ChemCatChem

Review
doi.org/10.1002/cctc.202500730

Chemistry Europe
European Chemical Societies Publishing

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MXene-Based Nanozymes: Current Challenges and Future Prospects

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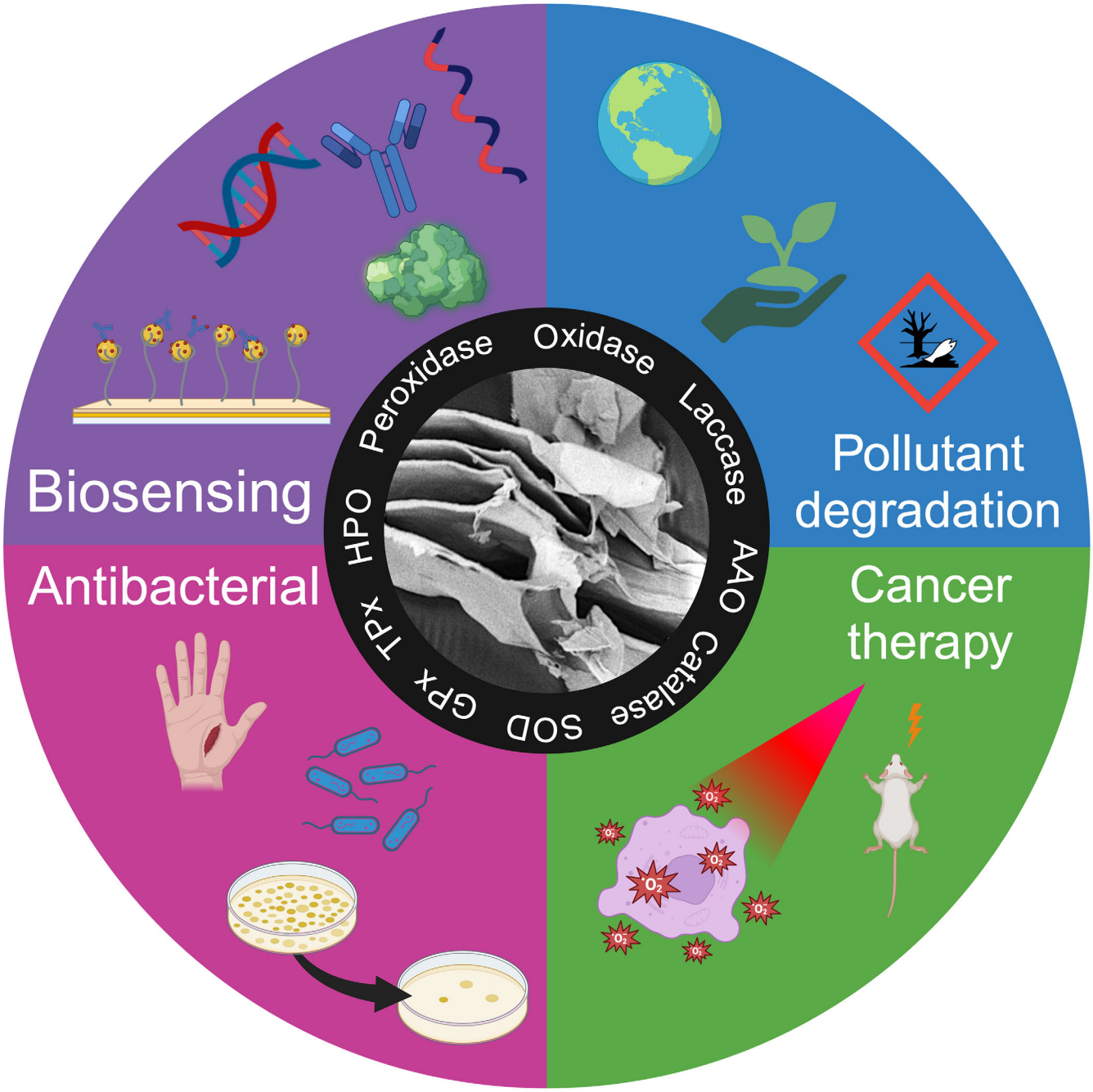

MXene-based nanozymes (recently called MXenzymes) have emerged as promising candidates for environmental remediation, biomedical, (bio-)catalytic, and sensing technologies due to their surface tunability, tailored electronic properties, remarkable electrical conductivity, and high surface area. These materials offer significant advantages over traditional enzymes, such as enhanced stability, tunable catalytic activity, and multifunctionality. However, despite the increasing number of studies in this field, critical challenges remain, including the long-term stability, the lack of studies on structure–activity relationships to better understand the catalytic mechanisms, and the scalability required for real-world applications. This mini-review provides a comprehensive overview of the most recent advancements in MXenzymes, focusing on the type of MXenes used, the reported enzyme-like activity, and the role of the photothermal effects in enhancing their catalytic performance. Moreover, key limitations, such as oxidation susceptibility, biocompatibility concerns, and the scarce in-depth mechanistic studies, are critically examined. Last, the necessary steps to transition from proof-of-concept studies to real-world applications are discussed. By addressing the listed fundamental challenges, MXenzymes could represent a valuable and effective alternative to natural enzymes used in catalysis, medicine, and environmental science.

1. Introduction

MXenes, a relatively new class of two-dimensional (2D) transition metal carbides, nitrides, and carbonitrides, have gained significant attention due to their exceptional physicochemical properties.[1–5] First discovered at Drexel University in 2011,[6] MXenes are derived from their parent MAX phases, which consist of layered ternary carbides or nitrides with the general formula $M_{n+1}AX_n$, where M represents an early transition metal (such as Ti, V, Nb, Ta and Mo), A is an element from groups 13 or 14 (as Al or Si), and X denotes carbon and/or nitrogen. By selectively removing the A element, a distinctive accordion-like structure of $M_{n+1}X_nT_x$ MXene is obtained, characterized by high surface area and tunable surface chemistry (T_x). These materials have been reported to possess outstanding electrochemical features,[7–9] exceptional mechanical properties,[10,11] and chemically versatile surfaces,[12,13] making them suitable for a kaleidoscope of possible applications, as in energy storage,[9,14] catalysis,[15] sensing,[16,17] and biomedical technologies.[18] This led to their recognition as one of the top ten emerging technologies in chemistry by IUPAC in 2024. Besides, in the case of MXenes produced by selective etching of MAX phases using aqueous solutions (typically, HF/HCl etching protocols), their inherent hydrophilicity, coupled with tunable surface functional groups (—OH, =O, —F), enhances their dispersibility in pure water and aqueous solutions and expands further their applicability.

Parallel to the rise of MXenes, nanozymes have emerged as powerful alternatives to biological catalysts.[19–22] They are generally defined as next-generation artificial enzymes based on engineered nanomaterials that mimic the catalytic activity of natural enzymes. Since their discovery in 2007 by Yan and coworkers,[23,24] nanozymes have demonstrated significant advantages over traditional enzymes, including enhanced activity and stability, scalability at a low cost, and greater multifunctionality.[23] As a result, IUPAC named them one of the top ten emerging technologies in chemistry in 2022. Indeed, natural enzymes, notwithstanding their high specificity and efficiency, are often limited by their sensitivity to environmental conditions such as extreme temperatures, pH fluctuations, and denaturation over time.[19,20] Conversely, nanozymes can offer robustness under harsh conditions and can be chemically modified to enhance the final catalytic activity. These artificial enzymes have been extensively used in various fields, including biocatalysis, medicine, and environmental remediation.[19,21,25,26] For instance, they showed favorable chemical reactions in biocatalysis, akin to natural enzymes but with greater stability and reusability.[27] In the biomedical field, nanozymes have been explored for potential biosensing platforms, antibacterial treatments, and cancer therapy, where the ability to generate reactive oxygen species plays a crucial role.[28–30] Additionally, nanozymes have also been reported to be useful for pollutant degradation and water purification, offering sustainable solutions for environmental challenges.[22,26,28]

