

Bio-Functionalized MXenes: Synthesis and Versatile Applications

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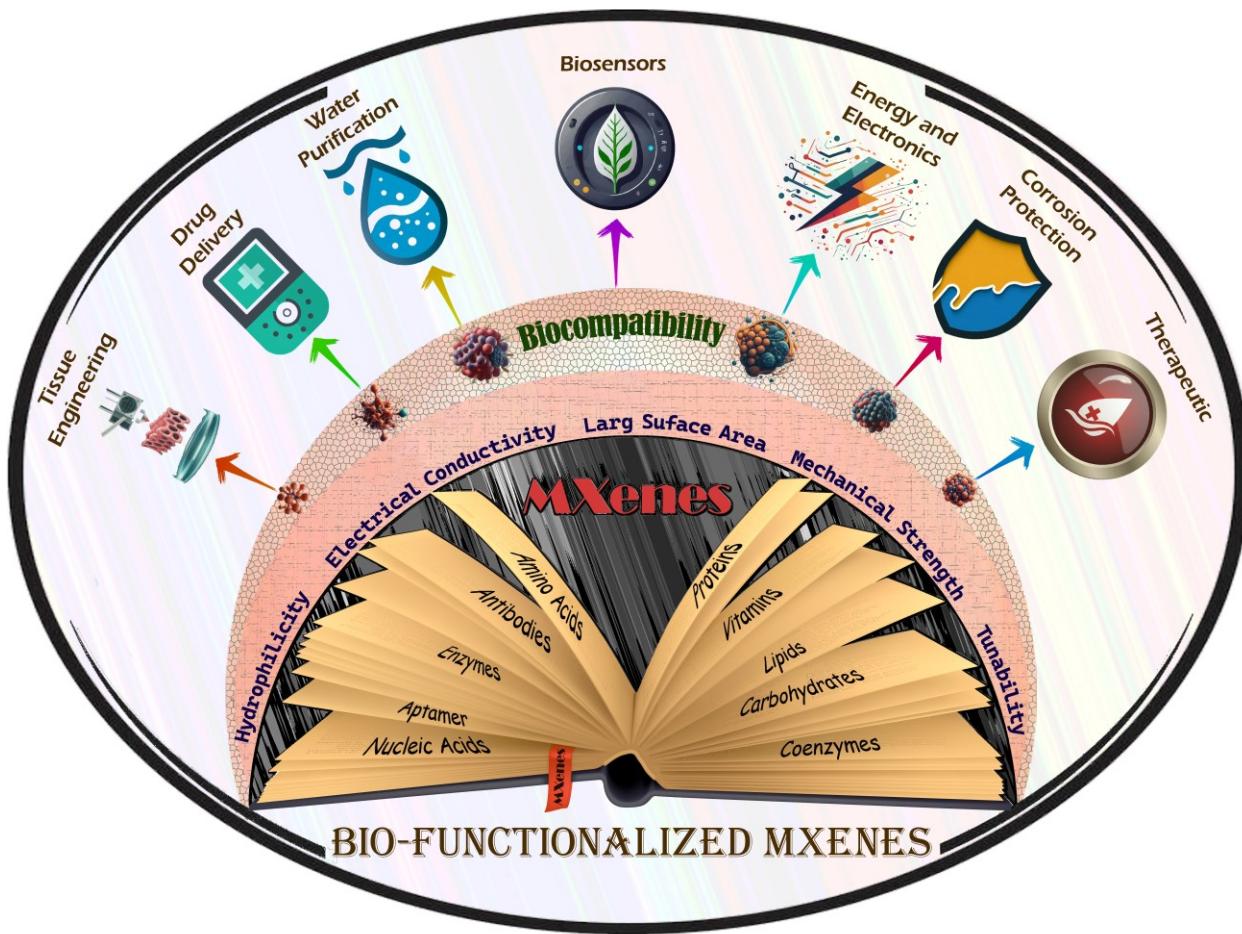
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Abstract

MXenes, synthesized predominantly through selective etching of MAX phases, exhibit remarkable properties, including high electrical conductivity, tunable surface chemistry, outstanding mechanical strength, and notable hydrophilicity. Recent advancements in bio-functionalization have further enhanced these intrinsic characteristics, unlocking unprecedented opportunities for MXenes across a wide spectrum of applications in both biomedical and environmental domains. This review provides an in-depth analysis of the synthesis strategies and functionalization techniques that improve MXenes' biocompatibility and expand their potential uses in cutting-edge applications, including implantable and wearable devices, drug delivery systems, cancer therapies, tissue engineering, and advanced sensing technologies. Moreover, the review explores the utility of bio-functionalized MXenes in areas such as corrosion protection, water purification, and food safety sensors, underscoring their versatility in addressing urgent global challenges. By conducting a critical evaluation of current research, this review not only highlights the immense potential of bio-functionalized MXenes but also identifies pivotal gaps in the literature, offering clear pathways for future exploration and innovation in this rapidly evolving field.

Graphical Abstract



1. Introduction

MXenes, a reasonably new class of two-dimensional (2D) materials, has gained significant attention in recent years for their unique properties and practical applications [1–7]. MXenes are a family of carbides, nitrides, or carbonitrides typically formed by selectively etching their parent structures, MAX phases [8–12]. MXenes have high surface area [13,14], excellent electrical conductivity [15,16], and a rich surface chemistry that can be tailored for various applications [17–23]. In addition to MXenes, other 2D materials such as graphene oxide (GO) and molybdenum disulfide (MoS₂) have also attracted significant attention. The exploration of these 2D materials, alongside MXenes, underscores the expanding landscape of 2D nanomaterials for advanced technological applications [24–31].

MXenes have gained significant attention in several fields because of their unique structure and surface chemistry [1,32,33]. For specific applications, however, they often require further modification to achieve optimal performance, particularly in biomedical [34–36], environmental [37–39], and energy [40–42] sectors. Various methods have been explored for tailoring surface properties, improving stability, and improving biocompatibility [43–45].

The most common approach involves polymer [46–48], organic ligand [49–51], and biomolecules [52–54] being covalently or non-covalently functionalized on MXene surfaces. Covalent functionalization ensures stable and long-term modifications by forming chemical bonds with surface functional groups like hydroxyl or fluorine [55–57]. Whereas non-covalent functionalization preserves MXene's intrinsic properties through weaker interactions like electrostatic forces or π - π stacking [58–60].

Another modification technique is the intercalation of various ions or molecules between MXene layers. As a result, the electrical, mechanical, and electrochemical properties of the

material are altered [61–65]. Energy storage applications benefit from intercalation because it increases interlayer spacing, which enhances ion diffusion [66–68]. Additionally, this modification improves MXene's water purification and biomedical performance [69–71].

MXenes can also be combined with other materials, such as graphene [72,73], polymers [48,74], and nanoparticles [75,76], to form hybrid structures. Hybrid materials have improved mechanical strength, electrical conductivity, and multifunctionality, making them suitable for use in composite materials, sensors, and catalysis. By modifying MXenes, new applications can be developed for them in cutting-edge technology for highly specific purposes [77–81].

Bio-functionalization is the modification of a material with biological molecules to enhance the interaction of the material with biological systems [82–84]. Specifically, bio-functionalization of MXenes can expand their capabilities to biomedical sciences [85], environmental sciences [86], and energy applications [87]. By attaching biomolecules such as proteins, enzymes, antibodies, or DNA to MXene surfaces, researchers have been able to develop hybrid materials with improved biocompatibility, specificity, and functionality [88–91].

This review provides a comprehensive overview of bio-functionalized MXenes, referred to as BioMXenes, covering their synthesis, characterization, and diverse applications. Unlike previous reviews that have concentrated on bio-functionalizing 2D materials other than MXenes (particularly on graphene and its derivatives), this review focuses solely on MXenes. It not only fills the gap that currently exists in the literature but also paves the way for further exploring MXenes' potentials. We will discuss the various methods employed to synthesize MXenes and functionalize them with biological agents. We will also explore the techniques used in characterization of the BioMXenes to understand their chemical, physical, and biological properties. The review will further investigate the diverse applications of BioMXenes, highlighting

their potential in various fields including implantable and wearable devices, drug delivery, biosensing, and tissue engineering, as well water purification, sensing, energy, and catalysis, demonstrating the versatility and broad impact of these nanomaterials. Despite their numerous advantages, BioMXenes present certain challenges, which this review examines. The review also provides future perspectives, identifying emerging trends, potential applications, and directions for further research in this promising area. This comprehensive analysis also provides BioMXenes' insights into their synthesis, characterization, applications, and future prospects, facilitating improved understanding and development of these MXene-based materials (**Figure 1**).

Figure 1. Flowchart depicting the organization of this review.

2. Production and Bio-functionalization of MXenes

MXenes' properties and potential applications are impacted by their synthesis and functionalization [92–96]. The methods for synthesizing and bio-functionalizing MXenes are discussed in this section.

2.1. Methods of MXene Synthesis

As MXene synthesis methods have been discussed in numerous published scientific papers in detail [97–103], very briefly synthesis techniques for MXenes are reviewed in this section. MXenes are synthesized from their parent MAX phases, which are layered ternary carbides, nitrides, or carbonitrides. The general formula for MAX phases is $M_{n+1}AX_n$, where $n = 1$ to 4, M is an early transition metal, A is an A-group element (mostly IIIA and IVA), and X is carbon and/or nitrogen. There are two general types of synthesis approaches for MXenes: top down and bottom up (**Figure 2**) [104–110]. MXenes have been synthesized mostly via the selective etching of the A layers from the MAX phases, which is a top-down approach.

Figure 2. Synthesis of MXene. a) A top-down approach via selective etching. Reproduced with permission [110–112]. Copyright 2016, Wiley b) a bottom-up approach to prepare Mo₂C via a CVD process. Reproduced with permission [110–112]. Copyright 2022, Elsevier.

Top-down approaches

The top-down approaches produce MXenes by exfoliating layers of MAX phases. Because of their simplicity and effectiveness, these approaches are popular among researchers [113–115]. Here we discuss three top-down approaches briefly.

Chemical Etching. Using fluoride-containing acids such as hydrofluoric acid (HF) or hydrochloric acid (HCl) and lithium fluoride (LiF), chemical etching selectively removes A layers from MAX phases. Various types of MXenes can be produced with high yield and quality by choosing appropriate MAX phase precursors. However, the use of HF poses significant risks, defects and impurities may be introduced during the etching process, affecting the properties of MXenes [116–120].

Electrochemical Etching. As an alternative to chemical etching, electrochemical etching removes the A layers by applying an electric field to the MAX phase in an electrolyte solution. This approach provides more control on the etching process and the resultant MXene properties. Electrochemical etching can be performed under milder conditions than chemical etching, reducing hazardous chemicals risk. Among challenges of this approach are the need for careful process optimization and difficulties in scalability [121–125].

Mechanical Exfoliation. By using a mechanical procedure such as sonication, ball milling, and shearing, MAX phases are peeled off, resulting in MXenes. Mechanical exfoliation avoids the use of hazardous chemicals, making it a safer and more environmentally friendly method. The process is relatively simple and cost-effective. Compared to chemical and electrochemical

methods, the yield is typically lower, and the resulting MXenes can also suffer from defects due to mechanical exfoliation, resulting in non-uniform layer thickness ^[126–131].

Bottom-up approaches

MXenes are assembled from atomic or molecular precursors in a bottom-up approach. Material composition and structure can be precisely controlled through this method. Here, we very briefly discuss two commonly used bottom-up approaches.

Chemical Vapor Deposition (CVD). During CVD, volatile precursors are decomposed over a heated substrate to form MXene layers. Gaseous metal chlorides and carbon or nitrogen as typical elements are heated at high temperatures to produce the product. This approach can produce highly-pure MXenes with well-defined structures (with controlled thickness and crystallinity), making this approach suitable for applications requiring MXenes with precise specifications. However, it requires complex and expensive equipment as well as precise control of process conditions, and is challenging to scale up ^[12,132,133].

Solution-based Synthesis. Under hydrothermal or solvothermal conditions, metal salts react with carbon or nitrogen sources in a solvent. MXene size and morphology can be controlled by tuning the reaction parameters. Solution-based synthesis is performed at relatively lower temperatures than CVD and allows various dopants to tailor MXenes' properties. Achieving uniform size and thickness can be difficult with this approach, and the process may require post-synthesis treatments to enhance product quality ^[134–139].

2.2. Techniques for Bio-functionalization

MXenes are bio-functionalized by modifying their surfaces with biological molecules to enhance the interaction between MXenes and biological systems. Covalent and non-covalent interactions are formed to achieve this goal (**Table 1**).

Table 1. Overview of bio-functionalization techniques for MXenes, including covalent and non-covalent methods, their applications, advantages, and challenges.

| | Technique | Description | Applications | Advantages | Challenges | Ref |
|---------------------------|----------------------------|--|--|---|---|---------------|
| Covalent | Silane Coupling | Biomolecules linked to MXene using silanes (e.g., amines, thiols) with hydroxyl groups. | Biosensing, drug delivery, tissue engineering | Versatile, incorporation of diverse biomolecules, strong - stable attachment, customizes surface properties (e.g., zeta potential, dispersibility). | May affect MXene properties (e.g., agglomeration, changes in conductivity). | [52,140–150] |
| | Carbodiimide Chemistry | Activates carboxyl groups for covalent bonding with amino groups in biomolecules via compounds like EDC. | Biosensing, (e.g., protein conjugation, enzyme immobilization) | Biocompatible, minimal toxic by-products, high efficiency, especially useful for sequential bioactive molecule attachment. | Competing side reactions may reduce yields, reaction conditions must be carefully controlled. | [53,151–158] |
| | Click Chemistry | Specific reactions (e.g., azide-alkyne cycloadditions) enable high yield and stable covalent bonds. | Drug delivery, biosensing, tissue engineering | Efficient in aqueous environments, high yield, minimal by-products, preserves bioactivity in dynamic biological environments. | Weaker than other covalent bonds in harsh conditions. | [144,159–167] |
| Non-covalent interactions | Electrostatic Interactions | Positively charged biomolecules interact with negatively charged MXenes for reversible binding. | Drug delivery, biosensors, bioseparation | Reversible and tunable depending on pH and ionic strength, preserves bioactivity, especially useful for repeated cycles (e.g., biosensors). | Highly sensitive to environmental changes like pH and ionic strength. | [168–183] |
| | Hydrogen Bonding | Polar groups on biomolecules (e.g., hydroxyl, oxygen) form reversible hydrogen bonds with MXenes. | Biosensors, enzyme immobilization, drug delivery | Moderate strength allows for reversible attachment, preserves biomolecule conformation and bioactivity, suitable for dynamic conditions. | Sensitive to environmental changes (e.g., temperature, pH), weaker than covalent bonds. | [184–202] |
| | π-π Stacking | Interaction between delocalized π-electrons in aromatic biomolecules and MXenes. | Biosensing, targeted drug delivery | Maintains MXene's conductivity and flexibility, ideal for dynamic applications (e.g., real-time biosensing, repeated use). | Weaker interaction, susceptible to shear forces and changes in pH or ionic strength. | [203–216] |

| | | | | | |
|-------------------------|--|---|--|--|---------------|
| Van der Waals Forces | Universal weak forces based on molecular dipoles, useful for capturing a wide range of biomolecules. | Biosensing, environmental remediation | Gentle, non-invasive, preserves MXene properties, facilitates dynamic applications (e.g., controlled drug release). | Weaker binding, less stability in varying environmental conditions. | [213,217–230] |
| Layer-by-Layer Assembly | Sequential deposition of oppositely charged biomolecules and polyelectrolytes to create multilayered structures. | Biosensing, drug delivery, tissue engineering, environmental applications | Allows customization of surface functionalities, scalable, adaptable for different biomolecules, for dynamic and responsive systems (e.g., pH or temperature-sensitive). | Challenges in uniformity and reproducibility of layers, requires precise control of deposition conditions. | [175,231–237] |

Surface termination groups

A unique property of MXenes is the ease of their functionalization via their surface groups including =O, –OH, –F, –Cl, and –I. MXene properties, such as hydrophilicity, conductivity, and chemical reactivity, are strongly influenced by the concentrations of these termination groups. However, the determination of the exact concentrations of these surface groups (**Figure 3**) still remains a major challenge for several reasons [238,239].

Figure 3. Major surface groups of MXenes. Reproduced with permission [239]. Copyright 2023, Elsevier.

Challenges in surface termination quantification. First, it has been reported that distinguishing –OH from =O groups in high-resolution spectra is challenging [239]. Second, the measured composition of MXene surface groups depends on the instrument used to make the measurement. For example, XPS, NMR, and neutron pair distribution function (PDF) analyses of a MXene sample yielded number O:OH:F ratios of 1:0.07:4 [240], 1:0.07:0.3 [241], and 1:8:11 [242], respectively. XPS is a widely used technique, but its results may not agree with those of NMR and PDF. This discrepancy underscores the need for more accurate and standardized surface-group characterization techniques [238]. Combining experimental observations and computational

predictions can enhance our understanding of mixed-termination surfaces. While high-resolution microscopy and spectroscopy can provide more precise measurements, standardized protocols are still needed to be developed and widely adopted.

Dependence of the surface group concentrations on the MXene synthesis method used. The concentrations of the surface functional groups of a MXene strongly depend on the synthesis method used to produce the MXene. MXenes produced using HCl/LiF or HF have been reported to have –OH, =O, and –F surface groups. The etching and delamination conditions and durations also affect the concentrations. Once Al atoms are etched out, Ti-O, Ti-OH, and Ti-F bonds replace Ti-Al bonds [239,243,244]. On the other hand, electrochemical etching has been reported to yield MXenes with –Cl, =O, and –OH surface groups, water-free molten salt etching generates MXenes with halogen terminations (–Cl, –Br, –I) [239,245], and alkali-based etching methods, such as those using KOH or NaOH, produce MXenes predominantly terminated with –OH and =O groups. Through alkali etching, $Ti_3C_2(OH)_2$ MXenes were successfully synthesized with a high purity of surface functionalization (92 wt.%) [239,246].

Surface termination groups suitable for biofunctionalization

MXenes' surface groups are highly reactive to form covalent bonds with biomolecules. –OH groups, for example, are known to interact covalently with a wide range of biomolecules. Proteins, peptides, and nucleic acids possess carboxyl groups and amine groups that can undergo esterification or amidation reactions with the –OH surface groups of MXenes [247–251]. Oxygen atoms in carbonyl (C=O) and oxide (O=Ti) functional groups of MXenes facilitate the formation of covalent bonds, resulting in the formation of imine or ester linkages crucial to stable bioconjugation when they react with amines (–NH₂) or hydroxyls (–OH) [252,253]. Under certain conditions, fluorinated MXenes can form strong covalent bonds with fluorophilic biomolecules or

can be used in chemically stable environments. MXenes terminated with halogen groups (–Cl, –Br, or –I) can also engage in covalent bonding. As an example, chlorine can react nucleophilically with amines and thiols in biomolecules, presenting a promising prospect for bio-functionalizing MXenes^[238,254,255].

MXene surface reactivity in the presence of steric effects. When there are multiple functional groups close to each other on MXene surface or when biomolecules reacting with MXenes are large, steric hindrance lowers MXene surface reactivity. A bulky biomolecule, such as an enzyme or protein, may cause steric hindrance, which can prevent covalent bond formation. Consequently, even when hydroxyls or halogens are present in significant amounts, only a few can form covalent bonds. A variety of strategies can be employed to mitigate steric hindrance, including selective functionalization to reduce the density of competing groups or using spacer molecules to increase accessibility^[256–258].

Covalent bonding

Covalent functionalization involves the formation of strong chemical bonds between the surface groups of MXenes (typically hydroxyl, oxygen, or fluorine groups) and bioactive molecules such as proteins, DNA, or enzymes. This technique ensures secure attachment and allows precise control over the surface chemistry of MXenes, which is crucial for applications requiring long-term stability and specific interactions with biological systems. BioMXenes with covalent bonds attaching biomolecules to MXene surface are suitable for in-vivo application in fluid-borne or enzyme-mediated degradation environments. Furthermore, they ensure durable activity and performance of molecules for extended periods^[141,149,150]. Common methods include silanization^[52] and carbodiimide coupling^[142].

Silane Coupling Agents. Biological molecules are linked to MXene surfaces using silanes with functional groups, such as amines and thiols that form covalent bonds with the hydroxyl groups on the MXene surface (**Figure 4a**) [52]. Functional groups able to interact with specific biomolecules can be selected, enhancing MXene-based systems' selectivity and specificity. MXene applications in liquid and solid phases can also be optimized through the selection of silane precursors, which allow the modification of surface properties such as zeta potential and dispersibility [52,184,259].

Silane coupling agents are versatile enough to bond with a wide range of biomolecules, including proteins, peptides, and nucleic acids. Various fields, including biosensing, drug delivery, and tissue engineering can benefit from silanes' adaptability. Functionalization begins with the hydrolysis of silane coupling agent, which produces reactive silanol groups that are able to react with hydroxyl groups on MXenes surface to form stable siloxane bonds. Covalent linkages not only secure biomolecules firmly to MXenes, but also facilitate a tailored interface for specific reactions. Furthermore, silane chemistry allows precise control over the degree of functionalization. The density of biomolecules on the MXene surface can be optimized by adjusting the concentration of the silane and the reaction conditions [52,140,143,151,260].

