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Review

Therapeutic Properties of Vanadium Complexes

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Abstract: Vanadium is a hard, silver-grey transition metal found in at least 60 minerals and fossil fuel deposits. Its oxide and other vanadium salts are toxic to humans, but the toxic effects depend on the vanadium form, dose, exposure duration, and route of intoxication. Vanadium is used by some life forms as an active center in enzymes, such as the vanadium bromoperoxidase of ocean algae and nitrogenases of bacteria. The structure and biochemistry of vanadate resemble those of phosphate, hence vanadate can be regarded as a phosphate competitor in a variety of biochemical enzymes such as kinases and phosphatases. In this review, we describe the biochemical pathways regulated by vanadium compounds and their potential therapeutic benefits for a range of disorders including type 2 diabetes, cancer, cardiovascular disease, and microbial pathology.

Keywords: vanadium complexes; anticancer; insulin; antimicrobial; osteogenic effect; cardiovascular system; COVID-19

1. Introduction

Vanadium was first discovered by the Mexican mineralogist Andrés Manuel del Rio in 1801 from a specimen of vanadinite, $Pb_5(VO_4)_3Cl$. The element is named after 'Vanadis', the old Norse name for the Scandinavian goddess Freyja representing youth and beauty [1]. However, vanadium was erroneously identified as a chromium mineral until 1831, when the Swedish chemist Nil Gabriel Selfström was investigating steel brittleness in Taberg, Småland, Sweden [2,3]. Vanadium's importance in biological systems has long

been recognized, and vanadium-based catalysts are widely used in industry [4]. Many researchers, like the Pessoa, Kiss, and Garribba groups, have concentrated on vanadium complexes and published tens of articles on the topic, probably owing to the chemical diversity of vanadium complexes and their medicinal and biological significance [4–14].

Among the discovered elements, vanadium is the 20th most abundant chemical element on Earth [15] and is naturally occurring in different minerals including carnotite, patronite vanadinite, roscoelite, and vanadium-bearing magnetite. Vanadium is also naturally found in certain crude oils in the form of vanadium organic complexes and vanadium-carbonaceous deposits from the Cryogenian and Cambrian periods [5].

Chemically, vanadium exhibits a broad range of oxidation states from +5 to −3, which can be easily interconverted. Moreover, at maximum oxidation states, vanadium can be a very good Lewis's acid. The multiple oxidation states of vanadium, along with its Lewis acid character, good oxophilicity, and ready hydrolysis, give it a rich reaction versatility compared with sulfur complexes and aggregated oxyanions, as well as broad applications of its by-products in catalysis and biology.

Similar to other transition metal complexes, such as copper [16], gold [17], iron [18], and zinc [19], vanadium complexes show a wide range of bioactivities. The interest in vanadium complexes in medicine started earlier than 1939 and rose gradually until the 1970s [11]. The number of published articles related to the promise of vanadium compounds/complexes in various therapeutic applications, including diabetes, microbial infections, and cancers, has increased rapidly since 1999 (Figure 1), which is mostly attributed to vanadium's biological properties, many of which are shared with phosphates [20]. A recent study showed that vanadium (and its complexes with inorganic and organic ligands) plays an important role in lipid, DNA and protein synthesis, glucose transport and metabolism, and insulin-mimetic activity, and has mitogenic effects on different types of cells. It also shows therapeutic potential against RNA viruses including COVID-19 [21]. A series of in vitro investigations have demonstrated that oxidovanadium VO^{2+} and vanadate $VO_4{}^{3-}$ decrease lipolysis and stimulate glucose oxidation, glycogen synthase, glucose transport, and tyrosine phosphorylation in rat adipocytes [22]. Vanadates also promote glycogen synthase glucose uptake, glucose, and glycolysis oxidation in striated muscle [23,24]. However, vanadium is a highly toxic element that inhibits some biochemical processes.

Finally, its multiple oxidation states and Lewis acid character make vanadium highly reactive and versatile for numerous industrial applications, such as the pigmentation of ceramics, glass manufacturing, coatings, and microelectronic devices [25]. The use of transition metal compounds in biomedical applications is under investigation because of their efficacy in lowering the toxicity of the free organic ligands and increasing their absorbance and stability [26,27]. For this purpose, vanadium is being investigated as a potential metallodrug for the treatment of cancer [28], diabetes [29], and infectious diseases [30].

In this review, we describe the role of vanadium in different biochemical processes and its potentially toxic effects. We especially focus on recent studies that examined the enzyme switching activity of vanadium compounds for the treatment of osteogenesis; type 2 diabetes mellitus (T2DM); cancer; and pathologies caused by viruses, microorganisms, and parasites.

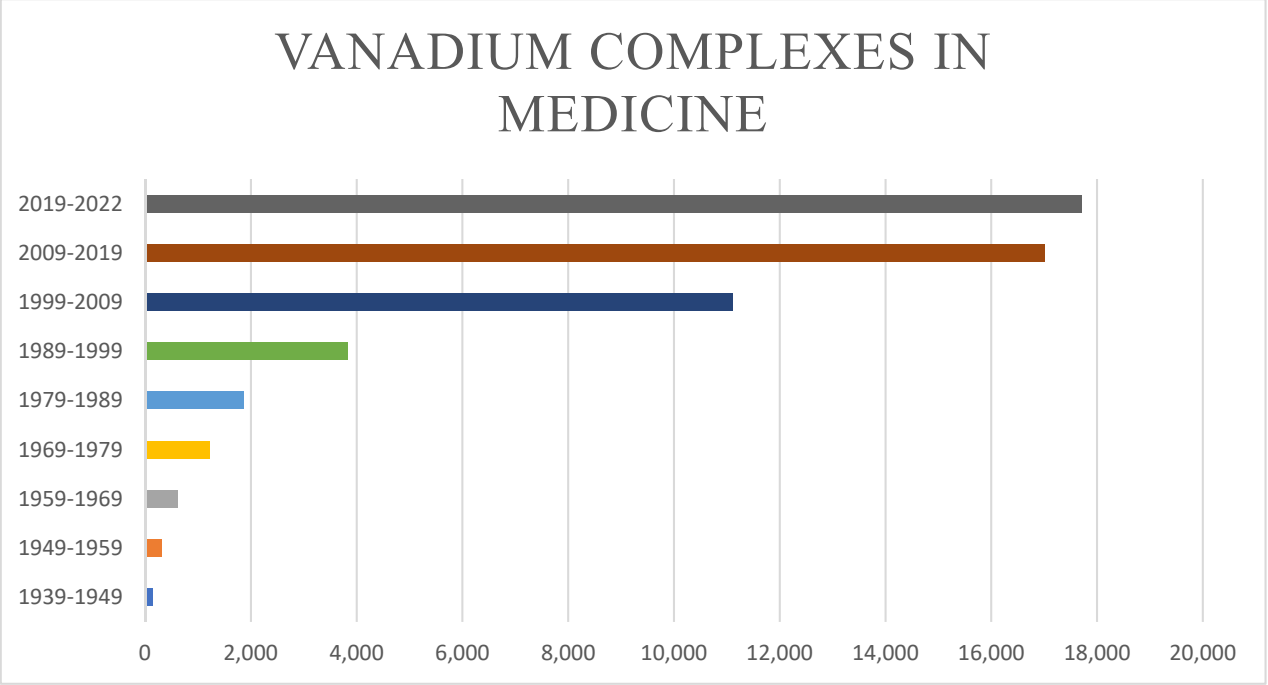

Figure 1. Published studies using vanadium complexes in medical applications. Studies were found by searching the exact phrase "vanadium complexes in medicine" on Google Scholar (http://scholar.google.com (accessed on 22 March 2022)).

