POLYOXOMETALATES

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REVIEW ARTICLE

# Study on the regulatory mechanisms of mitochondrial biosynthesis by polyoxometalates

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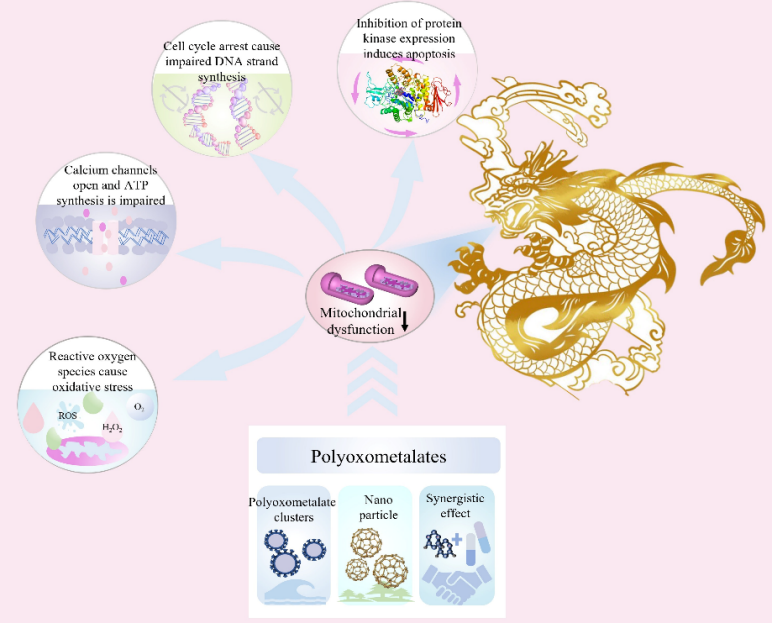
**ABSTRACT:** In recent years, polyoxometalates (POMs) have been extensively researched for their potential in treating diabetes, tumors, cancer, inflammation, and other diseases, both *in vitro* and *in vivo*. Their primary therapeutic mechanisms are related to the generation of reactive oxygen species (ROS), leading to oxidative stress. Because mitochondria are the main site of ROS production, POM treatment mechanisms may be associated with mitochondrial biosynthesis. This study explores one of the mechanisms by which POMs impact diabetes mellitus, focusing on the increase in ROS and the resulting oxidative stress. Additionally, POMs have been preliminarily studied for their antioxidant and antitumor properties in the treatment of diabetes mellitus and tumors. The antioxidant and antitumor properties of POMs are promising for future therapeutic drugs. By examining oxidative stress and its impact on various biomolecules, POMs have been recognized as a drug therapy mechanism closely linked to mitochondria. Investigating the relationship between POMs and mitochondrial biosynthesis, as well as their impact on mitochondria, provides a basis for future in-depth studies on the role of POMs in treating tumors, diabetes, and other diseases.




**KEYWORDS:** polyoxometalates, mitochondrial, antioxidant, antidiabetic, antitumor

## 1 Introduction

Polyoxometalates (POMs), also known as poly acids, are a class of nanoscale inorganic metal–oxygen cluster complexes. They are formed from the highly oxidized states of transition metals such as V, Mo, and W combined with oxygen [1]. The metal ions in POMs can be partially replaced by other transition metals to create substituted heteropolyacid compounds or the constituent elements can be intentionally chosen to modify their physical and chemical properties. Currently, POM-functionalized materials are attracting attention for their promising applications in photovoltaic materials [2, 3], energy materials [4], catalysis [5, 6], electrochemistry [7, 8], enzyme inhibition [9, 10], anticancer [11], antimicrobials [12], treatment of Alzheimer's disease [13, 14], and antidiabetes.

Diabetes, tumors, and cancers are becoming global epidemics owing to changes in lifestyle and diet. Diabetes encompasses type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D is characterized by genetic predisposition and environmental factors that trigger autoimmunity, resulting in the destruction of insulin-producing β-cells [15]. Bâlici et al. [16] synthesized two W-containing POMs (POM1 and POM2) to act on a diabetic rat model. Results showed that both POMs had a hypoglycemic effect on the diseased rats, as evidenced by monitoring blood glucose levels, observing the ultrastructure of β-cells, and recording the size of the secretory vesicles. POM1 exhibited a considerably more pronounced effect than POM2. The hypoglycemic effect of both POMs was attributed to the prevention of pancreatic β-cell apoptosis and the promotion of insulin synthesis. One of the causes of T2D is hyperglycemia and insulin resistance resulting from oxidative stress. This condition, often referred to as a metabolic disorder owing to mitochondrial

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dysfunction, occurs because mitochondria are the primary site of ROS production during oxidative stress. T2D accounts for 95% of all diabetes cases [17]. Chen et al. [18] reported that lipid-modified polyoxovanadates (ULPOVs) exhibited the ability to inhibit obesity-induced insulin resistance and lower glucose levels in a diet-induced obesity model, thus helping to maintain glucose homeostasis. Given our focus on type II diabetes, it is crucial to develop effective diabetes therapeutics and to identify the targets and molecular mechanisms of action of hypoglycemic agents.

Since the 1980s, studies on the antidiabetic properties of POMs have evolved from their role as insulin analogs to their current use as α-glucosidase inhibitors for blood glucose lowering and antidiabetic effects. These studies have enhanced the understanding of POMs as multifunctional therapeutic agents in type 2 diabetes mellitus (T2DM) and have created opportunities to design and screen POMs with reduced cytotoxicity and improved bioactivity. This can lead to the development of new therapeutic medications for diabetes. Diabetes mellitus (DM), a chronic multifactorial metabolic disease, is characterized by disrupted glucose homeostasis. One of the main carbohydrate hydrolases, α-glucosidase, inhibits glucose synthesis, making it an effective therapy and prevention strategy for diabetes [19]. It has been shown that in skeletal muscle, mitochondrial dysfunction—characterized by altered function, reduced adenosine triphosphate (ATP) synthesis, and increased ROS production—is a contributing factor to insulin resistance and the development of obesity and diabetes [20].