Strong and stable attachment to MXene is one of the primary advantages of silane coupling agents, ensuring longevity and reliability of interactions with biomolecules. Keeping biomolecules stable is especially important for applications requiring long-term activity, such as biosensors. Moreover, the ability to design silane-based linkers with specific chemical groups improves the selectivity of the functionalized MXenes. Developing highly targeted therapeutic or diagnostic systems can be achieved by selecting silanes with functional groups that specifically interact with certain receptors or cells [52,144,145,261].

Despite their many advantages, silane coupling agents present a number of challenges. Silanes can unfavorably affect the properties of MXenes, potentially leading to agglomeration or changes in electrical conductivity and mechanical strength. Moreover, the choice of silane precursor influences surface properties such as zeta potential and dispersibility of functionalized MXenes. Optimizing MXene applications in both liquid and solid-phase systems requires consideration of these factors. Briefly, silane coupling agents offer a powerful strategy for bio-functionalizing MXenes, allowing strong and specific attachment of biomolecules by optimizing silane types and functionalization conditions [146–148].

Carbodiimide Chemistry. Carbodiimide chemistry is widely used for functionalizing MXene surfaces by activating carboxyl groups to facilitate amide bonds with amino groups. Many biomedical applications can be achieved through carbodiimide coupling, particularly in the conjugation of proteins, peptides, and other amine-containing molecules on MXenes' surface (**Figure 4b**) [142]. During this process, carboxyl groups are activated by carbodiimide compounds, such as EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide). Activation causes the formation of reactive O-acylisourea intermediates that readily form stable amide bonds with amino groups in biomolecules. Various factors, including pH, temperature, and reactant concentration, can influence the efficiency of this reaction. Under certain conditions, competing reactions may occur with carbodiimide coupling. For instance, hydrolysis of activated intermediates can lead to decreased yields and unwanted side products, necessitating careful reaction condition optimization [53,142,152–154].

Biocompatibility is one of the primary advantages of carbodiimide coupling. Using reagents without toxic by-products makes this method especially suitable for biomedical applications that require safety. By utilizing this feature, functionalized MXenes can be

successfully developed for use *in vivo* as well as in sensitive biological environments. Researchers can also covalently attach different layers of bioactive molecules successively using carbodiimide chemistry due to their versatility. To improve therapeutic or diagnostic performance, MXene surfaces must be able to integrate different functionalities using complex architectures [142,155,156].

Carbodiimide coupling efficiency can be improved by implementing strategies such as EDC concentration, pH, reaction time, and temperature optimization and control. By optimizing these conditions and increasing the number of activated MXenes carboxyl functional groups, yields can be increased, and the rates of unwanted side reactions can be decreased. Typically, N-hydroxysuccinimide (NHS) is used to stabilize O-acylisourea esters, resulting in more stable intermediates. In summary, carbodiimide chemistry allows the bio-functionalization of MXenes with stable covalent bonds with a variety of biomolecules by leveraging multi-step functionalization potential [142,157,158].

"Click" Chemistry. Due to its specificity and efficiency, click chemistry is a powerful and versatile bio-functionalization strategy for MXenes. Click reactions allow robust conjugation of various bioactive entities, enhancing MXene functionality in biomedical applications. Additionally, click chemistry's ability to function efficiently in aqueous environments further emphasizes its suitability for biological applications (**Figure 4c**) [159,260]. Typically, click reactions involve strong covalent bonds, such as azide-alkyne cycloadditions (Huisgen reactions) or thiol-ene reactions. Unlike traditional coupling methods, these reactions are not only rapid but also produce high yields and minimal by-products. By precisely tuning reaction conditions, such as temperature and pH, click chemistry allows MXenes to functionalize in any context [160–163,260]. A hallmark of click chemistry is its compatibility with different functional groups and reaction environments. Multiple bioactive substances can be decorated on MXenes, making the chemistry

suitable for a wide variety of biological applications, including drug delivery, biosensing, and tissue engineering. A conjugated biomolecule can maintain its bioactivity and functional integrity despite dynamic interactions commonly observed *in vivo* using this method. A click reaction can improve drug delivery systems by incorporating targeting ligands, therapeutic agents, or probe imaging agents. Overall, click chemistry is a robust, versatile, and compatible method of bio-functionalizing MXenes, due to its specificity, versatility, and biocompatibility [164-167,260].

Covalent functionalization is widely used in biomedical application to ensure the stable conjugation of therapeutic agents, in biosensors for the immobilization of enzymes or antibodies, and in tissue engineering scaffolds to promote cell adhesion and growth [52].

Figure 4. a) Silane coupling between a MXene and carboxyl groups present in the Fc region of the bio receptor (anti-CEA). Reproduced with permission [52]. Copyright 2018, Elsevier. b) Schematic of a detection procedure for the SPR biosensor prepared by carbodiimide chemistry. Reproduced with permission [262]. Copyright 2020, ACS. c) Schematic illustration of the PNA-MXene electrochemical biosensor for miRNA detection based on chemical functionalization of the MXene nanosheets followed by bio-orthogonal copper-free click chemistry. Reproduced with permission [260]. Copyright 2024, RSC.

Non-covalent interactions

Biomolecules and the MXene surface interact less strongly and reversibly via non-covalent interactions. Non-covalent functionalization relies on weaker interactions such as van der Waals forces, hydrogen bonding, π - π stacking, and electrostatic interactions. This approach preserves the intrinsic properties of MXenes, such as electrical conductivity and mechanical flexibility, which may be compromised by covalent bonding. Techniques include physical adsorption that allows for the attachment of biomolecules without altering the MXene's structure [203].

Non-covalent functionalization is particularly suitable for applications where the conductivity of a MXene is crucial, such as biosensors, energy storage devices, and electronic devices. Unlike covalent bonds, non-covalent methods allow biomolecules to be attached without altering the MXenes' advantageous properties [263,264].

Electrostatic Interactions. Positively charged biomolecules interact electrostatically with negatively charged MXene surface to facilitate reversible functionalization. Typically terminated with –OH, –F, or –O groups, MXene surfaces serve as negatively charged binding and attraction sites for proteins, enzymes, and positive biopolymers. This method allows biomolecules to be attached without complex chemical reactions, making it ideal for reversible and simple applications. Electrostatic interactions can attach and detach biomolecules depending on pH and ionic strength. Especially advantageous are reversible bindings in dynamic applications such as biosensors or drug delivery systems, in which biomolecules must be captured and released repeatedly. Furthermore, the electrostatic approach ensures that proteins, DNA, and enzymes remain bioactive after attachment while preserving the native conformation and functionality of biomolecules. Depending on the surrounding medium pH, these interactions can be tuned by adjusting the charge state of the MXene surface as well as the biomolecules. By selecting MXenes with specific surface terminations, the strength and specificity of electrostatic interactions can be enhanced. By optimizing the surface charge of MXenes, biosensing platforms or bio-separation techniques can be more selective and more effective by attracting certain biomolecules while repelling others. Depending on the charge of the biomolecule, different layers can also be created, which increases the potential for multifunctional applications (**Figure 5a**) [168,169,176–178,265,266].

By changing the surrounding conditions, electrostatic interactions are inherently reversible, allowing bonded biomolecules to be released or desorbed. For example, lowering the pH can

reduce the electrostatic attraction by neutralizing the charges on the MXene surface and the biomolecules, resulting in faster desorption. Purification processes can also use electrostatic interactions to capture biomolecules under one set of conditions and then release them by altering pH or ionic strength. By utilizing this feature, MXene-based separation technologies can capture and purify biomolecules from complex mixtures, increasing their scalability and efficacy [176,179–182].

Even though electrostatic interactions are widely used to allow for functionalizing MXenes, there are challenges. These interactions are highly sensitive to environmental conditions. By unfavorably increasing the ionic strength of the solution, the charges on the MXene surface and the biomolecules can be screened, weakening electrostatic attraction, and potentially leading to desorption. Electrostatic functionalization cannot be used in environments where conditions fluctuate or are difficult to control, such as physiological or industrial environments [170,183,267,268]. MXene functional groups allow for adjusting MXene surface properties to enhance charge retention. Furthermore, selecting biomolecules with strong charge localization can improve the robustness of electrostatic binding, ensuring that interactions remain effective even under challenging environmental conditions. To maintain biomolecule attachment over extended periods, alternative functionalization strategies may be necessary, such as covalent bonds [171,172,268,269]. Reversible electrostatic interactions are particularly useful for certain applications. For instance, electrostatic attachment permits easy regeneration of sensor surfaces in biosensing applications, where biomolecules such as antibodies or enzymes need to be replaced frequently. pH-sensitive delivery platforms can be developed using electrostatic interactions, where drug molecules are bound to MXenes under neutral or basic conditions and released in acidic environments, such as tumor microenvironments [173–175,270–272].

Hydrogen Bonding. Proteins, enzymes, and nucleic acids form hydrogen bonds with MXenes due to their polar groups (such as hydroxyl or oxygen terminations). By using this type of interaction, biomolecules can be effectively attached to MXenes while preserving their intrinsic properties and chemical structure. Hydrogen bonds are moderate in strength, allowing reversible and dynamic attachments of biomolecules, which are essential for applications that require temporary interactions or frequent replacements of biomolecules (**Figure 5b**) [149,273].

Reversible hydrogen bonds are especially beneficial in biosensor applications, where biomolecule regeneration ensures repeated functionality. Hydrogen bonds can be used to attach antibodies or enzymes and enable them to be replaced or regenerated after each detection cycle without compromising the MXene's surface or functionality. Because of this versatility, hydrogen bonding is an important mechanism for functionalizing MXenes under dynamic biological or chemical conditions. Due to their rich surface terminations (e.g., hydroxyl, oxygen), MXenes have multiple hydrogen bonding sites for interacting with polar biomolecules like amines, carboxyls, and phosphate groups. A highly significant interaction occurs when nucleic acids, proteins, and enzymes bind to the MXene surface, where their structural and functional groups can align to form stable hydrogen bonds [149,185,195,196,273].

Biomolecules with complex three-dimensional structures, like proteins and enzymes, are especially suited to hydrogen bonding when maintaining their native conformation is crucial to their functionality. Non-covalent hydrogen bonds allow biomolecules to retain their natural folded structure upon binding, ensuring their biological activity. Catalytic activity must be retained in applications such as enzyme immobilization, where this feature is critical [197–200,274].

The moderate strength of hydrogen bonds is appealing for reversible or tunable biomolecular attachments. MXene remains electrically, mechanically, and chemically unaltered by

this type of interaction. By using hydrogen bonding, MXenes can retain their conductive properties for applications such as electrochemical sensors, while also enabling the controlled attachment and detachment of biomolecules. Furthermore, hydrogen bonding is beneficial in cases where biomolecules need to be temporarily attached, such as for single-use devices like disposable biosensors. Biomolecules can be easily released from the MXene surface without harsh chemical treatments using hydrogen bonding, ensuring that the MXene substrate remains intact and can be reused again [186,201,202].

Despite their many advantages, hydrogen bonds are sensitive to environmental factors. Temperature, pH, and solvent composition can significantly affect hydrogen bond strength and stability. By increasing the temperature, for instance, the relatively weak hydrogen bonds can be overcome, causing biomolecules to detach from the MXene surface. Variations in pH or ionic strength can alter the protonation state of the biomolecule's functional groups or the MXene surface terminations, weakening hydrogen bonding interactions and causing desorption. Depending on the application, this can be a limitation, especially when operating in conditions that fluctuate or are extreme, such as industrial processes or in-vivo biomedical systems, where maintaining consistent pH levels and temperatures is challenging. Nevertheless, this sensitivity can be utilized in controlled laboratory and diagnostic environments in order to create systems that respond to specific stimuli (for example, temperature-sensitive drug delivery systems), in which environmental changes trigger the release of attached biomolecules [186–188,275,276].

Hydrogen bonding is also useful in applications that require moderate and reversible binding. Biosensors, for example, use hydrogen bonding to attach biomolecules such as antibodies or enzymes, which need to be replaced after each use. By connecting drugs to the MXene surface, hydrogen bonds control the release of drugs in response to environmental changes, like pH changes

and temperature fluctuations. Separation technologies can also benefit from hydrogen bonding, as biomolecules can be captured under specific conditions (e.g., pH or temperature) and released by adjusting the environment. Due to this reversibility, high-throughput separation processes can be achieved, especially in capturing and releasing sensitive biomolecules such as proteins or DNA. Moreover, hydrogen bonding can be used to create multifunctional systems for biomedical and environmental applications using MXene-based hybrid materials [189–194].

π - π Stacking. MXenes interact with aromatic biomolecules, such as nucleic acids and proteins, through π - π stacking interactions. Through this non-covalent mechanism, biomolecules can be attached to MXene while preserving its surface chemistry and structural properties. π - π stacking refers to the attractive interactions between the delocalized π -electron systems of aromatic rings, which is particularly significant in biomolecules that exhibit aromatic characteristics (**Figure 5c**) [203]. The specificity of π - π stacking enhances the possibility of biosensing and targeted drug delivery. For instance, the ability of MXenes to capture specific DNA sequences or proteins through π - π interactions can facilitate the development of highly sensitive diagnostic platforms. The mechanism of π - π stacking involves the alignment of aromatic rings in a face-to-face or edge-to-face orientation, facilitating optimal overlap of π -orbitals. Depending on the geometric configuration as well as the nature of the aromatic groups involved, there is a strong effect on the strength of these interactions. Aromatic surfaces can approach closely, resulting in significant electron cloud overlap and strong binding [204,209,210,277]. Furthermore, by modifying the surface properties of MXenes, their ability to engage in stacking can be further enhanced. For example, changing the terminations on the surface or doping the MXenes with different elements can change their electronic structure, optimizing their interaction with aromatic molecules [211,212,278].

One of the main advantages of using π - π stacking for the attachment of biomolecules is that it preserves the intrinsic properties of MXenes such as their electrical conductivity and mechanical flexibility. The maintenance of these properties is crucial for applications such as electrochemical sensors, when their performance heavily depends on the ability to maintain these characteristics. The mild nature of π - π stacking also facilitates easy recovery and regeneration of the biomolecules, allowing for repeated use of MXene-based platforms without the need for harsh conditions that might compromise the integrity of the biomolecules. A reversible structure is particularly advantageous in real-time biosensing applications, where frequent cycles of binding and releasing are required in the biosensing process [213–216,277,279].

While π - π stacking offers numerous advantages, its relatively weak nature compared to covalent bonds can pose challenges in applications requiring robust and stable biomolecule attachment. Stable binding may be difficult in environments with shear forces, pH changes, or ionic strength variations. To enhance the robustness of π - π stacking, researchers are exploring hybrid strategies that combine these interactions with other binding mechanisms, such as electrostatic or covalent interactions, to enhance their robustness. Functionalized surfaces can be significantly improved by optimizing the surface characteristics of MXenes, for example by increasing surface roughness or by introducing functional groups that promote cooperative interactions [205–208,280].

Van der Waals Forces. MXenes also interact with a wide range of biomolecules through van der Waals forces, which are universal non-covalent interactions. The interactions occur when molecular dipoles vary in density, providing a versatile way to modify MXenes without altering their chemical properties. Van der Waals forces are particularly useful in applications that do not require strong binding specificity. Depending on the application, MXenes can capture a large range

of biomolecules, which makes them suitable for biosensing and environmental remediation (**Figure 5d**) [203,213,217,223].

Molecular interactions are influenced by the distance between molecules, closer proximity results in stronger interactions. By optimizing the surface area and porosity of MXenes, it is possible to increase the contact between the MXene surface and the biomolecules. One key advantage of using van der Waals forces for biomolecule attachment is the gentle and non-invasive nature of the binding process. Having this characteristic preserves the intrinsic properties of MXenes, which is crucial in applications requiring high conductivity and mechanical flexibility [224–226]. Van der Waals forces facilitate the detachment and renewal of biomolecules, allowing for dynamic applications. As an example, drug delivery systems can achieve a controlled release of therapeutic agents by controlling environmental factors like temperature and ionic strength [227–230].

Despite their versatility, van der Waals forces pose a challenge when it comes to binding stability. Under varying conditions, their relatively weak nature may not suffice to keep biomolecules from desorbing. Several strategies can be employed to address these challenges, including combining van der Waals forces with other functionalization methods. Incorporating van der Waals interactions with complementary bonding mechanisms, such as electrostatic attraction or stacking, researchers can make MXene-biomolecule systems more stable and effective, thereby extending their usefulness in practical applications [218–222].

Layer-by-Layer Assembly. Layer-by-layer (LbL) assembly involves sequentially depositing oppositely charged polyelectrolytes and biomolecules over MXene surfaces. Self-assembled coatings can have variable compositions, thicknesses, and functionality due to their multilayered structure. Especially in applications where customizability and scalability are critical, LbL

assembly is an excellent approach for bio-functionalizing MXenes. Because of the technique's inherent flexibility, biomolecules like proteins, DNA, and enzymes can be incorporated along with polyelectrolytes, allowing specific surface functionalities to be tailored for specific applications, such as biosensing or targeted drug delivery (**Figure 5e**)^[231,281]. MXenes are typically negatively charged, and polyelectrolytes are positively charged, resulting in electrostatic attraction, followed by the adsorption of biomolecules with complementary charges. Each deposition cycle results in the growth of a multilayered structure, whose thickness is determined by the number of layers deposited. Assemblies can also be strengthened by using non-covalent interactions, such as hydrogen bonds or van der Waals forces^[232,282,283]. Furthermore, LbL assembly can produce dynamic systems that respond to environmental changes, such as pH or temperature, by incorporating stimuli-responsive materials. Controlled releases or activations of biomolecules are especially beneficial in biomedical applications^[233,234,284–286].

However, LbL assembly faces challenges related to uniformity and reproducibility of the coatings. The performance of functionalized MXenes can be affected by variation in layer thickness or composition if deposition conditions are not tightly controlled. To overcome these challenges, researchers are exploring advanced characterization techniques that monitor layer formation in real time and optimize deposition parameters in these systems^[175,235–237,281,287–290].

Non-covalent functionalization is particularly useful in applications where weak interactions are required, such as in stimuli-responsive drug delivery, where the release of therapeutic agents is triggered by environmental changes^[273,291].

Figure 5. a) Coating MXenes with Collagen by electrostatic interaction for controlling cytotoxicity. Reproduced with permission^[292]. Copyright 2020, Elsevier. b) Interfacial hydrogen bonds between serine-modified MXene nanosheets and serine-grafted epoxidized natural rubber (S-ENR) chains. Reproduced with permission^[150]. Copyright 2020, ACS. c) DNA-encoded MXene-Pt nanzyme by π - π stacking for enhanced colorimetric sensing of mercury ions. Reproduced with permission^[293]. Copyright 2022, Elsevier. d)

Correlation between the adsorption energy of each nucleobase-MXenes and their van der Waals volume. Reproduced with permission [294]. Copyright 2021, Elsevier. e) Schematic diagram of MXene/chitosan-quercetin multilayers (MCQMs) composed of MXene flakes and chitosan-quercetin membranes by layer-by-layer assembly. Reproduced with permission [282]. Copyright 2021, Elsevier.

3. BioMXenes Applications

BioMXenes offer a wide range of applications due to their unique properties, including high electrical conductivity, large surface area, and tunable surface chemistry [168,295,296]. This section explores the diverse applications of these materials including water purification, separation, corrosion protection, coating, drug delivery, therapeutic, tissue engineering, energy, electronics, material science, engineering, and biosensors (**Figure 6**).

