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The age of vanadium-based nanozymes: Synthesis, catalytic mechanisms, regulation and biomedical applications

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ABSTRACT

Nanomaterials with enzyme-mimic (nanozyme) activity have garnered considerable attention as a potential alternative to natural enzymes, thanks to their low preparation cost, high activity, ease of preservation, and unique physicochemical properties. Vanadium (V) is a transition metal that integrates the benefits of valence-richness, low cost, and non-toxicity, making it a desirable candidate for developing a range of emerging nanozymes. In this review, we provide the first systematic summary of recent research progress on V-based nanozymes. First, we summarize the preparation of V-based nanozymes using both top-down and bottom-up synthesis methods. Next, we review the mechanism of V-based nanozymes that mimic the activity of various enzymes. We then discuss methods for regulating V-based nanozyme activity, including morphology, size, valence engineering, defect engineering, external triggering, and surface engineering. Afterward, we outline various biomedical applications, including therapeutic, anti-inflammatory, antibacterial, and biosensing. Finally, we prospect the challenges and countermeasures for V-based nanozymes based on their development. By summarizing recent research progress on V-based nanozymes, we hope to provide useful insights for researchers to further explore their potential applications and overcome their existing challenges.

1. Introduction

In recent years, the field of nanotechnology has seen rapid development, and nanozymes, which are nanomaterial-based nanomimicase enzymes, have garnered significant attention [1]. Nanozymes are able to catalyze enzymatic substrates with a level of efficiency that rivals natural enzymes, while following enzyme kinetics under physiological conditions [2,3]. Compared with natural enzymes, nanozymes have advantages that natural enzymes lack, such as better stability and robustness under extreme conditions, ease to surface modification, versatility, lower manufacturing cost, and recyclability [4,5]. Since the discovery of intrinsic peroxidase (POD)-like activities of magnetic Fe_3O_4 nanoparticles (NPs) in 2007, various enzymes-like properties have been developed such as POD-, oxidase (OXD)-, catalase (CAT)-, superoxide dismutase (SOD)- and glutathione peroxidase (GPx)-like activities [5–7]. Based on unique catalytic activity and versatility, nanozymes have been applied in many fields such as biosensing [8–10], cancer therapy [11,12], antibacterial [13,14], and anti-inflammatory. Until now, reported nanozymes have included transition metals, noble metals and carbon-based materials. In general, the catalytic process of nanozymes involves the change of the valence state of the active center, so the transition metal nanomaterials with transformable multivalence state may have redox enzymes activity, among which the metals that have been widely reported include Fe, Mn, Ce, Co, Mo, Cu, V, Au, *etc.* [1]. Nano-catalytic systems composed of transition metals are among the most promising nanomaterials for environmental protection and biomedical applications, and vanadium (V)-based nanomaterials have received extensive attention in recent years due to their unique physicochemical and optoelectronic properties they exhibit [15,16].

V is known to be one of the forty trace elements essential to living systems for the regulation of normal life activities [17]. It is well known that V-based nanomaterials with multivalent states have a wide range of applications in electrocatalysis, organocatalysis, *etc.* [18,19]. Therefore, it is reasonably anticipated that the construction of transition metal V-based nanomaterials may mimic the catalytic activities of natural redox enzymes, including POD, SOD, CAT and GPx activities. To date, different types of V-based nanomaterials have been reported to mimic the activity of a variety of enzymes, mainly including zero-dimensional ma-

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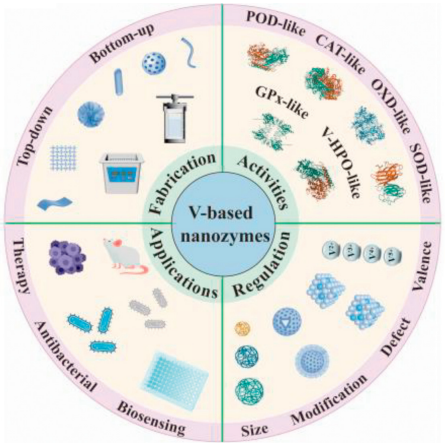

Fig. 1. Synthesis, classification, activity regulation and biomedical application of V-based nanozymes.

terials (VOx quantum dots/nanospheres) [20,21], one-dimensional materials (V_2O_5 nanorods/nanofibers/nanowires) [22–25] and two-dimensional materials (VC_2/VN_2/VS_2/VSe_2 nanosheets) [19,26-29]. In addition, the inherent physicochemical properties of V-based nanomaterials can be used for a variety of biomedical applications, such as photothermal/photodynamic effects for tumor therapy, large surface area loading of drug molecules for targeted therapies and cytotoxicity for antimicrobial therapy [29–31]. Therefore, there is great potential to design efficient V-based nanozymes for environmental, agricultural and biomedical applications.

In recent years, several reviews have summarized the research progress of transition metal nanozymes, including Mo [32], Fe [33], Ce [34] and Mn [35]. In this review, for the first time, a comprehensive review of the research progress of V-based nanozymes is presented (Fig. 1). The number of research articles focusing on V-based nanozymes in recent years has been depicted in Fig. S1 (Supporting information), reflecting the increasing interest among researchers in this field. Given the significant potential and value of V-based nanozymes in various applications, a comprehensive review is needed to provide a systematic summary of the research progress in this area. In this review, we first elucidate the method of synthesis based on V-based nanozymes. We then scrutinize the catalytic mechanism involving V-based nanozymes in mimicking natural enzymatic processes. Some of the factors used to regulate V-based nanozymes activity were also summarized. We further describe the application of V-based nanozymes in biomedical applications, including cancer therapy, anti-inflammatory therapy, antimicrobial, and biosensing. Finally, we present the current challenges encountered by V-based nanozymes and provide an outlook for future developments. We hope that this comprehensive review on V-based nanozymes will serve as a valuable resource for researchers and scientists working in the field of nanomaterials and catalysis, and that it will stimulate further research on the design, synthesis, and applications of V-based nanozymes in diverse fields.

2. Fabrication of V-based nanozymes

Nanozymes have shown promise in mimicking the catalytic activity of natural enzymes, but their activity levels remain inferior to those of natural enzymes that have evolved have undergone billions of years of evolution [36,37]. The high activity and substrate selectivity of natural enzymes are attributed to factors such as exposed catalytic sites, substrate binding pockets and high electron mobility [38]. Therefore, rational design and ingenious synthetic methods are essential to shorten or surpass natural enzymes. V-based nanozymes can be synthesized using two main strategies: bottom-up and top-down. The following section will introduce these two synthesis strategies in detail.