2. Vanadium as an Enzyme Switch

Vanadium is necessary for the activity or functionality of proteins in many species on the planet. Some vanadium-using species have highly effective and specialized protein-dependent vanadium absorption and transport mechanisms [31]. Under physiological settings, vanadium compounds in biological systems can quickly interconvert, and multiple vanadium-containing moieties can form and bind to proteins. These interactions are crucial for the form that is transported in the circulation, cell uptake, inhibitory characteristics, and mode of action of essential and pharmacologically active vanadium species [6]. Vanadium complexes conduct biological activities through their ability to activate or inactive certain enzymes [11,32]. Vanadate $(VO_4)^{3-}$ structure is remarkably like that of phosphate $(PO_4)^{-3}$ and has similar chemistry. For instance, $(H_2PO_4)^-$ has a pKa = 7.2, whereas $(H_2VO_4)^-$ has a pKa = 7.8 [30]. Phosphorous can typically be coordinated by more than five ligands, while vanadium can accept a maximum of six donor atoms. Nevertheless, both participate in esterification-type reactions, demonstrating that vanadate can be regarded as a phosphate competitor. Indeed, if vanadate replaces phosphate in an enzyme readily, it can form stable complexes with the enzyme target, thus inhibiting the enzyme [33]. Accordingly, some vanadium complexes activate and/or inhibit several enzymes, including phosphatases, ATPases, nucleases, and kinases, among others [30].

The ability of vanadium to activate enzymes is mostly attributed to complexing with the ligand. For instance, the anionic form of vanadium $(VO_4)^{-3}$ activates glucose-6-phosphate dehydrogenase in mammalian cells. Moreover, vanadate compounds activate the tyrosine kinases $p56^{lck}$ and $p59^{fyn}$ [34,35]. They also activate protein kinase B (PKB) or Akt, as well as extracellular-signal-regulated kinases (ERKs), which are involved in antilipolytic and cell cycle regulation processes (Figure 2).

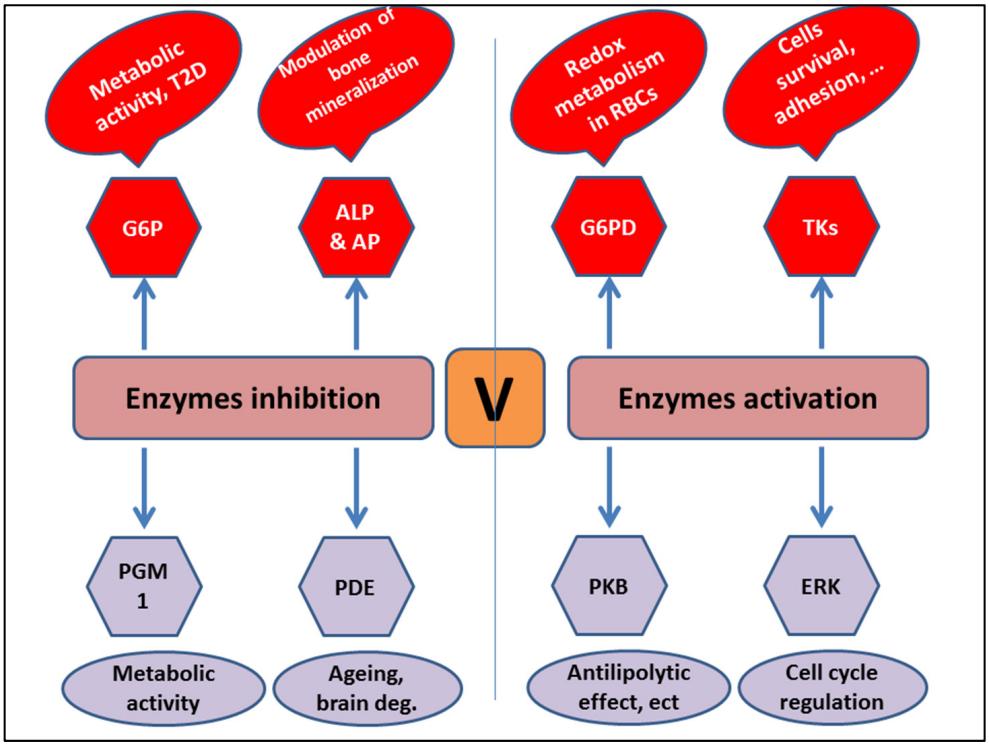

Figure 2. Main enzyme targets of vanadium complexes.

Conversely, vanadium can inhibit several enzymes, such as alkaline phosphatase (ALP) and acid phosphatase (AP), both of which are involved in bone mineralization [36,37], as well as glucose-6-phosphatase (G6P) [38,39], phosphodiesterases [40,41], and phosphoglucomutase [42,43] (Figure 2). Together, these findings suggest that vanadium complexes control numerous biological processes.

Vanadium and its compounds stimulate the biosynthesis of glycogen and lipids in muscle, liver, and adipose tissues. The insulin-mimetic action of vanadium is mediated by the inhibition of gluconeogenesis through blocking of phosphoenol pyruvate carboxykinase (PEPCK) [33] and G6P [38] and inhibition of lipolytic pathways [22]. Vanadium reverses peripheral insulin resistance and improves glucose uptake by perpetuating the nitric oxide (NO)/cGMP/protein kinase (PKG) signaling pathway through inhibition of phosphodiesterases [40].

Vanadium inhibits protein tyrosine phosphatases (PTPs) by generating reactive oxygen species (ROS) [44], and suppresses the dephosphorylation of tyrosine residues of the beta subunit of insulin receptors [45]; this ability is due to the structural homology of the vanadate group with the phosphate group [46,47]. The inhibition of protein tyrosine phosphatase 1B (PTP-1B) results in the activation of insulin receptor and phosphorylation of insulin substrate 1 (IRS-1), leading to activation of the 3-phosphatidylinositol kinase/Akt protein kinase (PI3K-Akt) pathway [48], which in turn increases the number of glucose-type 4 (GLUT4) transporters, and thus their translocation [49]. Moreover, the inhibitory effect of vanadium on PTP results in the increased activity of insulin-like growth factors, which in turn leads to the stimulation of glycogenesis, impairment of the gluconeogenic pathway, and increased production of GLUT4 [50]. Furthermore, it has been reported that the interaction of vanadium with cell membranes results in the stabilization of vanadium complexes and produces changes in membrane proteins that may further contribute to the insulin-mimetic action [51].

3. Insulin-Mimetic Activity of Vanadium Compounds

Metabolic disorders lead to obesity, diabetes, and insulin resistance. T2DM accounts for approximately 90% of global diabetes cases (463 million in 2019; 578 million are es-

timated by 2030 [52]). It is a multifaceted disorder characterized by impaired insulin secretion, diminished cellular response to insulin, increased glucose production, and reduced peripheral glucose uptake [53]. Current drug therapies reverse the blood glucose increase, but do not prevent the disease progression.

