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Review

Polyoxovanadates with emerging biomedical activities

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ABSTRACT

Polyoxovanadates (POVs) are a subclass of a larger family of polyanionic group V and VI metal-oxo clusters that are known as polyoxometalates (POMs). POMs have been found to have antidiabetic, antibacterial, antiprotozoal, antiviral and anticancer activities, which have sparked interest in their use as bioinorganic drugs. Among POVs, decavanadate ($[V_{10}O_{28}]^{6-}$; V_{10}) is an isopolyoxovanadate recently described to have several medicinal applications. In the present review, recent insights into POVs with emergent anticancer, antimicrobial and antiviral applications are described. Additionally, POVs' stability and speciation under experimental biological conditions as well as POVs (in particular, V_{10}) *in vivo* and *ex-vivo* effects are highlighted. Finally, we report the most important 21st century studies of POVs' effects and/or targets against cancer, bacteria and viruses including: apoptosis, cell cycle arrest, interference with ions transport system, inhibition of mRNA synthesis, cell morphology changes, changes in metabolic pathways, phosphorylase enzyme inhibition and cell signaling, formation of reactive oxygen species, lipid peroxidation, inhibition of viral mRNA polymerase, inhibition of virus binding to the host cell, penetration and interaction with virus protein cages.

Abbreviations: A549, human lung cancer cells; ADME, absorption, distribution, metabolism and excretion; AsPC-1, pancreatic cancer cells; ABC-transporters, ATPases, ATP binding-cassette ATPases; AMA, amavadin; BALB/c, albino, laboratory-bred strain of the house mouse; BMOV, bis-maltolato-oxovanadium(IV); CAT, catalase; Ca^{2+}-ATPase, calcium adenosine triphosphatase; CTS-$Ca_3V_{10}O_{28}$, chitosan-$Ca_3V_{10}O_{28}(NH_4)_6$; CT26WT, mouse colon carcinoma cell line; CHO, Chinese hampster ovaries; di-4-ANEPPDHQ, aminonaphthylethenylpyridinium-based dye; DPPC, dipalmitoylphosphatidylcholine; DTNB, 5,5'-dithiobis-(2-nitrobenzoic acid); E-NTPDase, ecto-nucleotide triphosphate diphosphohydrolase; EC_{50}, half maximal effective concentration; en, ethylenediamine; EXAFS, extended X-ray absorption fine structure; FcεRI, type I Fcε receptors; FluV, influenza virus; FIPV, feline infectious peritonitis virus; F-actin, filamentous polymerized actin; 5-FU, 5-fluorouracil; GI_{50}, half maximal growth inhibition concentration; G-actin, monomeric actin; GPCRs, G protein-coupled receptor; GPx, glutathione peroxidase; gp120, glycoprotein expressed by HIV; HCB, hepatitis B virus; hCG, human chorionic gonadotropin; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HDAC, histone deacetylase; HeLa, human cervical cancer cell line; HEK 293, human embryonic kidney cell line; HepG2, human liver cancer cell line; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HMTA, hexamethylenetetramine; IC_{50}, half maximal inhibitory concentration; IPOV, isopolyoxovanadate; L-02, human normal hepatocytes; LHR, luteinizing hormone receptor; MDA-MB-231, human breast adenocarcinoma cell line; MDCK, madin-darby canine kidney cells; MCF-7, human breast cancer cell line; Me, methyl; MIC, minimum inhibitory concentration; MRB, mitochondrial respiration buffer; MRSA, methicillin-resistant *Staphylococcus aureus*; MT-4, human Lymphocyte cells; NCI-H460, human non-small cell lung cell lines; P388, murine leukemia cells; RBL-2H3, rat basophilic leukemia; ROS, reactive oxygen species; SARS, severe acute respiratory syndrome; SF-268, human brain tumor cell line; SR, sarcoplasmatic reticulum; S1, myosin subfragment 1; SMMC-7721, Cellosaurus cell line; SOD, superoxide dismutase; SKOV-3, human ovary cancer cell line; TBA, tetrabutylammonium; tmen, N,N,N′,N′-tetramethylethylenediamine; U-87, human primary glioblastoma cell line; ^{51}V-NMR, vanadium-51 NMR; V_1, monomeric vanadate, simplest oxovanadate; V_{10}, ($V_{10}O_{28}^{6-}$) decavanadate, decameric oxovanadate; V^V-dipic, 2,6-pyridinedicarboxylatodioxovanadium(V); Vero, kidney epithelial cells; VRSA, vancomycin-resistant *Staphylococcus aureus*; BSA, bovine serum albumin; HA, hemagglutinin A; HSA, human serum albumin.

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1. Introduction

Polyoxometalates (POMs) are oxo-clusters of transition metal ions, such as Mo, W, V, Nb and Ta [1–3] forming a variety of structures within a wide range of applications, not only in chemistry but in many other fields, from environmental science to medicine [4-14]. The metal oxo-clusters consist in building blocks of metal-oxo components, generally octahedral, and can be classified in homo- or hetero-polyoxometalates containing only one or multiple metal ions, respectively. The ability to replace a small part of the cluster with a different metal-oxo component further diversifies the properties and supports a range of reactivities which, from the first synthesis by Berzelius two centuries ago, has fascinated scientists with their seemingly endless possibilities. As such POMs are divided up into specific families, such as polyoxotungstates (POTs), polyoxovanadates (POVs), polyoxomolybdates (POMos), and polyoxoniobates (PONbs), although heteropolyoxometalates may belong to more than one of these families.

A literature search since 1985 in Web of Science finds more than eleven thousand articles using the search word "Polyoxometalate" including pure inorganic, organic-hybrid, encapsulated, nanoparticle, or other POM-based composites (Fig. 1). In the last decade (2011–2020) the number of papers has more than tripled in comparison to the previous decade (2001–2010) (Fig. 1A). Also, several review papers on different aspects and applications of POMs have been published covering chemical engineering [15], catalysis [16], environmental chemistry [17], material science [18], biochemistry, biology, pharmacology and medicine [4,8,11,19–21]. This testifies the growing and expanding interest in POMs, amenable to a variety of structural transformations, in several scientific areas from basic to applied sciences [1–19]. In this review we will describe the subclass of POVs either as iso- or hetero-polyoxometalates in which vanadium is part of a cluster in POTs and POMos families.

In the last 20 years, the number of medicinal applications is increasing with several studies describing POMs with anticancer, antibacterial and antiviral activities [4,7,8,12,22–30]. POMs were found to be insulin mimetic agents [31,32], inhibitors of amyloid β-peptides aggregation and known to be associated with Alzheimer's disease [33–35] as well as enzyme inhibitors [4,36–40]. About 200 papers in the Web of Science concern the potential application of POMs as anticancer, antibacterial and antiviral agents, with 57% of those focusing on cancer, 17% on bacterial and 26% on virus studies, with the latter growing particularly in 2020 (Fig. 1B).

The first reports of anticancer, antiviral and antibacterial activities of POMs, were in 1965 [41], 1971 [42] and 1993 [43], respectively (Fig. 2). Over the years, POMs were reported to have beneficial properties against cancer and even been licensed toward the chemotherapy of solid tumors (such as human gastric cancer

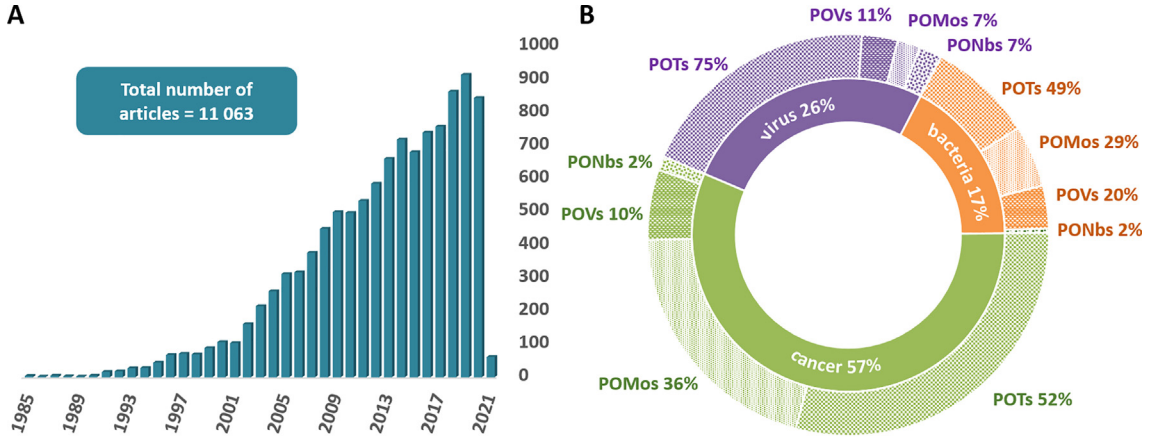

Fig. 1. Publication of studies involving POMs. A) Number of publications along the last 35 years (Web of Science); B) Relative contribution of POMs are divided up into specific families' of polyoxovanadates (POVs), polyoxomolybdates (POMos), polyoxoniobates (PONbs), and polyoxotungstates (POTs) and their application in anticancer, antibacterial and antiviral studies in each biomedical area.