The bottom-up strategy refers to the synthesis of larger complex structures from smaller structures by self-assembly based on crystal anisotropy. The hydrothermal/solveothermal method is a widely used approach for synthesizing nanomaterials due to its simplicity of operation, cost-effectiveness, and controllability. The morphology and chemical properties of the products can be influenced by factors such as solvent type, temperature, and reaction time. For instance, Ma *et al.* prepared VO_x quantum dots (QDs) using vanadium trichloride (VCl_3) as the V source and ethanol as the solvent under hydrothermal conditions, and found that the size of the product varies significantly and is negatively correlated with temperature [39]. In addition, the pH of the reaction system has effect the yield of the product. The preparation of highly active VO_2 required hydrolysis of V acetylacetonate oxide ($VO(acac)_2$) under hydrothermal conditions. However, the precursor $VO(acac)_2$ was almost insoluble in water, which limited the large-scale preparation of VO_2. Nie *et al.* achieved an effective way to prepare monoclinic VO_2 (B) on a large scale by adding an appropriate amount of hydrochloric acid to the reaction system to improve the hydrothermal reaction [40]. Recently, the synthesis from bottom to top by electrospinning has also attracted a lot of attention. Niu *et al.* prepared $VO(acac)_2$-polyacrylonitrile nanofibers by electrospinning using polyacrylonitrile, $VO(acac)_2$ and DMF solutions as precursors,which were annealed at high temperature to obtain VN@CNFs with high active POD-like and SOD-like activities [41]. Bottom-up synthesis methods enable atomic-level control of nanomaterials, allowing for highly customized nanostructures. These methods are typically employed in the preparation of complex nanomaterials and nanocomposites.

Top-down fabrication techniques involve the conversion of structurally complex parent or bulk crystals into smaller nanosheets or nanodots [42]. These methods typically employ mechanical force-assisted exfoliation, chemical etching, and ionic intercalation. The chemical peeling method, for example, entails the use of etching agents to destroy the intermediate layer of the precursor, thereby weakening the van der Waals forces between layers. Subsequently, ultrasound is used to disperse the multilayer nanosheets into a single layer. Feng *et al.* synthesized two-dimensional (2D) V_2C MXene by combining the stripping method with intercalation program synthesis [26]. Using V_2AlC as the precursor, hydrofluoric acid (HF) etching was used to selectively remove the intermediate aluminum layer, which could make multi-layer V_2C MXene exhibit regular hexagonal lattice characteristics. Then, utilizing tetramethylammonium hydroxide (TPAOH) as an intercalating agent, a V_2C-MXene monolayer with a thickness of about 2.7 nm was formed by ultrasound. Although the prepared V_2C MXene has a good layered structure, HF is a highly corrosive and dangerous substance. Thus, safer and more efficient green methods are still required to protect the environment from pollution and improve the safety of experiments. In V-based nanozymes synthesis, top-down methods offer flexibility and precision in controlling size, shape, and composition, particularly for nanosheet or nanodot structures. However, these methods can be cost-prohibitive, requiring expensive equipment and materials, and face challenges in scaling up for large or complex structured nanomaterials.

Because of its high abundance on Earth, V has the potential to prepare large-scale preparations of V-based nanozymes. However, many difficulties still exist in the large-scale preparation of V-based nanozymes, and new preparation methods need to be explored for various applications.

3. Catalytic mechanisms of V-based nanozymes

V-based nanomaterials are well-established catalysts due to their variable valence states and advanced preparation methods. It has been shown that V-based nanozymes express a variety of natural-like enzymatic activities such as POD-, OXD-, SOD- and CAT-like. In this chapter, we describe the different enzymatic mechanisms exhibited by V-based nanozymes, and present a classification of their catalytic activities (Table S1 in Supporting information).

3.1. Peroxidase activity of V-based nanozymes using H_2O_2 as a substrate

3.1.1. POD-like activity

The peroxidase family occupies a large part of nanozymes, which catalyze the oxidation of substrates by breaking down H_2O_2. More than half of the nanozymes exhibited POD-like activity [43]. Thus far, various mechanisms have been proposed to explain the POD-like catalytic activity of these nanozymes, which can be broadly divided into two types: Fenton/Fenton-like reactions and electron transfer [14].

Fenton/Fenton-like reaction, which are catalyzed by low-valence metal ions, generate the most harmful $^{\bullet}OH$, by breaking down H_2O_2 [44]. For example, Chen *et al*. explored the possible mechanism of POD activity of TA@VOxNSs, and proposed that the low-valence state V in TA@VOxNSs is able to undergo a Fenton-like reaction to produce $^{\bullet}OH$ [45]. The low-valence state V^{4+} is oxidized by H_2O_2 to V^{5+} and generates $^{\bullet}OH$. Meanwhile, H_2O_2 and $^{\bullet}OH$ combine to form $OH_2^{\bullet}$. The high-valence V^{5+} can then be reduced to V^{4+} by H_2O_2 and $OH_2^{\bullet}$, forming an effective cyclic process. The possible catalytic processes of TA@VOx NSs for H_2O_2 are as follows Eqs. 1–4.

$$V^{4+} + H_2O_2 + H^+ \rightarrow V^{5+} + {}^{\bullet}OH + H_2O \quad (1)$$

$${}^{\bullet}OH + H_2O_2 \rightarrow HO_2^{\bullet} + H_2O \quad (2)$$

$$V^{5+} + H_2O_2 \rightarrow V^{4+} + HO_2^{\bullet} + H^+ \quad (3)$$

$$V^{5+} + HO_2^{\bullet} \rightarrow V^{4+} + H_2O + O_2 \quad (4)$$

André *et al*. demonstrated that V_2O_5 nanowires catalyzes the oxidation of the substrate 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) *via* an electron transfer mechanism [46]. Fig. 2A shows that V coordination sites on different crystallographic planes of V_2O_5 nanowires vary in their arrangement. Specifically, the V coordination geometry on the [010] crystalline face of V_2O_5 nanowires resembles that of the natural V haloperoxidases (V-HPO) active site, with the V atom and bridging oxygen atom acting as Lewis acid-base sites, respectively. The reaction starts with H_2O_2 attacking the active site of V_2O_5 nanowires to produce a peroxide intermediate, followed by nucleophilic attack by ABTS on the V peroxide intermediate and production of the oxide $ABTS^{*+}$ with one electron loss. Moreover, the V on the [001] face of the surface has a saturated oxygen coordination with weak adsorption to the substrate, leading to selective oxidation of ABTS, while the [110] face is capable of complete oxidation due to the breakage of the V-O bond.