Recent advancements in nanozymes focus on their engineering, catalytic mechanisms, and optimization strategies.[23] As such, researchers have explored multienzyme-like properties, biorthogonal nanozymes, single-atom catalysts, and machine learning-assisted design, alongside with surface engineering and defect engineering to enhance the final activity and selectivity.[23] Among the wide array of nanomaterials investigated for enzyme-mimetic activity, MXenes have emerged as particularly promising candidates due to their exceptional surface and redox properties (Figure 1).[25,31–33]

Indeed, their high surface area, together with the abundance of active sites for catalytic reactions, and their metallic or near-metallic conductivity, can facilitate efficient electron transfer, making them ideal for catalytic applications, such as high-sensitivity electrochemical biosensing.[34] Furthermore, the

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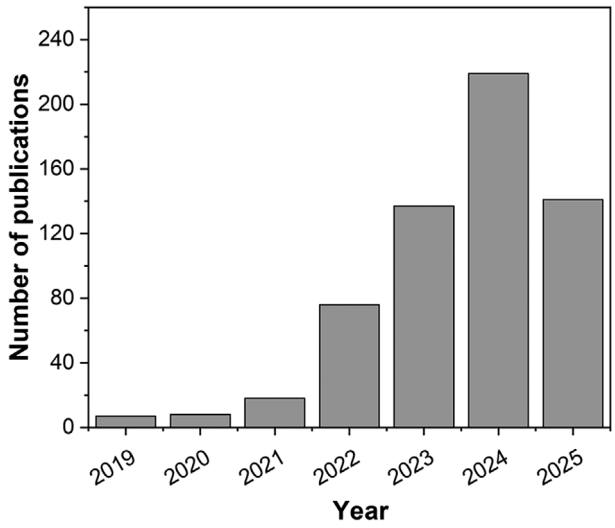


Figure 1. Histogram showing the number of scientific publications (original articles and reviews) on MXenes-based nanozymes over time. Source: Scopus, April, 2025.

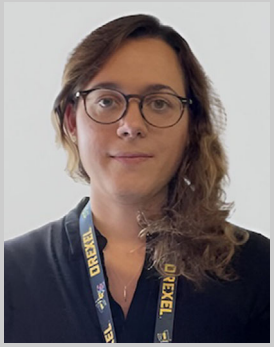
surface terminations of MXenes can be precisely tuned, allowing for optimization in various reaction environments. Their hydrophilicity may also further support stable catalytic performance, enabling robust charge transfer without the structural degradation commonly observed in conventional nanozymes during prolonged exposure.[35] Delving deeper into their surface properties, the chemistry of surface terminations, defects, the type of transition metal atoms, and the possible metal doping determine the final catalytic mechanism. Surface terminations directly modulate the electron density at catalytic sites, tuning the Fermi level and the redox potential, thus enabling the final enzyme-like activity. For instance, Wang et al.[36] showed that O-rich surfaces enhance peroxidase activity, whereas F-terminations may suppress redox interactions. Structural defects (such as vacancies, edge sites, or step discontinuities) create high-energy active sites that enhance the adsorption of reactants like hydrogen peroxide, molecular oxygen, and biomolecules, thereby accelerating reaction kinetics. The exposed transition metal atoms on the surface (e.g., Ti, V, Mo, and Nb), often in lower oxidation states, further act as catalytically active centers, capable of driving redox transformations through electron-transfer mechanisms,[26,37,38] and the chemically rich and functionalized MXene surface facilitates the stable immobilization of metal nanoparticles or single atoms (e.g., Pt, Fe, and Cu), forming composite materials. Additionally, MXenes can resist proteolytic cleavage, a major limitation of natural enzymes, thereby extending their shelf life and operational stability in both biomedical and environmental settings.[35]

Hence, due to these peculiar characteristics, MXene-based nanozymes (recently shortened as MXenzymes) can be highly versatile and efficient, with potential applications spanning from biosensing to disease diagnostics and environmental remediation.[25,26,28,31,39] Continued research into their functionalization, stability, and catalytic mechanisms will be crucial for realizing their full potential in both fundamental science and practical applications. However, the field still has many open questions as, for instance, the somewhat ambiguous catalytic mechanisms, MXenes' stability in physiological conditions, and the presence of mainly proof-of-concept studies, which fail to corroborate their effectiveness in real-world applications.

Therefore, in this mini-review, the recent progress in the enzyme-mimetic properties of MXene-based nanozymes will be thoroughly discussed, emphasizing the major reported achievements and highlighting the advantages associated with their use. Nevertheless, a critical assessment of the current limitations and future research directions will also be presented, suggesting a path toward their practical implementation.

2. Types of MXenes Used in Nanozymes

Among the already documented MXenzymes, mainly Ti-,[33,38,39,40–42] V-,[43–46] and Nb-based[2,29,31,47,48] ones have



Dr. Eleonora Pargoletti earned her B.S. (2013) and M.S. (2015) with Honors in chemistry at the University of Milan, where she also completed her Ph.D. in industrial chemistry (2020, Prof. G. Cappelletti), including a research period at the Australian National University. She was a post-doctoral researcher in Milan (2020–2022, Prof. A. Vertova) and Sydney (2022–2023, Prof. A. Tricoli), and a visiting scientist at Drexel University (9/2024–3/2025, Prof. Y. Gogotsi). In January 2025, she was appointed tenure-track assistant professor at the University of Milan. Her research focuses on low-dimensional and 3D nanocomposites mainly for energy and sensing applications.

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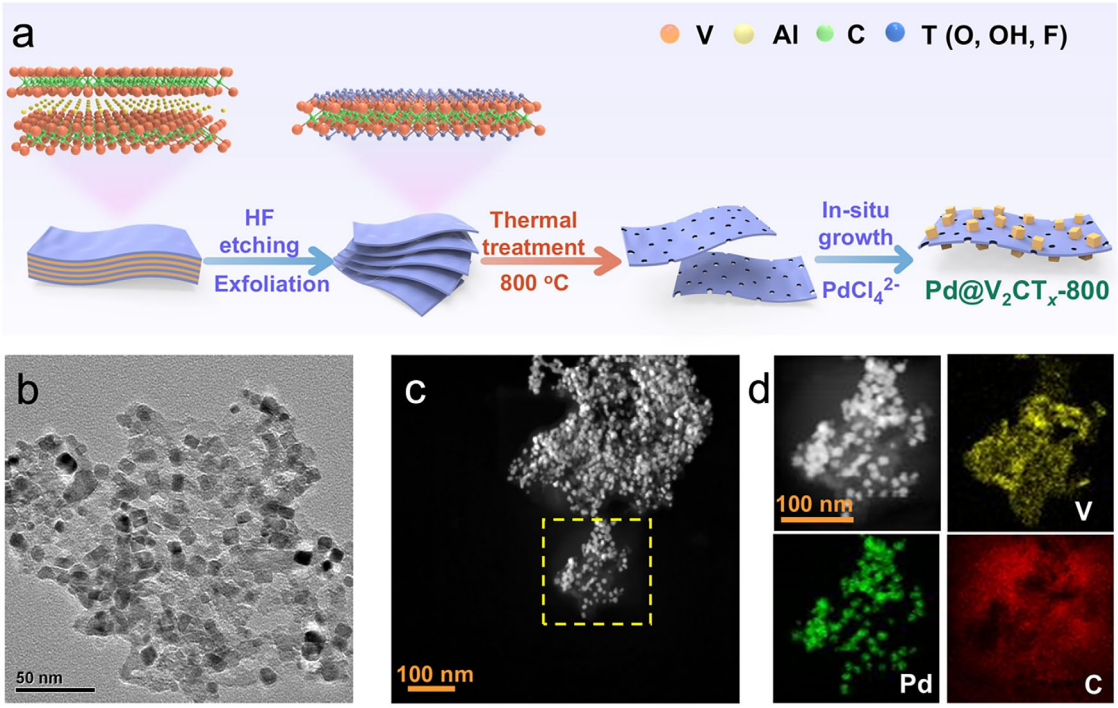