The antihyperglycemic effect of vanadium was first reported in diabetic patients more than 100 years ago [54]. In vivo and in vitro studies have shown that vanadium compounds have metabolic effects on glycemic control in diabetic patients similar to that of insulin [55]. The role of the red blood cells and serum in vanadium transport, the role of GIT in vanadium absorption, and the role of cell components such as ATP and glutathione that exert redox reaction and complex formation with vanadium have been reported to integrate the vanadium insulin mimetic activity [56]. In addition, the binding liability of vanadium and blood components such as albumin and human serum apo-transferrin have been reported as potential transporters of vanadium to the target cells [57,58]. At a physiological ratio, the majority of the VO^{2+} ion is present as (VO) in human serum apo-transferrin and a little amount is present as (VO) in human serum albumin, according to research by Sanna et al. Transferrin is a stronger binder to vanadium than albumin in aqueous solution [7]. The complex bis(sallixinato) oxovanadium(IV) (Figure 3A) is a potent anti-diabetic agent, presented by the Adachi group [59]. They used both in vitro and in vivo studies to investigate the antidiabetic potency of bis(3-hydroxy-4-pyronato)oxovanadium(IV) and bis(allixinato)oxovanadium(IV) complexes with $VO(O_4)$. These complexes contain allixin, a garlic component high in in vitro insulin-mimetic activity in terms of both free fatty acid (FFA)-release inhibitory and glucose-uptake enhancing activity in isolated rat adipocytes. Second-generation pyrone derivatives, such as bis((5-hydroxy-4-oxo-4H-pyran-2-yl)methylbenzoatato)oxovanadium(IV) (BBOV), which are less toxic than bis (maltolato) oxovanadium (BMOV), have been developed and can be administered at 1000-fold lower doses than their first generation counterparts [60].

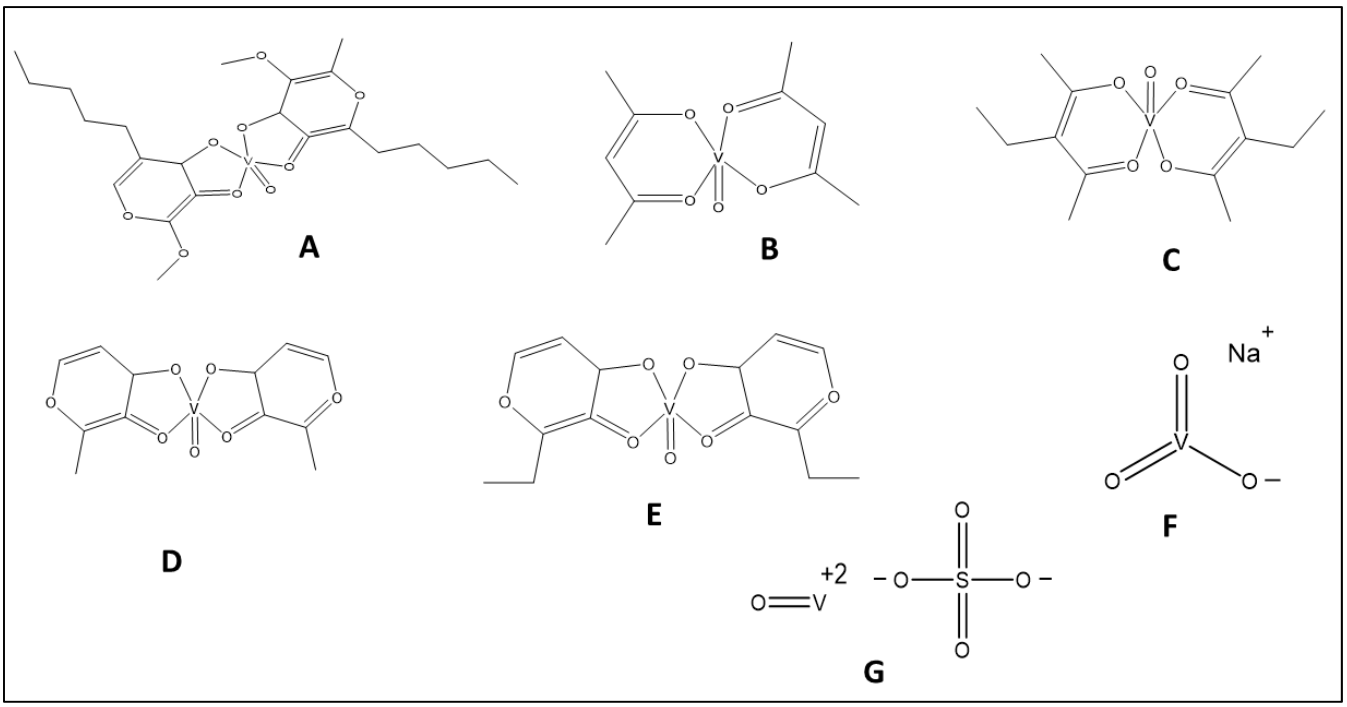

Figure 3. The structure of vanadium complexes with insulin-mimetic activity. (**A**) Bis(sallixinato) oxovanadium. (**B**) Vanadyl acetylacetonate. (**C**) Vanadyl 3-ethylacetylacetonate. (**D**) Bis(maltolato) oxovanadium. (**E**) Bis(2-ethyl-3-hydroxy-4-pyronato)oxovanadium(IV). (**F**) Sodium metavanadate. (**G**) Vanadyl sulfate.

Vanadium compounds, such as vanadyl acetylacetonate (Vac; Figure 3B), vanadyl 3-ethylacetylacetonate (Vet; Figure 3C), and BMOV (Figure 3D), show better glycemic control and restoration of the hepatic glycolytic pathway by upregulating and downregulating the mRNA expression of glucokinase and L-type pyruvate kinase and phosphoenolpyruvate carboxykinase (PEPCK), respectively, compared with vanadium sulfate in diabetic rat hepatocytes [61]. Further, several other organic complexes of vanadium such as bis(2-ethyl-3-hydroxy-4-pyronato)oxovanadium(IV) (BEOV; Figure 3E) and bis(maltolato) oxovanadium also exhibited improved antidiabetic effects compared with inorganic salts against streptozocin (STZ)-induced diabetes in rats [62,63]. Although BEOV is the first vanadium complex that entered clinical trials, its testing was suspended because of renal problems in some of the treated patients [64].

The oral administration (125 mg/day) of sodium metavanadate, which refers to mixtures such as $[H_2VO_4]^-$, $[H_2V_2O_7]^{2-}$, and $[V_4O_{12}]^{4-}$ (Figure 3F) [47], in insulin-dependent diabetes mellitus patients (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) patients for 2 weeks led to a 3.9-fold increase in the basal activity of mitogen-activated protein kinase (MAPK), a reduction in the cholesterol level in both groups, and a reduction in the insulin requirement in IDDM patients [65]. Another study showed that sodium metavanadate moderately decreased blood glucose levels in two out of three diabetic patients without adverse effects [55].

Rehder et al. tested the insulin mimetic characteristics of 41 vanadium compounds and found that these complexes exerted toxic effects at a dose of 1 mM. However, these compounds exerted insulin mimetic activity similar to or more potent than insulin with a non-toxic effect at the concentration of 0.01 mM or below [66]. In addition, insulin mimetic activity of three vanadium complexes, [((papy)(VO))$_2$ μ-O)], [(glysal)VO(H_2O)], and [(salam)$_2$VO], has been examined. Over a pH range of 2–10, the speciation of complexes [((papy)(VO))$_2$ μ-O)] and [(glysal)VO(H_2O)] was investigated. Only complexes [(glysal)VO(H_2O)] and [(salam)$_2$VO] display an insulin-mimetic action, while [((papy)(VO))$_2$ μ-O)] exhibits better stability over the entire pH range [67].