When considering illness, people often think of cancer and tumor development owing to their complex mechanisms, which has led many scholars to compete in researching these causes. One contributing factor is oxidative stress, which causes cellular dysfunction and is the basis of cancer and tumor formation. The role of POMs in this context, particularly as a therapeutic approach, remains underexplored. In this study, we discuss POMs in relation to antidiabetic mechanisms and extend the discussion to their mitochondrial regulatory mechanisms in the context of antitumor activity.

## 2 POMs and antidiabetic mechanisms

### 2.1 Mechanism of $Na^+/K^+$-ATPase and $Ca^{2+}$-ATPase inhibition by antidiabetic drugs

Mitochondrial ATP is crucial as the cell's energy source and a major source of reactive oxygen species (ROS). In all higher eukaryotes, a transmembrane protein complex known as the $Na^+/K^+$-ATPase (sodium-potassium pump) plays a crucial role. This energy-consuming pump maintains the cell's ionic and osmotic balance. The $Na^+/K^+$-ATPase enzyme facilitates ATP breakdown to provide energy, maintains membrane potential, regulates cellular osmolarity, and supports impulse conduction in nerve and muscle cells. Additionally, it drives the transport of $Na^+$ and $K^+$ across the cell membrane in opposite directions. In addition to regulating osmotic pressure and supplying energy through ATP hydrolysis, $Na^+/K^+$-ATPase also facilitates the transport of $Na^+$ and $K^+$ across the membrane in opposite directions, maintains membrane potential, and promotes nutrient uptake. It is crucial for impulse conduction in nerve and muscle cells. $Ca^{2+}$-ATPase, another important enzyme, greatly influences heart and muscle contraction, nerve cell action potential conduction, and cell secretion and proliferation by stabilizing intracellular $Ca^{2+}$ concentrations. Inhibitors of these enzymes are used to treat various conditions, including diabetes and heart failure. Bošnjaković-Pavlović et al. [21] investigated the effect of 12-tungstophosphate on the conversion of ATP to adenosine diphosphate (ADP) by $Na^+/K^+$-ATPase. The results demonstrated that 12-tungstophosphate negatively affected $Na^+/K^+$-ATPase enzyme activity. Gumerova et al. [22] compared the effects of nine different heterotungstates on the induction of two P-type ATPases. Their study revealed that large heteropolytungstates $K_9(C_2H_8N)_5[H_{10}Se_2W_{29}O_{103}]$ ($Se_2W_{29}$) and Dawson-type heteropolytungstates $K_6[\alpha\text{-}P_2W_{18}O_{62}]$ ($P_2W_{18}$) exhibited the strongest inhibitory effects on the enzyme. Fraqueza et al. [23, 24] further extended the application of POMs as effective inhibitors of $Na^+/K^+$-ATPase and $Ca^{2+}$-ATPase by investigating Keggin-type $Cs_{5.6}H_{3.4}PV_{14}O_{42}$ ($PV_{14}$), decavanadate ($V_{10}$), and monovanadate ($V_1$). The results indicated that $PV_{14}$ exhibited stronger inhibition of both $Na^+/K^+$-ATPase and $Ca^{2+}$-ATPase compared to $V_{10}$ and $V_1$. Additionally, $PV_{14}$ demonstrated considerable potential as an *in vivo* suppressor of $Na^+/K^+$-ATPase, particularly in relation to chloride secretion.

### 2.2 Mechanisms of oxidative stress in antidiabetic drugs with POMs

Liao et al. [15] selected biologically favorable gelatin methacrylate (GelMA) hydrogel combined with molybdenum-based POMs nanoclusters (GelMA/POM) for an *ex vivo* therapeutic study on bone damage in diabetic patients caused by excessive ROS production. *In vitro* studies revealed that GelMA/POM inhibited ROS production and reduced cellular oxidative stress. In diabetes, reduced electron carriers from the tricarboxylic acid cycle, which primarily produce glucose, disrupt redox balance and lead to metabolic disorders. This results in the accumulation of reactive oxygen and nitrogen radicals over time, causing considerable oxidative stress [25]. The role of diabetes is shown in Fig. 1. Mechanisms that contribute to diabetes, such as the polyol pathway and the formation of advanced glycation end products (AGEs), can also produce ROS. These pathways interact to exacerbate oxidative stress [26]. Protein kinase C (PKC)-dependent activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase can stimulate ROS/RNS (RNS = reactive nitrogen species) production via elevated glucose levels [27]. Numerous studies have indicated that oxidative stress contributes to the pathophysiology of T2D. Recent findings suggest that the mechanism of many antidiabetic drugs is linked to their antioxidant properties. For example, metformin, a medication used to treat T2D, reduces the generation of ROS and exhibits antioxidant effects [28]. Understanding the relationship between diabetes and antioxidants reinforces the theoretical basis for using POM antioxidants as a therapeutic strategy for diabetes. Recent studies have explored the potential of POMs' antioxidant properties as therapeutic agents for diabetes.