Figure 2. (a) Synthetic route of Pd-decorated V_2CT_x. (b–d) TEM and HAADF-STEM images together with elemental mapping of $Pd@V_2CT_x$. Adapted from Ref. [45]. Copyright (2025), with permission from Elsevier.

been explored for their catalytic activities, often mimicking peroxidase,[37] oxidase,[44] or other enzyme-like electron transfer processes.[28,49] However, most of these studies investigated heterogeneous systems where MXene is coupled to metal oxides and/or its surface is modified by noble metal nanoparticles[26,32,40,50] or heteroatoms.[51]

Similar to other applications, Ti-based MXenes (particularly $Ti_3C_2T_x$) are the most widely explored as MXenzymes, with several studies reporting their promising peroxidase- or oxidase enzyme-mimicking behavior.[52–59] Even if the surface terminations (—OH, —F, and =O) are reported to play a pivotal role in shaping the final catalytic efficiency, this aspect is often overlooked. Indeed, some studies attribute the high reactivity of $Ti_3C_2T_x$ to its ability to help the electron transfer and generate reactive oxygen species (ROS); however, the exact mechanism is not fully understood. Besides, a structurally similar but less explored Ti_2CT_x has also been explored for nonenzymatic catalytic reactions.[60] Nevertheless, its rapid oxidation/hydrolysis to TiO_2 limit its long-term usability, raising concerns about its feasibility under practical conditions.

Other MXenes have also been investigated. Most studies on V-based ones, such as V_2CT_x, revolve around their use as supports for catalytic nanostructures rather than standalone nanozymes.[43,61] Just recently, Liu et al.[45] reported the synthesis of porous V_2CT_x nanosheets loaded with Pd nanocubes, in which MXene serves as a conductive scaffold for the noble metal nanocatalyst, as shown in the TEM images of Figure 2. Even if the enhanced enzymatic activity is often ascribed to the MXene itself, a more critical perspective may suggest that the true catalytic properties come from the noble metal nanoparticles, and the role of V_2CT_x is less prominent. MXene's high surface area and electronic conductivity undoubtedly improve charge transfer, but the direct role it plays in catalytic reactions remains debated. Furthermore, the claimed antibacterial properties are primarily linked to palladium catalytic activity rather than any intrinsic behavior of V_2CT_x.

Only one study, reported by Feng et al.[46] in 2021, emphasized the use of V_2CT_x as a standalone nanozyme, exhibiting the ability to mimic up to six natural enzymes, including superoxide dismutase (SOD), catalase (CAT), peroxidase (POD), glutathione peroxidase (GPx), thiol peroxidase (TPx), and haloperoxidase (HPO). These findings might suggest that this MXenzyme possesses intrinsic catalytic activity beyond acting as a mere support. On the flip side, its long-term stability in physiological environments remains uncertain since V-based MXene is prone to oxidation.[3]

Lately, the catalytic behavior of Nb-based MXenes has also been elucidated. Nb_2CT_x has drawn attention to its potential as MXenzyme, particularly in catalytic and sensing applications.[31,47,48,62] While studies remain limited, preliminary findings suggest that its unique electronic properties and surface chemistry may have a remarkable impact. Some studies suggest that Nb_2CT_x exhibits peroxidase-mimicry, facilitating the decomposition of hydrogen peroxide in a manner similar to other transition metal-based nanozymes.[2] Other studies show an amplified electroluminescence and a significant peroxidase-like behavior when coupled with noble metal nanoparticles (Ag-Au or Pd-Pt), suggesting promise as a sensing platform.[47] Nevertheless, as previously hinted for other MXenes, the key question remains: is Nb_2CT_x intrinsically catalytic, or does the observed catalytic behavior stem from material impurities, surface defects, or cocatalysts? Furthermore, like other M_2C MXenes,

Table 1. Catalytic performance metrics of bioinspired nanozymes compared to the natural enzyme (horseradish peroxidase, HRP).

Enzyme/Nanozyme Type	Enzyme-Like Activity	Substrate	K_m/mM	V_{max}/μM s^{-1}	K_{cat}/s^{-1}	Specific Activity/ U mg^{-1}	Ref.
Natural enzyme (HRP)	Peroxidase	TMB/H_2O_2	0.43	8.23	2.50	250	[35]
Fe_3O_4 NPs	Peroxidase	TMB/H_2O_2	0.098	0.58	1.80	180	[35]
V_2O_5 nanowires	Peroxidase	ABTS/H_2O_2	0.12	0.75	1.92	170	[64]
GO-COOH	Peroxidase	TMB/H_2O_2	0.45	0.62	1.75	160	[65]
Pt NPs	Peroxidase/catalase	TMB/H_2O_2	0.60	0.95	2.40	220	[66]
Fe-MIL-88NH_2	Peroxidase	TMB/H_2O_2	0.084	0.68	1.85	175	[67]
MIL-53(Fe)	Peroxidase	TMB/H_2O_2	0.083	0.74	1.98	200	[68]
MXene $Ti_3C_2T_x$	Peroxidase	TMB/H_2O_2	0.13	0.72	2.10	210	[54]
Fe_3O_4@$Ti_3C_2T_x$-Au nanocomposite	Peroxidase	TMB/H_2O_2	0.12	0.75	1.92	170	[69]
Ag-$Ti_3C_2T_x$ nanocomposite	Peroxidase	TMB/H_2O_2	0.15	0.80	2.10	200	[37]

Nb_2CT_x exhibits a certain degree of instability over time, especially in the presence of aqueous solvents, which may compromise its catalytic performance in real-world applications over extended periods.

Last, the available literature primarily reports evidence of its redox activity and charge transfer properties, but with insufficient experimental and theoretical analyses, resulting in a scarcity of mechanistic insights into the catalytic processes.

3. Enzyme-Like Catalytic Processes of MXenzymes

Very recently, MXene-based nanozymes have been reported to show enzyme-mimicking behavior, including peroxidase (POD), oxidase (OXD), catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), thiol peroxidase (TPx), and haloperoxidase (HPO)-like activities.[39,46] Despite MXenes' intrinsic characteristics, such as high conductivity and tunable surface chemistry, a deeper mechanistic evaluation has so far been lacking, and rigorous experimental analysis integrated with theoretical calculations is needed to enable their use in real-world catalytic applications. Therefore, to provide guidelines for future pathways in this field, it is essential to critically evaluate the mechanistic insights that have been identified so far.

3.1. Peroxidase- and Oxidase-Like Activity

Peroxidase-like (POD) activity, associated with the concomitant presence of hydrogen peroxide molecules, stands out among the earliest and most studied MXenzyme behaviors.[63] Table 1 provides a side-by-side comparison of the POD-like catalytic performance of some MXenzymes, traditional nanozymes (e.g., Fe_3O_4), and natural enzymes (e.g., horseradish peroxidase, HRP). The metrics included in the table are the most representative ones, such as the Michaelis–Menten constant (K_m), the maximum reaction rate (V_{max}), the catalytic efficiency (K_{cat}), and the specific activity. It is interesting to observe that MXenzymes have similar performances to the well-known benchmark, that is, Fe_3O_4 NPs. Moreover, unlike natural enzymes, MXenzymes and other bioinspired nanozymes exhibit better catalytic activity at elevated temperatures (up to 60 °C–70 °C).[35]

Digging deeper, Wu et al.[59] demonstrated that histidine-functionalized $Ti_3C_2T_x$ nanosheets exhibit significantly enhanced peroxidase-like activity, which was attributed to their high electron transfer efficiency and favorable adsorption of both hydrogen peroxide and 3,3′,5,5′-tetramethylbenzindine (TMB) substrates. The latter is the common substrate used in colorimetric assays, as it is easily detectable when oxidized to its blue form by the POD enzyme. Interestingly, the proposed spontaneous switching of Ti sites' valence state is hypothesized to catalyze the concomitant reduction of H_2O_2 and oxidation of TMB. Indeed, the large specific surface area and, subsequently, the greater number of active sites of $Ti_3C_2T_x$ nanosheets can facilitate the adsorption of TMB onto their surface, enabling the transfer of unpaired electrons from the amino groups of TMB to the MXene. Subsequently, the accumulated electrons enhance their transfer to the nearby H_2O_2 molecules. This results in the oxidation of TMB and the concomitant reduction of H_2O_2 to water. Moreover, the spontaneous transition between oxidized and reduced states of Ti enables the continuous catalytic cycle.