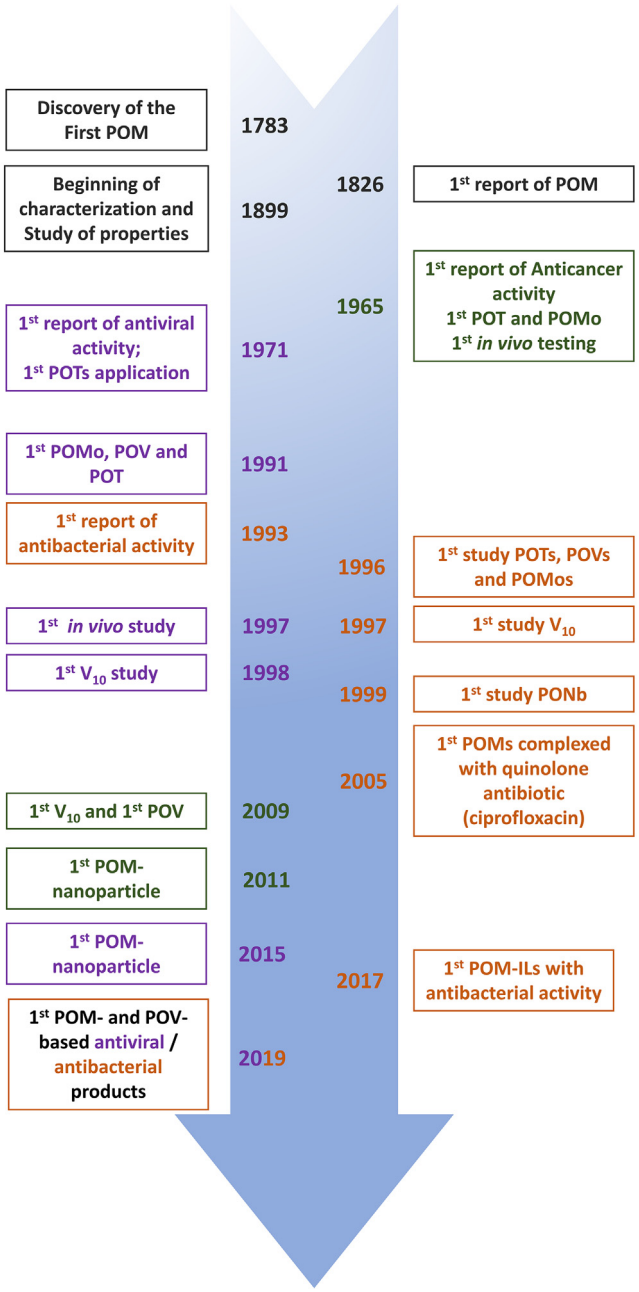

Fig. 2. Discovery (black) of the first biological studies described for polyoxotungstates (POTs), polyoxomolybdates (POMos), polyoxovanadates (POVs) and decavanadate (V_{10}), polyoxoniobates (PONbs) as well as for POM-nanoparticle and POM-Ionic liquids (ILs) anions in the treatment of cancer (green), viral (purple) and bacterial (orange) infections highlighting also *in vivo* animal studies.

and pancreatic cancer) [7,44,45], as well as against viruses (such as herpes simplex virus (HSV), human immunodeficiency virus (HIV), influenza, and severe acute respiratory syndrome (SARS)) [46], and drug-resistant bacteria (such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Staphylococcus aureus* (VRSA)) [44]. Some milestones related to biomedical POMs' applications are listed chronologically in Fig. 2. After Hill's first review about medical application of POMs in 1998 [6], two fundamental papers pushing forward the understanding of POMs in medicine were published in 2005 [19,20]. In the case of vanadium, whose status as an essential element in humans is highly controversial, an extensive body of literature documented that simple vanadium salts had antidiabetic properties and extensive exploration of other vanadium compounds has been carried out [47–49]. These studies include the effects of smaller oxovanadates [50] as well as the larger POVs such as V_{10} [31,51]. Recent studies point to beneficial properties of POVs against drug-resistant bacteria and have recently been added to anti-virus and anti-bacterial products [52], which might be caused by the versatility of the vanadium coordination modes and oxidation states (V^{III}, V^{IV} and V^{V}) compared to other POMos and POTs. In this review, we combine the information on vanadium coordination complexes with the knowledge of the molecular and cellular processing and interactions of POMs in bacteria and in cancer cells [7,8] to describe the potential for the subclass of POVs.

For organic drugs, unless they are prodrugs, is known that they reach the target organs in an unaltered form. It is not the case for a metal-based drug because of its speciation chemistry. In fact, in biological fluids a metal-based drug can undergo many chemical changes, including ligand exchange, redox reactions at the metal ion and on proteins and metabolites, hydrolysis and several metabolic transformations once the metal ion binds to metabolites and proteins [53,54]. Although several metal-based compounds have been used for diagnostics and treatments of various pathologies, many aspects of the ADME (absorption, distribution, metabolism and excretion) remain to be further investigated and the speciation in aqueous solution and its redox reactions must be determined to identify the active POM species in body fluids and cells and finally understand POMs' mechanism of action [6,7,8,14,53–57]. In the present review the most important 21st century studies of POVs' effects and/or targets against cancer, bacteria and viruses are highlighted. Although POVs' mechanism of action against cancer cells remains unclear, as described throughout the review, the effects include among others, changes in the morphology of cells and activation of apoptosis pathways [20,58–61]. Similarly, the antibacterial mechanisms of action described for several POVs also comprise changes in the morphology of cells [20,62], besides the interference with ions' transport system, inhibition of mRNA synthesis, interference with metabolic pathways and signaling processes [8,63,64]. Finally, POVs' antiviral modes of action are based on the inhibition of viral mRNA polymerase, inhibition of virus binding to the host cell, inhibition of virus penetration and interaction with virus protein cages [65,66].

POMs structures have various sizes and shapes and may include other heteropolyoxido anions such as P^{V} and As^{V}. The anions consist of $\{VO_4\}$ tetrahedral or $\{VO_6\}$ octahedral components to generate small oligomers or compact larger POVs. Even though POVs in general contain vanadium in the oxidation state +5, recent reports have described POVs with both oxidation states, V(IV) and V(V). These multi-valence POVs can also contain metal ions in $\{VO_5\}$ square-pyramidal units to generate structures that differ from the classical POMs and dramatically enrich POVs chemistry. Furthermore, in POMs structure one or more of the addenda metal oxoanions M = O (M = W^{VI}, Mo^{VI}, V^{V}, etc.) can be absent and/or substituted by transition metal ions (e. g. Co^{II}, Mn^{II}). Examples of pure inorganic and hybrid POVs structures described along this review are given in Fig. 3. However, the interested readers can find excellent reviews about POV structures elsewhere [1,2,5–8,14,19,21].

2. Polyoxovanadates' speciation and stability in biological media

The chemistry of POVs have been investigated using a range of different methods including potentiometry, ^{51}V NMR, EPR spectroscopy, FT-IR spectroscopy, UV–Vis spectroscopy, X-ray crystallography, EXAFS and other spectroscopies [3,50,54]. Although some of the POVs are stable under physiological conditions others are not and it is important to establish the speciation of

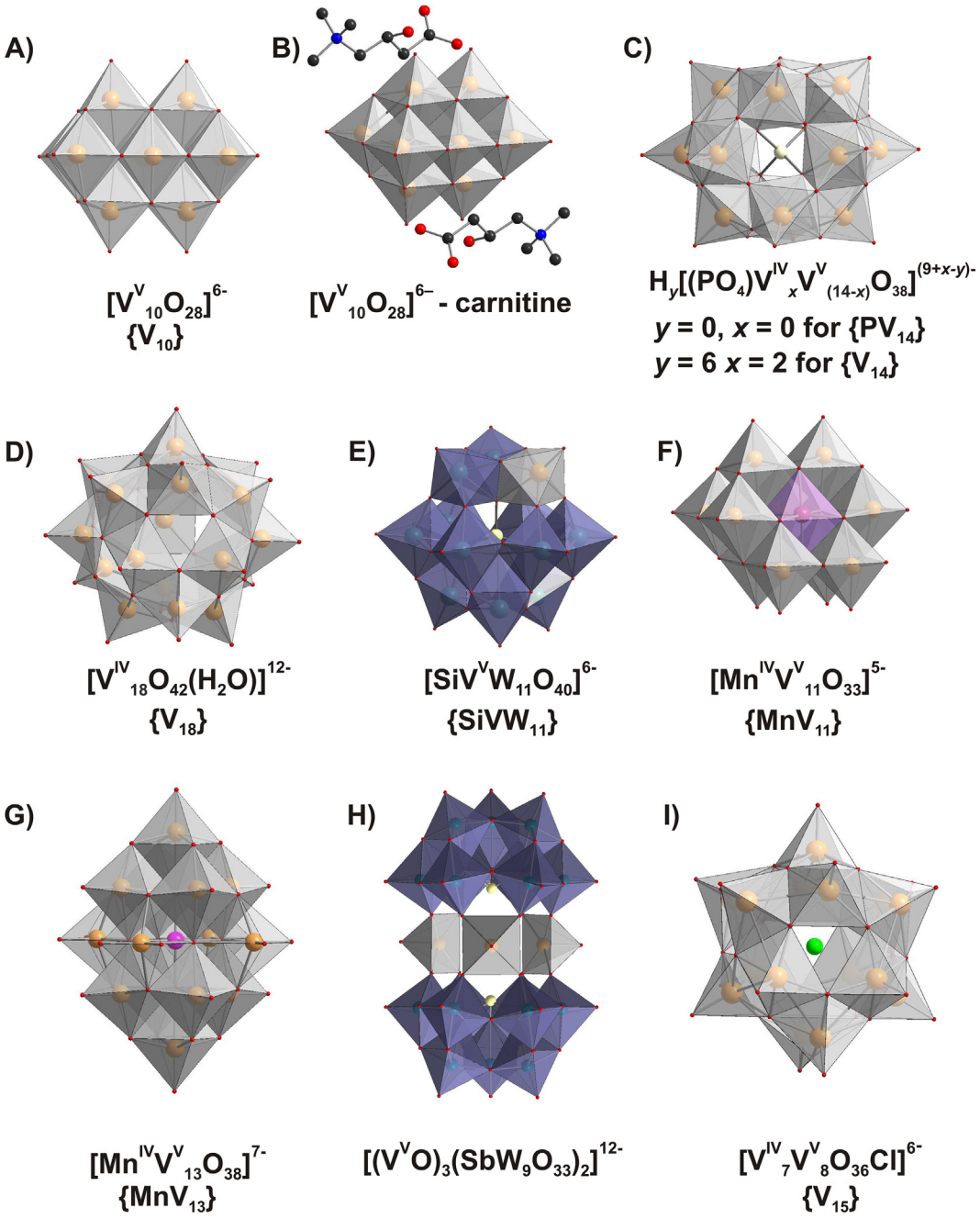

Fig. 3. POVs and mixed POVs-POTs structures, which exhibit biological activity. In MnV_{13} (G) structure four equatorial V atoms have 75% occupancy [67] and so in total correspond to three V atoms with full occupancy in the sum formula. Color code: $\{VO_x\}$, grey; $\{WO_6\}$, violet; P or Sb, yellow; Mn, pink; Cl, green; O, red; C, black; N, blue.

compounds in order to properly attribute the species present causing biological activities. The studies investigating the effects of POVs should always take into consideration the stability of the POV under the given experimental conditions. Often, the lack of information about POVs' stability might contribute to misinterpretations about their effects for any biomedical or biological application. When POVs are incubated with proteins and/or exposed to cell cultures during long periods of time (up to 72 h) and physiological temperature (37 °C) in aqueous or semi-aqueous environments, their stability may be affected by the specific experimental conditions [4,54,68–73]. Therefore, without a clear demonstration that a POV species is stable under the given conditions, attributing the observed effects to the structure of the solid compound is a mere speculation.