## 3 T2D, tumor therapeutic agents and intrinsic antioxidant mechanisms, antitumor mechanisms

In diabetes, uncoupling of oxidative phosphorylation leads to inefficient ATP synthesis and the production of superoxide anions. Therefore, a potential treatment approach is to mitigate the damage caused by oxidative stress [29]. In 2012, Bagul et al. showed that resveratrol, by reducing the excessive ROS emission from the

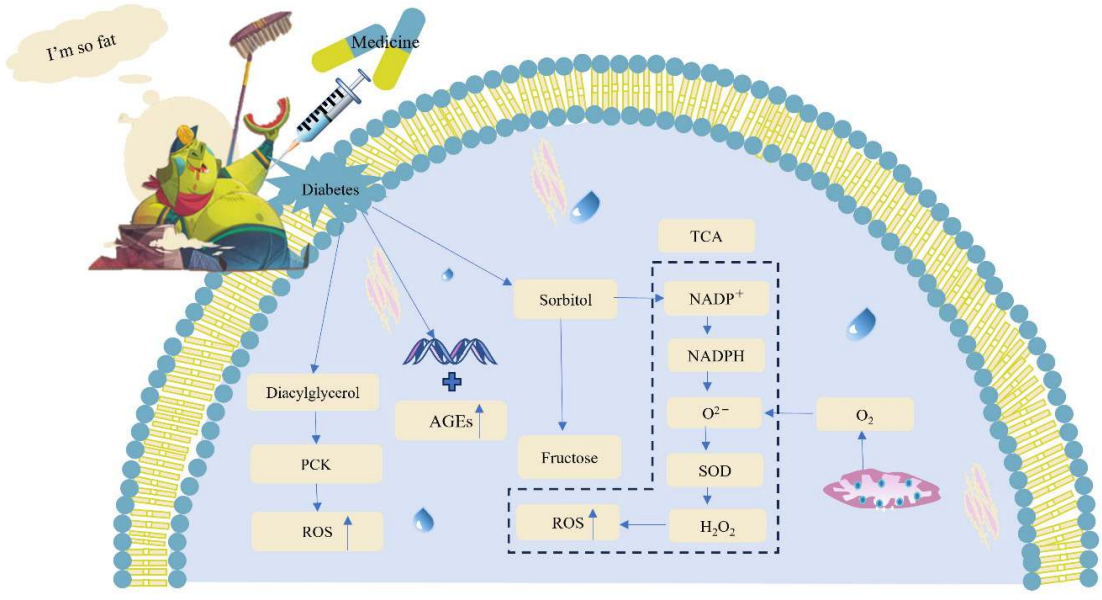


**Figure 1** Mechanisms of action in the development of diabetes.

succinate cycle, was able to correct insulin resistance in diabetic mice induced by oxidative stress [30]. Resveratrol from grapes has potent antioxidant qualities that reduce insulin resistance and activate SIRT1, a gene that protects cells from oxidative stress and inflammation [31]. It also stimulates peroxisome proliferator activated receptor γ coactivator-1α (PGC-1α), which promotes mitochondrial biogenesis and glucose uptake [32–35]. Van der Schaft and colleagues reported in a large epidemiological study that a diet rich in antioxidants was associated with improved insulin sensitivity in patients with T2DM [36]. In 2015, Agil et al. demonstrated that melatonin enhances its antioxidant properties by preserving mitochondrial function, which in turn improves insulin resistance in diabetic mice [37]. This evidence suggested that some antioxidants could reduce oxidative stress-induced insulin resistance and maintain glucose homeostasis [38]. Mitochondria-targeted antioxidants, such as SS-31, have been shown to inhibit enzyme activity and cytokine expression by modulating mitochondrial membrane potential ($\Delta\Psi_m$) and ATP levels. Additionally, they stimulate p38 protein kinase (p38 MAPK) and NADPH oxidase activities in hyperglycemic conditions and upregulate the expression of thioredoxin 2 (TRX2), demonstrating promising therapeutic effects for diabetic nephropathy [39]. Therefore, designing mitochondria-targeted antioxidants offers a more precise and effective strategy for developing drugs to treat diabetes mellitus.

Because one of the mechanisms of diabetes treatment drugs involves suppressing oxidative stress in the body, and tumor development may also be related to oxidative stress, it is plausible that patients with diabetes might be at an increased risk of developing tumors. Sharma et al. [40] determined that diabetic patients were at a higher risk of developing tumors, cancers, and other diseases compared to non-diabetic individuals. This was determined by analyzing the depth of invasion, tumor cross-sections, and other diagnostic studies through pathology, imaging, and research reports. It is suggested that the carcinogenic mechanisms in diabetic patients may be linked to hyperglycemia, cell proliferation, inflammatory cytokines, and other factors. The study more directly demonstrates that oxidative stress plays a considerable role in the interactions between cancer, tumors, and diabetes, including gene expression and signaling [41]. For instance, oxidative stress further reduces ATP synthesis levels through the pentose phosphate pathway, a key pathway for energy production. This pathway generates NADPH, which is crucial for insulin secretion, but also promotes tumor growth. Genetic factors regulated by NADPH are essential for malignant tumor development. High levels of ROS can contribute to carcinogenesis by damaging DNA, proteins, and lipids, inducing genomic instability, and activating factors such as NF-κB and apoptotic protein kinases. Additionally, elevated ROS levels may also contribute to the development of T2DM [42].

Furthermore, cellular and preclinical studies have demonstrated that metformin, the preferred drug for treating T2D [43], also possesses antitumor effects [44]. These effects are achieved through the inhibition of mitochondrial oxidative phosphorylation. It has also been demonstrated [45] that metformin's ability to restrict tumor growth *in vivo* relies on its interaction with mitochondrial complex I while also reducing insulin levels [46], which has also encouraged the development of an economically licensed drug for the treatment of cancer and diabetes [47].

