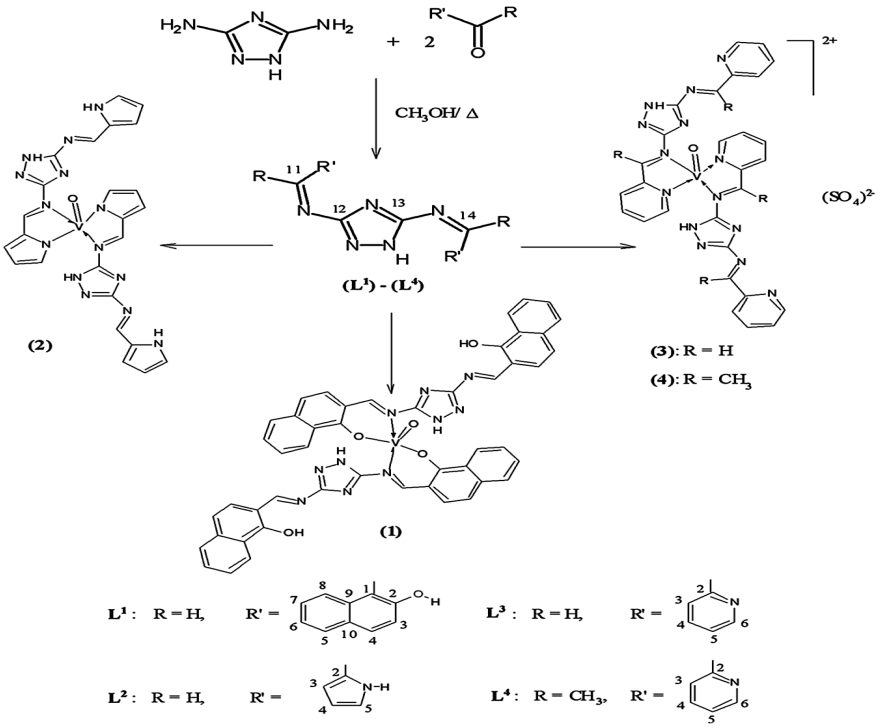


Figure 2. Synthesis of the triazole ligands (L1)-(L4) and their complexes (1)-(4).

aldehyde, pyridine-2-carboxaldehyde and acetyl pyridine-2-carboxaldehyde, respectively by Zahid H *et al.*(Figure 2) (37). The biological activity of the complexes have been studied against four Gram-negative (*Escherichia coli*, *Shigellaflexenari*, *Pseudomonas aeruginosa*, *Salmonella typhi*) and two Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*) bacterial strains, *in vitro* antifungal activity was studied against *Trichophytonlongifucus*, *Candida albican*, *Aspergillus flavus*, *Microscopum canis*, *Fusarium solani* and *Candida glaberata*. The Schiff bases showed weaker significant activity against one or more bacterial and fungal strains.

In most of the cases, a higher activity was exhibited upon coordination with vanadium(IV) metal. Brine shrimp bioassay was also carried out for in vitro cytotoxic properties against *Artemia salina*. This bioassay is an important tool for the preliminary cytotoxicity assay of plant extract and others based on the ability to kill a laboratory cultured larvae (38).

5. Antifungal activity

The oxovanadium(IV) complexes were tested for their antifungal activity against different fungal cultures such as: *Aspergillus flavus*, *Aspergillus niger*, *Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavus*, and *Candida glaberata* using standard methods. Several methods for detecting activity are available, but since they are not equally sensitive or not based upon the same principle, results will be profoundly influenced by the method. The methodology for testing compounds for determination of antifungal activity is variable and each research group employs different types of tests. The most used are bio-autography, disk diffusion, agar dilution and dilution tests (39).

A comparative study of the ligand and its complexes (MIC values) indicates that complexes exhibit higher antifungal activity than the free ligand. From the MIC (the minimum inhibitory concentrations) values, it was found that the compound VOL is more potent among the other investigated metal complexes and the Schiff base. Such increased activity of the complexes can be explained on the basis of Overtone's concept (36) and Tweedy's Chelation theory. On chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization π-electrons over the whole chelate ring and enhances the lipophilicity of the complexes. The increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of the proteins that restricts further growth of the organism. Furthermore, the mode of action of the compound may involve formation of a hydrogen bond through the azomethine group with the active centre of cell constitutes resulting in interference with the normal cell process (40).

6. Conclusion

Studies on the vanadyl Schiff base complexes have shown that some of them are involved in important biological processes, such as antidiabetic, antioxidant, antibacterial and antifungal activity. The mechanism by which vanadium compounds exert anti-diabetic actions may involve a combination of the stimulation of glucose uptake as well as glycogen and lipid synthesis in muscle, adipose and hepatic tissues and inhibition of gluconeogenesis and activities of the gluconeogenic enzymes PEPCK and G6Pase in the liver and kidney as well as lipolysis in fat cells. In addition to animal studies, clinical trials in diabetic human subjects have documented improvements in glycaemic control and insulin sensitivity. These studies are encouraging, but improvements are less than those in animal models.

Antimicrobial results indicated that all the oxovanadium (IV) complexes possessed enhanced biological activity against one or more bacterial/fungal strains as compared to their uncomplexed ligands. In general, it is believed that the functional groups present in the compounds such as azomethine-N and other heteroatoms such as oxygen and nitrogen are responsible for improved biological activity. In most of the cases, the oxovanadium (IV) complexes showed higher antimicrobial effect than free ligands. It is therefore, evident that coordination makes the ligands strong antibacte-

rial agents and inhibits the growth of bacteria more than the parent uncomplexed ligand.

The results of antibacterial and antifungal studies of these complexes lead us to the conclusion that those compounds that are not biologically active become biologically active, and those that are biologically active become more active, upon coordination/chelation with the metal ions.

Conflict of Interest

None declared.

7. References

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