A randomized placebo-controlled clinical trial involving T2DM patients given 100 mg sodium monovanadate once a day for six weeks found no significant reduction in fasting blood glucose (FBS), glycosylated hemoglobin (HbA1C), total cholesterol (TC), or low-density lipoproteins (LDLs) [68]. On the other hand, vanadyl sulfate (Figure 3G) orally administered for 6 weeks in 16 T2DM patients lowered FBG, HbA1c, and total TC without any significant change in hemodynamic parameters. In addition, the treatment produced a significant increase in the insulin-mediated activation of insulin receptors, Shc, IRS-1 protein kinase, and PI3K, without an increase in insulin secretion [69]. Vanadyl sulfate has also been reported to improve carbohydrate and lipid metabolism [70] and hepatic and peripheral insulin sensitivity in NIDDM patients [71], except in nondiabetic individuals with obesity [72]. A recent study showed that vanadyl sulfate (25 mg/kg) not only produced a significant reduction in blood glucose and insulin secretion, but also alleviated oxidative stress and inflammatory markers in renal tissues of type 2 diabetic rats [73]. However, some studies reported negative effects of vanadium sulfate therapy. For example, 0.25 mg/kg and 1.2 mg/kg vanadyl sulfate for 24 weeks produced a dose-dependent reduction in blood glucose and insulin levels, but had a negative effect on the lipid profile, as evidenced by the significant decrease in high-density lipoprotein c (HDL-c) and increase in LDL-c and triacylglycerols (TGs) in healthy rats [74]. Another study showed that vanadyl sulfate administration (50 mg twice daily for 4 weeks) produced a significant increase in serum triglyceride without an improvement in insulin sensitivity in obese type 2 diabetic patients with impaired glucose tolerance compared with placebo [75]. Finally, Jakusch et al. have shown that vanadium ion exerts antidiabetic activity. However, the role of drug candidate ligands of the original vanadium complexes is that of a carrier function until the vanadium is taken up into the serum [12]. The breakdown of the initially neutral VO(IV) molecules and subsequent ternary complex formation with endogenous or foreign ligands in the organism significantly alters their ability to be absorbed. Transferrin plays a

crucial function in transferring VO(IV) to the cell by displacing the carrier ligands from the VO(IV) molecules during transport in the bloodstream [76]. The dissociation of vanadium complexes prior to antidiabetic activity also supports the activity of the vanadium ion itself and limited the ability of the complexes to enhance the absorption of the free active metabolite, vanadium in the oxidation state (V^V) [56].

4. Osteogenic Activity of Vanadium Compounds

In animals, vanadium is mainly stored in bones and has a positive effect on osteogenesis owing to its growth-factor-mimicking properties [77,78]. Therefore, vanadium compounds have been investigated for their osteogenic activity. Experimental studies on osteosarcoma epithelial (UMR106) cells showed that vanadium derivatives (vanadate, vanadyl, and vanadium peroxide complexes) improve cell differentiation and proliferation and enhance alkaline phosphatase enzyme activity [79].

Furthermore, vanadium derivatives stimulate two insulin signaling pathways, PI3K and MAPK, responsible for bone mineralization, bone density, and bone formation in mammalians [80]. Two bone-derived cell lines (Vertebra Sparus aurata; VSa13 and VSa16) treated with metavanadate and decavanadate (Figure 4A) solutions exhibited similar effects as treatments with insulin and IGF-1 in the short-term; namely, VSa13 cell proliferation and extracellular matrix mineralization inhibition [80].

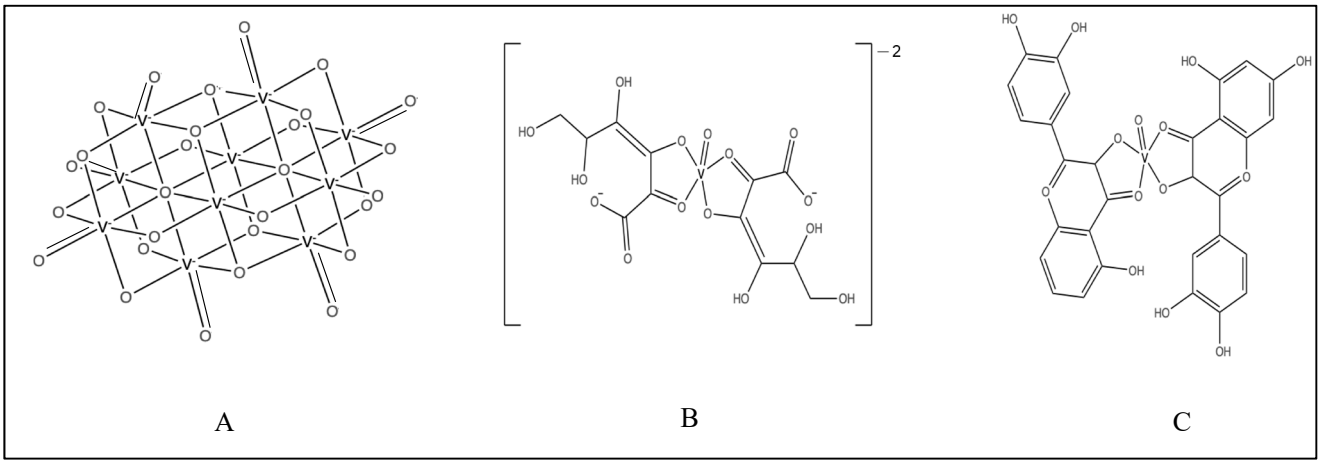

Figure 4. Structures of vanadium complexes of (**A**) decavanadate, (**B**) 2,3-diketogulonic acid, and (**C**) quercetin.

Vanadyl(IV) complex of 2,3-diketogulonic acid (Figure 4B) was found to allow proliferation of UMR106, but not mouse-calvaria-derived cells (MC3T3E1) [81]. It also activated type-I collagen production in osteoblasts and activated P-ERK in a dose-dependent manner. The effects on the osteoblasts were partially inhibited by a *PI3K* inhibitor (wortmannin) and calcium channel blocker (nifedipine).

Nano vanadium dioxide (VO_2) deposited on biomedical titanium demonstrated osteogenic activity in rat mesenchymal stem cells by regulating ROS levels [82].

In a recent study, the titanium aluminium vanadium ($TiAl_6V_4$) complex enhanced the osteogenic differentiation and adhesion of osteoblasts and mesenchymal stem and progenitor cells [83].

A vanadium complex with quercetin (Figure 4C) exhibited osteogenic effects by stimulating type I collagen production and ERK phosphorylation in a dose–response manner [84]. Vanadium-loaded collagen scaffolds have been fabricated for osteochondral tissue engineering purposes. These scaffolds exerted better adhesion, growth, osteoblastic, and chondrocytic differentiation compared with no loading in rat bone marrow progenitor cells [85].

5. Anticancer Potency

Vanadium compounds have various cancer treating properties, where different cancer pathways may be targeted, such as MAPK/ERK and PI3K/AKT, or caspase signaling pathways [86]. The anticancer mechanism includes defensive effects against chemical carcinogenesis and as inhibitors of cancer cell metastatic potential by reversing drug resistance and changing cellular adhesion [87]. Moreover, it could be the activation of xenobiotic enzymes, inhibition of PTPs and/or activation of protein tyrosine kinases, production of free radicals, and DNA cleavage [87].