## 4 POMs and mitochondrial regulatory mechanisms

Mitochondrial dysfunction—an adverse effect of T2D characterized by high production of ROS, reduced ATP levels, impaired regulation of mitochondrial proteins, and various other responses [48]—extends to mechanisms of tumorigenesis. Research shows that mitochondrial synthesis and enzymes on the cellular membrane are closely linked to changes in ROS levels. A major source of mitochondrial ROS is the electron transport chain. Damage to this chain, resulting from mitochondrial metabolic disorders, leads to persistent opening of the permeability transition pore in the mitochondrial membrane, reduced mitochondrial membrane potential, increased $Ca^{2+}$ accumulation, elevated ROS levels, impaired redox balance, limited ATP synthesis, and a detrimental impact on mitochondrial function [49]. When

mitochondrial activity is impaired, apoptotic factors such as cytochrome C and associated proteases, including caspases, are released. This disruption can lead to gene mutations and trigger apoptosis [50]. Excessive amounts of ROS can damage proteins, lipids, and DNA, leading to severe oxidative stress and contributing to conditions such as degenerative diseases and cancer. Mitochondrial DNA (mtDNA) is especially vulnerable to ROS-induced damage owing to its lack of repair mechanisms and histones [51]. Meanwhile, studies have found that in cancer cells, there is a state of persistent oxidative stress caused by mitochondrial dysfunction and metabolic changes [29]. The role of mitochondria is illustrated in Fig. 2. Excessive ROS, mitochondrial dysfunction, and the stimulation of cancer cell proliferation are linked to gene mutations, genetic abnormalities, and additional damage to proteins and lipids. These factors collectively contribute to tumor and cancer development [52]. Numerous studies have shown that the intrinsic mechanisms underlying diabetes, tumors, and cancer are closely linked to mitochondrial regulatory mechanisms. In this study, we explore how POMs interact with mitochondrial regulatory mechanisms in three distinct ways: (1) by affecting mitochondrial oxidative stress and ROS production, (2) by influencing mitochondrial ATP synthesis and the electron transport chain, and (3) by modulating mitochondrial protein kinases and gene expression processes that regulate mitochondrial function [53] (see Table 1 for a summary).

### 4.1 POMs and mitochondrial oxidative stress ROS generation

Hyperglycemia triggers the production of superoxide, and insulin can also induce the formation of ROS [54]. The rise in ROS and oxidative stress occur mainly in mitochondria [17]. Several experimental studies have found that elevated glucose levels in diabetic patients lead to excessive production of ROS. This excess ROS results in mitochondrial metabolic disorders and tissue damage characterized by oxidative stress injury [15]. Raza et al. [55] observed a considerable increase in ROS in both the brain and liver of ZDF mice, suggesting that oxidative stress is linked to mitochondrial dysfunction in these mice. Additionally, a related historical study indicated that high ROS levels are associated with tumorigenesis [56]. Tungsten-based POM nanodots [57], novel POMs synthesized using W atoms, have attracted considerable attention from many scholars. Song et al. [58] designed giant tungsten-oxonate cluster fragments coligated with $Ce^{3+}$ and $Ag^{+}$ linkers, specifically $\{[Ce_{10}Ag_6(DMEA)(H_2O)_{27}W_{22}O_{70}][B\text{-}\alpha\text{-}TeW_9O_{33}]_9\}_2^{88-}$ (Ang-Te-Ag-CeNPs). They found that this POM inhibited glioma cell growth by up to 74.8% and exhibited s trong antitumor properties. The article highlighted that the antitumor activity was due to the activation of ROS production through the Ag active site, which induced oxidative imbalance and cellular death. Additionally, the team performed related research on the biological functions of large POM superclusters and synthesized $\{[(Sn(CH_3)_2)_2O]_4\{[CeW_5O_{18}][TeW_4O_{16}][CeSn(CH_3)_2]_4[TeW_8O_{31}]_4\}_2\}^{46-}$, which is the first report of an organotin/lanthanide functional group with antitumor activity [59]. León et al. [60] investigated the effects of copper heteropolytungstate on mitochondrial oxidative stress by synthesizing it as an antitumor compound. They found that when $PW_9Cu$ was applied to toxic cells, it induced oxidative stress, increased ROS levels, and decreased GSH production in the mitochondria. This demonstrated that the compound impaired mitochondrial metabolism and cellular function, contributing to its antitumor effects. Additionally, diabetes can lead to acute kidney injury (AKI) owing to damage to renal tubules and disturbances in the mitochondrial electron chain, resulting in excessive production of ROS. Huang's team designed small tungsten-based nanodots (TWNDs), noting that W-atoms exhibit extremely high antioxidant activity. These TWNDs were shown to effectively reduce $O_2^-$, $H_2O_2$, and other ROS. The study also found that TWNDs had a mitochondria-targeting effect, capable of restoring mitochondrial membrane potential, reducing damage to the mitochondrial respiratory chain, and effectively treating AKI [61]. Jia et al. [62] synthesized a novel compound $(Hdmap)_3[\{CoNa_2(H_2O)_8(BiWO_3)\}\{BiW_8O_{30}\}]\cdot 2H_2O$ containing a stabilized sandwich structure of $\{BiW_8\}$. The researchers were concerned with the close correlation between POMs and ROS production. They found that $\{BiW_8\}$ reduced GSH levels in both cellular and chemical environments while increasing ROS levels in MG63 cells. The results suggested that the decrease in GSH levels induced by $\{BiW_8\}$ led to ROS-induced DNA damage, which may