The most commonly used speciation model (Fig. 4) was constructed about thirty five years ago as a result of rigorous ^{51}V NMR investigations in conjunction with potentiometric titration studies [74–81]. To testify the interest in such models, various computation methods were developed. In the 1980′s speciation programs were based on calculations using the LAKE software [79], and since then more user friendly programs have been used. Recently, computational efforts point toward the automated search of POMs nucleation mechanism, providing speciation diagrams from first-principles [82].

The speciation model for vanadate solutions without heteroions postulates that, at pH higher than 6, polymers with one to five vanadium centers are formed, where many of these also undergo several individual protonation steps (Fig. 4). These oligomeric

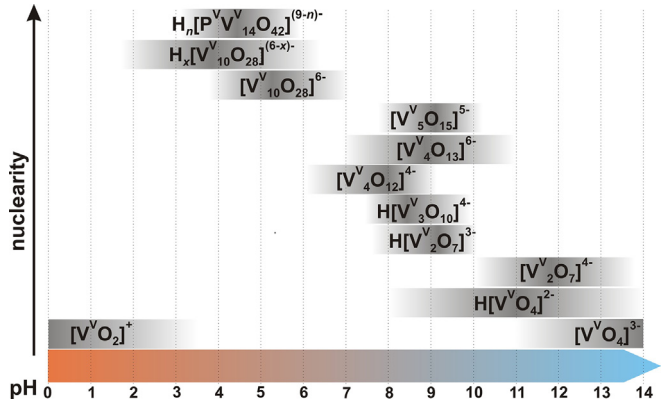

Fig. 4. pH stability ranges for POVs and PV_{14} in an aqueous solution with a total concentration of vanadium ions of more than 0.1 mM based on [74,75,77,78,85]. The maximum intensity of grey color in each box with a single species corresponds to its maximum concentration in the chosen pH region, e.g. the maximum concentration of $[V^V_2O_7]^{4-}$ is at pH 12. The species (in grey) along the y-axis are positioned according to increasing nuclearity, but do not represent their relative concentration at a certain pH range. *x* in $H_x[V^V_{10}O_{28}]^{(6-x)-}$ is 1–3, *n* in $H_n[P^VV^V_{14}O_{42}]^{(9-n)-}$ is 3–5. The molecular structures of V_{10} and PV_{14} are depicted in Fig. 3 A and C, respectively. For concentration lower than 100 μM, the formation of V^V species with lower nuclearity is favored, although V_{10} could persist under physiological conditions in extracellular and intracellular fluids, mainly due to its kinetic stability.

species such as tetramer or dimer are in rapid equilibria [75] and can generate selective responses including inhibition of enzyme activities [83] as well as effecting the growth of yeast [84]. In contrast, under acidic conditions (pH < 6), only two major species are formed, namely V_{10} and the dioxovanadium(V) ion $[V^VO_2]^+$ (Fig. 4).

In biological systems, components such as amino acids, proteins and phosphate interfere with the vanadium chemistry giving rise to new coordination compounds and complex speciation profiles [54,86–88]. Phosphate is a frequent and abundant component of biological systems and the vanadate speciation in the presence of phosphate is particularly relevant. The predominant species in the aqueous H^+–$H_2V^VO_4^-$–$H_2PO_4^-$ system between pH 2 and 4 is PV_{14} (Fig. 3C), which has a trans-bicapped α-Keggin structure [88].

Reaching equilibrium in the system H^+–$H_2V^VO_4^-$–$H_2PO_4^-$ is generally fast at neutral and alkaline conditions requiring less than 15 min, but at pH 3–5 the equilibration is slow. Formation of PV_{14} (Fig. 3C) occurs from pH 2 to 4.5 and the equilibration is reached very slowly over at least three months. High total concentrations of vanadate and acidic pH values favor the formation of PV_{14}, but the presence of V_{10} will also facilitate its formation [88]. Additional V-P species form outside the pH region where PV_{14} is stable as shown in the speciation diagram in Fig. 5.

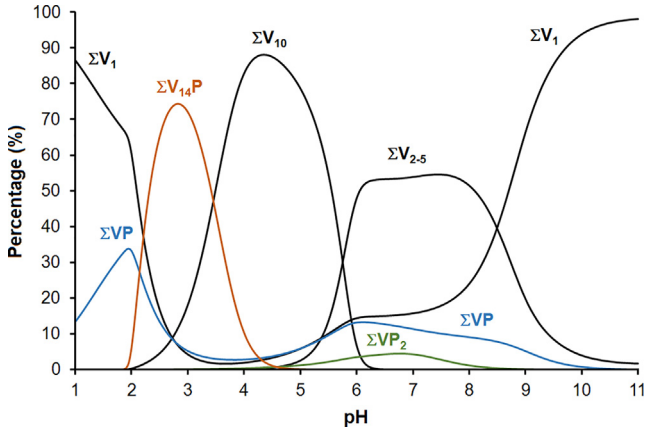

Fig. 5. Percentage of the species formed as a function of pH in the system H^+–$H_2V^VO_4^-$–$H_2PO_4^-$ with $[V]_{tot}$ = 5 mM and $[P]_{tot}$ = 60 mM. Curves are calculated using the model reported in [88]. Sum of the species are shown for clarity. Modified from reference [88].

Decavanadate $[V_{10}O_{28}]^{6-}$ (Fig. 3A) [89,90] is an isopolyoxovanadate (IPOV) without other metal ions and represents an example of a stable POV; the study of its reactivity and of its derivatives is important to deduce its biological effects. This large anion [89,90] has a compact structure, with dimensions of 8.3 × 7.7 × 5.4 Å [91]. With ^{51}V NMR spectroscopy, three different types of vanadium ions can be distinguished, reflecting the two types of vanadium ions, internal or in the surface of the anion. A specific absorption between 600 and 400 nm, attributed to V_{10} species and responsible for the yellow or bright orange color of vanadium(V) solutions, can be detected by UV/Vis spectroscopy [72,89,90]. Using the latter technique, V_{10} stability can be followed, even at μM concentrations like those observed in the organism after its administration [89,92,93]. Decavanadate has a half-life in serum (pH = 7, NaCl 0.9%) of 15 h at ambient temperature [92], however at increased 37 °C and at pH of 7.4 in mitochondrial respiration buffer (MRB: sucrose, 0.2 M; KH_2PO_4, 5 mM; KCl, 10 mM; $MgCl_2$, 5 mM; Tris–HCl, 10 mM; pyruvate, 5 mM; malate, 0.5 mM) a 5 mM V_{10} solution shows a half-life of only 3 h [68]. In our understanding of decavanadate speciation the different biological environments have to be considered, so that the observed response can be attributed to the active species under the applied conditions [90,92].

V_{10} is stable below pH 6.5 and can be formed upon acidification of neutral solutions [89]. It was previously suggested that V_{10} species may eventually form intracellularly in the cytosol, which overall has a neutral pH. The local acidification was suggested to be caused by H^+-transport by ionic pumps into the cytoplasm [90]. Since POVs' speciation depends on pH (Fig. 4), V_{10} can also form in acidic cell compartments such as endosomes and lysosomes [90]. Willsky's group demonstrated the intracellular formation of V_{10} from administration of V_1 to *Saccharomyces cerevisiae* using a combination of ^{51}V NMR and EPR spectroscopic studies; the detection of V_{10} in yeast cells containing vanadate at pH 6.5 implies that V_{10} is concentrated in subcellular organelles where the pH reaches values near 5.0 [94,95].

This review describes the few *in vivo* and *ex-vivo* studies in mitochondria which are very valuable for POVs, and necessary to support future biomedical applications. Moreover, the studies on the antidiabetic action of POVs were resumed since the relationship between vanadium and diabetes is well known for more than 100 years, even before the discovery of insulin by Banting and colleagues [96,97]. Other putative POV targets in proteins *in vitro* studies and/or others putative cellular targets are reviewed in [7,8]. Thus, in the following sections, we will describe reports of a number of biological systems treated with POVs. Because of the high number of reports, we have organized this review with separate sections for studies of effects on mitochondrial functions, of anticancer activity, of bacterial and antiviral treatments by POVs. All other results *in vivo* and *ex-vivo* are described in the first section where fundamental studies as well as reports on the antidiabetic treatments and other papers are described.

3. POVs *in vivo* and *ex-vivo* studies

3.1. Effects of POVs on fundamental metabolic processes

The main studies of POVs investigated *in vivo* and/or *ex-vivo* are mainly focused on V_{10} and summarized in Table 1. Studies following the early *in vivo* experiments with decavanadate in 2002 [98] continued to use fish models in order to determine the contribu-

Table 1
POVs *in vivo* and *ex-vivo* studies in the 21st century.

POV	Organ(s) tissue	Effects	Administration mode*	Year	Ref.
V_{10} (Fig. 3A)	Heart, Fish	Antioxidant enzymes	i.p.*	2002	[98]
V_{10} (Fig. 3A)	Heart, kidney, liver, Fish	Histological effects	i.p.	2003	[101]
V_{10} (Fig. 3A)	Liver Fish	Vanadium accumulation/Antioxidant enzymes	i.v.*	2005	[93]
V_{10} (Fig. 3A)	Heart, blood, Fish	Vanadium accumulation	i.v	2006	[99]
V_{10} (Fig. 3A)	Heart, Fish	Lipid peroxidation/Antioxidant enzymes	i.v.	2007	[100]
V_{10} (Fig. 3A)	Rat	Antidiabetic parameters	*in vivo Ad libertum*	2007	[51]
V_2O_5 (Fig. 7A) Modelled by V_{10} (Fig. 3A)	Male F344 Rat Lungs	Pulmonary Immunotoxicity/ Pneumonia inducing *Listeria monocytogenes*	Airborne particles *in vivo*	2007	[102]
V_{10} (Fig. 3A)	Heart, Fish	Vanadium accumulation/Antioxidant enzymes	i.v.	2008	[68]
V_{10} (Fig. 3A)	Rat adipocytes	Antidiabetic parameters	*ex-vivo*	2009	[31]
V_2O_5 (Fig. 7A) Modelled by V_{10} (Fig. 3A)	Male F344 Rat Lungs	Pulmonary Immunotoxicity/ Pneumonia inducing *Listeria monocytogenes*	Airborne particles *in vivo*	2010	[103]
V_{10} (Fig. 3A) Model for V_2O_5	RBL-2H3 cells Leukemia cells	Cell degranulation FcεRI signaling	*ex-vivo*	2013	[104]
V_{10} (Fig. 3A), metformium complex	Rat	Antidiabetic parameters	*in vivo Ad libertum*	2016	[96]
V_{10} (Fig. 3A), metformium complex	Rat	Antidiabetic parameters	*In vivo Ad libertum*	2018	[97]
V_{10} (Fig. 3A), metformium complex	Rat	Antidiabetic parameters	*In vivo Ad libertum*	2019	[105]
PV_{14} (Fig. 3C)	Epithelia, Fish	Na^+/K^+-ATPase	*ex-vivo*	2019	[106]
V_{10} (Fig. 3A) $Na_3[H_3V_{10}O_{28}]$	CHO cells	Signal Transduction luteinizing hormone receptor (LHR)	*ex-vivo*	2020	[107]
$K(NH_4)_4[H_6V_{14}O_{38}(PO_4)]$ $MVPV_{14}$ (Fig. 3C)	CHO cells	Signal Transduction LHR	*ex-vivo*	2020	[107]
$[(CH_3)_4N]_6[V_{15}O_{36}(Cl)]$ MVV_{15} (Fig. 3I)	CHO cells	Signal Transduction LHR	*ex-vivo*	2020	[107]