3.1.2. GPx-like activity

GPx is a crucial enzyme found in living organisms and can effectively catalyze the reduction substrate glutathione (GSH). This process reduces toxic H_2O_2 to H_2O, protecting biofilms and other cellular components from damage by reactive oxygen species (ROS) [48,49]. To date, although many nanomaterials have been reported to mimic GPx-like activity, nanozymes with V as the catalytic center generally have the highest GPx-like activity, including metal oxides, metal-organic frame (MOFs), and single-atom nanozymes [47,50,51]. Zhang *et al.* [51] prepared several single-atom nanozymes containing different catalytic centers, including RhN_4, VN_4, and Fe-Cu-N_6. VN_4 exhibited a 7-fold higher activity than natural GPx, while RhN_4 and Fe-Cu-N_6 lacked GPx-like activity. D'Silva *et al*. [47] experimentally demonstrated that V_2O_5 nanowires (Vn) exhibited significant antioxidant activity under physiologically relevant conditions, and found that Vn can use GSH as a cofactor to eliminate H_2O_2 in the system without affecting the reduction process of glutathione disulfide (GSSG) conversion to GSH. In the catalytic process shown in Fig. 2B, the highly exposed V oxygen active center is susceptible to attack by H_2O_2 to produce peroxy intermediate **1**. GSH can then attack the active intermediate **1** to form the unstable sulfenate-bound intermediate **2**, which upon hydrolysis produces glutathione sulfite (**3**, GSOH) and dihydroxy intermediate **4**. Finally, intermediate **4** reacts with H_2O_2 back to the first intermediate for the next cycle. This catalytic process was similar to that of natural GPx, where by-products **3** and **5** were also characterized and confirmed.

3.1.3. V-HPO-like activity

The antibacterial effects of natural V-HPO found in certain seaweeds have been extensively explored for the development of antibacterial coatings [52]. These V-HPOs are able to catalyze the production of the corresponding hypohalous acids (HOX) from various halogen ions in the ocean using H_2O_2 as an oxidant. After revealing the inherent POD-like activity of V_2O_5 NWs, Tremel group further found that V_2O_5 NWs also had the ability to mimic halogenoperoxidase and can be used as a substitute for natural V-HPOs to prevent biofouling on marine vessels surfaces [16]. Based on their proposed peroxidase mechanism, the group suggested that V_2O_5 NWs mimic haloperoxidases by exposing lattice planes with a local V coordination geometry similar to the active site of V-HPOs. Here, V acts as a reactive site to adsorb H_2O_2 to produce intermediate peroxides. The generated peroxide species reduces the electron density of the oxygen atom, which facilitates the attack of halide ion to produce HOX in the absence of an organic acceptor, as shown in Fig. 2C.

3.2. OXD-like activity

Oxidases typically consume O_2 to catalyze the substrate for redox reactions, and O_2 as an electron acceptor can be reduced to H_2O_2 *via* the $2e^-$ pathway or to H_2O *via* the $4e^-$ pathway [53]. To date, V-based nanozymes with oxidative activity have attracted significant attention in the field of biosensing and antibacterial. Hu *et al*. synthesized a 2D V nitride (V_2N) monolayer membrane using an improved chemical peeling process, which generates abundant ROS [19,54]. Experiments proved that V_2N had excellent OXD-like activity, and its mechanism was further elucidated. Low-valence V (V^{3+}, V^{4+}) is oxidized to the high-valence state by O_2 to produce H_2O_2, which then reacts with the low-valent V in a Fenton-like reaction to produce the lethal $^{\bullet}OH$. The process is shown in Eqs. 5 and 6. In addition, H_2O_2 can also undergo the process shown in Eq. 2, producing $HO_2^{\bullet}$. Eventually the high-valence state of V is able to return to the low-valence state by a process similar to Eqs. 3 and 4. After the catalytic reaction, the authors observed a decrease in the proportion of low-valent V and an increase in the proportion of high-valent V, indicating that low-valent V participated in the simulation of oxidase activity.

$$2V^{4+} + V^{3+} + 2O_2 + 4H^+ \rightarrow 3V^{5+} + 2H_2O_2 \quad (5)$$

$$V^{4+} + V^{3+} + 3H_2O_2 + 3H^+ \rightarrow 2V^{5+} + 3H_2O + 3{}^{\bullet}OH \quad (6)$$