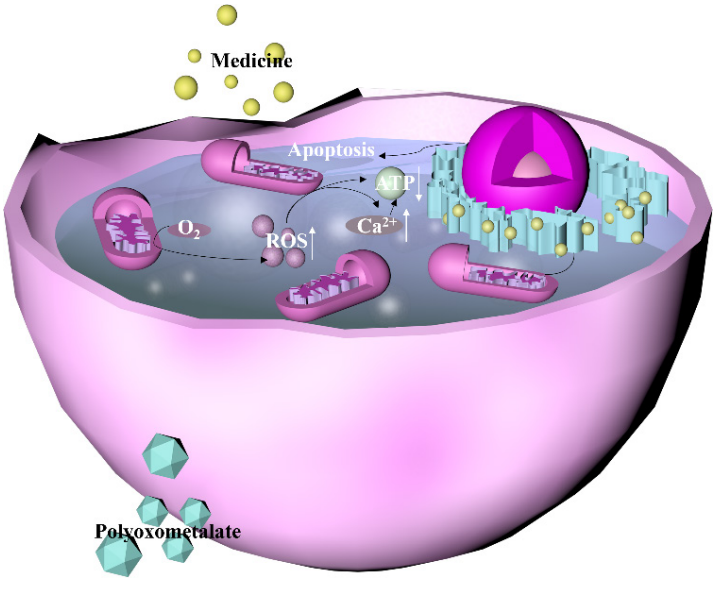


**Figure 2** Mitochondrial action diagram.

**Table 1** Polyoxometalates and mitochondrial regulatory mechanisms

| | Characteristics | Main findings | References |
|---|---|---|---|
| Oxidative stress, reactive oxygen species production | Gelatin methacrylate with molybdenum-based POM cluster | Inhibit the production of reactive oxygen species, reduce oxidative stress and alleviate bone damage | [15] |
| | Tungsten-based clusters connected to $Ce^{3+}$ and $Ag^{+}$ | Ag active site activates ROS production, triggers oxidative imbalance and inhibits tumor cell proliferation | [58] |
| | Tungsten-based nanodots, ultra-high antioxidant activity of W-atoms | Reduction of $O^{2-}$, $H_2O_2$, mitochondrial targeting | [57, 61] |
| | Stabilized sandwich structure containing $\{BiW_8\}$, nanoclusters with $Se_2W_{18}$ sandwich structure | Reduces GSH levels and enhances ROS generation | [62, 63] |
| | Preparation of $GdW_{10}$@CS nanospheres | Synergistic action of $W^{6+}$ oxidizes GSH and generates sufficient ROS | [64] |
| | Ph-sensitive POM clusters | Decreased ROS levels and POM as a ROS scavenger to treat inflammation | [68] |
| | Nano-enzymes, photothermal co-catalysis | NIR laser irradiation generates large amounts of reactive oxygen species, leading to oxidative stress and cancer cell apoptosis | [69] |
| | Lipid droplet-specific photosensitizer (DPCMP) | White light irradiation generates ROS to trigger lipid peroxidation and induce endoplasmic reticulum oxidative stress | [70] |
| | Oxygen vacancy ($O_V$) bimetallic silicate nanoenzymes with Fe-Ca dual active sites | Fe-Ca dual active site, ROS production | [72] |
| | Zeolite imidazole modification, tumor microenvironment, synergistic therapy | Increase the level of ROS production in tumor | [73] |
| ATP synthesis and the electron transport chain | Containing 10 nuclear heteroatoms $\{SbW_8O_{30}\}$ | Inhibits mitochondrial ATP synthesis, impedes electron respiration chain function, hinders metabolic function *in vivo*, and generates large amounts of ROS | [76] |
| | $[Mo_7O_{24}]^{6-}$ redox | Formation of FMN complexes to inhibit ATP synthesis | [78, 79] |
| Cytokines, cycle and protein expression | Large POM with $\{SbW_9O_{33}\}$, $\{SbW_8O_{31}\}$ | Stalls the cell cycle in S phase, induces apoptosis, and inhibits cell proliferation | [90, 91] |
| | Large POM containing Sb | Sb triggers p53-dependent apoptotic pathway | [92] |
| | Sandwich construction (BWCN) | Induction of apoptosis by activation of caspase-3 expression | [95] |
| | Containing Si nanoparticles | Inhibits Bcl-2 protein levels, activates caspase3 protein expression and promotes apoptosis | [93] |
| | Multifunctional selenium nanoparticles (SeNPs) loaded with drugs | Up-regulates pro-apoptotic proteins Bcl-2 and Bcl-xl, down-regulates anti-apoptotic protein Bax, inhibits activation of the p53(MAPK) pathway, reduces ROS concentration, and prevents mitochondrial dysfunction | [96] |
| | Binding of metformin to vanadate | Inhibition of NADH oxidation, inhibition of mitochondrial II and III complexes, inhibition of FADH oxidation | [99] |

be responsible for the cell death observed in MG63 cells. $Fe_4Se_2W_{18}$ [63], also a sandwich-structured nanocluster, exhibited an antitumor activity mechanism similar to that of reducing intracellular GSH levels and enhancing ROS production, leading to the elimination of tumor cells. Furthermore, Yuan et al. [64] described the formation of $GdW_{10}$@CS nanospheres after preparing $Na_9[Gd(W_5O_{18})_2]\cdot xH_2O$. They used 2',7'-dichlorofluorescein (DCF) as a probe to stimulate the generation of excess cytotoxic ROS. High-energy X-rays, in combination with the synergistic effect of $W^{6+}$, were used to oxidize glutathione, generating sufficient ROS to enhance the therapeutic efficacy of radiotherapy. Liao et al. [15] designed and synthesized Mo-based POMs along with a novel advanced nanohydrogel system [65]. Dalong et al. [66] designed molybdenum-based POM nanoclusters as novel nano-antioxidants for renal protection. Because renal tubules are susceptible to oxidative stress, the overproduction of ROS causes mitochondrial functional impairment, leading to cell death and resulting in AKI [67]. Dalong found that pretreating HEK293 cells with POM nanoclusters before $H_2O_2$ treatment decreased ROS concentration and reduced oxidative stress, thereby protecting the cells from ROS damage. Yang et al. [68] developed a pH-sensitive molybdenum-based POM nanocluster. Given POM's high antioxidant properties, they investigated its potential to scavenge ROS in cells and found that ROS levels decreased considerably in POM-pretreated cells under drug stimulation, indicating a strong ROS scavenging effect. They concluded that such clusters were preferred as ROS scavengers for treating colitis, facilitating the transition from laboratory research to clinical treatment. In recent years, new materials based on POM have attracted considerable attention for realizing photothermal synergistic therapy and photodynamic therapy for treating tumors and cancers using externally induced light (such as near-infrared light and daylight) and micro-environments such as tumors and acidity. Tang et al. [69] synthesized nano-enzymes, termed POMotors, using a one-pot method, and achieved photothermal catalytic synergistic oncology therapy by constructing a near-infrared (NIR) laser irradiation model. In both *in vivo* and *ex vivo* studies of POMotors, it was found that the nano-enzyme generated many ROS under NIR laser irradiation, leading to oxidative stress and subsequent apoptosis. Other researchers developed a photosensitizer with lipid droplet specificity (DPCMP) [70]. It was determined that under white light irradiation, DPCMP could generate many ROS, which triggered lipid peroxidation and induced oxidative stress in the endoplasmic reticulum, ultimately leading to ferroptosis [71] in cancer cells and