The first vanadyl complexes shown to have anticancer activity against several cell lines were vanadocene dichloride and its derivatives, with IC_{50} values lower than cisplatin [88]. METVAN ([$VO(SO_4)(Me2phen)_2$], where Me2phen is 4,7-dimethyl-1,10-phenanthroline) also showed practical activity at low concentrations (micromolar or nanomolar) against many cell lines [89]. Moreover, antitumor properties of the $V^{(IV)}O$ complexes of flavonoids, such as quercetin, morin, chrysin, and silibinin, were found for osteosarcoma and breast cancer cell lines [20]. The antiproliferative activity against ovarian (A2780) and prostate (PC3) human cancer cells for three aroylhydrazones and the corresponding vanadium complexes (one oxido and two nonoxido compounds) were evaluated by Dinda's group [90]. This work showed a significant inhibition of [$V^{V}O$(L1)(OEt)] among the tested complexes. Moreover, the measured cytotoxicity values were better than the free ligand owing to the presence of several species such as $V^{V}O_2$, $V^{IV}O$, and V^{IV} in the aqueous solution, which gave more ability to bind to the model proteins, ubiquitin (Ub) and lysozyme (Lyz). In addition, four different vanadium species have been examined for their antiproliferative potency against two malignant melanoma cell lines, A375 and CN-mel cells [91]. These four species, namely, inorganic anion vanadate, [$V^{IV}O$(1,2-dimethyl-3-hydroxy-4(1*H*)-pyridinonate)$_2$], [$V^{IV}O$(1-methyl-3-hydroxy-4(1*H*)-pyridinonate)$_2$], and [$V^{IV}O$(1-phenyl-2-methyl-3-hydroxy-4(1*H*)-pyridinonate)$_2$], have exerted marked cytotoxic effects in a dose-dependent manner and showed IC_{50} values of 2.4 to 14 μM [91].

Schiff base oxidovanadium(IV) complexes were studied in vitro for their anti-cancer effects [92] on hepatocellular carcinoma (HepG2), human hepatic carcinoma cells (Hep3B), breast adenocarcinoma (MCF7), and colon carcinoma (HCT-116) cell lines. The DSHNVO complex (Figure 5A) showed a higher cytotoxic effect compared with the free ligand, with the biggest effect on MCF-7 [92]. The complexes presented in Figure 5B have considerable cytotoxicity on Hep3B and remain stable for 3 days in cell culture media [93].

Recently, Nunes et al. has reported the potential anticancer effect of Copper(II) and oxidovanadium (IV) complexes of chromone Schiff bases that effectively produce genotoxic damage, elevate ROS production, and promote cell death by apoptosis in various human cancer cell lines (breast, brain, cervix, and ovary) preferentially compared with normal cells [94]

Mixed–ligand oxidovanadium(IV) compounds, such as complex ([VO(ox)(phen)(H_2O)] (ox = oxalic acid dihydrates and phen = 1,10-phenanthroline)), show high cytotoxicity against SMMC-7721 and HepG2 cells with IC_{50} values of 5.34 and 29.07 μM, respectively [95] (Figure 5C).

Introducing metal ions reduces the toxicity of free drugs. Additionally, metal ions can enhance the lipophilicity of the drugs to penetrate the cell and increase their absorbance and stability [96]. Four approved drugs, sulfonamide (antibacterial), cetirizine (antihistamine), carbimazole (antithyroid), and lornoxicam (anti-inflammatory), have been used as ligands to form oxidovanadium(IV) complexes with potential anticancer activity in colon cancer cells (3IG7) [97]. Cetirizine-based oxidovanadium (IV) complex (Figure 5D) showed greater selectivity and potential than cisplatin, cleaving DNA with a predicted binding constant of $K_b = 1.40 \times 10^6\ M^{-1}$.

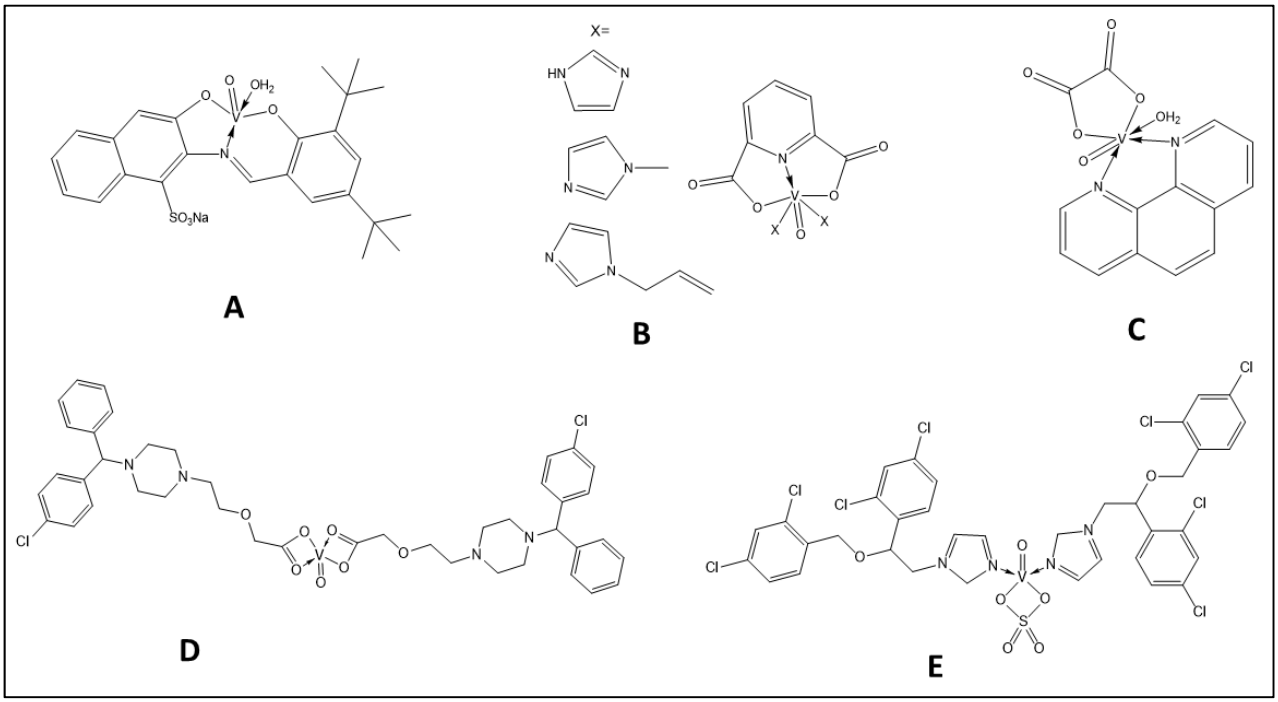

Figure 5. The structure of some vanadium complexes with anticancer activity.

Imidazole derivatives have remarkable pharmaceutical potencies. They can bind to DNA and proteins with multiple modes of interaction such as electrostatic, intercalation, and groove binding [98]. Basaleh et al. [99] used three imidazole derivatives to synthesize novel vanadyl-based drug complexes from clotrimazole (CTNZ), miconazole (MNZ), and pantoprazole (PNZ). The investigated complexes bind to DNA non-covalently, and the $[VO(SO_4)(MNZ)_2]$ H_2O complex (Figure 5E) has a promising binding constant. Remarkably, all obtained metal complexes strongly inhibited HepG-2 and human breast cancer (HCF-7) cell lines.