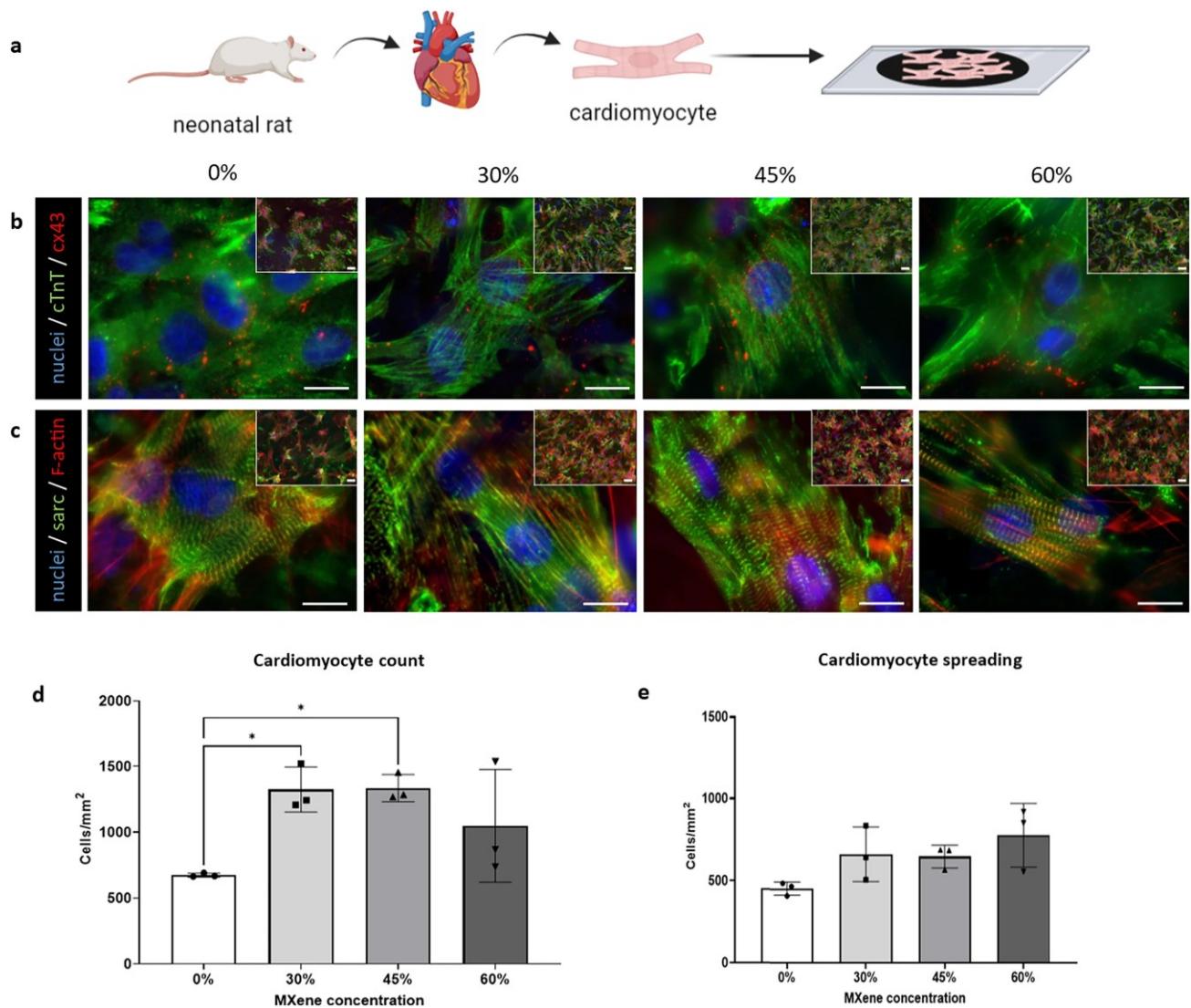


Figure 6. a) Schematic illustrating the setup of an experiment with extracted neonatal rat cardiomyocytes seeded onto biohybrid substrates containing 0%, 30%, 45% and 60% MXene and cultured for 7 days. b) Row of immunofluorescent staining micrographs with nuclei in blue, cardiac troponin T (cTnT) in green and connexin-43 (cx43) staining in red (scale bar: 20 μ m) at day 7. c) Row of immunofluorescent staining micrographs with nuclei in blue (sarcomeric α -actinin green and F-actin staining by staining with rhodamine phalloidin (scale bar: 10 μ m)) at day 7. d) Quantification of viability (cells mm^{-2}) on day 7. e) Cardiomyocytes spreading quantification ($\mu\text{m}^2 \text{ cell}^{-1}$). Statistical analysis was performed using a one-way ANOVA with Tukey's multiple comparison test, where a resultant p-value of less than or equal to 0.05 was considered significant. *Signifies a statistically significant difference between the groups indicated. All graphical data represents the mean value with error bars defining \pm standard deviation. Reproduced with permission [85]. Copyright 2023, Nature.

3.1. Water Purification and Membrane

BioMXenes have gained considerable interest due to their remarkable physicochemical properties, including large surface areas, hydrophilicity, and ease of surface modification. **Table 2** summarizes recently reported studies on nanofiltration, dye adsorption, and heavy metal ion removal.

Table 2. Overview of research projects investigating water purification and separation applications of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|---|---|---|--|-------|
| Ti ₃ C ₂ T _x | Glycine, L-Glutamic Acid, L-Lysine, L-Cysteine | Enhancement of nanofiltration (NF) performance and antifouling properties | Improved water permeability and separation performance with high salt rejection and antifouling properties | [297] |
| Ti ₂ CT _x | Chitosan, Lignosulfonate, Enzymatic Hydrolysis Lignin | Adsorption performance for Pb(II) ions | EHL-functionalized Ti ₂ CT _x showed the highest adsorption capacity for Pb(II) ions | [298] |
| Ti ₃ C ₂ T _x | L-Cysteine, L-Histidine | Separation of oil-water mixtures and dye wastewater | Achieved high separation efficiency and flux rates for various mixtures | [141] |
| Ti ₃ C ₂ T _x | Levodopa (DOPA) | Removal of heavy metal ions | Enhanced adsorption capacity and potential for further functionalization | [142] |
| Ti ₃ C ₂ T _x | Dialdehyde Starch Nanoparticles (DASNPs) | Removal of dyes and pharmaceutical residues | Excellent adsorption performance for dyes and pharmaceutical residues | [273] |
| Ti ₃ C ₂ T _x | Leather collagen, oxidized sodium alginate | Removal of Cr(VI) and water evaporation | High Cr(VI) adsorption capacity and enhanced water evaporation rate under solar illumination | [299] |

Nanosheets of MXene, particularly Ti₃C₂T_x, have been explored as building blocks for high-performance nanofiltration membranes. In a study by Luo *et al.*, amino acid-bonded Ti₃C₂T_x MXene membranes were introduced with enhanced performance (**Figure 7a**)^[297]. They achieved stable Ti–N bonds in the MXene nanosheets through the addition of glycine, l-glutamic acid, l-lysine, and l-cysteine. Among the various modifications, the glycine-bonded membrane demonstrated the best performance, with impressive salt rejection rates and superior antifouling capabilities. The results of this work demonstrate a straightforward approach to enhancing 2D MXene-based membranes that offers significant promise for water treatment^[297].

A BioMXene was synthesized for the adsorption of heavy metal ions, such as Pb(II) and Cr(VI). Using biosurfactants such as chitosan, lignosulfonate, and enzymatic hydrolysis lignin, Wang *et al.* enhanced Ti_2CT_x MXene's adsorption performance (**Figure 7b**) ^[298]. It appeared that EHL-functionalized Ti_2CT_x adsorbs 232.9 mg of Pb(II) ion very efficiently, which can be attributed to its active functional groups that prevent restacking and increase adsorption sites ^[298].

In another innovative approach, Wang *et al.* grafted polydopamine-pretreated $\text{Ti}_3\text{C}_2\text{T}_x$ MXene with l-cysteine and l-histidine to produce a modified material that efficiently separated oil-water mixtures and dye wastewater (**Figure 7c**) ^[141]. Coating these modified materials onto polyurethane sponge and polyamide membranes resulted in impressive separation efficiency and high permeability, demonstrating their potential for treating complex industrial wastewater streams ^[141].

Gan *et al.* synthesized MXene-based polymeric composites ($\text{Ti}_3\text{C}_2\text{T}_x$ -PDOPA) by combining MXenes with levodopa under mild conditions (**Figure 7d**) ^[142]. Compared to unmodified MXenes, the resultant composites displayed higher adsorption capacities for heavy metal ions. Through self-polymerization of levodopa, reactive functional groups can be added, providing opportunities for further functionalization, which makes these composites highly versatile and effective for environmental remediation ^[142].

According to Wang *et al.*, few-layer MXene can be combined with dialdehyde starch nanoparticles (DASNP) to create eco-friendly composite materials (**Figure 7e**) ^[273]. Based on the results from several industries, the resulting composites demonstrated excellent adsorption performance for prohibited dyes (Rhodamine B, Congo Red) and non-steroidal anti-inflammatory drug residues (Naproxen). During the adsorption process, hydrogen bonding, electrostatic forces,

and van der Waals forces were all involved, which contributed to the effective removal of the pollutants [273].

The same principle was applied by Zhou *et al.*, who developed a 3D macroscopic aerogel called MPAC (Macroscopic Aerogel Composite) composed of leather collagen, MXene@polydopamine, and oxidized sodium alginate (**Figure 7f**) [299]. A promising candidate for the treatment of heavy metal wastewater, the aerogel displayed excellent Cr(VI) adsorption capacities as well as photothermal conversion capabilities [299].

BioMXenes for water purification and adsorption demonstrate broad applicability and effectiveness in treating various water pollutants. By adsorbing heavy metals, separating oil-water mixtures, or filtering membranes, these materials offer sustainable solutions to global water contamination issues.

Figure 7. a) Schematic illustration of the amino acid-bonded $Ti_3C_2T_x$ MXene membrane preparation. Reproduced with permission [297]. Copyright 2024, Elsevier. b) The preparation process of biosurfactant-functionalized $Ti_3C_2T_x$. Reproduced with permission [298]. Copyright 2022, Elsevier. c) Preparation processes of L-Cysteine MXene (L-CPT), L-Histidine MXene (L-HPT), Polyurethane sponge L-Cysteine MXene (L-CPTPU), Polyurethane sponge L-Histidine MXene (L-HPTPU), Polyamide L-Cysteine MXene (L-CPTPA) and Polyamide L-Histidine MXene (L-HPTPA). Reproduced with permission [141]. Copyright 2023, Elsevier. d) The synthesis of $Ti_3C_2T_x$ -Levodopa Polymer (PDOPA) through mussel-inspired chemistry. Reproduced with permission [142]. Copyright 2020, Elsevier. e) Schematic illustration for the step-wise synthesis of Dialdehyde Starch Nanoparticles MXene (DSP-M) composite. Reproduced with permission [273]. Copyright 2023, Elsevier. f) Fabrication procedures of collagen, MXene, Macroscopic Aerogel Composite (MPAC) aerogel, and cross-linking mechanism of substances in MPAC aerogel. Reproduced with permission [299]. Copyright 2024, Elsevier.

3.2. Corrosion Protection and Coatings

By enhancing barrier properties and improving dispersibility and compatibility of protective coatings, BioMXenes have demonstrated significant promise for corrosion protection and coatings. **Table 3** summarizes recently published studies on this topic.

Table 3. Overview of research projects investigating the corrosion protection and coatings applications of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|--------------|-------------|---|---|-------|
| $Ti_3C_2T_x$ | L-Cysteine | Anti-corrosion in coatings | Improved corrosion resistance in epoxy coatings with higher impedance modulus. | [300] |
| $Ti_3C_2T_x$ | Glycine | Improvement of corrosion resistance in epoxy coatings | Enhanced dispersion and corrosion resistance in epoxy coatings. | [301] |
| $Ti_3C_2T_x$ | Dopamine | To enhance corrosion and wear resistance in waterborne coatings | Improved corrosion resistance, wear resistance, and compatibility in aqueous environments | [149] |

Li *et al.* [300] developed a hybrid material composed of functionalized $Ti_3C_2T_x$ MXene nanosheets and L-cysteine (**Figure 8a**), and incorporating the resulting materials into waterborne epoxy (WEP) coatings, leading to significant improvement of the corrosion resistance of the coatings. Biofunctionalized MXenes/WEP coatings had a higher impedance modulus at the lowest frequency in 3.5 wt.% NaCl solution after 30 days and had a lower corrosion rate than the unmodified WEP coatings. Due to the well-dispersed nanosheets within the WEP matrix, the coating had improved barrier properties. This study showed that the corrosion resistance of protective coatings can be boosted by the green modification of MXene materials [300].

Xiaoyu *et al.* [301] reported that glycine-functionalized $Ti_3C_2T_x$ (GT) improves the dispersibility and compatibility of MXenes in waterborne epoxy resins (**Figure 8b**). Adding glycine to epoxy resin alleviated the aggregation of $Ti_3C_2T_x$ nanosheets, as well as improved overall dispersion. Improvements in corrosion resistance were crucial to coating performance. Compared with the pure epoxy coating, the GT composite coating showed superior protection after 60 days of immersion, with an electrochemical impedance spectroscopy value of $|Z|f = 0.01$ Hz three orders of magnitude higher than that of the pure epoxy coating. Since glycine contains –COOH and –NH groups, it helped facilitate better interaction between $Ti_3C_2T_x$ and epoxy resin, strengthening the coating-metal bond. To enhance epoxy-based coating corrosion protection, this study provides an environmentally friendly method for modifying $Ti_3C_2T_x$ [301]. In another study, a waterborne polyurethane (WPU) and $Ti_3C_2T_x$ MXene hybrid coating showed exceptional corrosion and wear resistance (**Figure 8c**) [149]. Dopamine-grafted $Ti_3C_2T_x$ MXenes improved the material's compatibility and dispersibility in aqueous solutions, resulting in improved corrosion resistance. By adopting this approach, the stability of MXenes can be addressed and high-performance coatings can be produced [149]. Hence, BioMXenes, particularly those containing L-

cysteine and glycine, can provide valuable corrosion protection and coating benefits. By improving the dispersion of MXenes in protective coatings, they enhance barrier properties and, consequently, corrosion resistance. Furthermore, these modifications are environmentally friendly, which makes them suitable for use in protective coatings (**Figure 8**).

Figure 8. a) The schematic graph of the preparation process of a composite coating embedded with modified $\text{Ti}_3\text{C}_2\text{T}_x$. Reproduced with permission [300]. Copyright 2021, Elsevier. b) Glycine- $\text{Ti}_3\text{C}_2\text{T}_x$ hybrid material improves the electrochemical corrosion resistance of a water-borne epoxy coating. Reproduced with permission [301]. Copyright 2024, ACS. c) The schematic of the fabrication of MXene and functionalized MXene nanosheets. Reproduced with permission [149]. Copyright 2024, Elsevier.

3.3. Drug and Pesticide Delivery

BioMXenes have created new avenues for controlled and targeted drug/pesticide delivery, enhancing therapeutic efficacy, and reducing side effects. The development of a smart pesticide delivery system (PDS) using a nanocarrier platform incorporating tannic acid-modified MXene ($\text{Ti}_3\text{C}_2\text{T}_x$) has been reported (**Figure 9a**) [291]. By self-polymerizing tannic acid on the MXene surface, TA-modified MXene was synthesized to exhibit a high pesticide loading rate of 44.69% through physical adsorption. An important feature of this PDS was its pH-responsive controlled release behavior, which increased efficiency in acidic environments. Agricultural settings with varying pH are particularly suited to this characteristic. Furthermore, the surface modification with TA increased the nanopesticide's affinity for leaves, ensuring better adherence and prolonged activity. Using *Culex pipiens pallens*, this nanopesticide was evaluated for insecticidal activity, and the results showed that it maintained high insecticidal activity even after 28 days, surpassing the performance of technical β -CYF. Biosafety evaluations demonstrated that the PDS was not toxic to maize or *Vigna radiata* (Linn.) Wilczek, underscoring its potential for safe agricultural use. Throughout this study, MXene-based delivery systems were demonstrated to be versatile in

controlled release applications, including agricultural pest control. Enhanced plant adhesion, pH-responsive behavior, and high loading capacity demonstrate the potential of MXene-based PDSs [291]. The synergistic effects of photothermal-chemotherapeutic cancer therapies using $Ti_3C_2T_x$ -based MXenes and DNA hydrogels have been studied (**Figure 9b**) [302]. As photothermal agents, MXenes act as photothermal agents, while doxorubicin (DOX) acts as a chemotherapeutic agent. Near-infrared (NIR) light triggers a reversible gel-to-solution transition in the DNA hydrogel, releasing DOX for targeted cancer therapy. After NIR irradiation ceases, the hydrogel matrix reforms, allowing for controlled drug delivery. Based on both *in vitro* and *in vivo* studies, the MXene-DNA hydrogel system demonstrated excellent biocompatibility, efficient NIR-triggered drug delivery, and localized cancer treatment. Combining photothermal effects with stimuli-responsive hydrogels may enhance cancer treatment outcomes, as demonstrated in this study [302]. These studies summarized in **Table 4** highlights the broader implications of MXene-based bio-functionalized nanocarriers in the field of drug/pesticide delivery, where controlled release and targeted delivery principles can be applied to therapeutic agents, making treatments more efficient and effective with fewer side effects.

Figure 9. a) Preparation of the MXene-TA- β -CYF nanopesticide for pH-responsive β -CYF release. Reproduced with permission [291]. Copyright 2022, ACS. b) Schematic illustration of the construction of DOX-loaded MXene-DNA hydrogel and its application as a NIR-responsive injectable platform for the photothermal-chemo synergistic treatment of tumor. Reproduced with permission [302]. Copyright 2022, Wiley.

Table 4. Highlights key points of two recently reported studies.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|--------------|---------------------------------|---|--|-------|
| $Ti_3C_2T_x$ | Tannic Acid (TA) | Smart pesticide delivery system (PDS) | pH-responsive controlled release of β -cyfluthrin with improved leaf affinity and insecticidal activity. | [291] |
| $Ti_3C_2T_x$ | DNA Hydrogel, Doxorubicin (DOX) | Photothermal-chemo synergistic cancer therapy | Efficient localized cancer treatment with NIR-triggered drug delivery and minimal side effects. | [302] |

3.4. Therapeutic

Various medical fields, including oncology and antibacterial treatment, have benefited from the use of BioMXenes in therapeutic applications. 2D Ti_3C_2 MXene nanosheets functionalized with CeO_2 nanozymes and glucose oxidase (GOD) have been reported to be an effective cancer therapy (**Figure 10a**)^[90]. This nanocomposite targets challenges posed by the tumor microenvironment (TME), which includes high glucose levels, hypoxia, and low hydrogen peroxide levels. A combination of peroxidase-like and catalase-like activities are provided by CeO_2 nanozymes, which transform H_2O_2 into hydroxyl radicals and produce oxygen to relieve hypoxia. In parallel, GOD disrupts cancer cells' energy supply by increasing H_2O_2 levels. Photothermal therapy (PTT) and photodynamic therapy (PDT) are also enhanced by Ti_3C_2 MXenes when exposed to near-infrared (NIR) light. Both *in-vitro* and *in-vivo* tests showed significant tumor suppression using CeO_2/Ti_3C_2 -PEG-GOD nanocomposite, providing a strong example of an integrated therapy for cancer treatment combining multiple therapeutic modalities^[90]. Another study demonstrated the enhancement of photothermal effects and durability using $Ti_3C_2T_x$ MXene nanosheets functionalized with polydopamine (PDA) (**Figure 10b**)^[168]. Lysozyme, an antibacterial enzyme, was immobilized on this MXene-PDA hybrid platform (M@P@Lyso). Using the platform, it was possible to control local heat with precision and activate lysozyme on a photo-responsive basis by converting light into heat. Methicillin-resistant *Staphylococcus aureus* was effectively inhibited by this system in mice, and wound disinfection was significantly accelerated. MXene-PDA composites increased physical disruption and enhanced lysozyme activity, resulting in improved antibacterial performance. This work demonstrated that MXene-based platforms may be useful in overcoming bacterial resistance and enhancing enzymatic therapies by using stimuli-responsive mechanisms^[168]. In summary, BioMXenes offer innovative solutions for advanced therapeutic

applications, including multimodal cancer treatments and enhanced antibacterial strategies. By combining MXenes with bio-functional agents and stimuli-responsive systems, therapeutic interventions can be made more effective and specific. **Table 5** compares key points of these two reported studies.

Figure 10. a) CeO₂ and glucose oxidase Co-Enriched Ti₃C₂T_x MXene for hyperthermia-augmented nanocatalytic cancer therapy. Reproduced with permission [90]. Copyright 2024, ACS. b) Schematic diagram of the bio-interface engineering of lysozyme on MXene and the photothermal-enhanced photothermal antibacterial performance against MRSA. Reproduced with permission [168]. Copyright 2023, Elsevier.

Table 5. Overview of the two studies on the therapeutic application of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|---|---|--|--|-------|
| Ti ₃ C ₂ T _x | CeO ₂ Nanozymes, Glucose Oxidase (GOD) | Cancer therapy with multimodal treatment | Effective tumor suppression with integrated photothermal, photodynamic, and enzymatic therapy. | [90] |
| Ti ₃ C ₂ T _x | Polydopamine (PDA), Lysozyme | Enhanced antibacterial activity | High light-to-heat conversion and effective antibacterial activity against resistant strains. | [168] |

3.5. Tissue Engineering

Advances in material science have greatly benefited tissue engineering, particularly in the development of bio-functionalized materials that support and enhance tissue regeneration. MXenes, with their unique properties, have emerged as promising candidates in this field. A potential use of MXene (Ti₃C₂T_x)-based conductive biohybrid platforms in tissue engineering has been investigated (**Figure 11a**) [85]. In this work, covalently crosslinking collagen Type I with Ti₃C₂T_x provided substrates with increased electrical conductivity and stiffness. The platform was extremely biocompatible and supported increased proliferation and cell spreading of fibroblasts. Furthermore, it showed a reduced proliferative and attachment rate for bacteria. Interestingly, the incorporation of an external electric field enhanced cell growth and cx43 expression in cardiomyocytes, suggesting this conductive biohybrid platform could enhance cardiac tissue

regeneration [85]. MXene nanoparticles (NPs) have been integrated into poly(L-lactide-co- ϵ -caprolactone) and collagen nanofibrous matrices to develop novel scaffolds for bone tissue engineering (**Figure 11b**) [303]. Preosteoblasts (MC₃T₃-E₁) promoted spontaneous osteogenic differentiation when scaffolds were enhanced with MXene NPs. MXene-integrated nanofibrous materials were found to be effective at stimulating bone tissue regeneration due to enhanced interactions between cells and supportive matrix [303].

MXene nanosheets have been incorporated into oxidized alginate and gelatin hydrogels to create multifunctional conductive hydrogels (**Figure 11c**) [304]. The one-pot synthesis approach resulted in hydrogels with improved mechanical properties, electroactivity, and self-healing. It has been found that MXene-ADA-GELs are biocompatible and promote the attachment and spreading of fibroblasts. Hydrogels with these properties hold promise for wound healing and flexible bio-electronics applications [304].

These studies demonstrate the versatile applications of BioMXenes in tissue engineering by emphasizing their potential to increase tissue regeneration through enhanced conductivity, biocompatibility, and functionality. **Table 6** compares key points of these reported studies.