apoptosis. Liu et al. [72] reported oxygen vacancy ($O_V$)-rich bimetallic silicate nano-enzymes with Fe-Ca dual active sites. These nano-enzymes were created by modifying oxidized sodium alginate and loading gallic acid (GA) (OFeCaSA-V@GA). This modification allowed the nano-enzymes to adsorb and dissociate $H_2O_2$, stimulating the generation of ROS to achieve synergistic catalytic effects for targeted, aggregation-enhanced tumor therapy. Song et al. [73] used a zeolite imidazole framework to modify POM nanoparticles (POM@ZIF-8 NPs). They combined thermodynamic and electrodynamic therapies for tumor treatment, and the results showed that POM@ZIF-8 NPs generated many ROS and exhibited a high rate of demobilization in the presence of electric field stimulation and acidic tumor environments, indicating a strong antitumor effect. These novel POM materials provide diverse inspirations for future exploration of synergistic therapeutic approaches using POMs.

### 4.2 Mitochondrial ATP synthesis and the electron transport chain

NADH and $FADH_2$, produced by mitochondrial glucose oxidation, are oxidized in the electron transport chain (ETC) to generate ATP and ROS. This process is known as oxidative phosphorylation [17]. Protein kinases maintain energy homeostasis by simultaneously inhibiting ATP-consuming anabolic processes and promoting ATP-generating catabolic processes [74]. Insulin secretion is regulated by mitochondria. Elevated glucose levels trigger oxidative phosphorylation in insulin-producing β-cells, increasing the ATP/ADP ratio. This inhibits $K^+$ channels, depolarizes the plasma membrane, and subsequently increases intracellular $Ca^{2+}$ levels [48]. Excessive $Ca^{2+}$ accumulation leads to the formation of mitochondrial permeability transition pores (mtPTPs), resulting in the uncontrolled release of $Ca^{2+}$, apoptotic factors, and ROS [51]. This impairs the mitochondrial electron transport chain and ATP synthesis, causing oxidative stress and elevated ROS levels [75]. Research into the mechanisms of ATP synthesis in mitochondria is highly complex. Here, several novel POMs designed with W and Mo ions are highlighted. Gong's group [76] successfully synthesized a new POM, $Na_4Ni_2Sb_2W_2$-$SbW_8$, based on the 10-nuclear heteroatom $\{SbW_8O_{30}\}$. Their findings demonstrated that $Na_4Ni_2Sb_2W_2$-$SbW_8$ inhibited the citric acid cycle by disrupting mitochondrial ATP synthesis, impairing the electron transport chain, and affecting the expression of mitochondria-associated proteins. This disruption in fatty acid β-oxidation and oxidative phosphorylation impairs metabolic functions *in vivo*, leads to excessive ROS generation, and ultimately inhibits tumor cell proliferation. Fraqueza et al. [77] compared the inhibitory effects of decanovanadate, decanoate, vanadate, tungstate, and molybdate on $Ca^{2+}$-ATPase. These substances inhibit ATP production, affect calcium ion accumulation in calcium pumps, disrupt cell signaling, and block mitochondrial active sites. The study results indicated that decanoate and vanadate were the most effective inhibitors. However, owing to the complex mechanisms through which POMs exert their antitumor and antidiabetic effects, further research is needed to fully elucidate their therapeutic potential, particularly for compounds such as $V_{10}$. ATP synthesis is also related to flavin mononucleotide (FMN) complexes. Mitsui [78] and Ogata [79] et al. investigated the inhibitory effect of PM-8 on tumor cells. The observed antitumor activity is likely attributed to the repeated redox cycling of the anionic form of PM-8, $[Mo_7O_{24}]^{6-}$ in tumor cells. This process inhibits ATP production and interferes with the electron transfer from NADH to coenzyme Q on the inner mitochondrial membrane. $[Mo_7O_{24}]^{6-}$ forms a 1:1 complex with FMN on this membrane. FMN is an electron carrier, facilitating the transfer of electrons from NADH to coenzyme Q [80], and the complex formed with $[Mo_7O_{24}]^{6-}$ inhibited ATP synthesis, thereby contributing to antitumor activity. Razavi et al. [81] synthsized a nanolipid-loaded Preyssler (NLP) containing $H_{14}[NaP_5W_{30}O_{110}]$ as a large kind of POM and investigated its *in vitro* antitumor activity against HepG2 cancer cells. The study demonstrated that Preyssler POM charges could cross the cell membrane into the cytoplasm via active transport, contributing to apoptosis. Furthermore, once inside the mitochondria, these POMs can form complexes with FMN that inhibit ATP synthesis.