Mono-oxovanadium(V) complex with mixed ligands, tridentate hydrazine, and benzhydroxamic acid have shown significant inhibitory activity towards MCF-7 with an IC_{50} = 6.0 μM (cisplatin had IC_{50} = 22.8 μM under the same experimental condition) [100].

6. Antimicrobial, Antiviral, Antiparasitic, and Antifungal Activities of Vanadium Compounds

Vanadium is as a cofactor of several bacteria enzymes, such as haloperoxidases and nitrogenases. Several studies showed that vanadium can act as an antibacterial agent against tuberculosis and pneumonia. In a recent study, the inhibitory activities of three oxovanadium (IV) (Figure 6A–C) and three cis-dioxovanadium(V) complexes (Figure 6D–F) with thiosemicarbazone derivatives carrying varying lipophilicity moieties were tested against *Mycobacterium tuberculosis* strains (H37Rv ATCC27294) [101]. The diamagnetic cis-dioxovanadium(V) complexes $[VO_2(aptsc)]$, $[VO_2(apmtsc)]$, and $[VO_2(apptsc)]$ were formed as a result of oxidation of the vanadium (IV) complexes. In general, vanadium compounds have anti-*M. tuberculosis* activities comparable to or even greater than free thiosemicarbazone ligands, with MIC values ranging from 62.5 to 1.56 (g/mL) [102]. Of note, treating tuberculosis with free thiosemicarbazone ligands has been shown to affect diabetes mellitus [102].

A recent study focused on the antibacterial efficacy (methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*) of V_2O_3-, VO_2-, and V_2O_5-nanofilms on quartz glass and their interactions with human erythrocytes in a unique cell–bacteria co-culture model [101,103]. These VO_x-nanomaterials showed positive antibacterial action against bacteria, particularly *S. aureus*, and this impact increased with greater vanadium valence [102].

Elevated amounts of induced intracellular ROS could be one explanation for these findings. More crucially, the VO_x-nanofilms were found to kill prokaryotic cells, but not mammalian cells in hemolysis assays, indicating that they could be used to prevent implant-related hematogenous infections. In general, bloodstream infection, particularly when implants are involved, is a life-threatening illness with high death rates that places a significant burden on patients and medical systems. Such research could lead to novel biomedical applications for inorganic vanadium compounds, attracting more interest in the subject. This research has the potential to provide prophylaxis of bloodstream infections involving implantable biomedical devices. Indeed, recent studies showed that vanadium ions are released in a sustained way from VO_x-nanofilms, and low-valence films had higher biocompatibility with human fibroblasts [104].

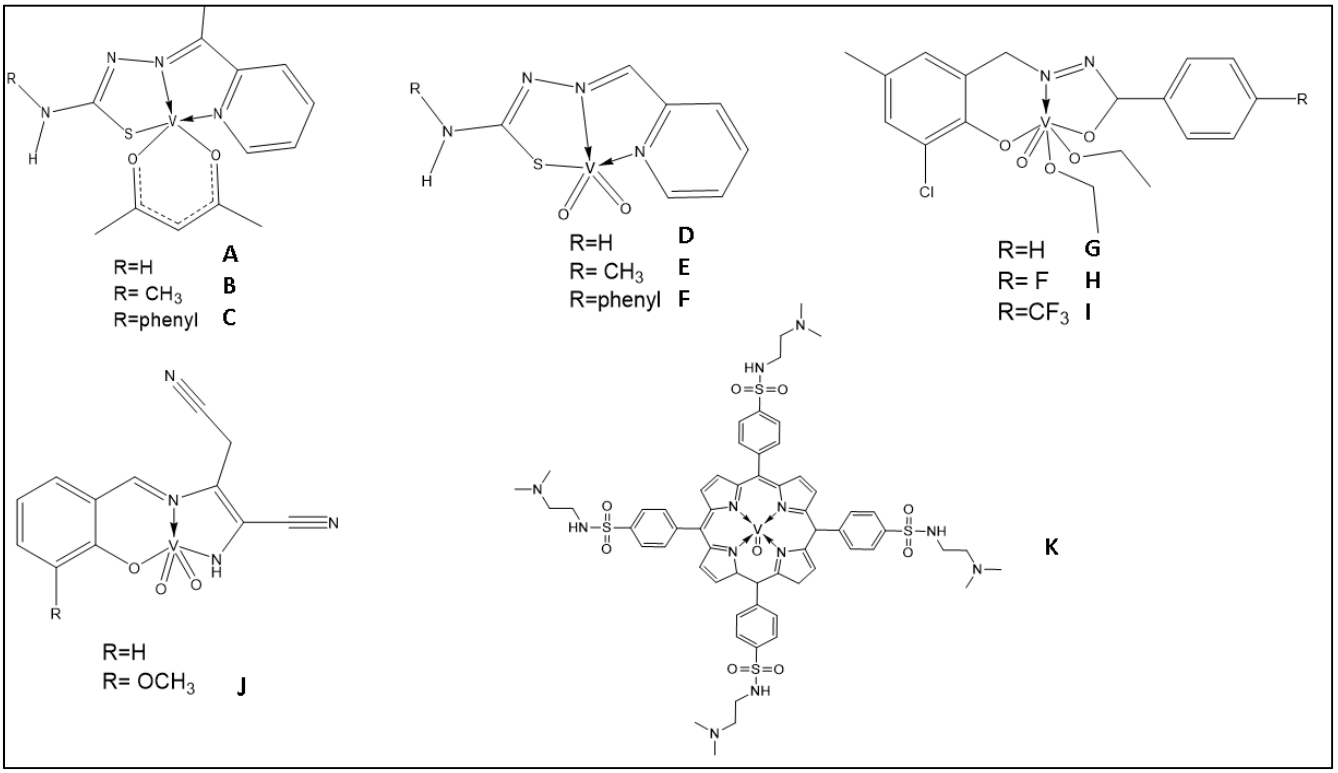

Figure 6. The structure of oxovanadium complexes with antimicrobial potency.

Another study used the agar diffusion method to investigate the antibacterial and antifungal efficacy of nanocrystalline vanadium pentoxide (V_2O_5) nanoparticles against *S. aureus* and *Aspergillus niger* [105]. The metal oxide was made using the sol–gel method, polyaniline (PANI) was made by chemical oxidation, and PANI/V_2O_5 composites were made using the in situ polymerization method with varying ratios of V_2O_5 in PANI (10, 20, 30, 40, and 50 weight percentage). The newly generated composites were analyzed by FTIR and powder X-ray diffraction (P-XRD), which revealed they are made of PANI/V_2O_5 nanocomposites.

Wu et al. studied three vanadium(V) hydrazone complexes (Figure 6G–I) that exhibited antibacterial activity against *B. subtilis*, *S. aureus*, and *E. coli*, with MICs ranging from 1.2 to 37.5 g/mL, which is significantly higher than the MICs of their free ligands (9.4 to >150 g/mL) [106].

Khaleghi et al. found that vanadium Schiff base complexes (Figure 6J) have antibacterial activity. The results from measuring the inhibition zone, however, are dependent on the bacteria tested, as demonstrated by the two vanadium complexes not showing activity against Gram-negative bacteria *P. aeruginosa*, *E. coli*, and *Klebsiella pneumonia*. Despite this limitation, these complexes were more active than vanadium sulfate or ciprofloxacin against

the Gram-positive bacteria *Listeria monocytogenes*, *E. faecalis*, and the fungus *Candida albicans* (MICs = 0.62, 1.25, and 2.5 mg/mL, respectively). Additionally, vanadium complexes inhibited the formation of biofilms in some bacteria [107].