Very recently, Facure et al.[63] deeply investigated a MXene-based composite made of ZnO-Ce_3O_4-$Ti_3C_2T_x$ that demonstrated peroxidase-like activity for ascorbic acid detection, showing very promising results (Figure 3), even if it is still characterized by a slightly lower catalytic activity with respect to the benchmark Fe_3O_4-based nanozyme (limit of detection of 0.6 versus 0.2 μmol L^{-1} in acetate buffer). Here, the authors claim that the peroxidase-like behavior originates from a synergistic effect between the MXene and the metal oxides, rather than from the 2D material itself, as confirmed by the lack of improvement when its amount is increased in the composite. Nevertheless, the study did not go deep into the possible mechanism through theoretical/experimental analyses.

Beyond peroxidase-mimicking activity, MXenes have also shown oxidase-like behavior, generating reactive oxygen species (ROS as O_2) without requiring hydrogen peroxide.[44,58] This property may be highly attractive for antibacterial and

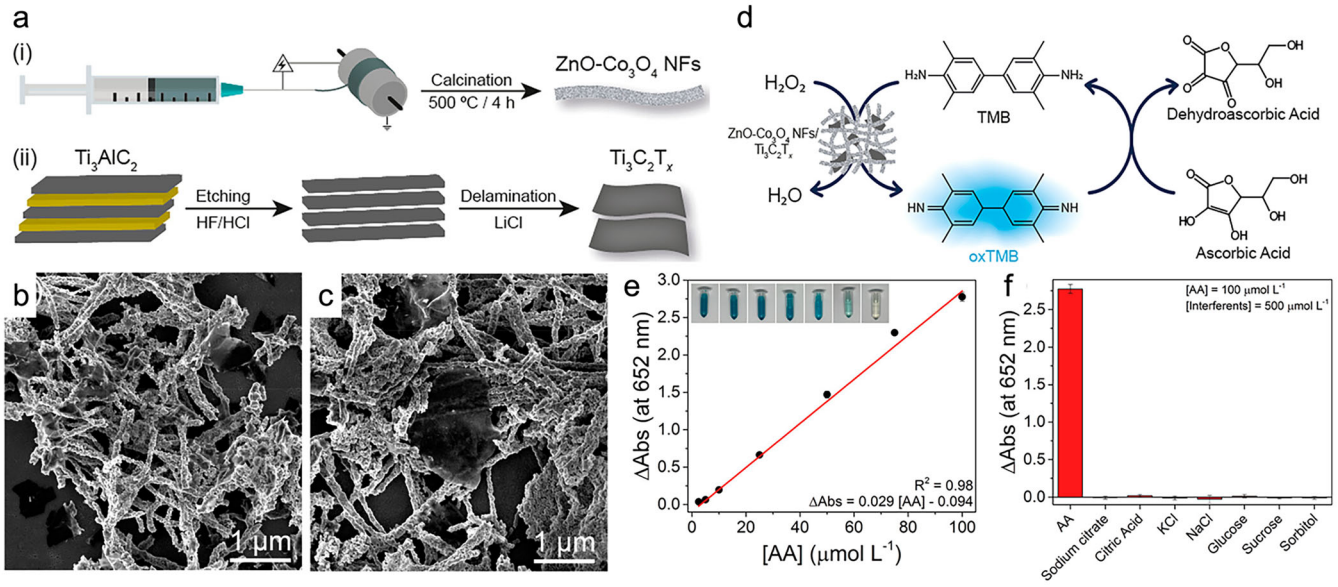

Figure 3. (a) Schematic illustration of the preparation of (i) ZnO-Co_3O_4 nanofibers and (ii) $Ti_3C_2T_x$ MXene. (b, c) SEM micrographs of ZnO-Ce_3O_4-$Ti_3C_2T_x$ nanocomposite, where darker areas refer to MXene sheets. (d) Peroxidase-like activity of the MXenzyme and the colorimetric detection of ascorbic acid based on TMB redox reaction. (e) Linear regression curve of ascorbic acid detection using the prepared MXenzyme (inset: photos showing the color change by varying the AA amount from 2.5 to 100 μmol L^{-1}). (f) Comparison of AA and possible interferents detection with the ZnO-Ce_3O_4-$Ti_3C_2T_x$ system. Adapted from Ref. [63]. Copyright (2024), with permission from the American Chemical Society under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).

pollutant degradation applications. However, the possible mechanism remains somewhat ambiguous. For instance, Jin et al.[58] pointed out the superior oxidase-like activity of $Ti_3C_2T_x$-derived nanozyme, in which the key role was played by the MXene-derived TiO_2 quantum dots rather than by the MXene itself. Thus, once again, this raises a crucial concern: is the observed catalytic activity an intrinsic property of the MXene, or is it an artifact of the oxidation reactions? In-depth experimental studies and theoretical calculations will be necessary to establish potential future directions.

3.2. Multienzyme Mimicry

It is worth pointing out a significant study by Feng et al.[46] in which authors reported a multi-enzymatic activity of V_2CT_x mimicking up to six different natural enzymes (i.e., superoxide dismutase (SOD), catalase (CAT), peroxidase (POD), glutathione peroxidase (GPx), thiol peroxidase (TPx), and haloperoxidase (HPO), Figure 4). V_2CT_x showed impressive reactive oxygen species-scavenging capability, protecting cell components against oxidative stress through catalytic reactions. The reported remarkable versatility was attributed to the MXene electron donation capability and strong surface interactions with reactive oxygen species, evidenced by results obtained via electron paramagnetic resonance (EPR), X-ray photoelectron spectroscopy (XPS), and infrared spectroscopy (FTIR) analyses.

Furthermore, unlike Ti-based MXenes, which predominantly rely on electron transfer processes, V_2CT_x can catalyze redox reactions through direct ROS scavenging. On the other hand, questions regarding its stability in physiological environments remain open, leading to uncertainties about its effectiveness over time. Very recently, Huang et al.[70] reported the synthesis of $Ti_3C_2T_x$-based metal composites (M/MXenes, where M = Cu, Co, Ni, Zn, Fe, Mn) exhibiting multi-enzyme mimicry properties. These materials demonstrated catalytic activities resembling peroxidase, catalase, ascorbic acid oxidase (AAO), superoxide dismutase, and laccase. Among the synthesized composites, the copper-decorated MXenes showed the most robust catalytic performance, particularly in mimicking laccase activity. Thus, the authors developed a colorimetric hydrogel sensor for detecting and degrading phenolic pollutants, such as hydroquinone and naphthalene-1,8-diol, exhibiting excellent stability and sensitivity (with a limit of detection in the tens of nM range). As such, they underscored the potential of the engineered MXenzymes for environmental remediation and sensor applications. Nevertheless, the authors did not dive deeper into the Cu/$Ti_3C_2T_x$ catalytic mechanism through theoretical simulations and/or experimental analyses (as in situ spectroscopic techniques). Therefore, it is not clear whether the MXene or the metal nanoparticles played the major role.