### 4.3 Mitochondrial genes and cytokine and protein kinase expression

The production of excessive ROS by mitochondria makes mtDNA particularly vulnerable to genetic mutations caused by oxidative stress and cell cycle arrest. This, in turn, disrupts transcription, impairs mitochondrial electron transport, hinders the assembly of mitochondrial ATP synthase, and reduces ATP production [17], further causing damage to the proteins encoded by mtDNA. Li et al. [82] reported the successful synthesis of two POMs functionalized with glycine. They found that compound 1 exhibited superior antitumor activity compared to compound 2, primarily by impeding the S-phase of the cell cycle and inducing apoptosis. Additionally, studies have shown that in obese patients, there is a general downregulation of mitochondrial oxidative pathways, including reduced levels of mtDNA, mtDNA-dependent translational systems, and oxidative phosphorylation mechanisms, compared to lean patients [83]. In the context of decreased insulin secretion owing to T2D, Nile et al. [84] determined that mtDNA deletion in simulated MIN6 cells resulted from the transcriptional silencing of mitochondrial transcription factors. This led to reduced mtDNA gene transcription and translation, impairing mitochondrial respiration and ATP production, which in turn affected insulin secretion. It was predicted that mtDNA transcriptional deletion accelerated aging and increased the risk of developing T2D. In addition to hyperglycemia, other metabolites involved in insulin resistance or diabetic states include free fatty acids (FFAs), specific cytokines such as tumor necrosis factor-α (TNF-α), and various transcription factors (e.g., FOXO, Nrf2, AP-1, NF-κB, PPARS, and Bach 1). These factors collectively contribute to excessive ROS production by mitochondria, which then regulates the activation of these factors in a reciprocal manner [85]. ROS production induced by oncogenes leads to mitochondrial dysfunction and mtDNA mutations, which further increase ROS levels and promote apoptosis. Additionally, mitochondrial DNA instability, primarily resulting from oxidative damage to mtDNA and elevated mtROS production, contributes to cancer development [56].

Over the past 30 years, research on POMs for antidiabetic purposes has steadily increased. Our findings indicate that POMs exhibit substantial antioxidant effects *in vitro* [86]. Despite the growing body of research on POMs, there are currently few reports on their transport into mitochondria. The development of mitochondria-targeted antioxidants has become a major focus for scientists. However, the mechanisms behind the mitochondria-mediated antioxidant functions of POMs remain unclear. Previous studies have demonstrated that mitochondria contain numerous

miRNAs (mt-miRNAs) that are involved in regulating mitochondrial biosynthesis and function. This raises the question: Is the antioxidant mechanism of POMs related to mt-miRNAs? To explore this, we performed a preliminary study [9]. The results indicated that treatment with POMs led to considerable changes in the expression of both genes. By modulating mitochondrial miRNAs, POMs influence the development of various genes involved in mitochondrial regulation, including their mt-miRNA target genes in cultured cells. This action effectively reduces ROS and scavenges free radicals. ROS are known to damage epithelial cells by inducing oncogenes through hypermethylation or by changing histone modification and miRNA expression, which disrupts epigenetic patterns and contributes to tumorigenesis and cancer progression [87].

Numerous POMs induce oxidative stress, leading to interactions between intracellular components and free radicals. This process opens the mitochondrial permeability transition pore, which activates the apoptotic pathway [88]. Currently, an increasing number of teams are adding Sb to POMs to create unique POMs that contain Sb. For instance, Sun et al. [89] discovered that POMs ($SbW_9$) inhibited protein kinase phosphorylation by activating the expression of PTEN (tensin homolog)-deficient proteins, upregulating the pro-apoptotic gene Bax (Bax = Bcl-2-associated X, Bcl-2 = b-cell lymphoma-2), and downregulating the anti-apoptotic gene Bcl-2. These effects ultimately suppressed the proliferation of NSCLC cells and induced apoptosis. Similarly, the compound $\{Na_{0.7}M_{5.3}(H_2O)_2(ii)_2(Himi)(SbW_9O_{33})_2\}^{6-}$ (where M = $Ni^{II}$ (1) and $Co^{II}$ (2) and ii = imidazole) [90] inhibited cell proliferation by causing a delay in the S-phase of the cell cycle and inducing apoptosis. Recent research has increasingly focused on the synthesis of large POMs. Zhang et al. prepared the homochiral POM anion $\{CoSb_6O_4(H_2O)_3[Co(hmta)SbW_8O_{31}]_3\}^{15-}$. Their results demonstrated that this POM complex was more cytotoxic than $\{Sb_9W_{21}\}$ alone. The increased cytotoxicity was attributed to the induction of apoptosis pathways. Subsequent analysis of cellular DNA content revealed that the POMs inhibited cell proliferation by blocking the cell cycle and reducing the synthesis of protein complexes with high affinity, which impaired cellular functions, leading to apoptosis and inhibition of cancer cell proliferation [91]. Xiao et al. [92] reported the synthesis of a large Sb-containing POM, $H_{27}[Sb_{15}Tb_7W_3O_{29}(OH)_3(DMF)(H_2O)_6(SbW_8O_{30})(SbW_9O_{33})_5]\cdot 30H_2O$. This compound exhibited considerably enhanced antitumor activity owing to its ability to activate the p53-dependent apoptotic pathway, disrupt mitochondrial membrane function, and induce apoptosis. These findings offer new insights into incorporating bioactive elements into POMs for developing novel anticancer drugs. Additionally, there are ongoing studies investigating the expression of POMs in mitochondrial genes and proteins, as well as the design of new nanoparticles and clusters.