Figure 11. a) Schematic illustration of the blending process protocol to create the biohybrid platforms of MXene and Collagen. Reproduced with permission [85]. Copyright 2023, Nature. b) Ternary MXene-loaded poly(L-lactide-co- ϵ -caprolactone (PLCL)/collagen nanofibrous scaffolds that promote spontaneous osteogenic differentiation. Reproduced with permission [303]. Copyright 2022, Springer. c) Schematic illustration of the fabrication of composite hydrogel composed of MXene nano-flakes, Alginate Aldehyde (ADA) and gelatin, and the multi-layered structure of MXene nano-flakes. Reproduced with permission [304]. Copyright 2022, MDPI.

Table 6. Overview of three reported studies on the tissue engineering application of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|---|---|--|---|-------|
| Ti ₃ C ₂ T _x | Collagen Type I | To engineer conductive biohybrid platforms for cardiac tissue regeneration | Increased cell spreading and viability, reduced bacterial attachment, enhanced cardiomyocyte growth with electric-field stimulation | [85] |
| Ti ₃ C ₂ T _x | Poly(L-lactide-co-ε-caprolactone), Collagen | To develop scaffolds for bone tissue engineering with enhanced osteogenic differentiation | Improved osteogenic differentiation, favorable interactions with preosteoblasts | [303] |
| Ti ₃ C ₂ T _x | Oxidized Alginate, Gelatin | To synthesize multifunctional conductive hydrogels for skin wound healing and flexible bio-electronics | Enhanced mechanical properties, self-healing, and conductivity, suitable for flexible bio-electronics | [304] |

3.6. Energy and Electronics

The superior conductivity, stability, and tunable properties of BioMXenes are making them attractive for use in energy storage and electronic systems. Different strategies are currently being explored to improve MXenes' performance and expand their applications in this area.

Table 7 summarizes key points of recently reported studies in this field.

Table 7. Highlights of recent studies on the energy and electronics applications of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|---|--|---|---|-------|
| Ti ₃ C ₂ T _x | Vitamin C | To develop oxidation-resistant EMI shielding materials | Improved EMI shielding stability, slight decrease in effectiveness over time compared to pure Ti ₃ C ₂ T _x | [305] |
| Ti ₃ C ₂ T _x | Glycine | To prevent restacking in MXene and enhance charge percolation for energy storage | Increased interlayer spacing and improved rate and cycling performance of hybrid films | [87] |
| Ti ₃ C ₂ T _x | Amino Acids | To modify work function and passivate defects in Ti ₃ C ₂ T _x for use in organic solar cells | Enhanced electrical properties and power conversion efficiency in OSCs | [306] |
| Ti ₃ C ₂ T _x | Synthetic Proteins with Tandem Repeats | To modulate hierarchical organization and electronic transport in MXene composites | Regulated electronic transport with varying tandem repeat units, highlighting both isotropic and anisotropic effects | [307] |
| Ti ₃ C ₂ T _x | Carbonized Eggshell Membrane (REM) | To develop flexible and customizable electrodes for supercapacitors | High capacitance, excellent flexibility, and stable capacitive behaviors during bending | [308] |
| Ti ₃ C ₂ T _x | Soybean Protein Isolate | To develop an interlayer for Li-S batteries to suppress shuttle effect | Improved cycling stability and rate performance of Li-S batteries | [309] |

The use of $\text{Ti}_3\text{C}_2\text{T}_x$ foam composites modified with vitamin C as electromagnetic interference (EMI) shields has been investigated (**Figure 12a**)^[305]. This study demonstrated that vitamin C enhances $\text{Ti}_3\text{C}_2\text{T}_x$'s oxidation resistance, significantly improving its EMI shielding effectiveness (EMI SE). Over 10 days, their experiment showed only a small decrease in EMI SE from 42.5 to 41 dB, in contrast with a significant decline in unmodified $\text{Ti}_3\text{C}_2\text{T}_x$ foam. The oxidation resistance study led to the development of a promising approach for the fabrication of MXene-based EMI shielding materials^[305].

Another study examined the effect of glycine on $\text{Ti}_3\text{C}_2\text{T}_x$ on restacking in MXene-based materials (**Figure 12b**)^[87,310]. Combining theoretical and experimental methods, this study demonstrated that glycine functionalization increases interlayer spacing and enhances charge percolation. Compared to pristine $\text{Ti}_3\text{C}_2\text{T}_x$, hybrid films of $\text{Ti}_3\text{C}_2\text{T}_x$ /glycine showed improved rate and cycling performance, suggesting that the organic modification enhances MXene electrochemical properties^[87,310].

Huang *et al.* modified $\text{Ti}_3\text{C}_2\text{T}_x$ using amino acids, leading to passivating $\text{Ti}_3\text{C}_2\text{T}_x$'s defects (**Figure 12c**)^[306]. They discovered that amino acids reduced $\text{Ti}_3\text{C}_2\text{T}_x$'s work function and enhanced its electrical properties. Through this modification, the organic solar cell (OSC) displayed over 18% power conversion efficiency. This study revealed that amino acid-functionalized MXenes can be used in electronic devices effectively^[306].

In a recent publication, Vural *et al.* presented a new method for improving MXene composites' physical properties using synthetic proteins (**Figure 12d**)^[307]. They developed protein-based biomimetic composites using $\text{Ti}_3\text{C}_2\text{T}_x$ MXene and showed that tandem repeat units in proteins controlled the distance between layers and modulated electronic transport. Increasing

the tandem repeats resulted in nonlinear I–V characteristics, suggesting that topologically organized biomaterials could regulate electronic properties [307].

Weimin Chen *et al.* developed a carbon-based interlayer coated with soybean protein isolate and MXene for lithium–sulfur (Li–S) batteries (**Figure 12e**) [308]. By chemically adsorbing and physically blocking lithium polysulfides, the composite interlayer effectively suppressed the shuttling effect. This interlayer improves the cycling stability and rate of Li–S batteries, showing a low-capacity decay rate of 0.071% per cycle at 0.5 C, indicating significant possibilities for commercialization [308].

Chen *et al.* examined the challenges posed by the shuttling of lithium polysulfides (LiPSS) in lithium sulfur (Li–S) batteries, which hinders their commercialization (**Figure 12f**) [309]. To overcome this problem, the researchers coated acidified carbon paper (ACP) with a mixture of soybean protein isolate and MXene. An interlayer labeled SM@ACP reduces the shuttle effect by combining chemical adsorption with physical blocking. Furthermore, the porous structure of the ACP enhances conductivity and facilitates Li ion diffusion, facilitating electron and ion conduction. Battery performances improved significantly with SM@ACP interlayers, demonstrating a notably low-capacity decay rate over 800 cycles of 0.071% per cycle at 0.5 C. By providing a rational design and commercial mass production of effective interlayers, this study advanced Li–S battery commercialization [309].

BioMXenes have demonstrated versatility and potential for advancing energy storage and electronic applications. From improving EMI shielding to enhancing battery performance and electronic device efficiency, BioMXenes continue to offer innovative solutions in these fields.

Figure 12. a) Schematic of the fabrication procedure of vitamin C/Ti₃C₂T_x foam. Reproduced with permission [305]. Copyright 2023, Elsevier. b) Several stable adsorbed configurations of Glycine on the Ti₂CO₂ MXene surface. Reproduced with permission [310]. Copyright 2020, ACS. c) The differential charge distribution diagram of glycine interacting with different functional groups –F, –O, –OH, vacancies of Ti atoms on Ti₃C₂T_x surface. Reproduced with permission [306]. Copyright 2023, Elsevier. d) Self-assembly of topologically networked protein-Ti₃C₂T_x MXene composites. Reproduced with permission [307]. Copyright 2020, ACS e) Schematic illustration showing the proposed strategy of reconstitution and low-temperature carbonization. Reproduced with permission [308]. Copyright 2023, Elsevier. f) Enlarged from left to right including the new configuration of Li–S batteries. Reproduced with permission [309]. Copyright 2024, Wiley.

3.7. Biosensors

Due to MXene's unique properties and versatility, BioMXene-based sensors have seen considerable progress. Here, we summarize recent research highlighting the use of MXenes in sensor applications.

Environmental safety sensors

Environmental safety sensors have been significantly influenced by BioMXenes, particularly in the detection of hazardous substances such as nitrite, acrylamide, lead ions, and iron ions. Due to their large surface area, excellent conductivity, and biocompatibility, MXenes presents a promising candidate for developing high bio-functionalized sensitive and selective sensors. BioMXene-based sensors for environmental safety have recently made considerable advances that highlight their potential. **Table 8** highlights key points of recently reported studies.

Table 8. Overview of research projects investigating environmental safety sensor applications of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|---|-----------------------------------|--|---|-------|
| Ti ₃ C ₂ T _x | Hemoglobin (Hb) | Mediator-free biosensor for environmental analysis (nitrite detection) | Wide linear range of 0.5–11800 μM, detection limit of 0.12 μM; good protein bioactivity and stability | [86] |
| Ti ₃ C ₂ T _x | Hemoglobin (Hb), Au@Ag Core-Shell | Detection of acrylamide in environmental samples | Detection limit of 3.46 μM, stability, reproducibility, and good analytical | [311] |

| Performance with potential for rapid sensory development | | | |
|--|--------------------------------------|---|---|
| $\text{Nb}_4\text{C}_3\text{T}_x$ | Lead-binding DNA oligonucleotide | Sensitive detection of Pb^{2+} ions | Achieved a detection limit of 4 nM for Pb^{2+} with high selectivity and a linear range of 10 nM to 5 μM . [312] |
| $\text{Ti}_3\text{C}_2\text{T}_x$ | GR5 DNAzyme | Detect Pb^{2+} with high sensitivity | Detection limit of 0.1 nM Pb^{2+} ; linear range from 0.5 to 32 nM [313] |
| $\text{Ti}_3\text{C}_2\text{T}_x$ | Bovine Serum Albumin (BSA) | Create a fluorescent sensor for detecting Fe^{3+} ions | BSA@MXene QDs showed a linear response for Fe^{3+} with a limit of detection and good selectivity [314] |
| $\text{Ti}_3\text{C}_2\text{T}_x$ | β -Cyclodextrin (β -CD) | Quantification of L-methionine (L-Met) | High sensitivity and stability with LOD of 0.03 μM [315] |

Liu *et al.* explored the application of a $\text{Ti}_3\text{C}_2\text{T}_x$ -based material for the fabrication of a mediator-free biosensor by immobilizing hemoglobin (Hb) (**Figure 13a**)^[86]. The $\text{Ti}_3\text{C}_2\text{T}_x$ -based biosensor demonstrated impressive performance in nitrite detection, with a linear range of 0.5 to 11,800 μM and a remarkably low detection limit of 0.12 μM . The study suggests that $\text{Ti}_3\text{C}_2\text{T}_x$ can be used in environmental monitoring, particularly for nitrite detection^[86].

By modifying a gold electrode with MXene nanosheets and an Au@Ag coreshell-Hb complex (Au@Ag CS-Hb/MXene/AuE), a biosensor for acrylamide detection was developed (**Figure 13b**)^[311]. The biosensor exhibited a detection limit of 3.46 μM and showed high analytical performance, stability, reproducibility, and repeatability. A good recovery rate was obtained when acrylamide was tested in spiked real samples. This biosensor needs to be further developed into a fast and portable acrylamide detector, which is essential for food safety and environmental protection^[311].

Using lead-specific DNA oligonucleotides on an Au@ $\text{Nb}_4\text{C}_3\text{T}_x$ MXene modified electrode, an electrochemical sensor for the ultrasensitive and sensitive detection of Pb^{2+} ions were developed (**Figure 13c**)^[312]. This sensor exhibited an ultra-low detection limit of 4 nM and a linear range from 10 nM to 5 μM . This study illustrated how $\text{Nb}_4\text{C}_3\text{T}_x$ MXene can be used for DNA immobilization, making it useful in environmental monitoring and biomedical applications^[312].

Using GR5 DNAzyme and modified glassy carbon electrodes containing $\text{Ti}_3\text{C}_2\text{T}_x$ MXene, an electrochemical biosensor was developed to detect Pb^{2+} (**Figure 13d**) ^[313]. The biosensor displayed a high specificity for Pb^{2+} with a detection limit of 0.1 nM and a linear range of 0.5 to 32 nM. This sensor can have potential applications in food safety inspection and environmental monitoring, especially in the detection of lead contamination ^[313].

Using a hydrothermal method, Bovine serum albumin (BSA)-functionalized fluorescent 2D $\text{Ti}_3\text{C}_2\text{T}_x$ MXene quantum dots (MXene QDs) were fabricated (**Figure 13e**) ^[314]. BSA-functionalized MXene QDs were then selectively quenched in the presence of Fe^{3+} ions, exhibiting a linear response from 0 to 150 μM . Both selectivity and practical applicability were demonstrated in real samples, while cytotoxicity studies indicated the MXene QDs were biocompatible. This sensor can detect Fe^{3+} ions in environmental samples with promising results ^[314].

Lastly, Rajeev *et al.* developed a β -cyclodextrin-MXene (β -CD-MXene) composite-based sensor for L-methionine (L-Met) quantification using carbon fiber paper electrodes (**Figure 13f**) ^[315]. The sensor showed high sensitivity and selectivity with a detection limit of 0.03 μM . The β -CD-MXene/CFP (carbon fiber paper) electrode showed excellent performance in non-interfering sensing of L-Met, which is significant for environmental safety monitoring, particularly in detecting amino acids and other organic compounds in various environmental contexts ^[315].

These studies together highlight the potential of biofunctionalized MXenes in the development of next-generation environmental safety sensors. Environmental safety and public health are ensured through the versatility and efficiency of these materials in detecting a wide range of pollutants.

Figure 13. a) Typical current-time response of the Nafion/Hb/Ti₃C₂T_x/GCE at -0.70 V to successive addition of NaNO₂ in stirred 0.1 M pH 5.5 PBS (The inset in figure is plot of steady state current vs. NaNO₂ concentration). Reproduced with permission [86]. Copyright 2015, Elsevier. b) Schematic working mechanism of the constructed biosensor for Acrylamide (AA) sensing [311]. c) Schematics of the sensor fabrication including the formation of G-quadruplex structure with Guanine base, and quantitative detection by differential pulse voltammetry (DPV) analysis. Reproduced with permission [312]. Copyright 2022, Wiley. d) The illustration for the preparation of GR5 DNAzyme/ Ti₃C₂T_x-GCE and its application in Pb²⁺ detection. Reproduced with permission [313]. Copyright 2022, Elsevier. e) Illustration of BSA@MXene QDs detection probe for Fe³⁺ ions. Reproduced with permission [314]. Copyright 2022, Wiley. f) Synthesis of β-CD-MXene composite for developing β-CD-MXene CFP electrode for electrochemical detection of L-Met. [315].

Cancer detection sensors

BioMXenes have been used to construct high-sensitivity cancer detection sensors for specific cancer biomarkers. We explain how the materials developed in the recent articles summarized in **Table 9** can potentially be used to detect cancer.

Table 9. Overview of research projects investigating the cancer detection sensors application of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|---|---|---|---|-------|
| Ti ₃ C ₂ T _x | Aminosilane (f-Ti ₃ C ₂ -MXene), Anti-CEA | Ultrasensitive detection of cancer biomarker (CEA) | Linear detection range of 0.0001–2000 ng mL ⁻¹ with sensitivity of 37.9 μA ng ⁻¹ mL cm ⁻² per decade; comparable to other 2D materials | [52] |
| Ti ₃ C ₂ T _x | Dual-signal-tagged chimeric DNA (dcDNA) | To create a nanoprobe for dual-signal analysis of cancer biomarkers MUC1 and miR-21 in living cells. | Enabled dual analysis with low-nanomolar sensitivity, providing a tool for reliable cancer diagnosis and monitoring biomarker expression changes. | [316] |
| Ti ₃ C ₂ T _x | β-Cyclodextrin (β-CD), Cu ²⁺ | Construct an overly sensitive electrochemical immunosensor for squamous cell carcinoma antigen (SCCA) | Sensor exhibited a wide linear range (0.05 pg mL ⁻¹ to 20.0 ng mL ⁻¹) and low detection limit (0.01 pg mL ⁻¹) | [317] |
| Ti ₃ C ₂ T _x | Thiolated single-stranded DNA | Detect BRCA1 for cancer diagnosis | Linear range 10 zM to 1 μM; detection limit of 1 zM; high specificity and reproducibility | [318] |
| Ti ₃ C ₂ T _x | Flavin adenine dinucleotide (FAD) | Improve electro-catalytic reduction of hydrogen peroxide | Detection limit of 5 nM; enhanced redox properties and stability | [319] |
| Ti ₃ C ₂ T _x | Peptide nucleic acids | Design amplification-free electrochemical biosensor for microRNA detection | Wide dynamic range; single-nucleotide specificity; detection limit of 40 aM | [260] |
| Ti ₃ C ₂ T _x | L-cysteine, magnetite nanoparticles | Detect CYFRA 21-1 biomarker for oral cancer | Detection limit of 0.023 ng mL ⁻¹ ; linear range from 0.5 to 30 ng mL ⁻¹ | [320] |
| Ti ₃ C ₂ T _x | CD9 aptamer | Detect exosomes for early cancer diagnosis | Detection limit of 10.64 pM; detection range of 6.41 × 10 ² to 1 × 10 ⁷ exosomes/mL | [321] |

In a study, Kumar *et al.* synthesized ultrathin $\text{Ti}_3\text{C}_2\text{T}_x$ -MXene nanosheets and functionalized them with aminosilane to develop a bio-functionalized MXene platform to detect carcinoembryonic antigen (CEA) (**Figure 14a**) ^[52]. By immobilizing anti-CEA on the surface of functionalized MXene ($\text{f-Ti}_3\text{C}_2\text{T}_x$ -MXene), the researchers achieved label-free and ultrasensitive detection. Using hexaammineruthenium ($[\text{Ru}(\text{NH}_3)_6]^{3+}$) as a redox probe, electrochemical behavior of $\text{f-Ti}_3\text{C}_2\text{T}_x$ -MXene was optimized, resulting in a linear detection range of 0.0001–2000 ng mL⁻¹ and a sensitivity of 37.9 A ng mL cm². This work demonstrates that $\text{f-Ti}_3\text{C}_2\text{T}_x$ -MXene is superior to previously reported 2D nanomaterials and even compares favorably to hybrid 2D materials, opening new avenues for the development of MXene-based biosensors ^[52].

Wang *et al.* designed a dual-signal-tagged chimeric DNA-functionalized titanium carbide MXenes nanoprobe (dcDNA– Ti_3C_2) for detecting cancer biomarkers with distinct cellular locations (**Figure 14b**) ^[316]. To enable simultaneous analysis of MUC1 and miR-21, the probe utilizes dual fluorescence signals. By interacting with its aptamer, MUC1 is detected by enhanced red fluorescence, while miR-21 is detected by hybridization with a hairpin probe. By combining these two signals, it is possible to monitor biomarker expression as well as the spatial distribution of biomarkers within MCF-7 breast cancer cells ^[316].

In another study, Jiang *et al.* presented an extremely sensitive electrochemical sandwich-like immunosensor for squamous cell carcinoma antigen (SCCA) (**Figure 14c**) ^[317]. This sensor utilizes gold nanoparticle/graphene nanosheet (Au/GN) nanohybrids as a sensing platform and β -cyclodextrin/ $\text{Ti}_3\text{C}_2\text{T}_x$ MXenes (β -CD/ $\text{Ti}_3\text{C}_2\text{T}_x$) as a signal amplifier. The biocompatibility and conductivity of the Au/GN platform facilitate effective loading of primary antibodies, while β -CD/ $\text{Ti}_3\text{C}_2\text{T}_x$ offered strong signal amplification through host–guest interactions. This innovative

signal amplification strategy in real human serum samples detected SCCA within a wide linear range of 0.05 pg mL^{-1} to 20.0 ng mL^{-1} . With a low detection limit of 0.01 pg mL^{-1} , it demonstrates its potential for cancer biomarker detection ^[317].

Divya *et al.* introduced a biomimetic bilayer lipid membrane supported MXene-based biosensor for detecting the BRCA1 biomarker, prevalent in breast cancer (**Figure 14d**) ^[318]. Detection of hybridization was achieved through the use of a 2D MXene nanosheet-anchored gold nanoparticle-decorated bilayer lipid membrane (AuNP@BLM). Combining these two technologies significantly enhanced the detection signal, resulting in a linear range of 10 zM to $1 \mu\text{m}$ and limit of detection (LOD) of 1 zM . The sensor's specificity was verified using non-complementary and double-base mismatch oligonucleotide sequences, indicating its potential for precise and reliable cancer biomarker detection ^[318].

Nagarajan *et al.* developed a novel biosensor by immobilizing flavin adenine dinucleotide (FAD) on 2D MXene ($\text{Ti}_3\text{C}_2\text{T}_x$) to enhance the redox properties of FAD and improve the electro-catalytic reduction of hydrogen peroxide (H_2O_2) in ovarian cancer cells (**Figure 14e**). Compared to bare electrodes, GCEs modified with FAD/ $\text{Ti}_3\text{C}_2\text{T}_x$ exhibited superior performance in detecting H_2O_2 , with a linear detection range from 5 nM to 2 m and a significant reduction in detection potential ^[319].