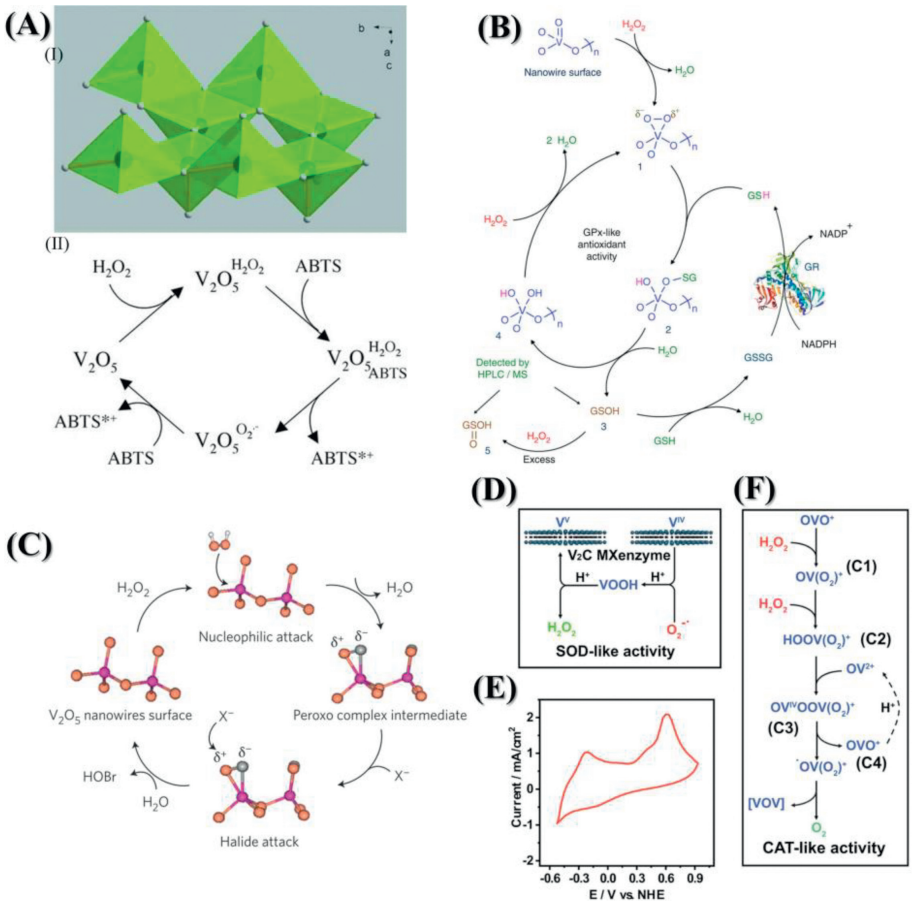

Fig. 2. (A) (I) Single layer from the V_2O_5 structure. (II) Proposed mechanism for the formation of ABTS with the formation of a V peroxidase complex intermediate and oxidation attack of ABTS and release of the product ($ABTS^{*+}$). Copied with permission [46]. Copyright 2011, Wiley Publishing Group. (B) Schematic diagram showing the mechanism of Vn GPx-like activity. Copied with permission [47]. Copyright 2014, Springer Nature. (C) V-HPO-like activity mechanism for the V_2O_5 nanowires. Copied with permission [16]. Copyright 2012, Springer Nature. (D) Schematic diagram of the mechanism of 2D V_2C MXenzyme SOD-like activity. (E) V_2C MXenzyme redox potential measured by cyclic voltammetry. (F) Schematic diagram of the mechanism of 2D V_2C MXenzyme CAT-like activity. Copied with permission [26]. Copyright 2021, Springer Nature.

3.3. SOD-like activity

Natural SOD is an enzyme that protects the body from oxidative stress damage by catalyzing the disproportionation of $O_2^{\bullet-}$ into O_2 and H_2O_2. Recent studies have shown that several V-based nanozymes with SOD enzymatic activities have been widely used in biomedical applications. Feng *et al.* [26] discovered that 2D V_2C with multispecies enzymatic activity can be used to scavenge ROS to alleviate inflammatory diseases. The multivalent V on the surface of V_2C is capable of catalyzing the conversion of $O_2^{\bullet-}$ to H_2O_2 by mimicking SOD-like enzymatic activity. Specifically, V^{4+} on the surface of V_2C captures $O_2^{\bullet-}$ with the assistance of H^+ to produce the VOOH intermediate, while electrons are transferred from V^{4+} to $O_2^{\bullet-}$. Subsequently, VOOH releases H_2O_2 with the help of another H^+ and produces V^{5+} (Fig. 2D). In general, nanomaterials simulating SOD-like enzymatic activity are thermodynamically required to satisfy a redox potential between $E(O_2/O_2^{\bullet-})$ and $E(O_2^{\bullet-}/H_2O_2)$ [55]. The redox potential of V_2C was further measured to be -0.11 V, which is between $E(O_2/O_2^{\bullet-}) = 0.91$ V and $E(O_2^{\bullet-}/H_2O_2) = -0.81$ V, thus confirming that V_2C has a simulated SOD-like enzyme activity (Fig. 2E).

3.4. CAT-like activity

CAT plays a crucial role in maintaining the oxidative balance in living systems. Some V-based nanozymes have been shown to mimic CAT activity by catalyzing H_2O_2 to generate O_2 and H_2O. Feng *et al.* [26] investigated the CAT-like activity of V_2C with a laminar structure and elucidated the underlying mechanism (Fig. 2F). Specifically, H_2O_2 oxidizes the V^{5+} species on the surface of V_2C to form the **C1** monooxovanadium species $OV(O_2)^+$. **C1** continues to be reacted by another molecule of H_2O_2 to produce the **C2** diperoxovanadium species $HOOV(O_2)^+$. The lower valence vanadium-oxygen species (OV^{2+}) further reacts with **C2** to produce a vanadium species with an m-peroxo bridge **C3**, which undergoes an intramolecular redox reaction to release the peroxyl radical $^{\bullet}OV(O_2)^+$. Eventually, $^{\bullet}OV(O_2)^+$ decomposes to produce oxygen and [VOV] which forms the next cycle.

It is evident that vanadium exhibits a pronounced affinity for oxygen, resulting in the formation of diverse vanadium oxide intermediates. These intermediates alter the charge distribution surrounding vanadium, which in turn endows it with the ability to emulate multiple enzymes, enabling it to react with a broad range of substrates.

4. Regulation of catalytic activity of V-based nanozymes

The catalytic activity of V-based nanozymes is governed by various factors such as their size, morphology, surface valence, defect engineering, external conditions and surface modification (Fig. S2 in Supporting information). In this section, we will discuss these factors in detail.

4.1. Size and morphology

Surface-active sites play a crucial role in determining the catalytic activity of nanozymes, which are highly dependent on the size and morphology of the materials. In general, nanozymes with larger specific surface areas and more exposure to active sites have better catalytic performance. On the other hand, smaller nanozymes exhibit higher enzyme-like activity due to their greater diffusion rates and smaller spatial efficiency, which can result in a stronger catalytic efficiency [14]. Li *et al*. [56] synthesized mesoporous vanadium oxide nanospheres (MVON) of different sizes with POD-like activity. The size of MVON-x (x is the amount of F127) obtained by the self-assembly method is inversely proportional to the amount of Pluronic F127 (surfactant). Despite MVON-0.3 having the smallest size, MVON-0.2, which had the largest surface area and the smallest pore size. Importantly, MVON-0.2 exhibited the highest OXD-like and POD-like activities. This indicates that MVON with a larger specific surface area can expose more active sites for enhanced activity, with less dependence on size effects.

Interestingly, Vernekar *et al*. [47] discovered that V_2O_5 nanomaterials with different morphologies displayed opposite enzyme-like activities. V_2O_5 nanowires (Vn) exhibited GPx-like activity and were able to significantly scavenge intracellular ROS significantly. Conversely, V_2O_5-bulk (Vb) and V_2O_5-foam (Vf) were capable of causing an increase in cellular peroxides under the same conditions.

Surface facets play an important role in determining the surface energy and reactivity of nanoparticles. It has been observed that nanoparticles with different morphologies may expose different surface facets [57]. For instance, Mugesh's group synthesized four different morphologies of V_2O_5 nanocrystals with significant GPx activity [58]. It was found that the specific surface area of different morphologies had a negligible effect on GPx activity, while the material exposed to different surfaace facets had a greater effect on the enzyme-like activity. Specifically, V_2O_5 nanospheres composed mainly of [100] and [010] facets have stronger GPx-like activity than V_2O_5 composed of other crystalline facets. Overall, these findings suggest that the surface facets, surface area and morphology of V-based nanozymes play a crucial role in determining their enzyme-like activity.