The study by Cao et al. [93] demonstrated the *in vitro* antiproliferative effects of POM@$SiO_2$ nanoparticles on MCF-7 cells through their synthesis. The authors detailed the apoptosis-promoting mechanism of POM@$SiO_2$ nanoparticles using flow cytometry, showing that as the nanoparticle concentration increased, the level of cleaved caspase 3 protein was considerably up-regulated while the Bcl-2 protein level notably decreased. The nanoparticles induced apoptosis by reducing Bcl-2 levels and enhancing caspase 3 expression, thereby exerting antiproliferative effects on MCF-7 cancer cells. Additionally, another study discussed the *in vitro* antiproliferative activity of $K_{12}[V_{18}O_{42}(H_2O)]\cdot 6H_2O$ ($V_{18}$) on MCF-7 and MDA-MB-231 cell lines, suggesting that $V_{18}$ might induce apoptosis in MCF-7 cells by up-regulating caspase-3 and down-regulating Bcl-2 [94]. Similarly, Wang et al. [95] characterized $(Himi)_2[Bi_2W_{20}O_{66}(OH)_4Co_2(H_2O)_6Na_4(H_2O)_{14}]\cdot 17H_2O$ (BWCN) through elemental analysis, infrared (IR) spectroscopy, thermogravimetric analysis (TGA), and single-crystal X-ray diffraction. They evaluated this compound as a chemotherapeutic agent in colon cancer HT-29 cells. The study found that BWCN inhibited cancer cell proliferation and induced apoptosis. In POMs-treated human colon cancer HT-29 cells, the expression of caspase-3 was examined. Results indicated that the expression of cleaved caspase-3 was considerably up-regulated after BWCN treatment. These findings suggest that BWCN promotes apoptosis in HT-29 cells by activating caspase-3. For effective treatment of spinal cord injuries, Rao et al. [96] used multifunctional selenium nanoparticles (SeNPs) modified with soluble polysaccharide-protein complexes (PTWs) and PG-6 peptides (PLGLAGs). These SeNPs were then loaded with therapeutic drugs tetrahexylsucrose ganglioside monosilane (GM1) and tetramethylpyrazine (TMP). By reducing the expression of anti-apoptotic proteins Bax and Bad (Bad = Bcl-2-associated cell death agonist) while enhancing the expression of pro-apoptotic proteins Bcl-2 and Bcl-xl (Bcl-xl = b-cell lymphoma-extra-large), SeNPs@GM1/TMP inhibited the p53 mitogen pathway. Furthermore, SeNPs prevented mitochondrial dysfunction, lowered ROS levels, and exhibited a preventive effect against apoptosis and G2/M phase arrest induced by tert-butyl hydroperoxide (t-BOOH). Aureliano et al. [97] provided a systematic review of polymetallic oxo vanadates (POVs) and their interactions with proteins or enzymes. The review focused specifically on the interactions between vanadates and antidiabetic proteins [98], which included the combination of metformin and vanadates to create a novel metformin decanoate (Metf-$V_{10}O_{28}$) [99, 100]. This compound was tested on a diabetes model in mice, and its mechanism of action was found to involve the inhibition of NADH oxidation by both the vanadium complex and metformin. Specifically, the vanadium complex inhibited the oxidation processes of mitochondrial complexes I, II, and III, while metformin also affected these complexes. Complexes II and III are involved in the oxidation of $FADH_2$, which is crucial for maintaining the electron transport chain and ATP production. However, the exact hypoglycemic effects require further investigation. Additionally, vanadate was shown to impede NADH oxidation and ATP production by disrupting the transfer of cytochrome C and cytochrome B1 in the electron transport chain [101]. Oliveri et al. [102] investigated acute porphyria in STZ-induced diabetic mice and studied the effects of vanadate treatment. They determined that vanadate reduces hepatocyte δ-aminolevulinic acid synthase 1 (ALAS1) expression. This reduction activates the phosphoinositide 3-kinase (PI3K)/Akt pathway, which in turn decreases the expression of the FOXO1-PGC-1α nuclear complex. These findings suggest that vanadate may also have potential therapeutic benefits for other diseases associated with diabetes.

## 5 Summary and outlook

Although we have compiled the latest findings on chemical pathways related to POMs and their effects on antitumor and antidiabetic disorders, a comprehensive, specific, and systematic analysis of their mechanisms remains incomplete. Further

exploration of cellular pathways and biomedical technologies may be necessary to fully elucidate these mechanisms. Future clinical studies should focus on promising mitochondria-targeted antioxidants [103, 104] to develop new therapeutic and preventive strategies. Antioxidants may offer therapeutic benefits in treating metabolic diseases such as insulin resistance, tumors associated with diabetes, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome. Additionally, several herbal remedies, such as curcumin and nanoparticles [105] containing POMs, have been determined to exhibit antioxidant properties [106]. These results may prove useful in the future [107]. Further research is needed to explore the synthesis, intrinsic antioxidant characteristics, and mitochondrial regulation of novel POMs, as well as the development of other biological properties. Because different types of POMs (e.g., Keggin-type, Dawson-type, and Anderson-type) possess different properties, attention should be paid not only to their antioxidant capabilities but also to their antitumor, anticancer, and other biological characteristics. In the rapidly evolving research, it is crucial to investigate how POMs interact with ROS, energy synthesis, and protein gene expression related to mitochondrial regulatory mechanisms. This includes examining various structures of POMs, such as those based on tungsten and molybdenum. Small, large, and clustered POMs, along with emerging types such as nanoplatforms, composites, and combined therapeutics, are gradually gaining attention. Owing to their diverse and rich properties, POMs offer considerable potential for development in the future, particularly in antitumor, anticancer, and antibacterial applications in biology and medicine.

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## Declaration of competing interest

The authors have no competing interests to declare that are relevant to the content of this article.

## Author contribution statement

S. L.: Conceptualization, investigation, writing manuscript. B. N. C.: Conceptualization, supervision. L. W.: Project administration, conceptualization, supervision. J. L.: Project administration, supervision. All the authors have approved the final manuscript.

## Informed consent

Not applicable.

## Ethics statement

Not applicable.

## Use of AI statement

None.

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