* - i.p. is intraperitoneal; i.v. is intravenous administration.

tion of the V_{10} species on the reported toxicological effects [90,93,99,100]. Several studies described intraperitoneal (i.p.) and intravenous (i.v.) administration of V_{10} in two different fish models, *Halobatrachus didactylus* also known as the Lusitanian toadfish and *Sparus aurata* also known as the gilthead seabream [93,99,100]. The studies were carried out with both orthovanadate $[VO_4]^{3-}$ (V_1) and V_{10} (Fig. 3A) solutions (although V_{10} solution pH was adjusted from 4 to near neutral, before administration, where vanadate exist as HVO_4^{2-} or $H_2VO_4^-$) and the effects were analyzed in several organs and/or tissues such as cardiac, hepatic, renal and blood, Table 1 [90,93,99,100]. It was found that V_{10} administration induces changes in sarcoplasmatic reticulum Ca^{2+}-pump, lipid peroxidation and antioxidant enzymes activities besides vanadium's subcellular accumulation and histological changes in heart and liver tissues (Table 1) [90,93,99,100]. It was proposed that oxidative stress responses, lipid peroxidation and vanadium subcellular distribution is dependent on V_1 or V_{10} present in the administration fluid [68,72,73,90,93,98–101]. V_{10} administration resulted in different effects not observed for monovanadate alone and, likewise, some effects observed for V_1 were not observed with V_{10} (Table 1), findings which suggest that these species are not rapidly interconverting under biological conditions or that the processing of V_{10} does not always result in V_1.

3.2. Studies carried out probing the effects of POVs as antidiabetic agents

Vanadium is well known to induce insulin-like or insulin-enhancing effects [47–51,108–111]. In 2021, it will be 100 years since insulin was discovered by Banting, Best and McLeod at the University of Toronto [112–114]. More than 350 million people are projected to suffer from diabetes mellitus in 2030 [115]. Diabetic patients are subject to other pathologies such as nephropathy, arterial and neurodegenerative diseases. The usage of vanadium compounds with putative applications as insulin-mimetic agents was due to early discoveries that the simple inorganic salts generate an insulin-like effect [47–51,116]. At least part of the insulin enhancing effects was soon attributed to an increase of protein phosphorylation or inhibition of protein tyrosine phosphatases [117,118]. However, vanadium compounds also induce formation of reactive oxygen species (ROS), some of which could arise from Fenton-like reactions [119]. POVs have an effect on phosphatases, glucosidases, dehydrogenases, aldolases and other enzymes that are important for glucose processing [50].

A large number of different vanadium salts and complexes have been investigated reporting insulin-enhancing properties [48–50,111], among which several POVs, in particular, derivatives of V_{10} [50,51]. V_{10} with an ammonium counter-ion based on a molecule comparison increases about 6-fold the basal glucose uptake in rat adipocytes compared with other active vanadium compounds like bis(maltolato)oxovanadium(IV) (BMOV) or about 3-fold with respect to 2,6-pyridinedicarboxylatodioxovanadium(V) (V^V-dipic) (Fig. 6A, orange columns) [31]. However, only the incubation of adipocytes with decavanadate in the presence of insulin reaches an increase of the glucose uptake, of about 50% at decavanadate concentration of 1 mM (total vanadium, which is 100 μM decameric vanadate, Fig. 6A blue columns). Therefore, V_{10} exerts *per se* insulin-like activity as well as is the unique V-based compound enhancing the glucose uptake also in presence of insulin (Fig. 6A blue columns).

Recent studies with different counterions showed that the effects of ammonium decavanadate $(NH_4)_6[V_{10}O_{28}]$ can be improved and the use of benzylammonium $C_7H_{10}N^+$ [51] or metforminium $C_4H_{12}N_5^+$ [97,105] salts appear to exceed the insulin-enhancing effects of ammonium V_{10} even more. However, in the latter case a different animal model system was used so that

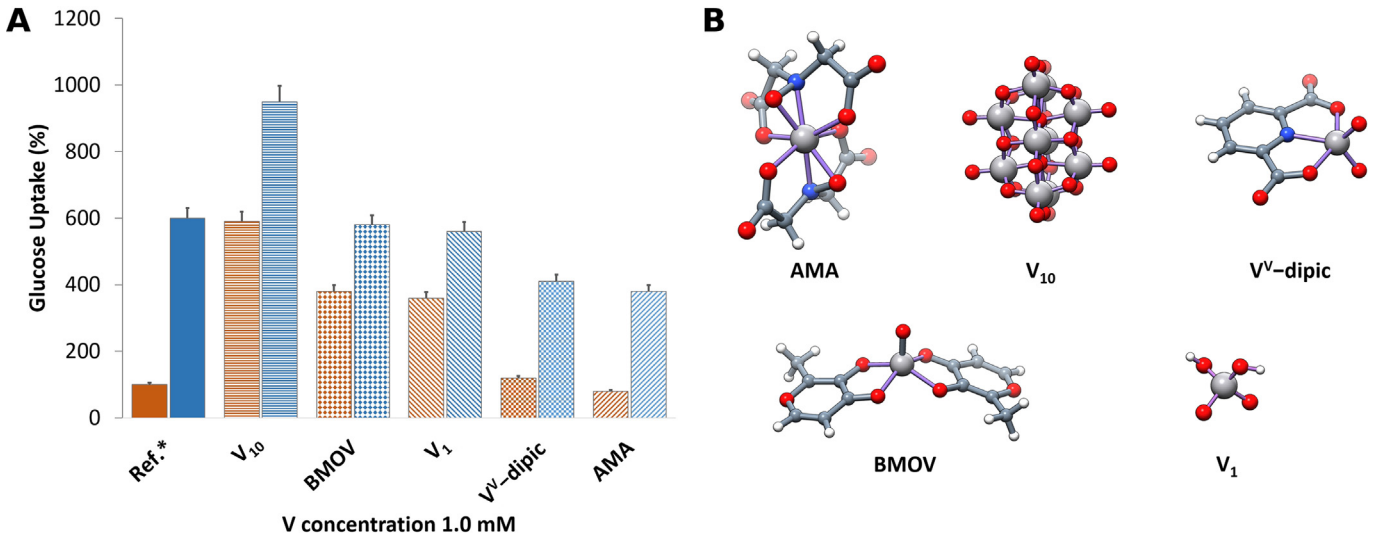

Fig. 6. A) Comparison of the [^{14}C] glucose uptake (%) between five different vanadium compounds (total vanadium concentration of 1.0 mM) measured in primary rat adipocytes. The samples are incubated for 45 min with vanadium compounds in the absence (orange) or in the presence (blue) of 10 nM insulin for 30 min. B) Structures for V_{10} (decavanadate); V_1 (orthovanadate, V_1); BMOV (Bis-maltolato-oxovanadium(IV)); V^V-dipic (2,6-pyridinedicarboxylatodioxovanadium(V)); AMA (amavadine). Vanadate (V_1) is illustrated as monomeric vanadate for simplicity although vanadate solutions at physiological pH values contains also others vanadate oligomers such as V_2 and V_4. Modified from reference [31].

comparisons are non-trivial and studies showing a direct comparison of these V_{10} salts would be desirable.

3.3. POVs as cellular activators

It has been suggested that V_{10} structurally resembles the surface of V_2O_5 oxide [104], which has been identified as low molecular weight sensitizing agent associated with occupational asthma and compromised pulmonary immune competence, Fig. 7 [103]. As V_2O_5 is a polymeric material with sheets of oxides which alter speciation upon dissolution, studies probing the effects of this material are controversial, because dissolution of V_{10} is observed. However, since V_2O_5 is an important heterogeneous catalyst, produced each year in high amount, there is significant interest in the biological effects of this material, which has been categorized as a toxic compound [120].

Due to this suggested structural analogy, the effects of V_{10} on biological systems and its interactions with lipid interfaces and membranes are of particular interest. In this context, the biological effects of V_{10} (Fig. 3A), used as model of V_2O_5, on plasma membrane lipid packing of leukemia cells (RBL-2H3) as well as on Langmuir monolayers were investigated [104]. Then, the possibility that V_{10} as a model for V_2O_5 may be initiating plasma membrane events associated with activation of Type I Fcε receptors (FcεRI) signal transduction using RBL-2H3 cells as a mast cell model was reported [28,104,123]. The exposure of RBL-2H3 cells to V_{10} caused a concentration-dependent increase in degranulation of RBL-2H3. In addition, an increase in plasma membrane lipid packing was observed as measured by the fluorescent probe, aminonaphthylethenylpyridinium-based dye (di-4-ANEPPDHQ). V_{10} also increases FcεRI accumulation in low-density membrane fragments, i.e., lipid rafts, which may facilitate FcεRI signaling. To determine whether V_{10} affects the packing of plasma membrane lipid, both V_1 and V_{10} were investigated. V_{10} increased the surface area of DPPC Langmuir monolayers by 6%, while V_1 decreased the surface area by 4%. These results are consistent with V_{10} interacting with this class of membrane lipids and altering dipalmitoylphosphatidylcholine (DPPC) packing and showed that V_{10} and V_1 act differently [104,124].