4.2. Valence engineering

Valence engineering is considered to be an important factor affecting nanozyme activity [14]. For V-based nanozymes, multiple valence states, including V^{2+}, V^{3+}, V^{4+}, and V^{5+}, have been identified. As discussed in catalytic mechanisms of V-based nanozymes, these valence states can be manipulated to produce a variety of vanadium-oxygen intermediates, which can satisfy the requirement for V-based nanozymes to exhibit multiple enzymatic activities. Recently, Zheng *et al*. [59] investigated the effect of vanadium valency on multiple enzyme activities, including POD-like, OXD-like, and CAT-like, by adjusting the ratio of precursor V_2O_5 and $NaBH_4$ during synthesis of vanadium oxide nanozymes. Their findings showed that as the ratio of $NaBH_4$ increased, the high-valent V in V_2O_5 gradually transformed to low-valent V, resulting in vanadium oxides with higher POD-like and OXD-like activities, which may be attributed to the more efficient catalysis of ROS production from H_2O_2 or O_2 by the lower valence vanadium, as summarized in catalytic mechanisms of V-based nanozymes. Additionally, the CAT-like activity was found to be proportional to the higher valence V, indicating that V^{5+} plays a key role in exerting the CAT-like activity of vanadium oxides.

4.3. Defect engineering

Defect engineering of nanozymes has emerged as a promising strategy to enhance their enzyme-like activity and catalytic specificity [60]. Among various types of defects, oxygen vacancies are the most common defect engineering in metal oxides [38,61]. For instance, Hou *et al*. [62] reported that higher oxygen vacancy V_6O_{13} (Od-V_6O_{13}) showed better halogenated peroxidase mimetic activity and photothermal effects than V_6O_{13}. Density functional theory (DFT) calculations indicated that H_2O_2 and Br^- have lower adsorption free energy on Od-V_6O_{13}, which contributes to enhanced decomposition of H_2O_2 and formation of HBrO.

In addition to oxygen vacancies, researchers have developed several efficient strategies for defect-containing V-based nanozyme, including metal doping and nitrogen doping. Heteroatom doping can modulate a variety of physicochemical properties of V-based nanozymes to enhance enzyme-like activity, *e.g.*, band gap, charge distribution, valence state and oxygen vacancy concentration [27,63–67]. In V_2O_5, the V-d_z^2 electron in the V center readily formed strong sigma bonds with the O-p_z orbital [68]. Therefore, V as the catalytic center of V_2O_5 readily interacted with the oxygen atom in H_2O_2 and limited the dissociation of the oxygen intermediate. To facilitate the dissociation of oxygen intermediates and accelerate the catalytic kinetics of V_2O_5 nanozymes, Li *et al*. [64] reconstituted the *d* electrons in the V center by doping the Zn atom. Compared with V^{5+} (V_2O_5), Zn^{2+} has redox inertness and lower electronegativity, so the construction of Zn-O-V bridge can realize the charge transfer between Zn to V. The *d* electrons in Zn^{2+} pass through the Zn-O-V bridge, filling the V-d_{yz} orbital with charge near the Fermi energy level, which limited the formation of sigma-bonds between the V-d_z^2 and O-p_z (H_2O_2) orbitals. Zn-doped V_2O_5 exhibited outstanding peroxidase activity by optimizing the adsorption and dissociation of oxygen intermediates.

4.4. External triggers

Previous research has established that the performance of V-based nanozymes can be influenced by a variety of external factors, including pH, ions, light, and sound waves [69]. It is generally accepted that acidic conditions are more favorable for the simulation of oxidases such as OXD and POD, while neutral conditions favor the simulation of reductases like SOD and CAT [70].

Illumination is largely able to significantly affect the activity of nanozyme-like enzymes with band gaps of different widths, thus having a great impact on their biomedical applications. Yang *et al*. prepared highly biocompatible photosensitizer VNPBs nanosheets and found that these nanosheets can promote the production of ROS under laser irradiation [71]. V^{3+} releases free electrons and produces V^{4+} when irradiated by near infrared (NIR) light. The free electrons are then captured by oxygen and undergo photochemical reactions, leading to the production various ROS. Moreover, the photothermal effect can also trigger the generation of ROS by inducing oxygen in solution. Additionally, V-based nanozymes with a laminar structure can act as aphotic acoustic sensitizers to generate ROS under ultrasound irradiation [27,72].

4.5. Surface engineering

The catalytic activity of nanozymes primarily stems from the exposed active sites on their surface, and the surrounding environment of these active sites exerts a significant impact on their catalytic activity. Surface engineering have been applied to tune their various properties, such as improving colloidal stability, targeting ability, catalytic activity, and biocompatibility [73,74]. For instance, Song *et al*. found that fluoride significantly enhanced the OXD-like activity of V_6O_{13}-rGO [75]. F overlay on V_6O_{13}-rGO surface can

change the surface charge of the nanozyme and thus increase the electron transfer rate between the substrate and the nanozyme.

5. V-based biomedical applications

5.1. Therapy

The global burden of cancer is a major public health concern, with high incidence and mortality rates in virtually every country worldwide [76–78]. The development of safe and effective cancer treatments is thus of utmost importance, as traditional therapies are often associated with significant side effects and drug resistance issues [79,80]. In recent years, several emerging therapeutic approaches, including chemodynamic therapy (CDT) [81], photothermal therapy (PTT) [82], photodynamic therapy (PDT) and sonodynamic therapy (SDT) [83], have shown great promise for the minimally invasive and effective treatments of oncological diseases. V-based nanozymes have a attracted significant attention due to their multispecies enzymatic activity, good photothermal effect and tunable band gap, all of which contribute to their potential as powerful antitumor agents [45].