3.3. MXenzymes Catalytic Enhancement by Photothermics

An emerging trend in MXene-based nanozymes is their integration with photothermal therapy (PTT) to enhance the final catalytic performance, especially in the biomedical field.[38,71–75] Actually, localized heating enhances the reaction rates, can activate multi-enzyme functions, and amplify ROS generation. The local heating generated by MXene absorption in the NIR region can accelerate catalytic redox reactions (e.g.,

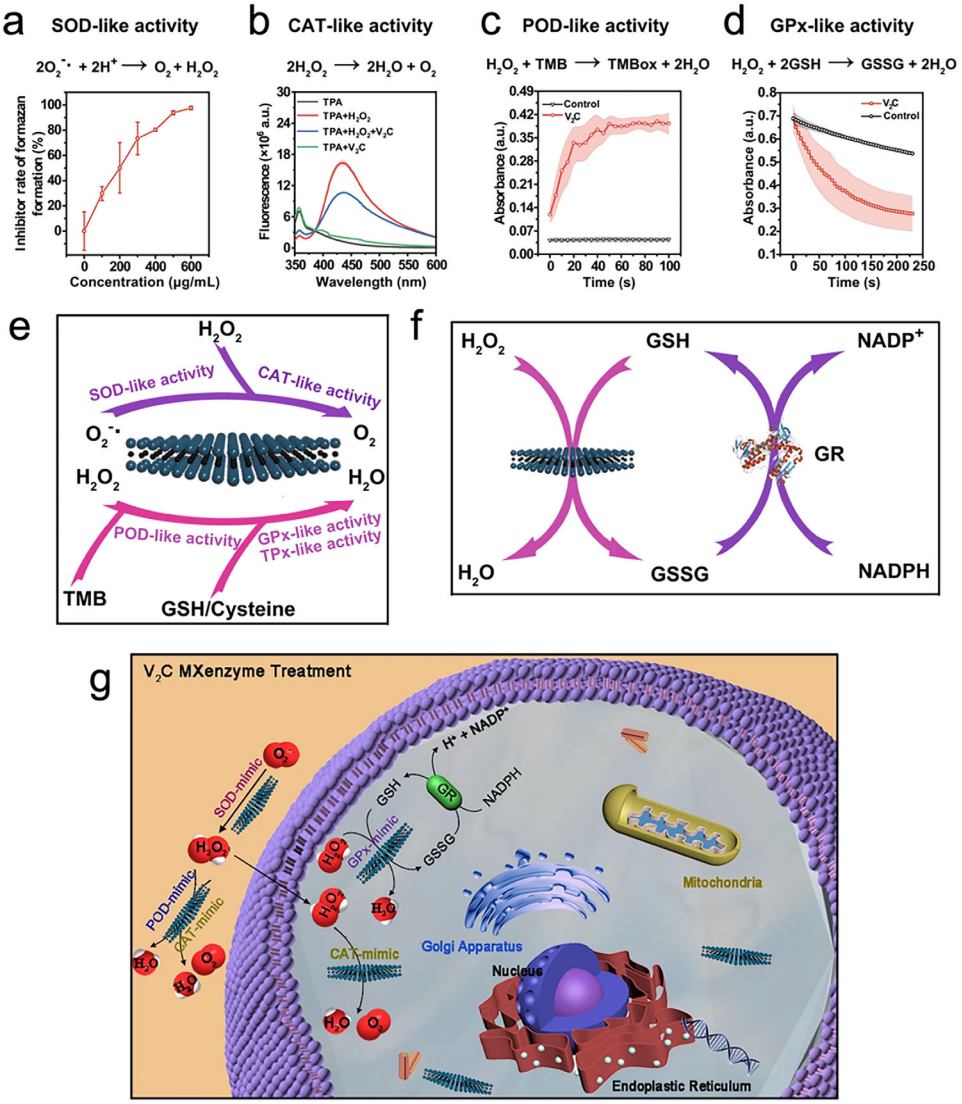

Figure 4. (a) SOD-like, (b) CAT-like, (c) POD-like, and (d) GPx-like activity of V_2CT_x MXenzyme (3 replicates for each group). (e, f) Schematics of enzyme-mimicking activities of V_2CT_x. (g) Sketch of ROS-scavenging activities of V_2CT_x-based MXenzyme showing multifunctionality: it catalyzes $O_2^{-\bullet}$ into H_2O_2 and O_2, decomposes H_2O_2 into O_2 and H_2O, and removes $^{\bullet}OH$. Adapted from Ref. [46]. Copyright (2021), with permission from Springer Nature under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).

peroxidase-mimicking H_2O_2 decomposition) by increasing kinetic energy and reducing activation barriers.[76] In addition, in composite systems (e.g., Fe_3O_4-MXene and Pt-MXene), photothermal activation not only enhances single-enzyme mimicry but can also trigger sequential cascade reactions, thereby improving efficiency in complex media such as tumor microenvironments or biofluids.[38] Furthermore, photothermal stimulation can improve reactive oxygen species generation, which is crucial in antibacterial or cancer therapy contexts.[77] Different approaches can be used to optimize this combined strategy, as: *i*) the incorporation of noble metals (e.g., Au and Pt) or semiconducting nanostructures that can improve the light absorption and photothermal conversion efficiency; *ii*) the structure engineering since vertically aligned or few-layered MXenes exhibit higher absorption and heat dissipation control; *iii*) the tailoring of irradiation parameters, for example by varying laser power, wavelength, or exposure duration, thus offering stimulus-responsiveness.

As such, it is worth noting the work reported by Zhu et al.[38] in which they described a Pt-decorated $Ti_3C_2T_x$-based system that showed a significant increase in peroxidase-like activity when irradiated with near-infrared (NIR-II) light. This enhancement was mainly attributed to a local temperature-induced acceleration of catalytic reactions thanks to the MXene's photothermal effect, suggesting that the MXenzymes could be used in hyperthermia-amplified enzyme therapy. However, authors also claimed that Pt nanoparticles are responsible for the peroxidase-like activity, resulting in an efficient in situ catalytic reaction of H_2O_2 to reactive hydroxyl radicals.

On a similar note, He et al.[78] demonstrated a dramatic improvement in the catalytic activity of V_2CT_x-based nanozyme through photothermal effects by decorating its surface with platinum nanoparticles (Figure 5a). This platform displayed a significant photothermal conversion efficiency (PCE) of around 60% under near-infrared (NIR-II) irradiation, leading to an