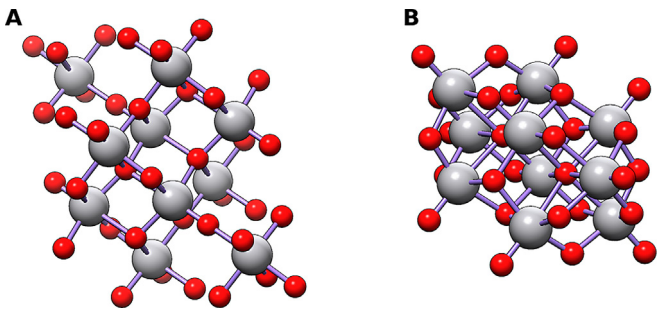

Fig. 7. Representation of: A) the partial structure (10 units) for V_2O_5 sheet [121]; and B) the structure for the discrete decavanadate anion (V_{10}) [122]. While V_2O_5 falls apart in solution; the discrete V_{10} anion retains its structure upon dissolution. Adapted with permission from reference [104].

The luteinizing hormone receptor (LHR), a G protein-coupled receptor (GPCRs), can initiate signaling in the presence of two mixed-valence POVs, $K(NH_4)_4[H_6V_{14}O_{38}(PO_4)]$ ($MVPV_{14}$, Fig. 3C) and $[(CH_3)_4N]_6[V_{15}O_{36}(Cl)]$ (MVV_{15}, Fig. 3I) or V_{10} (Fig. 3A) and V_1 [107]. The ability of LHR expressed in Chinese hamster ovaries (CHO) cells to initiate signaling in the presence of highly charged, water-soluble and redox active POVs, $MVPV_{14}$ and MVV_{15}, is a result of the vanadium compound interactions with the membrane lipids and/or the cell membrane lipid interface [107]. Interactions of the vanadium compounds with CHO cells decreased the packing of membrane lipids, drove aggregation of LHR and increased signal transduction by LHR. For V_{10}, $MVPV_{14}$ and MVV_{15}, cell responses were greater than those observed for cells treated with human chorionic gonadotropin (hCG), a naturally-occurring LHR ligand produced in early pregnancy in humans. POV effects were observed for CHO cells where LHR was expressed at 10,000 or 32,000 LHR per cell but not when LHR was overexpressed with receptor numbers >100,000 LHR per cell. The speciation of V_1, V_{10}, $MVPV_{14}$ or MVV_{15} in cell medium was monitored using ^{51}V NMR and EPR spectroscopy. In the case of both V_1 and $MVPV_{14}$ the conversion to trace levels of V_{10} and the smaller oligomers was observed after 3–10 h of incubation in the cell medium. All the POVs and V_1 initiated signaling, but V_{10} (Fig. 3A), $MVPV_{14}$ (Fig. 3C) and MVV_{15} (Fig. 3I) had the greatest effects on cell function, while V_1 was sig-

nificantly less active. The observed IC_{50} per each V compounds were 56.5, 3.2, 6.1 and 8.2 μM or expressed per V-atom 56.5, 32, 85 and 123 μM, respectively [107]. However, the chemistry of these mixed valence polyoxovanadates include oxidation of the POV and in the case of MVV_{15} ($[(CH_3)_4N]_6[V^{V}_{7}V^{IV}_{8}O_{36}(Cl)]$, Fig. 3I) the oxidized anion is formed in solution. Because of the complex nature of vanadium compounds speciation, it cannot be ruled out that some of the observed effects on cell function may be due to vanadium species formed in the cell medium over time. Still, the data clearly do show that the three POVs exhibit different effects of each other and of V_1.

In summary, these results demonstrate that V_{10}, the major POV studied in these systems, shows effects different from those of V_1 in fundamental biochemical processes, including activating signal transduction. Furthermore, the data of the studies as an antidiabetic agent are rather promising and demonstrate that optimization of effects can be done by altering the nature of the counterion.

4. Mitochondria as a potential subcellular target for POVs

As referred above, POVs have distinct effects other than orthovanadate (V_1) or metavanadate (V_1, V_2, V_4) species in mitochondria. Studies with both vanadate and decavanadate (Fig. 3A) in two different fish models, *Halobatrachus didactylus* and *Sparus aurata,* following POVs administration, detected that more vanadium is accumulated in mitochondrial fractions than when treated with V_1 alone [98,100]. Moreover, *in vivo* administration of V_{10} resulted in specific effects in mitochondrial antioxidants enzyme activities [99,100].

In order to further explore the effects of V_{10} on mitochondria, studies were performed *in vitro*. In both hepatic and cardiac mitochondria V_{10} inhibits mitochondrial respiration and induces mitochondrial membrane depolarization [70]. For instance, V_{10} concentrations lower than 100 nM inhibit 50% of oxygen consumption in mitochondria, while a 100-fold higher concentration of V_1 (10 μM) (or 10-fold higher concentrations of V-atoms) is needed to induce the same effect. Moreover, V_{10} also induces mitochondrial depolarization (IC_{50} 0.5 μM) much more strongly than V_1 (IC_{50} 50 μM) [125]. Considering the concentrations and biodistribution of vanadium upon administration and the observation that nM concentration of decavanadate inhibits oxygen consumption and membrane depolarization, it could be argued that mitochondria are a potential cellular target organelle for V_{10} (Fig. 8) [70,100,124,125].

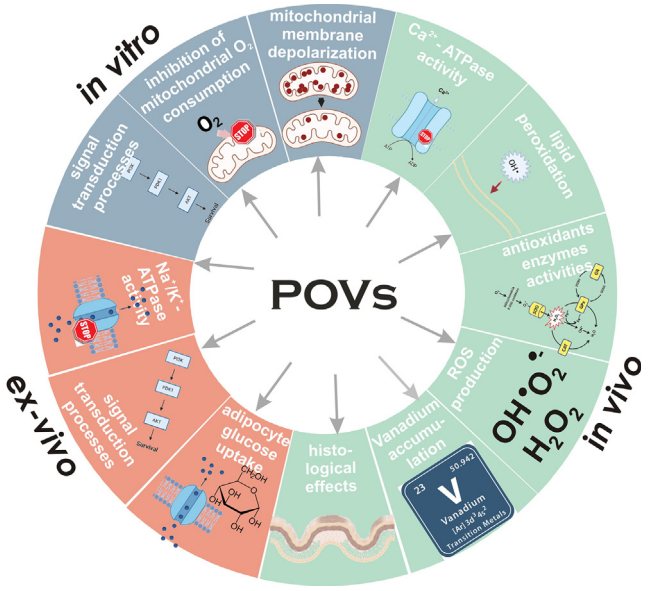

Fig. 8. Scheme of the described *in vitro*, *in vivo* and *ex-vivo* effects for POVs, mainly V_{10}. POVs *in vivo* effects in: 1) Ca^{2+}-ATPase activity; 2) lipid peroxidation; 3) antioxidants enzymes activities (SOD, CAT, GPx); 4) ROS production; 5) vanadium accumulation and 6) histological effects. POVs *ex-vivo* studies effects in: 7) Na^+/K^+-ATPase activity coupled with chloride secretion; 8) adipocytes glucose uptake; 9) signal transduction and *in vitro* POVs studies; 10) signal transduction processes; 11) inhibition of mitochondrial respiration and 12) mitochondrial membrane depolarization.

In summary, herein not only *in vitro*, but specially *in vivo* and *ex-vivo* effects for POVs, mainly decavanadate (V_{10}) are described and summarized in Fig. 8. Thus, regarding POVs *in vivo* studies many effects were reported in several organs and tissues such as heart, kidney, liver and blood in: 1) Ca^{2+}-ATPase activity; 2) lipid peroxidation; 3) antioxidants enzyme activity, in particular superoxide dismutase (SOD), involved in the elimination of superoxide radical anions, catalase (CAT) involved in the decomposition of hydrogen peroxide and glutathione peroxidase (GPx) involved in the recovery of glutathione (GSH); 4) reactive oxygen species (ROS) production; 5) vanadium accumulation; and 6) histological effects. In addition, recently *ex-vivo* studies effects were described for: 7) Na^+/K^+-ATPase activity coupled with chloride secretion; 8) adipocytes glucose uptake; 9) signal transduction. Finally, effects of *in vitro* POVs studies were associated with: 10) signal transduction processes; 11) inhibition of mitochondrial respiration; and 12) mitochondrial membrane depolarization (summarized in Fig. 8).

5. Recent insights into POVs' biomedical applications

5.1. Anticancer activities of POVs

A search in Web of Science shows that the number of papers published on the subjects "POMs and cancer", increased 7-fold in the past 10 years, in comparison to the previous decade, from 14 to 93 publications, representing 57% of POM papers in the biomedical field, with only 3 papers published prior to year 2000. Polyoxotungstates (52%) and polyoxomolybdates (36%) represent the majority of studied POMs, whereas the number of papers on polyoxovanadates (10%) and other types of POMs, such as polyoxoniobates (2%) is much less. For POTs and POMos the first studies on anticancer activity were described in 1965 [41], whereas the first report for V_{10} and/or POVs was published in 2009 [126]. The anticancer activity of POM-nanoparticle composites, which are promising candidates for the drug delivery in cancer therapy, as their particle size can be fine-tuned to ensure appropriate accommodation of guest molecules, was actively investigated (Fig. 2) [7,127,128]. Table 2 summarizes the results published with V_{10}, V-containing POMs and others POVs in cancer studies for the last 15 years.

Two decavanadate compounds, $(H_2tmen)_3[V_{10}O_{28}]$ (tmen = N,N,N′,N′-tetramethylethylenediamine) and $(H_2en)_3[V_{10}O_{28}]$ (en = ethylenediamine), were tested against human lung carcinoma cells (A549) and murine leukemia cells (P388) [26]. The IC_{50} values for A549 inhibition are 4.3±0.3 and 1.5±0.1 μM, for $(H_2tmen)_3[V_{10}O_{28}]$ and $(H_2en)_3[V_{10}O_{28}]$, respectively and for P388 inhibition 20.0±1.5 and 59.0±4.3 μM, respectively [26]. Considering that there are 10 V-atoms in one V_{10} anion, these values are 10-fold larger if focusing on concentrations of vanadium. Against human lung carcinoma cells, these POVs exhibited inhibition values 1.8–5.2 times lower than cisplatin (IC_{50} value: 7.8±0.5 nM for A549 and 5.2±0.3 nM for P388). The most lipophilic compound $(H_2tmen)_3[V_{10}O_{28}]$ showed higher cytotoxicity presumably due to a better uptake through the lipid bilayer [26]. The cytotoxicity of both H_2tmen^{2+} and H_2en^{2+} V_{10} salts was also measured on human normal hepatocytes (LO2) and resulted in IC_{50} of 6.5±0.6 μM for

Table 2
Studies published during the past 15 years on the anticancer activity of V_{10}, V-containing POMs and others POVs.