Vanadium complexes also have antiviral properties; oxovanadium complexes of thiourea [108], polyoxovanadates, and oxovanadium porphyrins are effective anti-HIV agents with more than 97 percent inhibition (Figure 6K). Computational studies have suggested that vanadium compounds bind to HIV-1 reverse transcriptase and CD4 protein, preventing virus transcription and cell entry [109]. Some polyoxovanadates containing silicon, tungsten and/or boron exhibit activity at concentrations as low as 1 μM ($K_5[SiVW_{11}O_{40}]$ and $K_7[BVW_{11}O_{40}]$) [110].

Other studies suggested vanadium compounds can neutralize human immunodeficiency virus 1 (HIV-1) gene expression [21]. Thus, they utilize computational approaches to emphasize the favorable binding properties of vanadium compounds targeting M^{pro}, which is the main protease of SARS-CoV-2 [21,111,112].

Reactions of Schiff bases produced from terephthalic acid, succinic acid, adipic acid, or salicylaldehyde and 2-hydroxyacetophenone with oxovanadium (IV) sulfate in 100% ethanol resulted in a series of oxovanadium (IV) complexes, which were tested for their antifungal activity against *A. niger*, *Curvularia pallescens*, and *Colletotrichum capsici* [109]. Other applications of vanadium antifungal activity were highlighted in other reviews and papers [109,113].

Pioneering studies on vanadium compounds with anti-parasite activity showed protozoicidal organic molecules as ligands for various transition metals, such as molybdenum, vanadium, and tungsten. They had lower IC_{50} values against *Entamoeba histolytica* than their respective ligands alone, with the best results obtained for a vanadium complex of 2-(salicylideneimine)benzimidazole, which had an IC_{50} value of 2.35 μM (compared with 9.20 μM for the ligand alone and 2.99 μM for the molybdenum complex) [114]. Several synthetic vanadium compounds have exerted antiamoebic activity better than standard metronidazole drugs. For example, $K_2[CH_2(V^VO_2(sal\text{-}sbdt))_2]\cdot 2H_2O$, $Cs_2[CH_2(V^VO_2(sal\text{-}sbdt))_2]\cdot 2H_2O$, and $K_2[CH_2(V^VO_2(sal\text{-}smdt))_2]\cdot 2H_2O$ have significantly lower IC_{50} values compared with metronidazole [115].

Vanadium complexes have also been developed to inhibit *Leishmania* species (a parasite that causes leishmaniosis and is related to *T. cruzi*). A vanadium–stilbene complex based on a salicylic acid moiety showed an IC_{50} against *L. amazonensis* of 3.51 μM, which is slightly higher than the IC_{50} of other vanadyl polypyridyl complexes [116]. The mechanism of action was proposed to involve mitochondria, and the study emphasized the importance of this target because parasite mitochondria work differently than mammalian mitochondria, resulting in higher selectivity and because parasites are unicellular species with only one mitochondrion [117].

Another example of a vanadium compound with activity against *Trypanosoma cruzi* is the metal complex with aminophen and bromosalycilaldehyde, with IC_{50} values ranging from 0.27 to 3.8 μM (similar to the standard drug nifurtimox) [118]. The compound was not toxic to murine macrophages, with an IC_{50} around 50 μM (nearly 200 times higher than against *T. cruzi*), indicating high selectivity. Only 2.4 percent of the dissolved complex was taken up by the parasites (a similar amount to what was observed for other metallodrugs such as cisplatin), and a high concentration of vanadium was observed within the DNA and RNA (0.089 ng of vanadium per g of DNA and 0.006 ng of vanadium per g of RNA), indicating a strong interaction with DNA. A mitochondrial deficiency was also hypothesized, owing to the high level of some orgonites in mitochondria. Furthermore, a protein expression analysis revealed that transporters and drug efflux proteins as well as some proteins involved in transcription were overexpressed. This observation is consistent with the presence of vanadium in DNA, mitochondrial deficiency, and overexpression of some proteins involved in reduction/oxidation (redox) pathways and hydrolysis, implying that the vanadium complex is responsible for some redox disorders [114,116]. However, a live/dead assay only resulted in a trypanostatic effect, with the parasites recovering

normal growth after removal of the complex. Additionally, three oxidovanadium (IV) complexes have micromolar IC_{50} values against T. cruzi and exhibit activity on a par with nifurtimox. Atomic force microscopy (AFM) was also used to assess DNA as a potential target, demonstrating the complexes' capacity to interact with this biomolecule [119].

7. Vanadium Compounds' Effect in the Cardiovascular System

Many studies have proposed different mechanisms for the cardioprotective effect of vanadium compounds. The intracellular responses to decavanadates and monomeric vanadium complexes are different [120]. However, monomeric vanadate is still released following decavanadate treatment in biological systems and will contribute to decavanadate-induced effects on PTPs [121,122]. There is an expanding repertoire of compounds containing monomeric vanadium coordinated by different classes of organic ligands, including but not limited to maltolato vanadium compounds, vandocenes, and peroxidovanadium complexes [123]. One key advantage of these larger complexes with organic ligands seems to be improved bioavailability in vivo compared with vanadate [55,62]. However, increasing evidence now suggests that these larger compounds often undergo a complex range of ligand exchange events once in circulation and/or in the cell, ultimately releasing uncomplexed vanadate as the active PTP-inhibiting moiety [124].

In general, the cardioprotective activity of vanadium compounds appears to be linked to their hypoglycemic, hypolipidemic, antiapoptotic, and antihypertensive properties. Furthermore, their inhibition of cardiac hypertrophy and control of vascular cell contraction may play an essential role [20]. Table 1 shows the effect of some vanadium compounds and their mode of action on different models.

Table 1. Cardioprotective effects of some reported vanadium compounds.

Models	Vanadium Compounds	Effect	Mode of Action	References
STZ-induced diabetic rats	Dioxidovanadium (V) complex	Cardioprotective in diabetes mellitus	Decrease in blood glucose concentration, MAP, and regulation of the redox system and lipid metabolism	[125]
Spontaneously hypertensive rats	Vanadyl sulfate	Cardioprotective	Not indicated	[126]
Ischemia/reperfusion-induced injury in rat heart	Vanadyl sulfate	Cardioprotective and cardiac functional recovery	Activation of PKC and induction of FLICE-inhibitory protein	[127]
Rat model of myocardial ischemic infarction	Sodium orthovanadate	Post-treatment rescued cardiomyocytes from ischemia/reperfusion injuries	Akt activation and inhibition of fodrin breakdown, thereby inhibiting apoptosis	[128]
Spontaneously hypertensive rats	bis(maltolato)oxovanadium (IV) (BMOV)	Attenuates hyperinsulinemia and hypertension		[129]
Rat model of myocardial infarction	bis(maltolato)oxovanadium (BMOV)	Cardioprotective by limiting reperfusion injury	Opening of cardiac K^+_{ATP} channels via increased tyrosine phosphorylation	[130]
STZ-induced diabetic rats	bis(maltolato)oxovanadiurn (IV) (BMOV)	Cardioprotective by preventing development of myocardial dysfunction		[131]
Overload-induced hypertrophy in ovariectomized female rats	bis(1-oxy-2-pyridinethiolato) oxovanadium	Inhibition of cardiac remodeling rescues isoproterenol-induced cardiac arrest	Activation of endothelial nitric oxide synthase	[132]
Male, 7-week-old mice	Orthovanadate (OVA)	Increase of mouse thoracic aortic contractility	Activation of Src, EGFR, MEK, Erk1/2, and Rho kinase, leading to inactivation of myosin light chain phosphatase via MYPT1 phosphorylation	[133]

8. Vanadium Toxicity

The cationic and anionic forms of vanadium are considered to be toxic, with the latter having higher toxicity [134]. Vanadium toxicity depends on the vanadate form, oxidation state, time, dose and route of intoxication [134,135]. Accumulation of vanadium may be fatal and lead to irreversible tissue damage due to the inhibition of enzymatic processes and oxidative stress, which lead to carcinogenesis, neurotoxicity, gastrointestinal complications, infertility, lung and kidney toxicity [136].