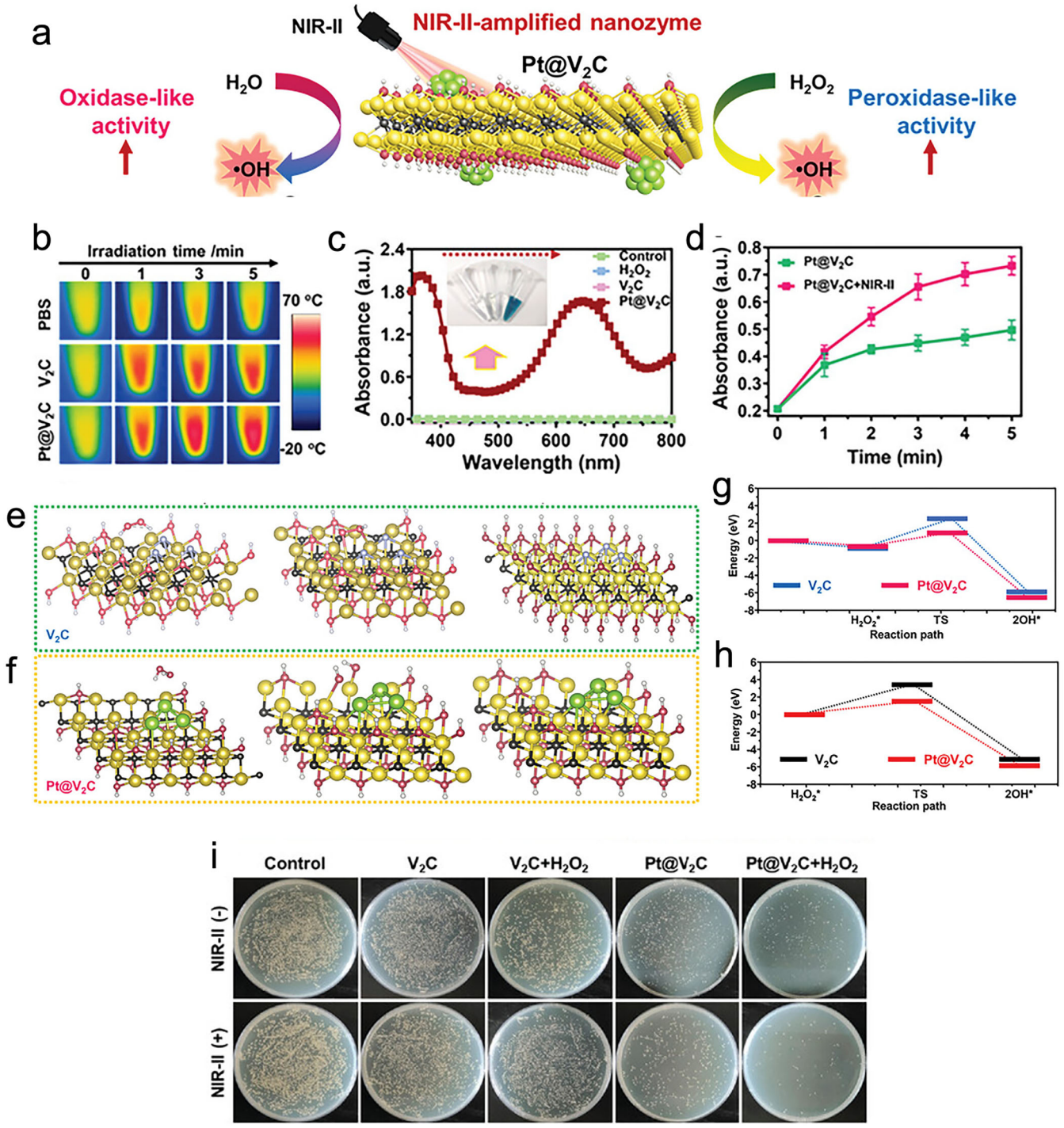

Figure 5. (a) Combined photothermal and chemodynamic therapy activities of Pt@V_2CT_x-based nanozyme. (b) Infrared thermal images of water (phosphate buffer saline, PBS), V_2CT_x, and Pt@V_2CT_x (80 ppm) under irradiation (1064 nm and 1 W cm^{-2}) for 5 min. (c) Peroxidase-like activity of V_2CT_x and Pt@V_2CT_x. (d) POD-like activity enhanced by NIR-II irradiation. Data are presented as mean ± SD ($n = 3$). DFT optimized structures of H_2O_2 and •OH adsorbed and catalytically decomposed on (e) V_2CT_x and (f) Pt@V_2CT_x at Pt and V sites. (g) Calculated Gibbs free energy change diagram from H_2O_2 to •OH on V_2CT_x and Pt@V_2CT_x. (h) Calculated H_2O_2 decomposition energy barrier on V_2CT_x and Pt@V_2CT_x. (i) Comparison of the antibacterial activity of different treatments against methicillin-resistant *Staphylococcus Aureus* determined by counting the number of bacterial colonies in the agar plate. Adapted from Ref. [78]. Copyright (2024), with permission from Wiley-VCHGmbH.

amplified oxidase- and peroxidase-like behavior (Figure 5b–d). Authors attributed this photothermally boosted enzymatic performance to the localized surface plasmon resonance (LSPR) phenomenon of Pt NPs, which facilitated electron transfer and improved catalytic efficiency. Interestingly, they tried to confirm the biocatalytic mechanism through density functional theory (DFT) calculations, showing that Pt nanoparticles do alter the electronic structure of V_2CT_x, lowering the

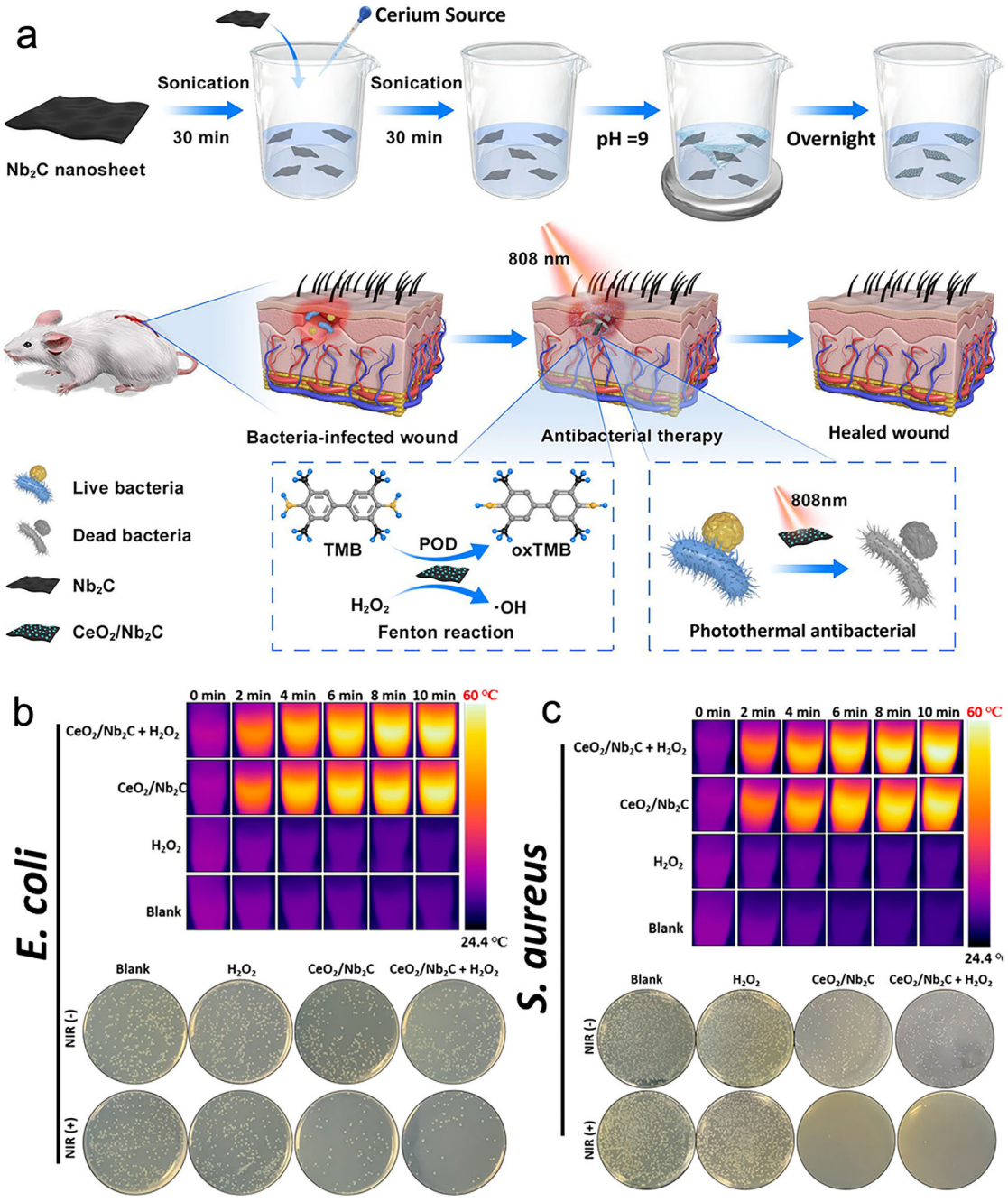

Figure 6. (a) Sketch of CeO_2/Nb_2C synthesis and its dual functionality. Infrared thermal images together with photos of (b) *Escherichia coli* and (c) *S. Aureus* colonies, when treated by phosphate buffer saline (PBS) solution, H_2O_2, CeO_2/Nb_2C nanocomposite, and $CeO_2/Nb_2C + H_2O_2$ under NIR irradiation. Adapted with permission from Ref. [29]. Copyright (2023), American Chemical Society.

activation energy for hydroxyl radicals (•OH) generation, which plays a critical role in oxidative stress-mediated antibacterial effects (Figure 5e–h).