Ali *et al.* engineered peptide nucleic acid-functionalized $\text{Ti}_3\text{C}_2\text{T}_x$ MXene nanosheets for the electrochemical detection of microRNA biomarkers, specifically targeting prostate cancer biomarker hsa-miR-141 (**Figure 14f**) ^[260]. Researchers functionalized MXene with peptide nucleic acid probes, achieving an impressive 40 aM detection limit by utilizing copper-free click chemistry. Cancer biomarkers may now be detected with high specificity, stability, and toxin sensitivity using this amplification-free, nanoparticle-free, and isothermal detection platform ^[260].

Choramle *et al.* developed a non-invasive, label-free electrochemical immunosensor for detecting the oral cancer biomarker CYFRA 21-1 (**Figure 14g**). A titanium carbide $Ti_3C_2T_x$ MXene nanosheet and L-cysteine-functionalized magnetite nanoparticle (L-Cyst@MNPs) nanohybrid was used to fabricate the sensor. By combining both surface area and electrochemical properties, this combination yielded a detection limit of 0.023 ng mL^{-1} and a linear range of $0.5\text{--}30 \text{ ng mL}^{-1}$ [320].

An *et al.* proposed a CD9 aptamer-based extended-gate field-effect transistor (EGFET)-type biosensor for detecting exosomes, which are promising biomarkers in early cancer diagnosis (**Figure 14h**). By monitoring the electrical signal changes of a disposable sensing membrane and an Au microelectrode, the sensor was able to detect exosomes. The sensor demonstrated a detection limit of 10.64 pM for CD9 proteins and a range from 10 pM to $1 \mu\text{M}$ in buffer. It also demonstrated reliable results in human serum samples. This aptasensor offers a powerful tool for the early diagnosis of cancer through exosome detection [321].

The combined results of these studies demonstrate the potential of BioMXenes in the development of sensitive and specific cancer detection sensors. Their applications range from detecting well-known cancer biomarkers like CEA and BRCA1 to innovative approaches to microRNA and exosome detection, providing new opportunities for early diagnosis and treatment monitoring in oncology.

Figure 14. a) Schematic illustration of $Ti_3C_2T_x$ -MXene functionalization. Reproduced with permission [52]. Copyright 2018, Elsevier. b) Multilayer imaging of plasma membrane glycoproteins MUC1 and cytoplasmic miR-21 using a dcDNA- $Ti_3C_2T_x$ composite nanoprobe. Reproduced with permission [316]. Copyright 2018, ACS. c) The formation and sensing principle of the sandwich-like immunosensor based on β -CD/ $Ti_3C_2T_x$ as the signal amplifier. [317]. d) Schematic representation of the constructed biosensor for BRCA1 gene hybridization detection for BC biomarker prognosis and diagnosis. [318]. e) Electro-deposition of FAD (from $0.1 \text{ M H}_2\text{SO}_4$ containing 10 nM FAD) on to biocompatible $Ti_3C_2T_x$ modified GCE for the electro-catalytic reduction of H_2O_2 . Reproduced with permission [319]. Copyright 2021, MDPI. f) Schematic illustration of the peptide nucleic acid (PNA)-MXene electrochemical biosensor for miRNA detection based on chemical functionalization of MXene nanosheets via silanization to introduce azido functionalities followed by bio-orthogonal copper-free click chemistry with a dibenzocyclooctyne (DBCO)-PNA probe, creating the

PNA-Ti₃C₂T_x nanosheets which are drop-casted on a glassy carbon electrode (GCE) working electrode. Reproduced with permission [260]. Copyright 2024, RSC. g) Synthesis of a L-Cyst@MNPs/Ti₃C₂T_x nanohybrid and development of a BSA/anti-CYFRA 21-1/L-Cyst@MNPs/Ti₃C₂T_x/GSPE immunosensor for CYFRA 21-1 detection. [320]. h) Schematic Diagram of Exosome Detection Using the EGFET sensor. Reproduced with permission [321]. Copyright 2023, ACS.

Food safety sensors

Recent developments in BioMXene-based sensors have demonstrated significant improvements in food safety diagnostics, leveraging their unique properties for enhanced detection and analysis. **Table 10** summarizes key points of recent reported studies.

Table 10. Overview of research projects investigating food safety sensor applications of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|---|---|--|--|-------|
| Ti ₃ C ₂ T _x | Dual-AFB1 aptamers, Cas12a, crRNA, FAM fluorophore-modified ssDNA | To create a fluorescence biosensor for rapid detection of aflatoxin B1 (AFB1) contamination in food. | Achieved detection within 80 minutes with a wide detection range (0.001 to 80 ng/mL) and a detection limit of 0.92 pg/mL, validated in real samples. | [54] |
| Ti ₃ C ₂ T _x | α -Cyclodextrin, Acrylamide, 5-Heneicosylresorcinol (AR21) | Design a molecularly imprinted electrochemical sensor for alkylresorcinols | Sensor provided a wide linear range (0.005 $\mu\text{g}\cdot\text{mL}^{-1}$ to 100 $\mu\text{g}\cdot\text{mL}^{-1}$) and an ultralow detection limit (2.52 $\text{ng}\cdot\text{mL}^{-1}$) | [322] |

Wu *et al.* developed a fluorescence biosensor utilizing CRISPR/Cas12a and MXenes for the rapid detection of aflatoxin B1 (AFB1), a hazardous contaminant in food (**Figure 15a**) [54]. The biosensor operates by employing MXenes to adsorb fluorophore-modified single-stranded DNA (ssDNA-FAM), which quenches fluorescence. By releasing the aptamer-bound activator, Cas12a degrades the ssDNA, restoring fluorescence. Real food samples can be detected effectively using this method, which offers a wide detection range from 0.001 to 80 ng/mL and a detection limit of 0.92 pg/mL. The biosensor's performance in peanut samples highlights its food safety applicability [54].

In another study, Wen *et al.* developed a novel electrochemical sensor incorporating MXene nanosheets and molecularly imprinted polymers (MIPs) for the detection of

alkylresorcinols, biomarkers for whole wheat (**Figure 15b**)^[322]. The sensor utilized α -cyclodextrin and acrylamide as dual-functional monomers to create a highly specific MIP with significant selectivity for alkylresorcinol. A molecular imprinting technique allows an electrochemical sensor to detect in a linear manner between 0.005 g/mL and 100 g/mL with a detection limit of 2.52 ng/mL. Using a commercial whole wheat product, the sensor enabled reliable detection of alkylresorcinols and validated its potential for determining food authenticity. The sensor demonstrated excellent stability and reproducibility^[322]. These two studies (reviewed in this and the previous paragraph) point to the versatile applications of BioMXenes as food safety sensors and to advances made in both sensitivity and specificity for detecting various contaminants and ensuring food quality.

Figure 15. a) A novel fluorescence biosensor based on CRISPR/Cas12a integrated MXenes for detecting Aflatoxin B1. Reproduced with permission^[54]. Copyright 2023, Elsevier. b) CV curves of DMIP/MXene/GE at different scan rates (from 2 to 150 $\text{mV}\cdot\text{s}^{-1}$) in the presence of $0.5 \mu\text{g}\cdot\text{mL}^{-1}$ AR21. Reproduced with permission^[322]. Copyright 2024, ACS.

DNA-based sensors

The integration of MXenes with DNA-based sensing technologies has emerged as a promising approach to enhance the sensitivity and specificity of biosensors. This section reviews recent articles on DNA-based MXenes sensors (summarized in **Table 11**), emphasizing their applications in detecting various biological and chemical targets.

Table 11. Overview of research projects investigating the DNA-based sensors application of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|---|---|--|---|-------|
| Ti ₃ C ₂ T _x | Tetrahedral DNA Nanostructures (TDNs) | Electrochemical DNA (E-DNA) biosensor for detecting gliotoxin | Detection ranges from 5 pM to 10 nM with a low limit of detection (LOD) of 5 pM; opened avenue for MXene-based E-DNA biosensors | [323] |
| Ti ₃ C ₂ T _x | Thiol-modified thrombin binding aptamer (TBA) | Develop a hybrid DNA hydrogel for thrombin detection | Achieved 90–92% accuracy in detecting thrombin with potential for customization | [324] |
| Ti ₃ C ₂ T _x | cDNA-MB (complementary DNA labeled with methylene blue) | To develop a competitive smartphone-based portable electrochemical aptasensor for detecting MC-LR. | Demonstrated a detection range of 0.0001–5 nM with an LOD of 4×10^{-5} nM, showing stability, reproducibility, and high recovery rate. | [325] |
| Ti ₃ C ₂ T _x | DNA, Pd/Pt nanoparticles | Develop sensitive dopamine sensors | Achieved a lower detection limit of 30 nM for dopamine with high selectivity and successful human serum sample testing. | [326] |

Wang *et al.* developed an electrochemical DNA (E-DNA) biosensor utilizing DNA nanostructure-modified MXene (Ti₃C₂) nanosheets for detecting gliotoxin (**Figure 16a**) ^[323]. This biosensor employs the excellent properties of MXenes, combined with tetrahedral DNA nanostructures (TDNs) that are immobilized through coordination interactions. The TDNs enhance the sensor's performance by facilitating rapid and efficient binding of target molecules, leading to amplified electrochemical signals. The detection range for the sensor was 5 pM to 10 nM, with a limit of detection (LOD) of 5 pM, demonstrating its capability to detect other mycotoxins. DNA probe modification is simplified using this approach, opening up new avenues for E-DNA biosensor development ^[323].

Morya *et al.* introduced a novel hybrid DNA hydrogel incorporating Ti₃C₂T_x MXene with a thiol-modified thrombin binding aptamer (TBA) to detect thrombin, a crucial enzyme in blood clotting (**Figure 16b**) ^[324]. A dense hydrogel matrix is formed by immobilizing TBA and complementary DNA oligos on MXene sheets. As the TBA binds to thrombin, it releases its complementary DNA, resulting in a loosening of the hydrogel and a change in resistance. Thrombin was detected with 90–92% accuracy in artificial samples, indicating that the method is

efficient and has the potential to create customizable biomedical sensing devices for multiple targets [324].

Fan *et al.* developed a portable, smartphone-controlled electrochemical aptamer sensing system for the detection of microcystin-LR (MC-LR) (**Figure 16c**) [325]. A screen-printed carbon electrode (SPCE) modified with gold nanoparticles and reduced graphene oxide is integrated into the system, with a smartphone app controlling the electrochemical setup and visualizing results. Signal amplification on MXenes was performed using complementary DNA labeled with methylene blue (cDNA-MB). This system exhibited a detection range from 0.0001 to 5 nM and a limit of detection of 4×10^{-5} nM, demonstrating excellent stability, reproducibility, and specificity. Its portability and low cost make it ideal for on-site MC-LR detection, meeting the need for rapid, field-deployable analytical tools [325].

To detect dopamine (DA), Zheng *et al.* developed a MXene-based nanocomposite (MXene/DNA/Pd/Pt) (**Figure 16d**) [326]. DNA adsorbed MXene nanosheets were used as a conductive matrix for loading and in-situ growing palladium (Pd) and platinum (Pt) nanoparticles. Nanocomposites with this configuration demonstrated higher electrocatalytic activity toward DA, with a linear amperometric response between 0.2 and 1000 μ M and a detection limit of 30 nM. Human serum samples were successfully analyzed with the sensor, indicating its potential for use in complex biological environments [326]. In summary, these studies have demonstrated the versatility and effectiveness of MXenes for enhancing DNA-based sensors.

Figure 16. a) Schematic illustration of the preparation of TDN/Ti₃C₂T_x modified electrode and the principle of TDN/ Ti₃C₂T_x-based electrochemical sensor for gliotoxin detection. Reproduced with permission [323]. Copyright 2019, Elsevier. b) Proposed thrombin detection set-up with Ti₃C₂T_x-DNA hybrid hydrogel. Reproduced with permission [324]. Copyright 2024, Cold Spring Harbor Laboratory. c) The image of modules of the portable electrochemical system were marked with letters, and schematic illustration

of the portable electrochemical system. Reproduced with permission [325]. Copyright 2022, Elsevier. d) The schematic diagram of the fabrication of $\text{Ti}_3\text{C}_2\text{T}_x/\text{DNA/Pd/Pt}$ nanocomposite. Reproduced with permission [326]. Copyright 2018, Elsevier.

Enzyme-based sensors

As an innovative solution for extremely sensitive and stable detection applications, enzyme-based sensors based on MXenes offer innovative solutions. Here, we review the two recent studies summarized in **Table 12**. These studies exemplify the advancement in enzyme-based sensors using MXenes, emphasizing their enhanced sensitivity, stability, and performance in detecting glucose.

Table 12. Overview of research projects investigating the enzyme-based sensors application of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|-----------------------------------|--|--|---|-------|
| $\text{Ti}_3\text{C}_2\text{T}_x$ | Glucose Oxidase (GOx), Poly-L-Lysine (PLL) | High-performance biosensor for glucose detection | Superior enzymatic activities; glucose detection limit of 2.6 μM due to Ti_3C_2 catalyzing H_2O_2 decomposition | [327] |
| $\text{Ti}_3\text{C}_2\text{T}_x$ | GOx polyananogel (PGOx) | Enzyme electrochemical biosensor for stable and continuous blood glucose detection | Linear range of 0.03–16.5 mM, sensitivity of 48.98 $\mu\text{A} \text{mM}^{-1} \cdot \text{cm}^{-2}$, detection limit of 3.1 μM , 85.83% current retention after 200 cycles | [328] |

Wu *et al.* demonstrated a robust glucose biosensor by immobilizing glucose oxidase (GOx) on $\text{Ti}_3\text{C}_2\text{T}_x$ MXene nanosheets modified with poly-L-lysine (PLL) (**Figure 17a**) [327]. By modifying the MXene surface with PLL, it enhanced the loading capacity and stability of the GOx on the surface. By decomposing hydrogen peroxide, a byproduct of glucose oxidation, the GOx-PLL-MXene nanosheets demonstrated enhanced catalytic activity. This sensor achieved a glucose detection limit of 2.6 μM , highlighting its potential for sensitive glucose monitoring [327].

Tong *et al.* developed a glucose biosensor using a nanocomposite of GOx polyananogel (PGOx) and MXene nanosheets, termed PGOx@MXene/CS (**Figure 17b**) [328]. By using this configuration, enzyme stability was improved through efficient electrostatic assembly. MXene's large surface area was utilized for effective enzyme loading and hydrogen peroxide decomposition. The sensor demonstrated a wide linear range (0.03–16.5 mM) and a high sensitivity of 48.98 μA

$\text{mM}^{-1} \cdot \text{cm}^{-2}$, with a detection limit of $3.1 \mu\text{M}$. This sensor maintained 85.83% of its initial current after 200 cycles, confirming its reliability and potential as a continuous glucose monitor ^[328].

Figure 17. a) Schematic illustration of the formation of $\text{Ti}_3\text{C}_2\text{T}_x$ -PLL-GOx nanoreactor and electrochemical glucose sensing. Reproduced with permission ^[327]. Copyright 2021, Elsevier. b) Schematic illustration of technical route for synthesis of PGox@MXene/CS nanocomposites. Reproduced with permission ^[328]. Copyright 2024, Elsevier.

Virus detection sensors

Recent advancements in virus detection have demonstrated the potential of BioMXenes to enhance biosensor performance through their unique properties (**Table 13**).

Table 13. Overview of research projects investigating the Virus Detection Sensors application of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|-----------------------------------|--|---|---|-------|
| $\text{Ti}_3\text{C}_2\text{T}_x$ | Truncated WNV aptamer | To develop a fast-response electrochemical biosensor for the detection of West Nile virus (WNV). | Achieved rapid detection of WNV within 10 minutes with a limit of detection (LOD) of 2.57 pM in water and 1.06 pM in human serum. | [329] |
| $\text{Ti}_3\text{C}_2\text{T}_x$ | INA BP2 peptide | To develop an electrochemical biosensing system for detecting neuraminidase (NA) of influenza H5N1 virus. | Achieved a detection limit of 0.098 nM and demonstrated good reproducibility, stability, and recovery even in spiked human plasma. | [330] |
| $\text{Ti}_3\text{C}_2\text{T}_x$ | CRISPR-Cas12a, MXene-probe DNA-Ag/Pt nanohybrids | Create a colorimetric biosensor for Hepatitis B virus (HBV) detection | Achieved subpicomolar detection limits and integration with smartphone platforms for visible detection | [331] |
| $\text{Ti}_3\text{C}_2\text{T}_x$ | Probe DNA | To develop a biosensor for the detection of SARS-CoV-2 using functionalized $\text{Ti}_3\text{C}_2\text{T}_x$ MXene electrodes. | Detected the SARS-CoV-2 N gene with a detection limit below 105 copies/mL in saliva, demonstrating high specificity against other viruses. | [203] |

Park *et al.* developed an electrochemical biosensor for the detection of West Nile virus (WNV) based on a truncated aptamer/MXene ($\text{Ti}_3\text{C}_2\text{T}_x$) bilayer (**Figure 18a**) ^[329]. To achieve a detection time of under 10 minutes, the sensor incorporates alternating current electrothermal flow (ACEF) technology. The biosensor was able to detect WNV at an LOD of 2.57 pM in deionized

water and 1.06 pM in 10% human serum, demonstrating high selectivity and potential for field deployment in flavivirus detection [329].

Kim *et al.* used a three-dimensional bovine serum albumin (BSA)/MXene matrix to enhance an affinity peptide-based electrochemical biosensor system for detecting influenza virus (**Figure 18b**) [330]. Using peptide INA BP2, which binds specifically to influenza H5N1 neuraminidase (NA), the BSA/MXene nanocomposite achieved a limit of detection (LOD) of 0.098 nM. Despite spiked human plasma samples, this system showed excellent reproducibility, stability, and recovery. The bioanalytical tool has proved effective for detecting influenza viruses [330].

CRISPR-Cas12a-based colorimetric biosensors have been reported to be effective at detecting Hepatitis B virus (HBV) (**Figure 18c**) [331]. This method utilized MXene-probe DNA-Ag/Pt nanohybrids, where HBV DNA drives Cas12a trans-cleavage, which inhibits DNA metallization and enzyme activity. With subpicomolar detection limits, the sensor exhibited exceptional sensitivity and performed well in human serum samples. Colorimetric detection was also compatible with smartphone platforms, making it suitable for low-resource settings [331].

The last study by Chen *et al.* explored the use of $Ti_3C_2T_x$ MXenes functionalized with probe DNA to detect the nucleocapsid (N) gene of SARS-CoV-2 by Winston (**Figure 18d**) [203]. This sensor utilized nucleic acid hybridization and chemoresistive transduction, achieving a detection limit below 10⁵ copies/mL in saliva. As a result of the MXenes' high surface area and electrical conductivity, the sensor was able to respond quickly and sensitively. SARS-CoV-2 had distinct characteristics from SARS-CoV-1 and MERS, highlighting its potential for COVID-19 diagnostics [203]. The studies reviewed in this section demonstrate BioMXenes' abilities to enhance sensor

performance in virus detection through increased sensitivity, rapid detection, and practical deployment.

Figure 18. a) Schematic of the biosensor for rapid electrochemical WNV detection based on MXene/Tr-WNV aptamer developed using ACEF technology. Reproduced with permission [329]. Copyright 2023, Elsevier. b) Highly sensitive and label-free detection of influenza H5N1 viral proteins using affinity peptide and porous BSA/MXene nanocomposite electrode. Reproduced with permission [330]. Copyright 2023, Elsevier. c) Schematic illustration of CRISPR/Cas12-triggered peroxidase-like catalytic behavior regulation of MXene-probe DNA-Ag/Pt nanohybrids for colorimetric DNA sensing. Reproduced with permission [331]. Copyright 2022, Elsevier. d) Schematic illustration of the process for etching and delamination of $Ti_3C_2T_x$ MXenes and surface functionalization of $Ti_3C_2T_x$ with ssDNA probes, forming ssDNA/ $Ti_3C_2T_x$ biosensors for the selective detection of SARS-CoV-2 nucleocapsid (N) gene. Reproduced with permission [203]. Copyright 2022, ACS.

Hormone detection sensors

A recent study on hormone detection sensors has leveraged a BioMXene's unique properties to enhance detection sensitivity and specificity (**Table 14**). Specifically, Lee *et al.* introduced an electrochemical sensor for dopamine (DA), an important biomarker for neurodegenerative diseases such as Alzheimer's (**Figure 19**) [91]. The sensor used MXene with quercetin-loaded liposomes functionalized with gold nanoparticles (MXene/Lip-Qu@AuNPs). Applied to a glassy carbon electrode, this configuration leveraged MXenes' high conductivity and quercetin's specific binding properties to detect DA selectively and sensitively. The sensor demonstrated detection limits of 0.35 and 0.72 μ M for DA with linear concentration ranges of 1–10 μ M. The sensor's ability to detect DA in human serum highlights its potential for use in neurological diagnostics [91]. This study indicates that bio-functionalized MXene-based sensors have the sensitivity and practicality needed for hormone detection.

Table 14. Overview of research projects investigating the hormone-detection sensor application of BioMXenes.

| MXenes | Biomolecules | Project's Aim | Project's Result | Ref. |
|---|---|----------------------------|--|------|
| Ti ₃ C ₂ T _x | Quercetin-loaded liposome, gold nanoparticles | Selective dopamine sensing | Detection limits of 0.35 and 0.72 μM; linear range 1–10 μM | [91] |

Figure 19. Schematic illustration representing the electrochemical significance of the individual materials and the final MXene/Lip-Qu@AuNPs for DA sensing. Reproduced with permission [91]. Copyright 2023, Wiley.

Wearable sensors

Recent studies on incorporating BioMXenes into sensor materials have improved wearable sensors' performance and functionality (**Table 15**).