POVs	Cell line	Effects	Year	Ref.
$[NiV_{13}O_{38}]^{7-}$ and $[V_{18}O_{42}(PO_4)]^{9-}$	Human melanoma	Antitumor parameters	2005	[129]
$[NiV_{13}O_{38}]^{7-}$ and $[V_{18}O_{42}(PO_4)]^{9-}$	Lung cancer cells	Antitumor parameters	2005	[130]
$Na_4Co(H_2O)_6V_{10}O_{28}{\cdot}18H_2O$ (CoV_{10}) (Fig. 3A)	SKOV-3 SMMC-7721	Growth reduction	2009	[126]
$(H_2tmen)_3[V_{10}O_{28}]$, tmen = N,N,N′,N′-tetramethylethylenediammonium (Fig. 3A)	A549 and P388	Growth reduction	2010	[26]
POV-bisphosphonate complexes: $V_6(Ale)_4$, $V_3(Zol)_3$, $V_5(Ale)_2$, $V_5(Zol)_2$, Ale = alendronate, Sul = (2-Hydroxy-2,2-bis-phosphono-ethyl)-dimethyl-sulfonium and Zol = zoledronate	NCI-H460, MCF-7, and SF-268	Growth reduction	2012	[131]
V_{10}-betaine complexes $K_2[(MeNC_5H_4COOH)_2][V_{10}O_{28}H_2]{\cdot}2H_2O$, $[(H_2NMe_2)_4][V_{10}O_{28}H_2][Me_3NCH_2COO]_2$, $[(Me_3NCH_2COOH)_4][V_{10}O_{28}H_2][Me_3NCH_2COO]_2{\cdot}2H_2O$ (anion Fig. 3A)	MCF-7, A549	Growth reduction	2013	[132]
$Na_5[PMo_{10}V_2O_{40}]$ (Keggin archetype Fig. 3E) encapsulated in starch or lipid nanoparticles	MCF-7 and HEK-293	Growth reduction	2015	[133]
$\{(Me_3N\text{-}CH_2\text{-}CH(OH)\text{-}CH_2\text{-}COOH)_2\}$ $\{Na_4(H_2O)_{16}[V_{10}O_{28}]\}{\cdot}MeOH$ V_{10}-carnitine (Fig. 3B)	MDA-MB-231 A549	Growth reduction	2016	[134]
$Na_{10}[V^{IV}_{11}V^{V}_{7}O_{44}(N_3)]$	Cervical cancer cells	Antitumor parameters	2016	[135]
$K_{12}[V^{IV}_{18}O_{42}(H_2O)]{\cdot}6H_2O$ (V_{18}, Fig. 3D)	MCF-7	DNA, BSA and HSA binding Induced apoptosis. G2/M phase cell cycle arrest	2017	[58]
$K_{12}[V^{IV}_{18}O_{42}(H_2O)]{\cdot}6H_2O$ (V_{18}, Fig. 3D)	MDA-MB-231	Growth reduction	2017	[58]
$(TBA)_4H_3[GeW_9V_3O_{40}]$, TBA - tetrabutylammonium (Keggin archetype Fig. 3E)	U-87	Growth reduction	2017	[127]
$Na_4\{(HOCH_2CH_2)_3NH\}_2[V_{10}O_{28}]{\cdot}6H_2O$ (Fig. 3A)	HeLa HepG2	Induced apoptosis	2018	[60]
V_1 at pH 3–5 V_{10} (Fig. 3A)	MDA-MB-231	Tumor decrease	2018	[60]
$\{V_5O_9Cl(COO)_4\}$ with TATB (VMOP-31)	SMMC-7721	Cell cycle arrest, DNA damage, induced apoptosis	2019	[59]

$(H_2tmen)_3[V_{10}O_{28}]$ and 7.2±0.7 μM for $(H_2en)_3[V_{10}O_{28}]$. In contrast, the V_{10}-carnitine complex (Fig. 3B) exhibits anti-tumor activity against various human cancer cells, whereas normal human cells were not affected even when it was applied at high concentrations [134]. V_{10}-carnitine had IC_{50} values of 0.72 and 1.8 μM against a human lung adenocarcinoma cell line (A549) and a human breast adenocarcinoma cell line (MDA-MB-231), respectively. Compared to cisplatin's cytotoxicity, V_{10}-carnitine exhibited lower cytotoxicity values against A549 [134]. The IC_{50} for the V_{10}-carnitine complex against MDA-MB-231 cells was 1.7 μM compared to 700 μM for cisplatin, showing that V_{10}-carnitine is 400 times more effective. Even when considering that V_{10} has ten metal ions and cisplatin only one, the V_{10}-carnitine complex is still more effective in the comparison of the efficacy of the two compounds per metal ion [126].

The sodium-cobalt(II) salt of V_{10}, $Na_4Co(H_2O)_6[V_{10}O_{28}]$ (CoV_{10}), was tested against human liver (SMMC-7721) and ovary (SKOV-3) cancer cell lines [126]. CoV_{10} inhibits cell proliferation by 95% and 90% of SMMC-7721 and SKOV-3, respectively, at 6.25 μg/mL with an IC_{50} value estimated lower than 0.26 μg/mL, for both cancer cell lines. Similarly, the potency of CoV_{10} as an antitumor drug was compared with the approved drug fluorouracil (5-FU) and verified to be 15 times more effective against SMMC-7721 [126]. Table 2 summarizes the results published for V_{10} and others POVs in cancer studies in the last 15 years. Regarding the mode of POVs' action as antitumour agents, several potential mechanisms leading to apoptosis have been evoked [24,25,61,136,137]. For some POVs, such as $K_{12}[V_{18}O_{42}(H_2O)]$ (V_{18}, Fig. 3D), the tumor inhibiting mechanism is identified and is based on the arrest of MCF-7 cells in the G2/M phase leading to the induction of apoptosis and necrosis [58].

In summary, these studies demonstrate that V_{10}, other V-containing POMs and POVs have desirable anticancer properties. Moreover, recent papers showed that their effects compete and exceed that of cisplatin and thus warrant consideration in the future regardless of their charge and high polarity. In the last few years, in order to reduce the toxicity of POMs and improve their structural stability, the trend has shifted from testing inorganic POMs to testing POM-based nanohybrids. This resulted in a significant increase of the number of studies with hybrid POMs as potential agents in the fight against cancer [138–141]. Moreover, due to the functionalization and/or encapsulation with organic ligands, POVs with novel properties arise [142–147].

5.2. Antibacterial activities of POVs

Antibiotic resistance represents a real threat to the world public health since a high proportion of bacteria show significant resistance [148]. Combinations of different antibiotic agents are commonly adopted to combat infections caused by multi-resistant bacteria. Since 1996 a total of 75 POVs studies are available measuring antibacterial effects, with a clear increase (~40%) in the last decade [8]. POMs were recently suggested as putative future drugs fighting against pathogenic bacteria [8]. Historically, POMs as antibacterial agents started serendipitously. Thus, in 1993 an unknown compound named initially as "Factor T" was observed to enhance the antibacterial effect of β-lactams inhibiting methicillin-resistant *S. aureus* (MRSA) strains [149]. The aged mixture of tungstate and phosphate named "Factor T" was later identified as $[PW_{11}O_{39}]^{7-}$, the first POT of many others following under investigation as antibacterial agents [43].

In an early study investigating the antibacterial activity of vanadates(V) and oxovanadium(IV) compounds *in vitro*, the minimum inhibitory concentration (MIC) values for V_1, V_{10}, and $[V^{IV}O]^{2+}$ for *S. pneumoniae* are between 4 and 32 μg/mL. In 1996, the first antibacterial studies applying POMos and POVs were described, whereas the first paper investigating V_{10}′ antibacterial power was reported in 1997 [8].

Table 3
Studies published during the past 16 years on the antibacterial activity of V_{10} and other POVs.

Sum formula of the solid decavanadate	Bacteria[a,b]	Quantitative characteristics	Year	Ref.
$(C_6H_{14}N_5O)_4[H_2V_{10}O_{28}]\cdot 9H_2O$ $(C_6H_{14}N_5O)_6[V_{10}O_{28}]\cdot 4H_2O$, $C_6H_{14}N_6O$ – moroxydine	*Staphylococcus aureus*,[b] *Staphylococcus epidermis*,[b] MRSA (methicillin-resistant *Staphylococcus aureus*),[b] MRSE (methicillin-resistant *Staphylococcus epidermis*)[b]	Growth inhibition	2004	[153]
chitosan–$Ca_3V_{10}O_{28}$	*Escherichia coli*,[a] *Staphylococcus aureus*[b]	MIC = 12.5 μM against both strains	2005	[63]
$[H_2V_{10}O_{28}][4\text{-picH}]_4\cdot 2H_2O$, 4-pic = 4-picoline	*Pseudomonas aeruginosa*[b], *Bacillus cirroflagellosus*[a]	Growth inhibition	2014	[154]
$[4\text{-}(CH_3O)C_6H_4CH_2NH_3]_6V_{10}O_{28}\cdot 2H_2O$	*Enterococcus feacium*[a]	only qualitative determination	2015	[155]
$K(NH_4)_4[H_6V_{14}O_{38}(PO_4)]$, $MVPV_{14}$ (Fig. 3C)	*E. coli*[a]	Growth inhibition	2016	[156]
$[(CH_3)_4N]_6[V_{15}O_{36}(Cl)]$, MVV_{15}	*E. coli*[a]	Protection against alkylating agents	2016	[156]
$Na_6V_{10}O_{28}$ (Fig. 3A)	*Mycobacterium smegmatis*,[ab] *Mycobacterium tuberculosis* [a,b]	EC_{50} (M. smeg) = 0.0037 mM; EC_{50} (M. tb) = 0.029 mM	2018	[151]
$Na_6V_{10}O_{28}$ (Fig. 3A), (3-Hpca)4 $[H_2V_{10}O_{28}]\cdot 2H_2O\cdot 2$(3-pca), 3-pca = 3-pyridinecarboxamide $(4\text{-Hpca})_4[H_2V_{10}O_{28}]\cdot 2$(4-pca), 4-pca = 4-pyridinecarboxamide	*E. coli*[a]	GI_{50} (Na salt) = 0.1 mM; GI_{50} (3-Hpca salt) = 0.47 mM; GI_{50} (4-Hpca salt) = 0.67 mM	2018	[152]
$(NH_4)_4$(HMTA—H)$_2V_{10}O_{28}\cdot 4H_2O$, HTMA – hexamethylenetetramine	*E. coli*[a] *Salmonella typhimurium*,[a] *Enterococcus feacium*,[b] *Streptocoque* B (*Streptococcus agalactiae*)[b]	only qualitative determination	2019	[157]
$(NH_4)_6V_{10}O_{28}$ (Fig. 3A)	*E. coli*[a]	GI_{50} = 1.1 mM	2019	[158]
MnV_{11} (Fig. 3F), MnV_{13} (Fig. 3G) and V_{10} (Fig. 3A)	*E. coli*[a]	GI_{50} of 0.21, 0.27, and 0.58 mM	2019	[158]
$Na_5PtV_9O_{28}$ $Na_5MoV_9O_{28}$ $Na_6V_{10}O_{28}$	*Mycobacteria smegmatus*[a,b]	EC_{50} ($Na_5PtV_9O_{28}$) = 0.0048 mM; EC_{50} ($Na_5MoV_9O_{28}$) = 0.0015 mM; EC_{50} ($Na_6V_{10}O_{28}$) = 0.0036 mM	2021	[64]
$(NH_4)_2(Me_4N)_5[V^{IV}_{12}V^{V}_{6}O_{42}I]\cdot Me_4NI\cdot 5H_2O$ ($V_{18}I$)	*E. coli*[a]	Protection against alkylating agents		[159]
$[\{K_6(OH_2)_{12}\ V^{IV}_{11}V^{V}_{7}O_{41}(PO_4)\cdot 4H_2O\}n]$ ($V_{18}P$)				
V_{10} (Fig. 3A)				