Furthermore, in vivo tests corroborated the antibacterial efficacy against methicillin-resistant *S. Aureus* infections. Combining photothermal and chemodynamic therapy (PTT/CDT) resulted in efficient bacterial eradication, thereby accelerating wound healing and reducing inflammation (Figure 5i).

Last, it is worth mentioning the work conducted by Yuan et al.[29] in which they described a CeO_2/Nb_2CT_x nanocomposite having dual functionality, as a peroxidase-like enzyme and as an excellent NIR photothermal material (Figure 6a), thus showing an 80% bactericide performance. They also demonstrated that this MXenzyme can accelerate the recovery of diabetic wounds of a mouse when infected by different bacteria (Figure 6b,c), such as *E. Coli* (Gram-negative bacteria) or *S. Aureus* (Gram-positive bacteria). The biosafety aspect was also discussed, achieving good results in in vitro and in vivo studies.

Overall, these findings underscore the potential of photothermal energy to modulate and enhance the catalytic prop-

erties of MXene-based nanozymes, expanding their final applicability in antibacterial strategies and the medical field.

4. Critical Gaps and Current Challenges

A common trend is evident across all available studies: a general lack of long-term stability investigations, in-depth mechanistic studies, biocompatibility and biodegradability assessments, and scalability issues. Without addressing these aspects, the potential of MXenzymes cannot be properly evaluated.

One of the potential barriers to practical application is the limited long-term stability, particularly in aqueous and biological environments. Indeed, unlike traditional Fe_3O_4 or CeO_2-based nanozymes, MXenes are susceptible to oxidation and hydrolysis in the presence of water molecules and oxygen, which lead to a gradual loss of the catalytic behavior due to their conversion into amorphous or crystalline oxides that can degrade surface conductivity and disrupt active sites over time, especially in biological or environmental settings. Moreover, terminations such as —F and —OH can desorb or undergo ligand exchange in complex fluids, altering surface reactivity and charge, which in turn impact colloidal stability and enzyme-mimicking activity. Alongside this, agglomeration and restacking pose a problem, as delaminated MXene sheets tend to restack due to van der Waals interactions, thereby reducing surface accessibility and catalytic performance during long-term storage or repeated use.[79] Concerning the quantification of the degradation behavior, $Ti_3C_2T_x$, which is the most widely studied MXene, may degrade in water if it is nonstoichiometric, has a high concentration of defects and a small flake size. Colloidal suspensions of first-generation $Ti_3C_2T_x$ indeed showed up to 42% degradation after 5 days, 85% after 10 days, and complete oxidation after 15 days at room temperature under ambient conditions, converting predominantly to TiO_2.[80] However, high-quality stoichiometric $Ti_3C_2T_x$ can be stored in dilute aqueous solution for at least a year.[81,82] In addition, under accelerated conditions (100% relative humidity, 70 °C). $Ti_3C_2T_x$ films may undergo significant conductivity loss and phase change unless stabilized.[83] At the same time, films stored in ambient air maintained metallic conductivity over 5 years.[84] On the contrary, Nb_2CT_x and, particularly, $Nb_4C_3T_x$ show improved oxidation resistance compared to Ti-based MXenes. The oxidation rate can be modeled by first-order kinetics, with the addition of antioxidants (e.g., ascorbic acid) and low-temperature storage significantly extending their shelf life.[85] Last, another MXene used in MXenzymes is V_2CT_x, which is particularly unstable in its delaminated form. However, Matthews et al.[3] demonstrated that ion exchange and flocculation can extend aqueous suspension shelf life from a few hours to several months.

Hence, to address the long-term stability problem, several stabilization strategies have already been explored, including (*i*) the use of polymer coatings (chitosan, polyvinyl alcohol, or polyethylene glycol);[74] (*ii*) hybridization with other materials (as metal oxides MOFs, or silica shells to inhibit interaction with water and oxygen);[60,63,86–88] (*iii*) low-temperature and inert atmosphere storage (e.g., −80 °C, Ar-filled vials) to suppress hydrolysis and oxidation reactions;[89] (*iv*) use of antioxidant additives (such as ascorbic acid) to scavenge reactive oxygen species and delay oxidation onset;[89] (*v*) solvent exchange protocols, including dispersion in ethanol or isopropanol, which can reduce oxidative degradation compared to aqueous systems;[90,91] (*vi*) hydrogen annealing treatments of MXene films to recover or enhance oxidation stability;[92] and (*vii*) surface terminations control to decrease the degradation. Nevertheless, the drawback of MXene modification is the introduction of additional complexity that may alter the final catalytic behavior, making it difficult to unveil the role played by the MXene itself. Using more stable M_4C_3 or M_5C_4 MXenes with the same M element instead of thin and vulnerable M_2C structures may provide a solution. Also, a lifetime of MXenes can be greatly improved by minimizing the point defects, increasing the flake size, and controlling M:X stoichiometry.[3]

Additionally, once again, a concept that remains incompletely understood is the intrinsic catalytic role of MXenes, particularly in hybrid nanocomposites. Many studies focus on the decoration or doping of 2D materials with noble metal nanoparticles (Pt, Pd, Au, or Ag) and/or metal oxides (ZnO-Co_3O_4,[63] TiO_2,[58,60] or CeO_2[27,29,90]), yet fail to distinguish and unravel the role of these materials. Hence, a proper, rigorous experimental/theoretical investigation to decouple the MXene activity from that of the cocatalysts and/or of the surface defects/presence of lattice impurities and to determine its standalone catalytic effect is required.

Regarding the long-term cytotoxicity, particularly in the biomedical field, multiple studies have confirmed that the cytotoxicity of MXenes is strongly dependent on dose, duration of exposure, cell type, surface chemistry, and flake size. For instance, Jastrzębska et al.[93] showed that $Ti_3C_2T_x$ had minimal cytotoxicity below 62.5 mg L^{-1}, with preferential toxicity toward cancer cells due to ROS overproduction. Yet, $Ti_3C_2T_x$'s impact can vary across cell lines, and its cytotoxic effects may accumulate with prolonged exposure. As far as it concerns the immune response, an advanced immune profiling was reported by Unal et al.[94] Using flow cytometry and single-cell mass cytometry on human immune subpopulations, it was revealed that $Ti_3C_2T_x$ and other MXenes are generally bio- and immunocompatible. Interestingly, these MXenes suppressed monocyte activation and reduced secretion of pro-inflammatory cytokines, suggesting anti-inflammatory properties. However, such findings require further validation across different biological systems. Lastly, concerning the biodegradability and clearance, a recent review[95] outlined that the biodegradability of MXenes varies with composition. Ti-based MXenes ($Ti_3C_2T_x$) exhibit limited in vivo degradation, raising concerns over long-term retention and bioaccumulation, particularly in reproductive organs. They can be made biodegradable by introducing defects and non-stoichiometry, which lead to hydrolysis, as described above. Conversely, non-Ti MXenes (e.g., Nb_2CT_x, V_2CT_x, and Mo_2CT_x) are emerging as more biodegradable alternatives with better biocompatibility profiles, showing promise in mitigating oxidative stress and avoiding chronic toxicity. Studies have documented that these materials undergo partial degradation and are cleared

through hepatobiliary or renal routes, depending on surface modifications and particle size.[96]