5.1.1. Tumor therapy

CDT is a promising anti-tumor strategy that relies on the Fenton or Fenton-like reactions to convert H_2O_2 in the tumor microenvironment to highly cytotoxic hydroxyl radicals, which induce oxidative damage to tumor cells [84,85]. Nie *et al.* designed 2D V-based nanosheets (V NSs) to enhance the photoelectric Fenton-like effect and improve the efficacy of CDT in treating tumors (Fig. S3A in Supporting information) [86]. The low-valent V on the surface of V NSs catalyzes the conversion of H_2O_2 to highly toxic $^{\bullet}OH$ to kill tumor cells. However, because CDT has strict requirements for response conditions and other factors, it is often difficult to solve tumor problems on its own and is often used in concert with other treatments to treat tumors [87]. V NSs have a narrow band gap, which allows for strong absorption at NIR and enhances thermal and electron conversion, leading to a significant increase in ROS production. Furthermore, V NSs can enhance the therapeutic effect on tumors by eliminating GSH (Figs. S3B and C in Supporting information). *In vitro* experiments have demonstrated that a single drug injection and a single NIR irradiation can achieve tumor eradication (Figs. 3D and E in Supporting information). More importantly, after hemolysis assays and blood tests, V NSs have been shown to have good hemocompatibility together with biosafety, and inorganic materials in tumor cells can be gradually removed from the body without causing harm (Figs. S3F and G in Supporting information). The observed degradation of vanadium-based nanomaterials to vanadate *in vivo* can be attributed to their inherent chemical nature.

Due to the limited H_2O_2 concentration in tumor tissues, it is difficult to achieve effective tumor treatment by CDT alone [87]. PTT is another tumor treatment process that converts light energy into heat energy through near-infrared light irradiation, which can effectively eliminate tumor cells by aggregating materials with photothermal conversion properties at the tumor cells through targeted identification technology [88]. The combination of CDT and PTT produces a synergistic effect that can effectively inhibit tumor growth. Chen *et al.* prepared a hybrid of natural polyphenol tannins (TA) and mixed-valence V oxide nanosheets (TA@VOxNSs) by a one-step assembly method [45]. The assembly of TA increased the NIR absorption of TA@VOxNSs, which enabled them to effectively play the role of PTT, converting light energy into heat energy. It is worth noting that VOx had multiple valence states that catalyze the conversion of H_2O_2 to the more toxic $^{\bullet}OH$. *In vitro* experiments verified that the lethality of TA@VOxNSs-treated MDA-MB-231 cells and 4T1 cells could reach more than 80% with better anti-tumor effect under the effect of laser irradiation and H_2O_2. TA@VOxNSs could achieve the synergistic effect of CDT/PTT which significantly improves the efficiency of tumor treatment. At present, CDT/PTT synergistic therapy provides a more ideal way for efficient treatment of tumors and offers more possibilities for the application of V oxide in tumor therapy [89].

SDT is another novel treatment for cancer that generates singleline oxygen and thus seizes electrons from tumor cells in the presence of ultrasound and acoustic sensitizers [90,91]. Cheng *et al.* doped vanadium (V) into TiO_2 to prepare a novel acoustic sensitizer V-TiO_2 nanospin for combined SDT-CDT of tumors (Fig. S4A in Supporting information) [72]. The doping of V reduced the band gap of V-TiO_2 nanospindles, improving the efficiency of ROS generated under ultrasound. Interestingly, the introduction of V also gave the V-TiO_2 nanospindles a Fenton-like effect that not only generates ROS to play an important role in CDT, but also further amplifies intracellular oxidative stress by depleting glutathione (Fig. S4B in Supporting information). *In vivo* and *in vitro* experiments have shown that V-TiO_2 nanospindles can be efficiently applied to tumor therapy. Their team also developed Fe doped VS_2 nanosheets (NSs) have also been developed as an effective acoustic sensitizer for the treatment of tumors [27]. The intrinsic Fenton-like reaction of Fe enhances Fe-VS_2 NS POD-like activity and therefore enhances the therapeutic effect of CDT combined with SDT. Fe-VS_2-PEG with a lamellar structure can be used for PA imaging and MRI imaging due to Fe doping (Figs. S4C and D in Supporting information). Overall, the combination of CDT with PTT or SDT provides a more ideal way for efficient treatment of tumors and offers more possibilities for the application of V-based nanozymes in tumor therapy.

5.1.2. Anti-inflammatory

ROS are signaling molecules composed of a variety of highly reactive substances containing oxygen. ROS are mainly composed of $O_2^{\bullet -}$, H_2O_2, $^{\bullet}OH$, and $^1O_2$ [92]. High levels of ROS often cause oxidative damage to intracellular biomolecules, inducing the development of various pathological diseases and even cell necrosis, and their levels are higher in the intracellular environment of tumor cells [93]. Low levels of ROS are essential for the regulation of normal intracellular physiological functions [94]. Therefore, reducing and maintaining normal intracellular ROS levels have become an attractive strategy for treating pathological diseases such as inflammation. V-based nanozymes possessing enzymatic activities of GPx-like, CAT-like, and SOD-like efficiently scavenge intracellular ROS and may be developed as potential anti-inflammatory drugs.

The efficiency of SOD enzyme significantly affects the amount of ATP production, which is closely related to various neurological-related diseases [95]. SOD enzymes regulate intracellular ATP levels by maintaining mitochondrial function. When SOD enzymes lose their activity, the mitochondrial membrane potential decreases rapidly, which leads to impaired mitochondrial function and greatly reduced energy production. Singh *et al.* found that the specific SOD-like enzyme activity of cerium vanadate ($CeVO_4$) nanozyme can replace natural SOD1 (Fig. S5A in Supporting information) [96]. CeO_2 and V_2O_5 nanozymes exhibit high CAT and GPx activities, respectively, whereas $CeVO_4$ has only SOD-like activity. Compared with V_2O_5 nanozymes, which can mimic GPx, $CeVO_4$ can replace natural SOD to reduce cell superoxide level as well as restore mitochondrial membrane potential and cell vitality. Other ROS reduction nanozymes classes, including CeO_2, NiO, MnO_2, and V_2O_5, have been reported to be less effective than $CeVO_4$. This can be attributed to the unique and specific SOD-like activity exhibited by $CeVO_4$, which serves as a mimetic catalyst. In addition, $CeVO_4$ can restore the levels of anti-apoptotic proteins (Bcl-2, Bcl-xL and Mcl-1) in SOD1-deficient cells and improve cell survival. These

findings indicate the promising potential of $CeVO_4$ nanozymes in ROS regulation and mitochondrial function restoration.