Animal studies have shown that subacute and chronic administration of vanadate leads to different toxic effects. A six-week administration of sodium metavanadate (Figure 3F; 1.25 mg/mL concentration) led to hematologic toxicity manifested as a reduction in body weight, fluid, and food intake, and a decrease in hematologic parameters such as red blood cell (RBC) count, hemoglobin (Hb), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) [137].

Dose-dependent toxicity of sodium metavanadate was reported in a rat model following its supplementation in drinking water for 12 weeks. These experiments showed neurobehavioral changes, demonstrated by an impairment in learning and memory, the decline in striatal acetylcholine (ACh) and 5-hydroxytryptamine (5-HT), an increase in gamma-aminobutyric acid (GABA) levels, and degenerative changes in the histopathology of the striatum [138].

The oral administration of vanadyl sulfate (Figure 3G) to pregnant mice provoked a range of toxic effects including maternal toxicity, embryotoxicity, fetal toxicity, and teratogenic potential. Maternal toxicity was evidenced by a decrease in body weight by the 18th day of gestation, a significant reduction in absolute weight of the liver and kidney, and a significant decrease in early resorption per litter. Moreover, fetal toxicity was evidenced by reduced fetal weight and fetal length [139].

Recent studies in murine models showed that 1 h per week inhalation of vanadium pentoxide for 4 weeks (Figure 7A; 0.02 M in saline) produced a negligible reduction in corporal weight, but a significant increase in uterine thickness and reduction in estrous cycling and serum progesterone levels in CD-1 mice [140]. Contrary to these findings, it has been reported that there are no significant hematological, biochemical, or histopathologic changes following the administration of vanadium for 5–12 months [141]. However, there is a significant reduction in systemic blood pressure and an increase in serum insulin in experimentally induced hypertensive rats [142].

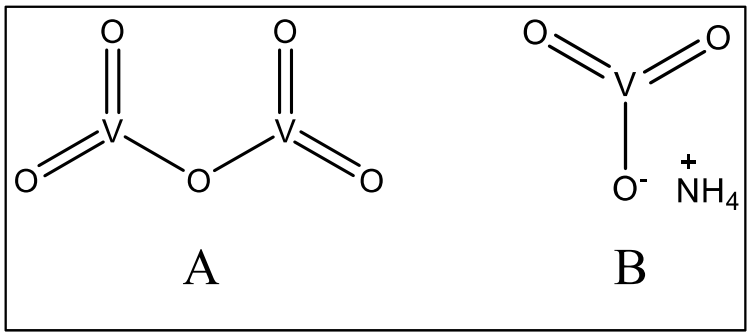

Figure 7. Structures of some vanadate compounds.

The brains of experimental animals exposed to vanadium showed morphological changes in neurons and astroglia cells [143]. The brain morphological alterations were attributed to increased oxidative stress in the presence of vanadium complexes in the cerebellum and hippocampus [144]. Moreover, vanadium compounds induced the proteolytic activation of caspase-3-dependent protein kinase C gamma (PKC-δ) and apoptosis via neurotoxicity in dopaminergic neuronal cells [145]. Spatial memory impairment in the experimental animals was attributed to changes in the hippocampus neuropiles and loss of dendritic spines [144].

Vanadium inhalation in mouse models increased thrombogenesis and enhanced platelet production (attributed to megakaryocytic proliferation) [146]. Long-term vanadium treatment in normal and pre-diabetic STZ rats led to bradycardia and a smaller leukocyte count in the peripheral blood of STZ-induced diabetic animals [142]. Moreover, five-months' administration of vanadyl sulfate to the streptozotocin-diabetic rat enhanced morphological alterations in kidneys [141,147].

The gastrointestinal (GI) system is most vulnerable to vanadium toxicity following inhalational or oral exposure. The ingestion of >14 mg of vanadium in humans causes GI symptoms [72]. The oral administration of vanadium salts often results in GI symptoms, such as abdominal cramps, diarrhea, vomiting, and weight reduction, in NIDDM patients with heart disease [69]. Oral administration of vanadium salts often results in gastrointestinal symptoms such as abdominal cramps, diarrhea, vomiting, and weight reduction in NIDDM patients with heart disease [69]. However, only slight GI distress was reported in diabetic patients with cardiovascular disorders following short-term treatment with vanadium derivatives [135]. Moreover, there was no hematologic alteration in blood cell count or biochemical markers for the liver and kidney after a three-month test period in athletes [148,149]. However, the continuous administration of vanadium may result in tissue accumulation accompanying the side effects in clinical settings. Experimental studies revealed that metal chelating agents, such as deferoxamine(N′-[5-(Acetyl-hydroxy-amino)pentyl]-N-[5-[3-(5-aminopentyl-hydroxy-carbamoyl) propanoylamino]pentyl]-N-hydroxy-butane diamide) and tiron (Disodium 4,5-dihydroxybenzene-1,3-disulfonate), significantly reduce vanadium accumulation in the kidney, bone, and liver [63].

The fatal intoxication of ammonium vanadate (Figure 7B) has been documented [150] in a 24-year-old woman admitted to the emergency department and presenting several GI tract complications, including pain, nausea, vomiting, and diarrhea, as well as hypoglycemia and severe acute renal failure with glomerular filtration rate.

Finally, people exposed to vanadium dust through work or other daily activities manifest respiratory system complications, such as cough, sputum, ENT (ear, nose, and throat) inflammation, exertional dyspnea, and wheezing [151]. Chinese workers exposed to vanadium showed increased negative emotions (e.g., excessive anger, depression, tiredness, and inertia) and decreased positive emotions (coordination, short-term memory, and interaction with others) [144].

9. Conclusions

Like other transition metals, such as copper, zinc, and iron, vanadium plays significant roles in many biological processes. More information is available on those other transition metals regarding their biological effects, and less attention has been given to vanadium for the synthesis of new complexes as candidate therapeutics. In this review, we highlighted the unique chemical structures and chemical properties of vanadium complexes as well as reviewed their significant biological effects.

Vanadium is a toxic metal ion, and its toxicity in humans mostly depends on the nature of its metal complexes (organic or inorganic), oxidation state, exposure route, time, and dose. However, vanadium compounds show beneficial effects as insulin-mimetic formulas in type 2 diabetes and enhance osteogenic processes in bone formation and mineralization. Moreover, selected vanadium compounds inhibit cell proliferation and thus could have anticancer potential. The distinct vanadium biochemistries of viruses, microorganisms, and parasites could be exploited to selectively target human pathogens with certain vanadium compounds. More study of vanadium biochemistry could lead to a new era in vanadium biomedicine.

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