[a] Gram-negative bacteria.
[b] Gram-positive bacteria.

In 2012, the first study with a POM complexed with the quinolone antibiotic (ciprofloxacin) was published [150]. V_{10} is the most common investigated POV also in antibacterial research, and Table 3 summarizes the antibacterial studies on V_{10}. Even when the starting compound is V_1, V_{10} forms in the growth media, which usually has an acidic pH, e.g. 6. In a study of *Saccharomyces cerevisiae* (*vide supra*) V_{10} was observed to be cell associated, which was interpreted as forming inside the cells in the acidic vacuoles through a proposed detoxification mechanism [94]. Willsky et al. was using ^{51}V NMR for the detection of vanadium(V) and saw the V_{10} signal forming as a function of time; they measured spectra of media and also consolidated cells (cell soup) and observed V_{10} both in cells and in growth media [94]. These studies were carried out with EPR spectroscopy which allowed monitoring the reduction of vanadate as a function of time [94].

V_{10} is more effective than V_1 and other rapidly converting smaller oxovanadates such as dimeric (V_2) and tetrameric vanadate (V_4), against Gram-positive bacteria, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Staphylococcus epidermis* [8]. Growth inhibition is also observed for Gram-negative bacteria such as *Escherichia coli* and *Salmonella typhimurium* [8]. V_{10} also inhibits the growth of *Mycobacterium smegmatis* and *Mycobacterium tuberculosis* more significantly than V_1 [151]. The higher efficacy of V_{10} over V_1 is due not only to the large number of V centers, but also to the general properties of POM, such as total net charge, size, and redox activity. The association of V_{10} with more complex cations such as (iso)nicotinamide ($C_6H_8N_2O^+$) [152], Ca^{2+}-chitosan [63] and other amine-based cations (Table 3) increases the toxicity towards *Escherichia coli*, proving that V_{10} also in a bacterial system can be fine-tuned by exchanging the counter-cation.

The symbiotic effect of chitosan together with V_{10} was investigated against *E. coli* and *S. aureus* [63]. The chitosan-V_{10} complex demonstrated the same antibacterial activity against both bacteria with a MIC value of 12.5 μM [63]. Chitosan is known for its antimicrobial activity as it inhibits the mRNA synthesis after penetration into the nuclei of microorganisms [160]. On the other hand, V_{10} alone inhibits P-type ATPases, such as Ca^{2+}-ATPase [73,161,162], leading to a disturbance in the molecular ion transport across the membrane and compromising the bacterial metabolism [63]. Thus, the mechanism of action of these combined POVs as antibacterial agents might include the inhibition of mRNA synthesis interfering with protein's production and the inhibition of P-type ATPases, destroying bacteria's metabolism and signaling. Several others possible mechanisms are discussed and reviewed in ref. [8].

Besides V_{10}, two manganese (Mn) containing polyoxovanadates, MnV_{11} (Fig. 3F) and MnV_{13} (Fig. 3G), were shown to inhibit the growth of *E. coli* [158]. MnV_{11}, MnV_{13} and V_{10} (pH of stock solution is 4) were all more effective inhibitors than simple V_1 (pH of stock solution is 10.5), with 50% maximal growth inhibition concentrations (GI_{50}) of 0.21, 0.27, and 0.58 mM, respectively, compared to 1.1 mM for simple vanadate. Strikingly, the V_{10} isostructural species decaniobate (Nb_{10}) showed only residual effects on *E. coli* growth [158].

The mixed valence polyoxovanadates $MVPV_{14}$ (Fig. 3C) and MVV_{15} (Fig. 3I) were evaluated for their chemoprotective activity

against the alkylating agent diethylsulphate in *Escherichia coli* DH5a cultures [156]. Their redox properties were examined as a potential protecting agent and compared to the effects of V_{10} and V_1 by monitoring the growth of *E. coli* treated with alkylating agent. $MVPV_{14}$ suffers rapid hydrolysis in both water and culture media, forming simple mononuclear complexes as well as larger aggregates such as $[H_4V^{V}_{14}O_{38}(PO_4)]^{5-}$ (Fig. 3C) or $[HV^{V}_{10}O_{28}]^{5-}$. This may explain the lack of chemoprotection by $MVPV_{14}$ and V_{10}, whereas MVV_{15} is effectively protecting the cells from alkylating agents. The observed chemoprotective effect is not only highly dependent on the solution stability of the polyoxometalates, but is also limited by the formation of decomposition products, such as V_{10} and V_1 species, which are not able to react and therefore do not deactivate the alkylating agent in the culture media of *E. coli*. In summary, the antibacterial effects of POVs vary based on speciation, although generally the POVs are more potent than V_1.

Recently, the chemoprotective activity of three POVs, $(NH_4)_2(Me_4N)_5[V^{IV}_{12}V^{V}_{6}O_{42}I]\cdot Me_4NI\cdot 5H_2O$ ($V_{18}I$), $[\{K_6(OH_2)_{12}V^{IV}_{11}V^{V}_{7}O_{41}(PO_4)\cdot 4H_2O\}_n]$ ($V_{18}P$), and V_{10}, towards the alkylating agent diethyl sulfate was assessed in *E. coli* cultures [159]. Comparing the results with previous findings described above for V_{14} and V_{15} [156], it was concluded that $V_{18}I$ is more stable than V_{15}, followed by $V_{18}P$ and V_{14}, and that the stability appears to originate from their interaction with cells and chemoprotective action against the deleterious effect of diethyl sulfate [159].

5.3. Antiviral activities of POVs

The number of studies testing metallodrugs which include POMs for treatment of viral infection has increased in 2020 due to the SARS-CoV2 pandemic [163–167]. Among the antiviral studies described so far for POMs, the investigations of POTs represent the largest contributions in this area (75%), followed by POVs (11%). The antiviral activity of POMs was initially studied and tested *in vivo* in France in 1973 by the Raynaud and Jasmin group [65]. They demonstrated that the POT $[NH_4]_{17}Na[Na(SbW_7O_{24})_3(SbO_7)_2]$ inhibits the RNA-dependent DNA polymerases of retroviruses and hence prevents the virus from spreading [65]. This discovery initiated testing of other POMs for their activity against the human immunodeficiency virus (HIV). Thus, POTs have been successfully demonstrated to inhibit the binding of HIV particles to cells through blocking the binding of gp120 [6,168,169]. Studies with other Keggin and Dawson type POTs proved that their antiviral effect was caused by inhibiting the binding of the virus to the host cell membrane and/or its penetration [168–171]. It is known that HIV specially targets CD4 cells present in T-lymphocytes, monocytes and macrophage lineage. A glycoprotein, termed gp120, allows binding of the virus on the CD4 cells and, consequently, the injection of viral material into the host cell [172]. POMs are active also against the SARS virus with promising EC_{50} values [173,174].

One of the most cited paper on the subject of V_{10} in biology is a study about its interaction within the protein cages of virions [66]. Besides preventing the formation of virions, V_{10} is also able to inhibit viral activities by preventing the virus-cell host binding [66]. In 2005, Yamase group has demonstrated that tungstovanadate mixed Keggin derivatives exhibit a wide-range of anti-RNA virus activities against MDCK, Vero, Hep-2 and MT-4 cells [20]. All tungstovanadates showed toxicity at concentrations above 200 μM (except on MT-4 cells, which are between 46 and 100 μM) [20]. Another study on a Keggin-type tungstovanadate, ($K_5[SiVW_{11}O_{40}]$, Fig. 3E) and two sandwich Keggin-type tungstovanadates, $K_{10}Na[(VO)_3(SbW_9O_{33})_2]$ (Fig. 3H) and $K_{11}H[(VO)_3(SbW_9O_{33})_2]$ (Fig. 3H) showed inhibition against the dengue virus (DFV), influenza virus (FluV A), respiratory syncytial virus (RSV), parainfluenza virus (PfluV 2), distemper virus (CDV) and HIV [173]. All three tungstovanadates showed high toxicity, as their effective concentration (EC) values were lower than 1 μM, in comparison to other Keggin POTs used in the study (EC_{50} > 10–60 μM). It was also demonstrated that $K_{10}Na[(VO)_3(SbW_9O_{33})_2]$ strongly inhibits the binding of the viral gp120 antibodies, in the step of syncytium formation between HIV-1-infected cells and uninfected cells [173].