V-based nanozymes with GPx-like activity have been used in the treatment of various diseases by depleting intracellular H_2O_2 levels [47]. Inspired by protein engineering, Wei group used the ligand of MOF to modulate the GPx mimicking activity of MIL-47(V) [50]. The group introduced substituents with varying electronic effects into the MOF ligand to produce MIL-47(V)-X, with X representing the different ligand substituents (Fig. S5B in Supporting information). The results showed that MIL-47(V)-NH_2 formed by -NH_2 substituted ligand had the highest GPx-like activity. *In vitro* studies have demonstrated that MIL-47(V)-NH_2 can protect cells from oxidative damage by regulating the balance of reactive oxygen species metabolism, resulting in a significant reduction of intracellular ROS levels. Moreover, clinical trials have shown that MIL-47(V)-NH_2 has a broad-spectrum anti-inflammatory effect in various inflammatory models, including otitis and colitis [50].

Hu *et al*. used a 2D V_2C nanozyme with multiple enzymatic activities for the treatment of ischemic stroke [97]. Few-layer V_2C simultaneously mimics four native enzyme activities, including SOD, CAT, POD, and GPx, enabling it to effectively scavenge various ROS and protect neural cells (Fig. S6A in Supporting information). The synergistic action of multiple enzymatic activities enables V_2C MXene to efficiently scavenge various ROS and protect neural cells. The *in vivo* treatment of ischemic stroke injury using V_2C MXene showed a substantial reduction in cerebral infarct volume, demonstrating its highly effective antioxidant capacity (Fig. S6B in Supporting information).

5.2. Antibacterial

As early as 2012, V-based nanozymes were used for antimicrobial applications [16]. Inspired by vanadium halide peroxides to combat marine pollution, Natalio *et al*. found that V_2O_5 nanowires could be used as an alternative to V-HPOs to prevent marine biofouling [16]. V_2O_5 nanowires were found to overcome the inherent limitations of traditional functional inorganic V-HPOs, such as poor solubility, the requirement of extremely low pH, and high cost, to catalyze Br^- and H_2O_2 and produce HOBr under seawater conditions (pH 8–8.2 and extremely low H_2O_2 concentration). HOBr reacts with H_2O_2 to produce highly toxic $^1O_2$, which exhibits high bactericidal properties against both Gram-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus aureus*) bacteria. The authors further verified the catalytic activity of V_2O_5 *via* simulated experiments where one stainless steel plate coated with V_2O_5 and another without V_2O_5 were placed under simulated marine conditions, respectively. And after 60 days, the stainless steel plate coated with V_2O_5 had extremely high bacterial scavenging rate with no signs of biological contamination compared to the stainless steel plate without V_2O_5 (Fig. S7A in Supporting information). And compared with other IMO-approved anti-fouling products, V_2O_5 nanowires are less harmful to other organisms in the ocean. With its low cost, significant antibacterial effect, and good biosafety, V_2O_5 nanowires have the potential to replace current commercial antibacterial agents for widespread use in life [98].

Bacterial infections pose a serious threat to human health, although a variety of antibiotics have been developed to treat bacterial infections. Unfortunately, increased bacterial resistance poses a challenge for new antibacterial drugs. In general, nanozymes with POD-like or OXD-like activity are competent to produce highly lethal ROS to kill bacteria effectively [99]. Therefore, nanozymes have great potential to replace antibiotics for the treatment of bacterial infections while avoiding the development of bacterial resistance [31,56]. Sun *et al*. developed V nitride MXene (V_2N) by chemical stripping, which provide to be an effective anti-infection method (Fig. S7B in Supporting information) [19]. VN_2 exhibited both OXD-like and POD-like dual enzymatic activities at pH levels similar to the biofilm microenvironment. In addition, the lamellar structure of VN_2 possesses a significant advantage in terms of its large specific surface area and narrow band gap, allowing for efficient photothermal conversion in the NIR-II window. The photothermal efficiency not only provided high temperature to kill bacteria but also the catalytic activity of the nanozyme was greatly enhanced by the photothermal effect. *In vitro* antimicrobial assay on mice revealed that the combination of $V_2N + H_2O_2 +$ NIR-II was effective in promoting abscess healing within 10 days (Figs. S7C–E in Supporting information). VN_2, with its biosafety, has the potential to replace antibiotics in the treatment of bacterial infections.

5.3. Biosensing

V-based nanozymes have gained widespread attention in the field of biosensing and detection due to their excellent enzymatic activity. Studies have shown that V-based nanozymes are typically generated using enzymatic activity to catalyze reactions and detect biologically active molecules by detecting color changes in the substrate. In addition, V-based nanozymes can be used for biomarker detection.

5.3.1. Biological small molecules

H_2O_2 is one of the metabolites of various biological small molecules, such as glucose, cholesterol and sarcosine [100–102]. Moreover, H_2O_2 is also a substrate catalyzed by POD-like enzymes. Based on the high POD-like activity of V-based nanozymes, a variety of sensitive V-based nanozymes biosensors have been developed for the detection of biomolecules. In general, chromogenic substrates, such as 3,3′,5,5′-tetramethylbenzidine (TMB), *o*-phenylenediamine (OPD) and ABTS, are often used to indicate POD-like and OXD-like activities. For instance, Huang *et al*. synthesized V disulfide nanosheets (VS_2 NPs) with POD-like activity by hydrothermal method [103]. The VS_2 NPs relied on their POD-like activity to catalyze the conversion of H_2O_2 to $^{\bullet}OH$, which caused the color reaction of TMB, and thus the intensity of the visible absorption peak at 652 nm can be used to assess the H_2O_2 content (Fig. S8A in Supporting information). The sensor has a low detection limit of 1.54 μmol/L for glucose, and it can indirectly reflect the amount of glucose by catalyzing the production of H_2O_2 from glucose using glucose oxidase (GOx).

Although many nanomaterials with peroxidase activity have been reported to detect glucose, natural GOx is still required for the construction of the sensor, which is expensive. Ding *et al*. found that V_2O_5 nanobelts possess both POD-like and GOx-like activities and constructed a non-enzymatic online relational assay platform (OODP) for continuous monitoring of rat brain glucose based on a cascade reaction of dual enzyme activities (Fig. S8B in Supporting information) [104]. The enzymatic cascade reaction in the V_2O_5 nanoribbon reduces the intermediate product transfer and increases the reaction rate based on the proximity effect and *in situ* reaction. The authors constructed an optical glucose online analysis system without natural enzymes and continuously monitored glucose in the striatum of the live rat brain (Figs. S8C and D in Supporting information). The OOPD platform allows for highly stable and sensitive detection of glucose concentrations in the central nervous system (CNS), and the data obtained are consistent with previously reported colorimetric methods.