Thus, to enhance safety profiles, several approaches can be hypothesized as: *i*) surface functionalization with biocompatible polymers (e.g., PEG and dextran) that may reduce the immune recognition and protein adsorption; *ii*) the engineering of flake size and oxidation states to minimize toxicity; *iii*) phospholipid bilayer coatings that mimic cell membranes, improving hemocompatibility; and *iv*) core-shell encapsulation with silica or protein cages, offering a more controlled exposure to biological fluids.[96]

Last, when evaluating the potential for large-scale production and real-world application of MXenzymes, several critical factors must be considered, including the scalability of synthesis and production costs. From a production standpoint, the cost of MAX phase precursors (e.g., Ti_3AlC_2 and Nb_2AlC) is currently moderate and it decreases as commercial availability expands. Although conventional wet chemical etching methods (such as HF- or HCl-based processes) remain widely used, they pose scalability and safety concerns. In response, alternative green synthesis approaches—including electrochemical, gaseous halogens, and molten salt etching or direct synthesis—are emerging as safer, more sustainable options for industrial-scale fabrication.[97] Notably, the scalability of MXene synthesis has already been demonstrated in pilot-scale settings for widely used materials, such as $Ti_3C_2T_x$. Techniques such as continuous-flow exfoliation, roll-to-roll deposition, and freeze-drying have enabled the production of multi-gram to kilogram scales. The successful printing of MXene inks on biosensor substrates further highlights their compatibility with industrial manufacturing workflows.[97] Furthermore, compared to traditional enzymes, MXenzymes offer several practical advantages that support their scalability. First, their synthesis is simpler and more amenable to scale-up, avoiding the need for complex biotechnological processes and cold-chain logistics. Second, while MXenes may exhibit batch-to-batch variability (e.g., in surface terminations or flake thickness), these parameters can be more easily standardized post-synthesis than the properties of biologically produced enzymes. Third, MXenzymes exhibit superior shelf stability under ambient conditions, eliminating the need for refrigerated storage, a major limitation for enzyme-based kits in field applications. Last, while initial synthesis costs may be non-negligible, industrial-scale production using methods like ball milling and batch reactors is feasible. This contrasts with natural enzymes, whose high purity and activity often necessitate expensive expression systems, purification steps, and stringent quality control measures. As such, a comprehensive assessment of all these aspects is urgently required to determine the practical applicability of MXenzymes.

5. Summary and Outlook

This mini-review highlights recent advancements in MXenzymes with a critical focus on the current challenges and open questions. Nanozymes hold promise for advancements in several cutting-edge fields, such as in biomedical applications, sensing, and environmental remediation. However, as research progresses, the still unresolved aspects must be unraveled. The majority of the available literature remains at the proof-of-concept stage, primarily focusing on qualitative demonstrations of the material's effectiveness rather than undertaking in-depth systematic investigations.

As far as concerns the synthetic route to produce MXene, which is strictly linked to surface tunability, other methods should also be considered. Only limited studies have been conducted on MXenes produced by molten salt synthesis, electrochemical etching, or direct gas-phase synthesis.[98] These different routes could open new avenues, as the obtained 2D materials have diverse surface chemistries (the surface hydrophilicity/hydrophobicity can be finely tuned), thus effectively slowing down degradation while potentially lowering production costs. In addition, the different synthesizing methods can also influence layer thickness, degree of delamination, as well as defects density and exposed transition metal atoms, thus resulting in potentially tailored catalytic properties.

Moreover, computational studies, combined with in-depth experimental investigations of the enzyme-like catalytic mechanisms, are needed. Control experiments using only MXene should be considered, and the results compared to those obtained with nanocomposites or modified MXenes. Kinetic studies (applying Michaelis–Menten kinetics, turnover frequency, and Arrhenius plots) performed with and without MXene surface modifications will be useful to understand the structure–activity relationship and to discern between simple electron transfer and surface redox reactions. Additionally, high-resolution structural characterizations, such as atomic force microscopy (AFM), will be useful for revealing layer thickness, defect density, and surface roughness. XPS and electron energy loss spectroscopy (EELS) will also be used to track oxidation states and local coordination environments of metal atoms, which are key to identifying active sites. Electron paramagnetic resonance (EPR), combined with operando techniques such as X-ray absorption spectroscopy (XAS), will be crucial in tracking possible reaction intermediates and shedding light on the catalytic mechanism.

Rational engineering of defects and dopants will also be fundamental: indeed, by introducing controlled vacancies, heteroatom dopants (e.g., N, S, and P), or single metal atoms, it is possible to examine how such modifications alter catalytic pathways, especially in multi-enzyme systems. Also, a comprehensive investigation of the type of MXene used (as Ti-, V-, and Nb-based ones, but also Mo- or Ta-MXenes) could be useful to fully grasp the possible role of the metal atoms and/or of defects and impurities intrinsic to the 2D material itself, as well as its role in the redox potentials and the intrinsic biocompatibility.

Besides, computational modeling (as DFT) and machine learning to predict optimal MXene structures for enzyme mimicry, model adsorption geometries, charge transfer processes, and reaction energetics could also be useful. Particularly, DFT-based identification of active sites is pivotal since low-valence transition metal centers (e.g., Ti(III) and Nb(IV)) can serve as key redox-active sites, and O-terminated surfaces are shown to facilitate the adsorption and dissociation of hydrogen peroxide more effectively than F-terminated ones, lowering

the activation energy for peroxidase-like reactions. Furthermore, regarding the charge transfer pathways, theoretical work suggests that electron delocalization across the MXene basal plane enables rapid charge redistribution during catalytic turnover. The presence of surface defects and dopants modifies the local density of states, thereby enhancing the catalytic electron transfer pathways. Indeed, for multi-enzyme mimicry, DFT simulations of MXene-metal NPs systems have demonstrated that the co-localization of distinct active centers allows for sequential reactions, enabling different enzyme-like behaviors within the same nanoplatform.[99]

Finally, before potential implementation in real-world applications, MXenes' toxicity and their environmental impact must be further investigated, for instance, through chronic toxicity tests, standard protocols, biodegradability studies over a long period of time, or lifecycle assessments. Additionally, recent studies reported their integration in hydrogels or microneedles for drug delivery purposes. However, some challenges can also arise here, as controlled degradation and biocompatibility must be ensured, whereas immune activation must be avoided.

Hence, future research should focus on MXenzymes stability, biocompatibility, scalability, mechanistic insights, and catalytic enhancement, also through cross-disciplinary collaborations, industry partnership, and consortia. By addressing these fundamental challenges, MXene nanozymes could emerge as powerful and versatile enzyme mimics with transformative potential in healthcare, energy, and environmental remediation. Furthermore, by leveraging cross-disciplinary approaches (machine learning), researchers can unlock new functionalities and drive MXene nanozymes toward groundbreaking applications, expanding their use into clinical diagnostics and implantable devices, engineering more hybrid multifunctional platforms, and developing regenerative catalytic systems for smart environments.

Acknowledgements

E.P. acknowledges the Italian Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP) – Mission 4 "Education and Research" – Investment 1.2 "Funding projects presented by young researchers", financed by NextGenerationEU, project number SOE_0000117. E.P. also acknowledges the University of Milan, Research Support Plan – Line 4, project number PSRL423EPARG_01. Y.G. was supported by the U.S. National Science Foundation under grant CHE-2318105 (M-STAR CCI).

Open access publishing facilitated by Universita degli Studi di Milano, as part of the Wiley - CRUI-CARE agreement.

Conflict of Interests

The authors declare no conflicts of interest.

Keywords: Enzyme catalysis · MXenes · MXenzymes · Nanozymes · Reaction mechanism

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Manuscript received: April 22, 2025
Revised manuscript received: June 4, 2025
Accepted manuscript online: June 10, 2025
Version of record online: July 3, 2025