It has been proposed that POMs have a dual mechanism of action in the inhibition of virus replication: firstly, POMs interaction with hemagglutinin A (HA), which is involved in viral attachment, impedes the fusion of viral particles into the cell [175]; secondly, inhibition of catalytic reactions promoted by sialyltransferases and sulfotransferases (neuraminidases) affect the carbohydrate chains in glycoproteins that play a major part in cell-viral recognition serving as a target for viral infections. Thus, by targeting virus membrane proteins, POMs affect the early stage of viral infection as illustrated schematically in Fig. 9.

The *Chlorella* virus was reported to be inhibited by V_{10} [176]. The *Paramecium bursaria Chlorella* virus is a large DNA virus that replicates in unicellular *Chlorella*-like algae [177]. The virus encodes an RNA triphosphatase which is involved in the synthesis of the RNA cap structure found at the 5′ end of the viral mRNAs. The *Chlorella* virus RNA triphosphatase is the smallest member of the metal-dependent RNA triphosphatases. The ability of various vanadate oxoanions to inhibit the phosphohydrolase activity of the enzyme was investigated by first examining the binding of V_{10} to the enzyme using fluorescence and CD spectroscopy [176]. The enzyme assay shows that V_{10} is a potent non-competitive inhibitor of the phosphohydrolase activity, and mutagenesis studies indicate that the binding of V_{10} does not involve amino acids located in the active site of the enzyme [176].

Oncolytic viruses are an emerging class of anticancer biotherapeutics that induce antitumor immunity through selective replication in conventional drug resistant tumor cells. Vanadate was found to increase antitumor efficacy in combination with oncolytic viruses in several syngeneic tumor models *in vitro* and *ex-vivo*, leading to systemic and durable responses, even in models otherwise refractory to oncolytic viruses and drugs alone [178]. The ability of vanadate to simultaneously maximize viral oncolysis and systemic anticancer immunity offers new avenues for the development of improved immunotherapy strategies.

Taking all these data together, the present review describes the activities of POVs against cancer, bacterial resistance and antiviral infection, which are summarized in Fig. 10. Recently, the putative mechanisms of POMs as anticancer and antibacterial agents were reviewed [7,8]. Still, taken into account the studies described above regarding POVs' anticancer activity, several possible mechanisms leading to apoptosis (Fig. 10, 1 h) have been evoked [59,60,174]. However, for other POVs, both apoptosis and necrosis was observed [53], whereas cell cycle arrest was also described (Fig. 10, 12 to 3 h in the clock).

Examples of antibacterial effects described for several POVs, such as V_{10}, include the interference with ions transport system, inhibition of mRNA synthesis, cell morphology changes besides affecting metabolic pathways and signaling [8,63,64] (Fig. 10, 3–8 h in the clock). POVs' virus effects include the inhibition of viral mRNA polymerase, inhibition of virus binding to the host cell, inhibition of virus penetration and interaction with virus protein cages [65,66,175] (Fig. 10, 8–12 h in the clock).

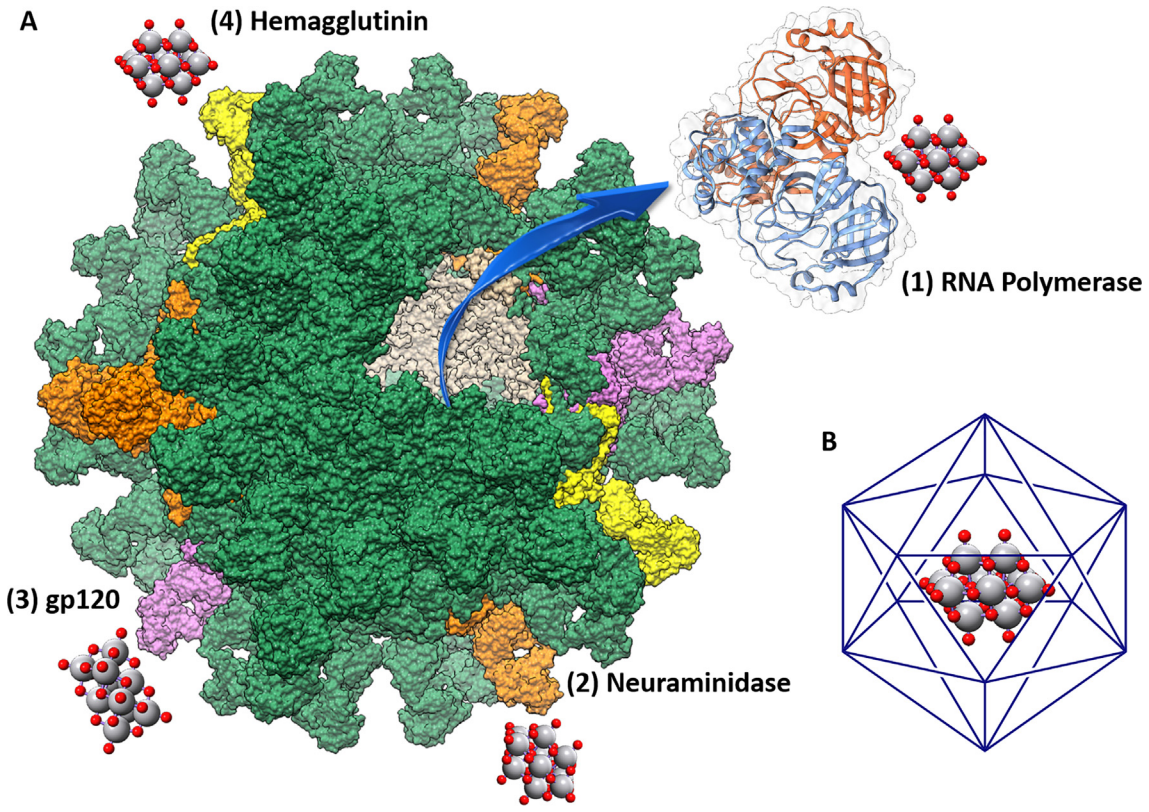

Fig. 9. A) POVs putative interactions with viral membrane proteins preventing an early stage of infection according to ref. [66]. In addition, the putative inhibition of neuraminidase prevents a later stage of infection. Color code: glycoprotein, dark pink; hemagglutinin, yellow; neuraminidase, orange. POM: vanadium, grey; oxygen, red. B) V_{10} interaction within the protein cages of HIV virions [66].

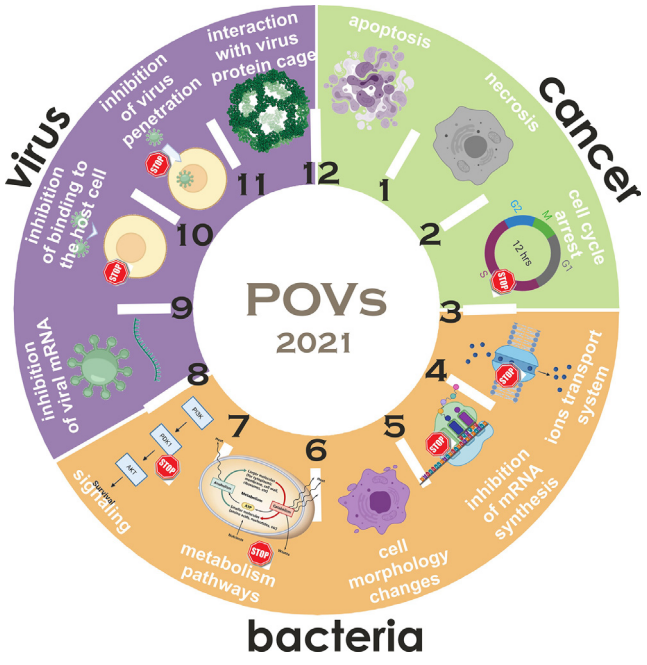

Fig. 10. POVs' clock in 2021 summarizing effects against cancer (green, Section 5.1), bacteria (orange, Section 5.2) and viruses (violet, Section 5.3). Some parts of this figure were created with BioRender.com.

6. Conclusions and perspectives

POVs, a subclass of POMs, are large anionic compounds that possess a rich diversity of structures and have shown biological and biomedical effects that are of interest and potential applications. POVs' stability and speciation studies, although essential for understanding which POMs species are inducing the biological effects, remain scarce. At this time few POMs *in vivo* and *ex-vivo* studies have been completed using POVs, with V_{10} being the major target compound. The *in vitro* studies carried out showed that POVs inhibits mitochondrial respiration.

To be approved as a drug, a POM must show higher activity against its biological target and low toxicity toward normal cells in comparison to the approved drugs. In addition, the development of potential compounds for therapeutic treatment must be economically feasible and hence synthetically accessible at the concentration levels needed. Only a few clinical studies with some POMs, in particular POTs such as SiW_{12} have been undertaken. These studies demonstrate that potential applications of such large anionic POVs are possible and so far these include POTs containing selected vanadium atoms. The fact that only a few pre-clinical studies have been carried out with POVs, although much work has been done with other vanadium compounds, points towards POVs' applicability in medical treatment. POVs present promising future applications toward the chemotherapy of solid tumors, DNA and RNA viruses and drug-resistant bacteria. Future approaches, in order to reduce toxicity and improve efficacy, include a shift from application of pure POVs to investigate vanadium-containing POM-based nanohybrids. Until now, the majority of the studies have addressed the potential of POVs to control cancer, bacterial growth and virus infections. A few studies have explored the mechanism of action of these compounds and their speciation. However, several aspects of the virulence and community life of bacteria, were not yet explored. Additionally, in order for POVs treatment of cancer to be considered, further studies are needed, since different mechanisms of action might

be involved. New strategies are needed allowing to obtain the first evidences of such potential, anticipating early changes in cellular metabolism induced by POVs. However, such studies are demanding with regard to resources, require interdisciplinary teams of technical skilled people to adhere to the regulations when developing materials for human consumption [179] and much pre-clinical work is needed to select which POMs or POVs are most suited for further development against a particular disease or infection.

In the present decade, we expect that important questions will be answered, for instance that we will be able to: (i) observe POVs at different subcellular domains and possible their formation since we already know that V_{10} can form in acidic vacuoles; (ii) clarify the processing and ADME of POVs after administration; (iii) understand the speciation of POVs under biological conditions and, finally, (iv) apply clinically POVs in the treatment of cancer, bacterial resistance and viral infections. These and other questions will require continuous development of new POVs and exploration of these and known compounds in biology and medicine. However, the observed activities *in vitro* as antibacterial and antiviral agents document the potential of this group of compounds, encourage more research and stimulate the interest especially in the light of the widespread rise of antimicrobial resistance and the recent SARS-CoV2 pandemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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