Table 15. Overview of research projects investigating the wearable sensors application of BioMXenes.

| MXene | Biomolecules | Project's Aim | Project's Result | Ref. |
|---|----------------------------|---|--|-------|
| Ti ₃ C ₂ T _x | Collagen, acrylic acid | Enhance mechanical properties and multifunctionality of collagen-based hydrogels | Improved tensile and compressive strengths, excellent biocompatibility, and effective bacteria killing under NIR. | [332] |
| Ti ₃ C ₂ T _x | Serine, elastomer | Develop self-healable sensor for wearable electronics | High gauge factor; low strain detection limit; capable of detecting subtle human motions | [150] |
| Ti ₃ C ₂ T _x | Anti-cortisol, L-cys/AuNPs | To create a thread-based electrochemical immunosensor for non-invasive cortisol detection in sweat. | Achieved high sensitivity with a detection limit of 0.54 ng/mL, showing high reproducibility and long-term stability (≥6 weeks). | [295] |

A collagen-based hydrogel reinforced with MXene nanosheets was developed by Zhang *et al.* (**Figure 20a**) [332]. A MXene-enhanced hydrogel achieved tensile and compressive strengths of 211.5 kPa and 7.8 MPa, respectively, values that are notably higher than conventional hydrogels. MXene-based hydrogels with excellent photothermal properties were able to monitor human body activities and provide effective antibacterial properties. Furthermore, the hydrogel demonstrated good biocompatibility, suggesting it is suitable for use in wearable health monitoring devices [332].

In a separate study, Guo *et al.* introduced a self-healing, MXene-modified elastomer for intelligent sensing applications (**Figure 20b**)^[150]. $\text{Ti}_3\text{C}_2\text{T}_x$ MXenes were functionalized with serine and incorporated into rubber-based supramolecular elastomers, resulting in materials with remarkable self-healing properties. Using self-healing MXene, the sensor displayed exceptional sensitivity, with a 1% strain detection limit and a 50 ms response time. As a wearable electronics and smart robotics sensor, the sensor can detect subtle human motions like speech and pulse, even after damage and healing^[150].

Laochai *et al.* designed a thread-based electrochemical immunosensor for cortisol detection in sweat without invasive testing (**Figure 20c**)^[295]. The sensor utilized a conductive electrode modified with L-cysteine (L-cys), gold nanoparticles (AuNPs), and MXene. By increasing the electrode's surface area and facilitating antibody immobilization, the sensor's sensitivity was enhanced significantly. The immunosensor demonstrated a wide linear detection range of 5–180 ng/mL and a low detection limit of 0.54 ng/mL. Wearable applications can easily incorporate it into wristbands for continuous cortisol monitoring because of its high reproducibility and long-term stability^[295]. The studies reviewed in this section demonstrate the versatility and improved performance of MXene-based materials for wearable health monitoring devices and intelligent sensing applications.

Figure 20. a) Schematic diagram of GCol-MX-PAA. Reproduced with permission^[332]. Copyright 2023, Wiley. b) Surface modification of MXene nanosheets by serine via the esterification reaction and construction of MXenes/rubber-based supramolecular elastomer (NMSE) via the latex assembly method. Reproduced with permission^[150]. Copyright 2020, ACS. c) Non-invasive electrochemical immunosensor for sweat cortisol based on L-cys/AuNPs/ MXene modified thread electrode. Reproduced with permission^[295]. Copyright 2022, Elsevier.

Aptamer-based sensors

A wide range of target analytes can be detected using aptamer-based sensors, including biomolecules, drugs, and environmental contaminants. Combining MXenes with these sensors, such as $Ti_3C_2T_x$, enhances their performance due to their superior electrical properties and large surface areas. An overview of recent studies on aptamer-based sensors using MXenes is provided below. **Table 16** highlights key points of these studies.

Table 16. Overview of research projects investigating the aptamer-based sensors application of BioMXenes.

| MXenes | Biomolecules | Project's Aim | Project's Result | Ref. |
|--------------|------------------------------|--|--|-------|
| $Ti_3C_2T_x$ | PD-L1-specific aptamer | Quantitative detection of PD-L1 biomarker | Achieved a detection limit of 7.8 pg/mL with a linear range of 0.01–100 ng/mL, demonstrating good specificity and stability. | [333] |
| $Ti_3C_2T_x$ | Aptamer | Detect antibiotic residues (kanamycin, tetracycline) | Detection limit of 1 fM; linear range 100 fM–1 μ M; high recovery rates | [334] |
| $Ti_3C_2T_x$ | cDNA-Ferrocene, MUC1 aptamer | Develop a competitive electrochemical aptasensor for detecting Mucin1 (MUC1) | Aptasensor achieved a wide linear range (1.0 pM–10 μ M) and a low detection limit (0.33 pM) | [335] |
| $Ti_3C_2T_x$ | Aptamer | Rapid detection of cytokine storm markers TNF- α and IFN- γ | Achieved rapid detection with low limits of detection (LOD) and high sensitivity. | [296] |

Li *et al.* presented a one-step potentiometric aptasensing method for the quantitative detection of programmed death-ligand 1 (PD-L1), a key biomarker in cancer immunotherapy (**Figure 21a**) [333]. $Ti_3C_2T_x$ nanosheet-functionalized electrodes were modified with PD-L1-specific aptamers to form the sensor. After interacting with PD-L1, the aptamer changed the spatial structure, which made the electrode's surface electric potential shift. The potentiometric aptasensor displayed a detection range of 0.01 to 100 ng/ml and a detection limit of 7.8 pg/ml. It also exhibited high specificity, reproducibility, stability, and accuracy, making it suitable for screening PD-L1 in

human serum samples. By enhancing sensitivity and decreasing detection limits over conventional aptamer-modified electrodes, $\text{Ti}_3\text{C}_2\text{T}_x$ provided better sensor performance [333].

Xiong *et al.* constructed a self-assembled sensing interface by functionalizing $\text{Ti}_3\text{C}_2\text{T}_x$ MXene with aptamers for antibiotic residue detection, specifically kanamycin and tetracycline (**Figure 21b**) [334]. The interface utilized the electrical properties of $\text{Ti}_3\text{C}_2\text{T}_x$ MXene and the specific recognition ability of aptamers to achieve high sensitivity. For both antibiotics, the sensor showed a linear detection range of 100 fM to 1 M and a detection limit of 1 M. Additionally, recovery rates for kanamycin and tetracycline were 97.15%–103.00% and 99.559%–106.36%, respectively. Self-assembled sensing interfaces enabled both ultrasensitive detection and aptamer configurational analysis. This work represents a significant advancement in highly sensitive food analysis technologies [334].

Wang *et al.* introduced a competitive electrochemical aptasensor designed to detect Mucin1 (MUC1), a breast cancer marker (**Figure 21c**). To enhance electrical signal detection, $\text{Ti}_3\text{C}_2\text{T}_x$ MXene nanosheets were used as carriers for aptamer probes and cDNA-ferrocene probes (cDNA-Fcs). cDNA-Fc/MXene probes were attached to the electrode surface, and Au–S bonds were used to immobilize MUC1-specific aptamers. During detection, cDNA-Fc/MXene probe competition with MUC1 reduced the electrical signal, which was used to quantify MUC1. A linear range of 1.0 pM to 10 pM and a low detection limit of 0.33 pM were achieved by the sensor. The electrochemical aptasensor is capable of detecting cancer biomarkers with high sensitivity and quantitative accuracy, making it a promising medical diagnostic device [335].

Noh *et al.* developed a rapid electrochemical dual-target biosensor using an aptamer/MXene ($\text{Ti}_3\text{C}_2\text{T}_x$) hybrid on an Au microgap electrode for detecting cytokine storm markers TNF- α and IFN- γ (**Figure 21d**). Biosensors employ alternating current electrothermal

flow (ACEF) to reduce detection time to under 10 minutes. Dual-type Au microgap electrodes enabled simultaneous measurement of both cytokines using $Ti_3C_2T_x$ MXene nanosheets. The sensor's detection range was 1 ng/mL to 10 ng/mL, and the limits of detection were 0.15 pg/mL for TNF- α and 0.12 pg/mL for IFN- γ . The biosensor also displayed high selectivity and sensitivity in human serum samples. Cytokine markers can be detected rapidly and accurately with the introduced tool [296]. The studies reviewed in this section point to significant advances made in the development of aptamer-based sensors with high sensitivity and selectivity, making them suitable for a wide range of applications, including clinical diagnostics and environmental monitoring.

Figure 21. a) Schematic illustration of the preparation procedure of potentiometric aptasensor on the glassy carbon electrode by using $Ti_3C_2T_x$ MXene nanosheets as the matrices; and one-step potentiometric measurement for target PD-L1 on the aptasensor. Reproduced with permission [333]. Copyright 2022, Wiley. b) The preparation process of the $Ti_3C_2T_x$ MXene and schematic illustration of the construction of a sensitive interface and detection of kanamycin (KANA) and tetracycline (TET). Reproduced with permission [334]. Copyright 2024, Elsevier. c) Schematic illustration of the fabrication procedure for the competitive electrochemical aptasensor. Reproduced with permission [335]. Copyright 2020, Elsevier. d) Schematic diagram of a rapid electrochemical cytokine storm biosensor based on the alternating current electrothermal flow (ACEF) technique. Reproduced with permission [296]. Copyright 2022, Elsevier.

Antibody-based sensors

Antibody-based sensors exploit antibodies' high specificity to detect and quantify target analytes, such as proteins and biomarkers. Incorporating MXenes, particularly $Ti_3C_2T_x$, into these sensors enhances their performance. Significant key developments in antibody-based sensors have been made using MXenes. **Table 17** highlights key points of these reported studies.

Table 17. Overview of research projects investigating the antibody-based Sensors application of BioMXenes.

| MXenes | Biomolecules | Project's Aim | Project's Result | Ref. |
|---|---------------------------------------|--|---|-------|
| Ti ₃ C ₂ T _x | Anti-PSA antibody, gold nanoparticles | Sensitive detection of prostate-specific antigen (PSA) | Detection limit of 0.031 ng mL ⁻¹ ; linear range from 0.1 to 50 ng mL ⁻¹ | [153] |
| Ti ₃ C ₂ T _x | Antibody, Bovine Serum Albumin (BSA) | Electrochemical biosensing of allergenic protein in food | Vertically aligned MXene electrode showed enhanced electrolyte diffusivity and higher current density than horizontally aligned | [336] |

Chen *et al.* designed an innovative interdigitated capacitance immunosensor system for the sensitive detection of prostate-specific antigen (PSA) (**Figure 21a**) ^[153]. To enhance sensitivity, this system integrated Ti₃C₂T_x MXenes with tyramine signal amplification. The immunosensor incorporated anti-PSA antibodies immobilized on Ti₃C₂T_x-coated electrodes. Gold nanoparticles functionalized with horseradish peroxidase (HRP) and detection antibodies served as signal-transducer tags. Using a sandwich-type immunoreaction, HRP was used to catalyze the precipitation of benzo-4-chlorohexadienone from 4-chloro-1-naphthol, altering the local capacitance of the sensor. With a detection range of 0.1 ng/mL to 50 ng/mL, the sensor showed a detection limit of 0.031 ng/mL. As well as outperforming commercial PSA ELISA kits, it demonstrated high reproducibility, specificity, and accuracy for analyzing human serum samples. The fabrication and performance of this Ti₃C₂T_x-based capacitance transducer highlight new possibilities for protein diagnostics and biosecurity ^[153].

Ogata *et al.* explored the use of vertically aligned Ti₃C₂T_x MXene electrodes to detect allergenic proteins in food (**Figure 22b**) ^[336]. The study addressed the challenge of MXenes' tendency to re-stack, which limits their effective surface area and diffusivity. The modified electrode, integrated with antibody-functionalized MXene and bovine serum albumin to prevent non-specific binding, showed enhanced performance in detecting allergenic proteins, offering a promising approach for food safety applications. By vertically arranging the MXene nanosheets,

the researchers significantly improved the electrolyte diffusivity and, consequently, the electrochemical performance of the biosensor. A vertically aligned MXene electrode exhibited a higher current density and better electrochemical characteristics than a horizontally aligned electrode, showing its potential to detect food allergens more accurately and sensitively^[336]. The two studies reviewed in this section indicate that in a variety of fields such as clinical diagnostics and environmental monitoring, BioMXenes have the potential to significantly enhance the performance of antibody-based sensors.

Figure 22. a) Schematic diagram of capacitance immunosensing system for the detection of prostate-specific antigen (PSA) on Ti_3C_2 MXenes-modified interdigitated micro-comb electrode (IDE) by coupling with enzyme labels, nano labels and tyamine signal amplification, accompanying enzymatic biocatalytic precipitation (Ab₁: capture antibody, HRP-Au-Ab₂: horseradish peroxidase and secondary/detection antibody-labeled gold nanoparticle; 4-CN: 4-chloro-1-naphthol). Reproduced with permission^[153]. Copyright 2019, Elsevier. b) Fabrication process of vertically aligned MXene electrode for biosensing.^[336]

Amino acid-based sensors

Amino acid-based sensors utilize the interaction between amino acids and various sensor components to detect and quantify specific analytes integrated with MXenes. **Table 18** highlights key points of a recently published work on this topic.

Table 18. Overview of a study on the amino acid-based application of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|--------------|---|--|---|-------|
| $Ti_3C_2T_x$ | ϵ -Poly-L-lysine (PLL), Cytochrome C (cyt-c) | Synthesize Ti_3C_2Tx quantum dots for detecting cytochrome c and trypsin | Developed a method with linear response for cyt-c and trypsin, applicable in spiked serum samples | [337] |

Liu *et al.* investigated titanium carbide quantum dots functionalized with ϵ -poly-L-lysine (PLL) for the detection of cytochrome c (cyt-c) and trypsin (**Figure 23**) [337]. Sonication cutting and hydrothermal methods were used to synthesize $\text{Ti}_3\text{C}_2\text{T}_x$ MXene quantum dots ($\text{Ti}_3\text{C}_2\text{T}_x$ MQDs) showed excitation wavelength-dependent blue photoluminescence with peaks at 330/415 nm and a quantum yield of 22%. Upon adding cyt-c to PLL-protected $\text{Ti}_3\text{C}_2\text{T}_x$ MQDs, an inner filter effect quenched their fluorescence. A detection limit of 20.5 nM was achieved for cyt-c in a concentration range of 0.2 to 40 M. By hydrolyzing cyt-c into smaller peptides and reducing Fe^{3+} to Fe^{2+} , the MQDs regenerated blue fluorescence. In spiked serum samples, the method was successfully applied to detect cyt-c and trypsin, demonstrating the practical utility of amino acid-functionalized Ti_3C_2 MQDs [337]. In summary, this study showed that MXene-based amino acid sensors can be used to detect proteins and enzymes in a sensitive and selective manner, taking advantage of MXene's unique optical and chemical properties.

Figure 23. Schematic presentation of the preparation of PLL-protected $\text{Ti}_3\text{C}_2\text{T}_x$ MQDs. [337].

3.8. Enhancing Properties for Future Research

MXenes are increasingly recognized for their potential applications in material science and engineering due to their unique properties. Their integration with biomaterials or bio-functionalization often leads to significant performance improvements and expands their utility in different fields. Their potential for material science and engineering can be seen in the following recent advancements. **Table 19** compares key points of these reported projects.

Table 19. Overview of research projects investigating the material science and engineering applications of BioMXenes.

| MXene | Biomolecule | Project's Aim | Project's Result | Ref. |
|---|--|---|--|-------|
| Ti ₃ C ₂ T _x | Immunoglobulin G (IgG) | To study the interactions between MXenes and IgG and their impact on protein stability | Ti ₃ C ₂ T _x exhibited significant IgG denaturation and aggregation, indicating high propensity for protein-corona formation | [338] |
| Ti ₃ C ₂ T _x | Polysaccharide | To fabricate a multifunctional hydrogel with high stretchability and conductivity | Excellent stretchability, self-healing, and photothermal conversion performance | [89] |
| Ti ₃ C ₂ T _x | Dopamine (DA), Serine (Ser) | To investigate the adsorption behavior of biological molecules on Ti ₃ C ₂ T _x for biosensing applications | Insight into adsorption energies and surface modifications for enhanced biosensing capabilities | [339] |
| Ti ₃ C ₂ T _x | L-Citrulline | To fabricate hydrogels with enhanced EMI shielding and mechanical properties | High tensile strength, ductility, and EMI shielding effectiveness suitable for electronic skin applications | [340] |
| Ti ₃ C ₂ T _x | Polydopamine, Bacterial Cellulose Nanofibers | Develop a moisture-responsive actuator with enhanced properties | Improved actuator with high conductivity (2848 S cm ⁻¹), tensile strength (406 MPa), and large deformation (176°). Functions as an electrical switch, robotic arm, and motor | [341] |

Huh *et al.* investigated the interactions between different MXenes and immunoglobulin G (IgG) to understand their biological and toxicological properties (**Figure 24a**) ^[338]. In their study, they found that different MXenes interact variably with IgG, affecting its stability and aggregation in diverse ways. In particular, Ti₃C₂T_x causes IgG destabilization due to its hydrophilicity and negative surface charge, which results in protein-corona formation. This study provided insights into how MXenes impact biological systems, guiding the design of MXene-based materials for biomedical applications ^[338].

He *et al.* developed a nanocomposite hydrogel by incorporating Ti₃C₂T_x MXene nanosheets into chondroitin sulfate/N,N-dimethylamino ethyl acrylate (DMAEA-Q) matrix (**Figure 24b**) ^[89]. This hydrogel has impressive properties, including high stretchability, rapid self-healing, and excellent electrical conductivity. Adding sulfonated Ti₃C₂T_x MXenes enhances the hydrogel's performance for real-time monitoring and photothermal conversion. The current study illustrates the versatility of MXenes for creating multifunctional materials with advanced properties ^[89].

Ozdemir *et al.* studied $Ti_3C_2T_x$ monolayers' interaction with dopamine and serine using density functional theory (DFT) (**Figure 24c**) [339]. Results revealed strong binding of these molecules to the Ti_3C_2 surface, with adsorption energies suggesting potential for biosensing applications. The study also explored how surface modifications affect adsorption properties, providing a foundation for developing functional materials based on Ti_3C_2 -MXenes [339].

The fabrication of a mechanically robust hydrogel composite that incorporates l-citrulline-modified $Ti_3C_2T_x$ MXene nanosheets has been reported [340] (**Figure 24d**). Besides offering excellent EMI shielding, this hydrogel also shows significant mechanical strength and ductility. In this composite, $Ti_3C_2T_x$ MXenes demonstrate both their mechanical resilience and high Electromagnetic Interference Shielding (EMI) capability [340].

Yang *et al.* developed a nacre-like composite film using polydopamine-modified $Ti_3C_2T_x$ MXenes and bacterial cellulose nanofibers (**Figure 24e**) [341]. Due to its high conductivity, mechanical strength, and moisture sensitivity, this film is suitable for use as a moisture-driven actuator. This work addressed some limitations of MXene actuators and opened the door to broader applications in smart devices [341]. The studies reviewed in this section collectively underscore the significant advancements achieved through the bio-functionalization and integration of MXenes, expanding the use of MXenes in various high-performance and innovative materials.

Figure 24. a) The surface property changes of antibodies on interacting with $Ti_3C_2T_x$, V_2CT_x , or $Mo_2TiC_2T_x$ MXenes. Reproduced with permission [338]. Copyright 2023, Springer. b) Schematic illustration of the formation of sulfonated MXene nanocomposite (SMC) hydrogel. Reproduced with permission [89]. Copyright 2022, Elsevier. c) Optimized atomic configuration of $Ti_3C_2T_x$ monolayer from top and side views. The 2D unit cell is highlighted within the yellow shaded area and relevant structural parameters (without (w/o) and with (w) Hubbard-U parameter where $U = 4.2\text{eV/Ti}$) are indicated. Reproduced with permission [339]. Copyright 2024, Elsevier. d) l-Citrulline-Modified $Ti_3C_2T_x$ MXene Nanosheets Embedded in Polyacrylamide/Sodium Alginate Hydrogels for EMI Shielding. Reproduced with permission [340]. Copyright 2022, ACS. e) Scheme showing the preparation process of polydopamine-modified $Ti_3C_2T_x$ MXenes and bacterial cellulose nanofibers (PDMM/BCNF) composite film. Reproduced with permission [341]. Copyright 2021, Wiley.

4. Specific Capabilities and Challenges

BioMXenes have a wide range of applications due to their unique properties and versatility. Prior to their implementation, they also face a variety of challenges. Taking these aspects into consideration is crucial for researchers and professionals seeking to use MXenes in a variety of fields, such as biomedicine, and environmental science. The purpose of this section is to highlight the key advantages and challenges of BioMXenes.

4.1. Specific Advantages of BioMXenes

BioMXenes are highly suitable for a wide range of biomedical and environmental applications due to their unique advantages. By integrating biological molecules with MXenes, their properties, such as biocompatibility [90], selectivity [333], and multifunctionality [302], are enhanced, making them superior to other nanomaterials. Here, we examine how BioMXenes contribute to their versatility and effectiveness in a variety of applications.