5.3.2. Biomarkers

The detection of biomarkers can reflect alterations that occur in living systems, organs, tissues and cells. Chen *et al*. designed VS_2 NS with POD-like activity and few layers for lateral flow immunochromatographic analysis (LFIA) [105]. Interestingly, due to the large specific surface area and electrostatic effect of

VS_2 NS allow for the easy adsorption of proteins on the surface of the material. The authors selected 17β-estradiol (E2), which can reflect male genital damage, as a biomarker. As shown in Fig. S9A in Supporting information, the T-line appears intense blue in the presence of E2, and the signal can be detected semi-quantitatively by the naked eye or quantitatively by analyzing the grayscale. Compared to commercial Au NPs-based LFIA, VS_2 NS achieves extremely low detection limits ($LOD_{VS_2NS} = 0.065$ ng/mL, $LOD_{Au\ NPs} = 0.406$ ng/mL) and a wider linear range.

T-2 toxin is one of the trichothecene mycotoxins produced by various fungi. Wang reported vanadium nanospheres (VNSs) with both SOD-like and POD-like enzyme activities [106]. VNSs with SOD enzyme activity can effectively scavenge 1,1-diphenyl-2-picryl-hydrazyl (DPPH$^{\bullet}$) and reduce its UV absorption at 517 nm. Additionally, VNSs with POD-like activity can catalyze TMB coloration. Using color reactions of different enzyme-like activities under the same conditions, the authors constructed a proportional nanozyme-linked immunosorbent assay (VNSs-RNLISA) for T-2 detection. As shown in Fig. S9B in Supporting information, T-2 toxin-modified BSA can capture VNSs-mAb Probe labeled with antibody, and thus, after similar operations to enzyme-linked immunosorbent assay (ELISA), the detection plate can catalyze TMB coloration while fading DPPH$^{\bullet}$. Conversely, when T-2 toxin appears in the test solution, VNSs-mAb Probe is occupied by T-2 toxin, and the washed plate cannot change the color of TMB and DPPH$^{\bullet}$. Compared to traditional ELISA, this proportional nanozyme-linked immunosorbent sensor has several advantages, including reduced cost, dual signals for self-calibration, and improved sensitivity and detection range.

6. Summary and perspective

V-based catalysts have been extensively used in industry, but the emerging interest in biosensing and biomedical applications has led to the development of novel V-based nanozymes with unique physicochemical properties and mimicking multiple enzymatic activities. This review systematically summarizes the research progress of V-based nanozymes in recent years. Due to the multiple valence states of V, these materials can mimic various redox enzymes, such as POD, V-HPO, GPx, OXD, CAT, and SOD. The mechanism of multi-species enzymatic activity of V-based nanozymes was further explored, and the formation of different types of V oxygen intermediates was found to be an important factor in simulating multienzyme activity. In addition, the catalytic activity of V-based nanozymes can be controlled through various methods such as size, morphology, valence, defect engineering, external triggering, and surface modifications. Importantly, due to their unique physicochemical properties and multispecies enzymatic activity, V-based nanozymes are now finding important applications in cancer therapy, anti-inflammatory, antibacterial and biosensing.

However, the research on V-based nanozymes is still in its early stages, and future studies need to focus on developing novel nanozymes, understanding the catalytic activity and mechanism, ensuring biosafety, among other aspects. In order to narrow down or surpass natural enzymes, V-based nanozymes need to work on several aspects, including novel nanozymes, catalytic activity, mechanism, biosafety, *etc*. (Fig. S10 in Supporting information). Considering the opportunities and challenges faced by V-based nanozymes, some potential research directions are proposed for expanding the research of V-based nanozymes.

(1) Developing new types of V-based nanozymes

The physicochemical properties and enzyme-like activity of V-based nanozymes are influenced by factors such as size, morphology, specific surface area, active site microenvironment, and crystallographic surface. Developing V-based nanozymes with specific structures is crucial in bridging the gap with natural enzymes. Current V-based nanozymes mainly include V oxides, oxygen-free V-based compounds, and a few vanadate and single-atom nanozymes. However, there are unexplored V-based nanomaterials, such as vanadates, MOF, and V phosphates, which offer great potential for studying catalytic mechanisms and preparing specific enzyme classes. Additionally, the development of V-based single-atom nanozymes with atomic dispersion can improve active site utilization and characterize the electronic state of catalytic processes. Exploring V-based nanozymes to mimic the activities of enzymes other than oxidoreductases is also important.

(2) Enhancement of catalytic activity and elucidation of the catalytic mechanism

Enhancing the catalytic activity of V-based nanozymes is crucial for matching or surpassing natural enzymes. Strategies such as exposing more active sites through special structures (hollow structures, low-dimensional structures, MOFs, and single-atom nanozymes) can enhance catalytic activity. Modulating the microenvironment of the active site, for example using molecular imprinting technology, enhances selectivity and activity. Understanding the changes in electronic structure during V-based nanozyme-substrate interactions and designing nanozymes with lower energy barriers for substrate reactions are areas that require further attention. Elucidating the catalytic mechanisms of different V-based nanozymes and establishing a theoretical system of catalysis through multidisciplinary research, including theoretical calculations and artificial intelligence, enables the prediction of highly active nanozymes.

(3) Enhancement of biosafety and biocompatibility

Biosafety and biocompatibility are critical considerations for the biomedical application of V-based nanozymes. Vanadate (VO_3^-) and vanadyl (VO^{2+}), the main forms of V ions in body fluids, are generally considered to have low toxicity. However, further studies are needed to assess the biological toxicity of V-based nanozymes composed of inorganic materials. Potential side effects, such as interference with cellular biochemical reactions, should be investigated. Surface engineering is important for biomedical applications, and exploring novel surface modification molecules that enhance biocompatibility, circulation time, and tumor targeting is necessary. Clinical research on V-containing compounds in diabetes treatment encourages further optimization of V-based nanozymes, potentially leading to their use as novel drugs.

(4) Broadening the application of V-based nanozymes

V-based nanozymes have been applied in cancer therapy, anti-inflammatory therapy, antibacterial therapy, and biosensing. Their unique enzyme-like activities, particularly in GPx-like and haloperoxidase activities, open avenues for cancer treatment and antimicrobial applications. Expanding V-based nanozymes to mimic the activity of other natural enzymes will broaden their application scope. In the future, V-based nanozymes with intelligent responsiveness to external stimuli can enable specific disease diagnosis and treatment. V-based nanozymes hold great potential for biomedical applications that warrant further exploration.

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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108793.

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