Enhanced biocompatibility

Grafting biomolecules such as peptides, proteins, and nucleic acids to MXenes can significantly enhance their biocompatibility. Bio-functionalization may reduce potential cytotoxicity and immune responses when interacting with biological systems. Enhanced biocompatibility is particularly beneficial for *in vivo* applications, such as targeted drug delivery and tissue engineering, where patient safety is a concern. For example, the surface modification of MXenes with biomolecules can mitigate adverse immune reactions and facilitate integration into biological tissues, promoting healing and reducing inflammation. Surface chemistry modifications can influence cellular adhesion, proliferation, and differentiation, ultimately affecting tissue regeneration. Furthermore, functionalized MXenes can interact with extracellular matrix (ECM) components to ensure bio-integration and avoid fibrosis or excessive scar formation. The tunability

of MXene surfaces also enables the optimization of key characteristics such as hydrophilicity, surface charge, and mechanical flexibility, all of which are essential for long-term biocompatibility. Medical devices and implants can take advantage of MXene's versatile properties by engineering them to meet the specific needs of different tissues and organs. Moreover, in the context of drug delivery, biofunctionalized MXenes can act as smart carriers, providing biocompatibility, and providing controlled release mechanisms by interacting with specific biological stimuli, such as pH, enzymes, or temperature [90,318,319].

Targeted specificity

The conjugation of targeting ligands (e.g., antibodies, aptamers) to MXenes can enable highly specific interactions with target cells or tissues. Molecular recognition capabilities of the conjugated ligands allow MXenes to selectively bind to overexpressed receptors or antigens on diseases such as cancer or inflammation. Specificity can enhance therapeutic delivery and diagnostic accuracy. Targeted drug delivery systems can precisely deliver therapeutics to cancer cells while minimizing off-target effects, improving treatment outcomes, and reducing side effects. For instance, antibody-functionalized MXenes can recognize and bind to tumor markers, ensuring chemotherapeutic agents are concentrated in targeted places and minimizing the risk of harming healthy tissues. By employing ligand-mediated targeting, MXene-based biosensors can be used for real-time monitoring of disease progression and treatment response, allowing clinicians to detect changes at the molecular level more accurately and quickly. Further research is examining multifunctional MXene platforms that combine drug delivery with diagnostic capabilities -- so-called theranostic platforms. Personalized treatment regimens could be offered based on real-time feedback from these platforms, responding dynamically to patient needs. The MXene platform

combines drug delivery, real-time monitoring, and targeted imaging into a single system for precision medicine [203,313,326,330,333].

Multifunctionality

BioMXenes can serve as multifunctional platforms combining therapeutic delivery, diagnostic imaging, and biosensing capabilities. Multifunctionality is achieved through simultaneous attachment of biomolecules with distinct functions. This multi-modal approach takes advantage of the intrinsic properties of MXenes, such as their high surface area, electrical conductivity, and ease of surface modification, to integrate various functionalities into a single platform. Developing smart nanoplatforms with synergistic capabilities is made possible by conjugating targeting ligands, therapeutic agents, and imaging probes on the same MXene surface. Therapeutic applications can be implemented on such platforms via integrated diagnosis and treatment systems, enhancing the efficiency of clinical interventions. As an example, a single MXene-based platform could simultaneously deliver chemotherapeutic agents to cancer cells, monitor therapeutic response using imaging modalities like MRIs or CTs, and detect biomarkers to measure disease progression. Accordingly, MXene-based structures can deliver drugs, provide real-time imaging feedback, and monitor disease markers, enabling personalized medicine and streamlining treatment. Personalized medicine can also benefit from BioMXenes because they are able to be tailored to individual patient needs. MXene platforms can be customized to respond to patient biomarkers, drug sensitivity, or resistance patterns by modifying surface properties and adjusting payloads. With the continued exploration of hybrid structures combining MXenes with other nanomaterials the potential for developing even more sophisticated multifunctional platforms grows, pushing the limits of precision and personalized medicine [90,168,291,302].

Versatile functionalization

The surface chemistry of MXenes enables versatile functionalization with a wide range of biomolecules. The versatility of MXenes stems from their abundant surface terminations, which can act as covalent and non-covalent sites for the attachment of functional biomolecules. Various surface groups can be modified to optimize MXenes for biomedical applications, allowing tailored interactions with biological systems. Due to its versatility, MXene can be customized for specific applications, such as gene therapy, immunotherapy, and biosensing. Customizable BioMXenes can deliver specific nucleic acids for gene editing or can detect specific biomarkers in complex biological samples. For example, MXenes functionalized with CRISPR-Cas9 can be employed for precise gene editing, offering potential treatments for genetic disorders at the DNA level. Through the conjugation of CRISPR-Cas9 components to MXenes, targeted gene editing can be achieved by efficiently delivering the gene-editing complex into cells. CRISPR-functionalized MXenes hold promise for treating genetic diseases by precisely targeting specific genetic loci. Moreover, MXene surfaces can be functionalized with antibodies or aptamers to enhance the specificity of these immunotherapies, allowing them to target cancer cells while sparing healthy tissue ^[54,316,332].

Enhanced stability

Biomolecules can be stabilized in biological environments with conjugation to MXenes. A strong interaction between biomolecules and MXene surfaces allows this stabilization, which protects sensitive biological structures from denaturation, degradation, or inactivation in hostile environments like high ionic strength. Stabilizing therapeutic agents and biosensors prolongs their functional lifetimes. As an example, MXenes provide consistent and reliable signal output over extended periods of time in biosensing applications. MXenes functionalized with enzymes maintain catalytic activity for extended periods, making them suitable for continuous glucose

monitoring in diabetics. Enhancing stability ensures that BioMXenes retain their functionality under harsh biological conditions, improving biomedical devices and treatments' reliability and durability. Furthermore, MXenes' ability to stabilize biomolecules under oxidative and enzymatic conditions is of particular relevance to implantable biomedical systems, which are subject to immune responses and biological degradation [149,305,308,309,311].

Improved performance in biological environments

Biologically functionalized MXenes exhibit improved performance in biological environments, such as increased binding affinity, and reduced non-specific interactions. MXene surfaces are precisely engineered, allowing for selective interactions with target biomolecules while minimizing off-target effects. MXenes can be functionalized with biomolecules, such as antibodies, to reduce non-specific protein adsorption and cellular uptake. To diagnose diseases accurately, high signal-to-noise ratios are essential for *in vivo* imaging applications. MXenes functionalized with suitable biomolecules can also escape the immune system, allowing for extended circulation in the bloodstream and better imaging of target tissues. Due to the rapid and reliable detection capability of MXenes, they can have a crucial role in point-of-care diagnostics and personalized medicine [90,302].

Efficient delivery and controlled release

BioMXenes safely can transport and release drugs and pesticides and to targeted sites, ensuring high therapeutic effectiveness with minimal side effects. MXenes are ideal candidates for developing efficient drug delivery systems due to their high surface area, tunable surface chemistry, and excellent biocompatibility. By leveraging these characteristics, a wide variety of therapeutic agents can attach to the surface, including small molecules, peptides, proteins, and nucleic acids. Chemotherapeutic can be delivered precisely to tumor sites, reducing systemic

toxicity of chemotherapy. Based on external stimuli or internal biological signals, MXenes with specific biomolecule functionalization can release therapeutic agents under controlled conditions. Different triggers, such as pH changes, temperature shifts, light, or magnetic fields, can cause stimuli-responsive MXenes to release their contents. As an example, MXenes can be engineered to release chemotherapeutic drugs in an acidic tumor microenvironment or under near-infrared light exposure, reducing the risk of drugs reaching non-targeted areas prematurely. A controlled release system can improve patient compliance and therapeutic outcomes by maintaining therapeutic levels over an extended period of time. A sustained delivery of drugs through MXenes is particularly beneficial for chronic conditions, in which maintaining therapeutic drug concentrations over long periods of time reduces the need for frequent dosing. Especially in diseases such as cancer, diabetes, and neurological disorders, consistent drug delivery can result in better management of the disease and improved patient outcomes. During sustained chemotherapy, prolonged release reduces peak doses, resulting in reduced systemic toxicity and fewer side effects. Furthermore, the ability of MXenes to deliver multiple therapeutic agents simultaneously makes them ideal for combination therapies, where different drugs can be delivered in a single platform with distinct release characteristics [291,302].

Enhanced imaging and diagnostic capabilities

MXenes can be biofunctionalized to enhance contrast in MRI, computed tomography (CT), and fluorescence imaging. Optical properties and high electrical conductivity make MXenes excellent candidates for enhancing imaging. Enhanced imaging contrast aids in early disease detection by improving the accuracy and sensitivity of diagnostic procedures. It is especially critical in conditions like cancer, where early detection has a dramatic impact on patient outcomes. MXene-enhanced imaging provides high resolution, which helps physicians detect early-stage tumors that

would otherwise go undetected with conventional imaging methods. Multi-biomolecule attachment to MXenes allows simultaneous detection of different biomarkers, creating a comprehensive diagnostic tool. Multiplexed imaging systems can be developed by attaching antibodies, aptamers, or peptides to the surface of MXenes in order to detect multiple disease markers simultaneously. Detecting multiple biomarkers simultaneously can improve treatment planning and provide a comprehensive picture of disease states in complex conditions like cancer and infectious diseases [260,316,318,320].

4.2. Challenges

Despite their promising potential, BioMXenes face several challenges that must be addressed to fully realize their application in various fields. Immunogenicity [342,343], stability [83,344,345], scalability [346,347], and regulatory [348,349] are examples of significant barriers to overcome in all bio-functionalized materials. This section discusses the primary challenges associated with BioMXenes, providing insights into the current limitations and areas where further research and development are necessary.

Complex functionalization processes

Bio-functionalization of MXenes with biomolecules can be complex, and precise control over reaction conditions is necessary to ensure the desired outcomes. Reproducibility can be hindered by this complexity, making it challenging to produce BioMXenes consistently and in enormous quantities. Scaling these processes is complicated by the intricacies of biofunctionalization, where factors such as steric hindrance and surface energy influence binding affinity and orientation. Optimizing functionalization conditions for high loading efficiencies and stability without compromising biomolecule activity requires a deep understanding of molecular interactions and surface chemistry. Unfavorable conditions can lead to low yields, reduced functionality, and

degradation of biomolecules. An example would be the formation of unstable linkages or the denaturation of proteins at high temperatures that limits biofunctionalized MXenes' overall effectiveness. Furthermore, a thorough understanding of surface chemistry is crucial to overcoming these challenges, since functional groups on MXenes determine the nature and strength of biomolecule attachment. Tailoring surface functional groups through chemical modifications can enhance biomolecule stability while minimizing desorption under physiological conditions [312,326,335,350–352].

Long-term stability and storage issues

Ensuring the long-term stability of BioMXenes, particularly in biological environments, is a significant concern. MXenes and immobilized biomolecules can both be rapidly degraded by changes in pH, ionic strength, and enzyme activity in biological systems.

Besides, as most biomolecules are inherently unstable, MXenes may degrade over time, particularly under oxidative or hydrolytic conditions, resulting in diminished effectiveness. The long-term stability of MXenes is influenced by their tendency to oxidize at their surfaces, especially when water and oxygen are present, which compromises their 2D structure and reduces their functionality. Reactive oxygen species (ROS) and various biomolecular interactions promote surface degradation in biological environments. Protective surface coatings, such as polymeric layers, lipid bilayers, and silica encapsulation, have been used to mitigate these effects while maintaining the active surface. To ensure the long-term performance of biofunctionalized MXenes, storage protocols must be developed in addition to functional coatings. Low-temperature storage, anoxic conditions, and light protection are often necessary to prevent both the degradation of MXenes and the denaturation or degradation of attached biomolecules. Despite these efforts, scalable, reliable storage protocols remain a significant challenge. For BioMXenes to remain

stable, real-time monitoring of storage conditions is necessary during transportation and handling. Nanoencapsulation strategies and responsive nanocapsules may provide solutions to maintain the stability and functionality of BioMXenes in the future. Furthermore, systematic studies are needed to establish clear guidelines for maintaining the bioactivity and structural integrity of MXene-based materials under different storage conditions [353–357].

Immunogenicity concerns

The presence of BioMXenes in the human body can potentially trigger immune responses, leading to inflammation or other adverse effects. MXenes and the immune system interact complexly not only because of their intrinsic properties, such as their size, shape, surface charge, and functional groups, but also because of the nature of the immobilized biomolecules. BioMXenes should be non-immunogenic to ensure their safety, particularly in applications where they come in direct contact with biological tissues or fluids. Studies on immunogenicity are therefore necessary to assess and mitigate potential immune reactions, since even subtle changes in surface properties can cause undesirable immune activation, posing a challenge to both the development and approval process. The immune system may recognize biomolecules introduced onto MXene surfaces as foreign, triggering the production of specific antibodies or activation of T cells. Specifically, prolonged exposure to immune cells can exacerbate these processes, resulting in chronic inflammation or immune clearance, thereby reducing the therapeutic efficacy of BioMXenes. To address these immunogenicity concerns, BioMXenes must undergo extensive preclinical testing, including both in vitro and in vivo tests. Furthermore, computational models and molecular simulations of immune receptor interactions can provide insights into potential immunogenicity and enable researchers to refine their designs before undertaking experimental testing. Functionalization strategies can be tailored by incorporating biocompatible coatings or stealth

layers that shield the BioMXene surface from immune detection. However, such modifications can alter MXenes' functional properties, as well as their ability to bind or interact with specific biomolecules. Bioactivity must be maintained while reducing immunogenicity. BioMXenes will benefit from future studies focused on optimizing surface modification techniques that preserve their desired functionality while minimizing immune responses. A comprehensive immunogenicity study will likely be required during the regulatory approval process, which can prolong clinical translation. To ensure the safety of BioMXenes in biomedical applications, early immunological assessment and iterative design modifications are essential [358–362].

Unstable biocompatibility

Several critical factors affect the biocompatibility of BioMXenes, including the type and density of biomolecules used for functionalization, the size and shape of the MXenes themselves, as well as the specific synthesis and post-functionalization procedures used. The variability in batches poses significant challenges in achieving consistent biocompatibility, particularly in clinical or therapeutic applications where reliable and safe performance is essential. MXenes can have a wide range of physiological effects based on their physicochemical properties as well as their environment, ranging from desirable effects such as cell proliferation and differentiation to adverse effects such as cytotoxicity and inflammation. Surface functional groups often influence BioMXenes' biocompatibility. By reducing non-specific protein adsorption and preventing immune cell activation, bioinert molecules such as polysaccharides and proteins can enhance biocompatibility. Biomolecules can also attach inefficiently to MXene surfaces, resulting in non-uniform biocompatibility. As an example, some synthesis methods may result in residual impurities such as solvents or byproducts that may be toxic. Furthermore, unbound biomolecules may leak into the surrounding environment if the attachment to MXenes is incomplete or unstable,

disrupting cellular homeostasis or triggering inflammatory responses. Biomolecules may degrade or change in the MXene surface chemistry during storage and handling due to pH, ionic strength, and temperature factors [363–367].

To mitigate these challenges, BioMXenes must undergo biocompatibility trials, including both in vitro and in vivo experiments, to assess cellular uptake, proliferation, and apoptosis under a variety of biological conditions. Surface plasmon resonance (SPR) and quartz crystal microbalance (QCM) can be used to monitor biomolecule stability and attachment efficiency over time [368–373].

To minimize batch-to-batch variability, it is crucial to adhere to standardized procedures and quality control protocols. To ensure consistent biomolecule attachment and surface modification, reproducible synthesis methods, such as controlled chemical vapor deposition (CVD) and solution-phase exfoliation, need to be used as well as real-time monitoring during functionalization. By integrating high-throughput screening methods, BioMXene biocompatibility can be assessed across multiple parameters simultaneously, ensuring that only the most stable and biocompatible formulations are tested in clinical trials. Standardized procedures are important for achieving reproducibility, but environmental factors such as temperature and humidity must also be carefully controlled when storing or using BioMXenes. Various factors can affect the long-term stability and biocompatibility of BioMXenes, including temperature, humidity, and exposure to oxidative agents. By developing advanced predictive models and machine learning algorithms in the field, we may be able to identify the optimal combination of functionalization strategies, synthesis methods, and environmental conditions that yield the most biocompatible BioMXenes [139,374–380].

Regulatory barriers

Regulatory approval of BioMXenes, like other MXene-based compounds, presents significant challenges because of the complexity of the regulatory pathways and the need for rigorous safety, efficacy, and quality assessment. Regulatory agencies, such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA), require extensive preclinical and clinical testing to demonstrate BioMXenes are safe for their intended applications, particularly in medical and therapeutic settings. MXenes are relatively new materials, so the regulatory framework governing their use is still evolving, adding layers of complexity and uncertainty to the approval process. Regulatory hurdles include the need for comprehensive characterization and standardization of BioMXenes. Regulatory bodies require precise documentation of BioMXenes' physicochemical properties, including size, morphology, surface chemistry, and possible impurities. To ensure predictable behavior of BioMXenes in biological systems, they must be well-defined and consistent across batches. Furthermore, MXenes can be functionalized with biomolecules, which introduces additional variables that can affect their stability, biocompatibility, and toxicity. Inconsistencies in functionalization efficiency, biomolecule attachment methods, and storage conditions can undermine reproducibility of experimental results and raise concerns during approval. Another crucial aspect of the regulatory process is toxicological studies. To evaluate their cytotoxicity, immunogenicity, biodistribution, and potential long-term effects, BioMXenes must undergo extensive in vitro and in vivo testing. MXene degradation products in biological environments, as well as the release of functionalized biomolecules, could cause toxicity or immune reactions. Furthermore, regulatory organizations often require comprehensive environmental impact assessments for MXene-based materials due to the possibility of environmental contamination or bioaccumulation. Addressing these concerns requires a thorough

understanding of BioMXene lifecycle, from synthesis and application to degradation and disposal. Researchers and developers have to navigate an increasingly complex regulatory landscape that includes both biocompatibilities testing as well as concerns regarding manufacturing. Following Good Manufacturing Practices (GMP) is crucial for reducing contamination and ensuring consistent BioMXene production. Validation of all manufacturing processes, from raw materials sourcing to final product packaging, and establishment of stringent quality control measures are included in this process. Additionally, the production of BioMXenes must comply with regulatory standards for the use of hazardous chemicals, especially when delamination processes involve substances such as hydrofluoric acid (HF), which can pose serious health risks if not properly managed [380–392].

Commercial scalability

Scaling up BioMXene production presents significant challenges, particularly in maintaining quality, consistency, and functionality when biomolecules are involved. Functionalization processes are complex, requiring precise control over surface modification, making it difficult to provide uniformity at larger scales. Variations in surface chemistry, biomolecule attachment efficiency, and MXene morphology can result in batch-to-batch inconsistencies, posing significant commercialization challenges. Commercially viable BioMXenes require cost-effective, scalable manufacturing processes that ensure high precision when functionalized. To ensure consistency, continuous-flow synthesis, automated functionalization methods, and advanced purification strategies can be employed. Moreover, small deviations in functionalization can have a significant impact on performance, making it necessary to apply strict quality control protocols during large-scale production. Optimizing the synthesis of MXenes, reducing the use of expensive biomolecules, and improving the efficiency of the functionalization process are also critical for

making BioMXenes accessible for widespread use in biotechnology, healthcare, and environmental science [393,394].

Integration with existing technologies

Incorporating BioMXenes into current medical devices and diagnostic platforms poses significant challenges due to differences in material properties, functionality, and performance standards. Many BioMXenes exhibit unique electrical, chemical, and mechanical properties, which require careful optimization to ensure compatibility. Specific characteristics of BioMXenes, such as their surface chemistry or conductivity, can be accommodated by redesigning devices, modifying sensor platforms, or adjusting protocols. The design and testing required to ensure BioMXenes can function effectively within established systems without compromising performance are extensive. MXene surface properties may need to be tailored to ensure compatibility with different diagnostic and therapeutic devices, as well as overcome challenges related to biomolecule stability. To use BioMXene-based technologies properly, healthcare professionals may need to adjust existing protocols and introduce new handling techniques. Clinical training programs and collaborations between biomedical engineers and material scientists will streamline this process. In real-world clinical settings, BioMXenes will have to succeed both in terms of their functional advantages as well as their seamless integration into established workflows and technologies. Researchers and healthcare providers must work closely together to address compatibility issues and accelerate the adoption of BioMXene-based solutions [156,395–398].

Long-term toxicity and environmental impact

While BioMXenes have enhanced biocompatibility compared to non-functionalized MXenes, long-term toxicity concerns and environmental impacts have yet to be addressed. Long-term exposure to BioMXenes poses a number of potential risks to human health, as well as to ecological

systems. Despite their novelty, MXenes behave strangely in biological environments, including their degradation pathways and potential accumulation in tissues and organs. To address these issues, comprehensive toxicological studies must examine not only the immediate effects of BioMXenes but also their long-term interactions with living organisms. MXenes or their degradation products should be assessed for their potential chronic toxicity or adverse ecological effects in biological systems or the environment in these studies. Bioaccumulation potential of these substances in organs and tissues as well as the possibility of contamination in the environment through water, soil, or air should be taken into consideration. Besides health risks, the environmental impacts of BioMXenes must also be assessed. Mitigating adverse effects can be achieved by designing biodegradable or environmentally friendly versions of MXenes, ensuring that degradation products are non-toxic, and implementing controlled disposal procedures. To prevent unintended harm to wildlife or aquatic ecosystems, researchers must also investigate BioMXene persistence. Integrated lifecycle assessments and environmental safety protocols are crucial to the safe and sustainable use of BioMXenes on a large scale. Designing appropriate containment and neutralization strategies for MXenes includes evaluating the potential release of MXenes during manufacturing, use, and disposal. Developing a comprehensive understanding of these long-term risks will require close collaboration between material scientists, toxicologists, and environmental researchers^[399–403].

Cost and resource availability

Bio-functionalizing MXenes is costly, primarily due to the high cost of biomolecules and the complicated chemical processes involved. Biomolecules used in functionalization are often expensive, and their synthesis or extraction increases BioMXene production costs. In addition, MXene preparation, functionalization, and purification require multiple steps, which are expensive

in terms of time and materials. Large-scale production methods must be developed in order to make BioMXenes commercially viable. By optimizing the functionalization process, less biomolecules will be required while maintaining performance, and synthetic analogs will be easier and more affordable. Chemical synthesis efficiency can be improved by recycling solvents and minimizing waste. Further reducing expenses may be possible by automating production systems and using continuous-flow techniques. Moreover, the cost-effectiveness of BioMXene technologies may also be adversely impacted by variations in the availability or price of raw materials. A collaboration between academia, industry, and government could lead to cost-saving measures or funding opportunities [404–408].

Hazardous materials in the synthesis process

MXenes may contain hazardous materials such as un-reacted HF and LiF (left in MXenes from in the synthesis steps), as impurities, which are hazardous to human health and the environment. Biocompatibility, chemical stability, and overall safety of MXenes can be affected by these impurities, especially in biomedical applications like drug delivery and tissue engineering. Even low concentrations of residual HF or LiF can cause adverse biological reactions in biomedical fields, as their potential toxicity poses a challenge for in-vivo applications. Furthermore, their presence in MXenes used for environmental remediation or water purification may lead to unintended contamination, negating their potential benefits. Alternative etching approaches have been investigated in order to mitigate these challenges, such as electrochemical etching and fluoride-free protocols, which aim to reduce the reliance on HF while maintaining MXene structural integrity and functionality. Impurities can also be minimized by post-synthesis purification techniques, such as extensive washing or ion exchange. Although these methods are often complex and costly, they may not completely eliminate trace contaminants [409–415].

To advance the development of MXene technologies in a safe and sustainable manner, it is imperative to address these challenges. Researchers should refine synthesis and purification techniques to remove hazardous impurities while maintaining the desired properties of MXenes in the future. A comprehensive toxicity assessment and environmental impact study are also required to evaluate full risks associated with residual chemicals in MXene applications, particularly in sensitive fields such as biomedicine and environmental science.

5. Future Perspectives

BioMXenes are rapidly evolving with significant advancements and emerging trends promising to expand their applications and enhance their performance. This section outlines potential future directions and innovations in this field.

5.1. Emerging trends and innovations

BioMXenes are at the cutting-edge of materials science, representing a significant leap forward due to their remarkable versatility ^[260,324] and multi-functionality ^[90]. Research and development on these 2D materials has revealed their potential for applications across a wide range of fields ^[142,315,316].

BioMXenes are transformative in advanced biomedical applications. Due to their unique surface chemistry, they are able to be functionalized in a targeted manner, enhancing their interaction with biological systems. This capability is leveraged for applications ranging from advanced drug delivery systems to cutting-edge biosensory ^[302,320]. Further research efforts should be made to address challenges such as immune responses, long-term biocompatibility, and biodistribution. Improving the clinical effectiveness of MXenes demands studies focusing on their molecular interactions with immune cells and cellular membranes. Biomedical technologies

incorporating MXenes enable the development of compassionate diagnostic tools and efficient therapeutic carriers, advancing personalized medicine and precision healthcare^[153,302].

Environmental safety is another crucial area in which BioMXenes have made significant advances. Their high surface area and tunable chemistry make them highly efficient adsorbents of pollutants, including heavy metals and organic contaminants, thus playing a significant role in water and soil purification. Besides detecting and neutralizing environmental hazards, BioMXenes may contribute to sustainable and eco-friendly solutions. Researchers should prioritize enhancing regeneration cycles and optimizing pollutant selectivity in future studies of MXene-based materials. Advanced catalytic regeneration techniques, including photothermal and electrochemical methods, hold significant potential for enabling more sustainable large-scale environmental remediation^[313,314].

Overall, the integration of BioMXenes into these critical domains reflects their transformative impact across multiple fields. Their ability to be tailored for specific applications underscores their potential to drive forward advancements in healthcare, environmental safety, and energy storage. As research evolves, MXenes are poised to offer innovative solutions and address complex challenges in these areas. Topics that require further research studies include developing MXene-based solutions, demonstrating their scalability, and validating their effectiveness in both biomedical and environmental applications as these technologies advance^[87,305].

Advanced bio-functionalization techniques

Researchers will likely focus on developing advanced bio-functionalization techniques to enhance the stability, specificity, and efficiency of MXene-based materials, particularly in biomedical and environmental applications^[416-420]. Functionalization will be achieved using precision and robust techniques such as click chemistry^[421-425]. By employing these methods, MXene materials can be

engineered with enhanced selectivity for specific biological targets, paving the way for the development of next-generation diagnostic platforms and therapeutic delivery systems. Furthermore, integrating MXenes with biological molecules such as peptides, antibodies, or nucleic acids can achieve unprecedented precision in targeting cellular processes, significantly improving therapeutic outcomes.

To advance MXenes' capability to selectively capture pollutants from complex environmental matrices, precision functionalization will be essential. Future research should focus on optimizing surface modifications to enhance the adsorption of emerging contaminants such as pharmaceuticals and microplastics. Additionally, MXenes with dual functionalities combining pollutant detection and remediation can facilitate the creation of integrated systems that not only monitor but also self-remediate in response to environmental changes, enabling real-time monitoring and sustainable environmental management.

In biomedical applications, these techniques will enable the creation of MXenes with superior biocompatibility and targeted delivery capabilities, improving the effectiveness of drug delivery systems and diagnostic tools. Precision functionalization will enable MXenes to detect and remove pollutants in environmental contexts, improving water purification and soil remediation. As these bio-functionalization strategies evolve, they will expand the applicability of MXenes, paving the way for innovative and sustainable technologies across various fields.

Hybrid and composite materials

To harness the unique properties of each nanomaterial, future research is also expected to concentrate on developing hybrid and composite materials that combine BioMXenes with graphene, carbon nanotubes, and metal nanoparticles. By integrating these materials, researchers can create composites that exhibit synergistic effects, leading to significant improvements in

various applications [426–428]. The synergy between MXenes and other nanomaterials, such as graphene, carbon nanotubes, and metal nanoparticles, can enable the creation of hybrid materials that leverage the unique properties of each component. To ensure structural integrity and stability under operational conditions, future research should focus on elucidating the interfacial properties and atomic-level interactions within these hybrids.

The development of MXene-based hybrids for energy storage applications, such as batteries and supercapacitors, holds significant promise. To achieve optimal charge/discharge performance and cycle stability, further investigations are needed to understand nanoscale interactions within MXene-graphene and MXene-metal hybrid systems. Breakthroughs in this area could pave the way for high-performance, scalable energy storage solutions featuring enhanced energy density and faster charge rates.

Similarly, incorporating MXenes into multifunctional catalysts offers potential for increasing energy conversion efficiency in applications such as hydrogen production and CO₂ reduction. This approach could unlock new pathways for designing advanced catalytic systems with improved performance and sustainability [429–431]. Biosensors and diagnostic tools can also be improved by combining MXenes with other nanomaterials, improving sensitivity and detection limits [432–434] while catalysis hybrids can improve reaction efficiency [435–437]. MXene-based technologies will benefit greatly from the continued exploration of these hybrid and composite materials [438–440].

Multifunctional platforms

Multifunctional platforms that integrate multiple BioMXenes will likely be developed for future research in biomedicine and environmental science with synergistic effect. By combining capabilities into a single platform, these multifunctional systems can offer comprehensive

solutions for disease diagnosis, treatment, and monitoring [441–443]. Researchers should strive to ensure the practicality of multifunctional systems by optimizing scalability and seamlessly integrating multiple functions into a single, cohesive device without compromising performance. One promising direction involves developing modular systems customized for specific patient needs in biomedicine or tailored to target specific environmental contaminants in remediation applications.

MXenes, with their dual role as sensors and remediation agents, can enable real-time environmental monitoring and dynamic pollution control. By combining MXene-based sensors with autonomous actuation mechanisms, hybrid systems can facilitate adaptive environmental remediation, responding in real time to detected pollutants for more efficient and sustainable pollution management. A single MXene-based platform could deliver therapeutic agents while simultaneously enabling real-time imaging and biosensing, making medical interventions more effective. Similarly, multifunctional platforms could detect pollutants and neutralize them, while monitoring environmental changes, leading to more efficient and sustainable solutions [365,444,445]. Developing such integrated systems will be crucial to addressing the multifaceted demands of modern science and technology.

5.2. Potential Future Applications

Personalized medicine

By enabling the development of customized drug delivery systems and biosensors tailored to individual patient profiles, BioMXenes can have a significant impact on personalized medicine. However, the effective scaling of these systems for clinical use requires addressing critical challenges, including batch-to-batch reproducibility, long-term storage stability, and adherence to regulatory compliance standards. Targeted therapies can be delivered in a more precise and

efficient manner with these MXene-based systems, which can help minimize side effects and improve therapeutic outcomes [446–448]. The integration of MXenes into diagnostic platforms capable of real-time monitoring of disease biomarkers has the potential to revolutionize the management of chronic diseases.

By combining MXene-based sensors with wearable devices, it becomes feasible to develop personalized treatment regimens informed by real-time data. This approach could transform personalized healthcare by merging drug delivery, diagnostics, and therapeutic interventions into a unified, multifunctional platform. Moreover, MXene-based diagnostic tools can offer real-time monitoring of disease markers, allowing for the continuous assessment of a patient's condition and the adjustment of treatment plans as needed [449–451]. Personalized and tailored medical care offers enhanced performance and higher quality of life for patients with this level of customization and adaptability [452–454].

Smart environmental monitoring and remediation

As environmental concerns intensify, BioMXenes offer promising solutions for advanced monitoring and remediation strategies. By harnessing their unique properties, these sensors can be used to develop smart highly selective and sensitive environmental sensors, capable of detecting and removing even trace levels of pollutants in the environment, including air and water [455–457]. To fully realize their potential, further research is required to overcome challenges related to sensor sensitivity, selectivity, and long-term stability. Additionally, advancing multifunctional MXene-based materials could enable the development of self-sustaining systems designed to effectively mitigate environmental contaminants.

Integrating MXenes with bio-inspired materials presents an exciting opportunity to create bio-hybrid systems that combine pollution detection with environmental recovery. These eco-

friendly solutions could address modern pollution challenges by providing sustainable and adaptive approaches to environmental management. For instance, MXenes can be engineered into efficient multifunctional materials for detection and removal of contaminants, such as heavy metals and organic pollutants, from environmental matrices ^[458-460]. By providing more effective tools for environmental protection and sustainability, these innovations can significantly mitigate issues like water and air pollution, contributing to a cleaner and healthier environment ^[461-463].

Enhanced energy systems

Energy storage devices, such as batteries and supercapacitors, require biocompatible materials for medical applications. These devices are especially important when they are intended for implantable electronics or systems that interact with living organisms. A non-biocompatible material can cause severe health complications, including chronic inflammation, the need for secondary surgery, and leakage, a major concern for devices implanted in the body. Alternatively, biocompatible materials are designed to avoid toxicity or immunological responses when in contact with tissue or fluids in the body ^[464,465]. For medical applications, the biocompatibility of MXenes is essential for designing immune-inhibiting energy storage solutions. To ensure the safety of implantable medical devices, extensive long-term studies on MXene-based energy systems are required to evaluate their performance, durability, and potential interactions with biological tissues.

Embedding BioMXenes into advanced energy systems can offer exciting potential for developing the next generation of biocompatible batteries, supercapacitors, and fuel cells. Optimizing BioMXenes with other energy storage materials integration can enable these systems to achieve significant increases in biocompatibility, energy density, lifespan, and efficiency. MXenes' high electrical conductivity and large surface area can be improved with biomolecules to

enhance charge storage and transfer in batteries and supercapacitors, leading to devices with faster charge/discharge rates and longer operational lives. Similarly, their incorporation into fuel cells can improve catalytic performance and energy conversion efficiency. Furthermore, the addition of biomolecules to MXenes enhances their biocompatibility, leading to the development of medical energy storage devices. These advancements can drive progress in energy storage and conversion technologies, supporting the transition to more sustainable and high-performance energy solutions [464–468]. Research efforts should focus on optimizing the integration of MXenes with other advanced materials to improve charge storage capacity, efficiency, and stability. Combining MXenes with conductive polymers or metal-organic frameworks (MOFs) offers significant potential for enhancing charge/discharge kinetics and cycle stability, making them more effective for use in batteries and supercapacitors.

5.3. Future Research Directions

Fundamental studies on mechanisms

A deeper understanding of the fundamental mechanisms behind MXene bio-functionalization and their interactions with biological molecules must be prioritized in future research. Surface chemistry of functionalized MXenes at the molecular level could be further explored to develop MXenes with optimized properties for biological and environmental applications. To develop better and more efficient bio-functionalized materials, these mechanisms need to be clarified at the atomic/molecular level [469–473]. MXenes are believed to influence cellular behavior through various molecular pathways, including inflammation, cellular uptake, and immune responses. Gaining a comprehensive understanding of these interactions will be essential for optimizing their clinical applications and ensuring their safe and effective deployment in medical settings. By gaining insights into how MXenes interact with biological systems, researchers are able to

optimize functionalization processes, enhance stability and specificity, and tailor their properties to meet the needs of specific applications. This knowledge will advance the development of MXenes for biomedical and environmental applications, leading to more precise and impactful technological solutions [223,313,318,339,474,475].

Long-term stability and safety

MXenes hold great promise for biomedical and environmental applications. However, long-term stability and safety remain pivotal areas for research. Comprehensive investigations into the degradation kinetics of MXenes under physiological and environmental conditions are essential, with a particular focus on their potential for bioaccumulation or long-term toxicity.

To address these challenges, advanced *in vivo* models and imaging technologies should be employed to examine the interactions of MXenes with tissues and cells. Studies on long-term biocompatibility and potential systemic effects will provide crucial insights, guiding the development of safer and more effective MXene-based materials for both clinical and environmental applications. BioMXenes need to be investigated with more specificity and consistency in future research. Degradation kinetics of BioMXenes should be examined under various environmental conditions, such as temperature fluctuations, humidity, and chemical exposure, to determine their stability for a long time. Detailed investigations are essential to determine the potential bioaccumulation, toxicity, and immunogenicity of bio-functionalized materials [476–481]. To assess the stability of BioMXenes in biological tissues and their impact on cellular and systemic functions, advanced analytical techniques should be employed, such as *in vivo* imaging and molecular profiling. To ensure the safe deployment of materials in clinical and environmental settings, robust safety profiles are necessary to establish through systematic toxicity

testing and risk assessments [482–484]. Researchers can advance the development of BioMXenes into reliable and safe materials for complex applications by focusing on these specialized aspects.

Scalability and commercialization

Transitioning BioMXenes from laboratory research to industrial production requires overcoming significant challenges related to scalability and cost-efficiency. Achieving mass adoption will depend on the development of high-yield, reproducible synthesis methods that preserve the structural integrity and bio-functional properties of MXenes. Advanced large-scale synthesis techniques, such as continuous-flow reactors or 3D printing, could provide cost-effective solutions for production.

Future research must focus on scaling up the laboratory successes of BioMXenes by optimizing synthesis and functionalization processes to ensure scalability. This requires developing methods that maintain consistency, enhance yield, and minimize production costs, paving the way for industrial-scale applications. This involves refining production techniques to enhance yield and reproducibility, and addressing issues related to material processing at larger scale [485,486]. To ensure successful commercialization, synthesis and functionalization procedures must comply with industry standards and regulatory requirements [487,488]. As a result, the widespread integration of BioMXenes into healthcare, environmental, and energy systems will only be feasible if clear regulatory frameworks are established to govern their synthesis, functionalization, and application. These frameworks will ensure safety, standardization, and compliance, facilitating their transition from research to real-world use. Collaboration between academia, industry, and regulatory bodies will be key to overcoming these challenges. Through these partnerships, BioMXenes can be widely adopted and integrated into existing industrial and commercial frameworks, facilitating the transition from research to application.

Interdisciplinary approaches

BioMXenes represent an inherently interdisciplinary field that requires close collaboration between materials scientists, chemists, biologists, engineers, and medical researchers. To advance this field effectively, fostering interdisciplinary approaches is crucial. By integrating diverse experiences and perspectives, we can drive innovation and address complex challenges in a more comprehensive manner. Material scientists and chemists can work together to refine the synthesis and bio-functionalization of MXenes, while biologists and medical researchers' study MXene interaction with biological systems and evaluate their therapeutic potential. Engineers can contribute by developing scalable fabrication techniques and integrating MXenes into practical devices. By promoting interdisciplinary research and establishing collaborative networks, the field can accelerate the development of BioMXenes and translate theoretical advances into practical applications [489,490].

5.4. Open Research Questions

BioMXenes and their applications have made considerable progress, but several critical questions remain.

- How do the size and shape of bio-functionalized MXenes affect their interaction with biological molecules and cells [491,492]?
- What are the strategies for the reusability and recycling of bio-functionalized MXenes, and how can their life cycle be extended [493,494]?
- How does the process of bio-functionalization affect the structural and chemical stability of MXenes [495,496]?
- How does the biocompatibility of BioMXenes vary across different types conjugated biomolecules [497,498]?

- How does bio-functionalization affect the inherent properties of MXenes, such as their electrical conductivity, mechanical strength, and thermal stability [499,500]?
- How does the number of layers in MXenes influence their interaction with biological systems and their overall functionality [501,502]?
- How can the consumer and public acceptance of bio-functionalized MXenes be improved, particularly in relation to their use in healthcare and everyday products [503,504]?
- What are the advancements in computational modeling for predicting the behavior of BioMXenes in complex biological systems, and how can these models guide experimental design [505,506]?
- What potential do bio-functionalized MXenes have in theragnostic, particularly in combining diagnostic imaging and therapeutic delivery into a single platform [507–509]?

6. Conclusion

Bio-functionalized MXenes (BioMXenes) sit at the cutting-edge of nanotechnology, materials science, and biomedical engineering, presenting a versatile platform with far-reaching potential for a wide range of applications. This review has highlighted the significant advancements in the synthesis and functionalization of MXenes, with a focus on their enhanced performance in biomedical and environmental systems.

MXenes' unique combination of high surface area, electrical conductivity, and facile functionalization with bioactive molecules has driven their successful integration into drug delivery systems, offering controlled and targeted release of therapeutic agents. Their exceptional sensitivity and specificity in cancer detection and treatment also open new doors for precision medicine, positioning BioMXenes as a promising tool for targeting and eradicating malignant cells.

In tissue engineering, BioMXenes provide critical advantages, including mechanical strength, electrical conductivity, and promotion of cell adhesion and proliferation. These properties support the regeneration of complex tissues such as neural, cardiac, and bone through electrical stimulation and structural reinforcement, with MXene scaffolds offering a potential breakthrough in mimicking the extracellular matrix for regenerative medicine.

Moreover, BioMXenes have demonstrated impressive capabilities in biosensing, detecting biomolecules, pathogens, and environmental toxins with remarkable sensitivity. Their ability to transduce biological interactions into high-fidelity electronic signals makes them ideal for real-time, on-site diagnostics. Coupled with their adaptability to various biorecognition elements, rapid response times, and stability, BioMXenes are poised to play a leading role in next-generation biosensors for medical diagnostics, food safety, and environmental monitoring.

In addition to their biomedical applications, MXenes offer significant promise in environmental domains, such as corrosion protection coatings, water purification systems, and food safety sensors. Their mechanical flexibility, biocompatibility, and ability to integrate bioactive molecules also make them suitable for wearable and implantable energy storage and electronic devices.

Despite their vast potential, challenges remain such as ensuring long-term stability, addressing toxicity concerns, improving production scalability, and mitigating environmental impacts. To fully harness the capabilities of BioMXenes, future research must focus on innovative bio-functionalization strategies, deeper insights into the bio-nano interface, and synergistic integration with other nanomaterials. Interdisciplinary collaboration among chemists, materials scientists, biologists, and engineers will be crucial to overcoming these hurdles and unlocking the full potential of BioMXenes.

In conclusion, bio-functionalized MXenes represent a transformative class of materials with the potential to significantly impact a broad range of fields. Continued research and development in this area will position BioMXenes as pivotal contributors to technological advancement, environmental sustainability, and the future of healthcare. Although BioMXenes hold significant potential for diverse applications, there is a pressing need for a deeper exploration of their synthesis, characterization, and functionality. Interdisciplinary approaches should be applied to refine bio-functionalization techniques, focusing on scalability, cost-effectiveness, and long-term stability. Computational models can play a pivotal role in elucidating interaction mechanisms at the atomic and molecular levels, thereby guiding experimental designs and enabling the development of innovative applications. Moreover, BioMXene platforms with multifunctional capabilities—serving simultaneously as diagnostics, therapeutics, and environmental tools—could bridge current gaps and expand their utility. Broad adoption of BioMXenes will depend on overcoming challenges such as cytotoxicity, stability in diverse environments, and regulatory compliance. Integrating expertise across disciplines will not only broaden their application spectrum but also enhance their practical deployment to address global challenges in healthcare, sustainability, and advanced technology.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.S. reports that financial support was provided by U.S. National Science Foundation; and H.V. declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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