A Seminar Paper on

Application of MXene in Cell and Bioengineering

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Application of MXene in Cell and Bioengineering[1]

By

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ABSTRACT

MXene is a multifaceted two dimensional (2D) material which is recently emerged in the world of two dimensional compounds. It is made up of surface-modified carbide which provides it flexibility and variable composition. The general formula of MXene is $M_{n+1}X_nT_x$, where M indicates early transition metals, X indicates layers of carbon or nitrogen (may contain n numbers of layers) and terminated with surface functional groups (denoted as T_x/ T_z). High electrical conductivity, exceptional mechanical stability, and great optical characteristics are just a few of the unique qualities that MXenes have to offer. MXenes also exhibit good biological properties, with high surface area for drug loading/delivery, good hydrophilicity for biocompatibility, and other electronic-related properties for computed tomography (CT) scans and magnetic resonance imaging (MRI).In the recent past only some of the biological properties of MXene have been explored and the types of MXene applied in the perspective of biomedical engineering and agriculture are limited to a few, titanium carbide and tantalum carbide families of MXenes. This review paper focuses on the structural properties of MXene, synthesis procedures followed and whether they are fluorine-based or fluorine-free etching methods to produce biocompatible MXenes. Both good and bad aspects of these synthesis procedure are discussed. MXenes can be further changed for applications in biosensing, cancer theranostics, drug delivery, and bio-imaging to increase their biodegradability and decrease their cytotoxicity. Discussions also included MXene's antibacterial properties and use in agricultural aspects. Some challenges for in vivo applications, pitfalls, and future outlooks for the deployment of MXene in bioengineering were included. Overall, this review puts into perspective the current advancements and prospects of MXenes in cell and bioengineering.

Keywords: Antimicrobial activity, Bioengineering, Biosensors, Cancer therapy, MXene

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CHAPTER I

INTRODUCTION

Two-dimensional (2D) materials are currently of keen interest to material researchers due to their excellent electronic, mechanical, and optical properties. On the other hand, early twentieth century classical physicists anticipated that thermal lattice fluctuations caused the thermodynamic stability of 2D materials. Yet, the finding of a 2D graphene monolayer in 2004 was a significant advance in the field of material science. (Zamhuri *et al*., 2021). In contrast to their 3D counterparts, 2D nanomaterials consist of layers of atomic to nanoscale thicknesses and have unique features of their own.

Recently, novel materials with significantly improved physical and chemical characteristics suited for a variety of research fields have been introduced. Because of its unique properties and adjustable chemical structures, "MXene" has gained significant attention in the field of 2D nanomaterials research. The first ever MXene was discovered by a group of researchers from Drexel University, Philadelphia, where they exfoliated 3D titanium aluminium carbide (Ti_3AlC_2) or known as MAX phase using hydrofluoric acid (HF), and produced 2D titanium-carbide (Ti_3C_2) layers. They share a general formula of $M_{n+1}X_n$ (n = 1–3), where M is an early transition metal (e.g. Sc, Ti, Zr, Hf, V, Nb, Ta, Cr, Mo), and X is a carbon or nitrogen. Since its initial discovery (Ti_3C_2) in 2011, MXenes have attracted a great deal of research interest in various fields, such as physics, energy evolution, environmental science, and nanomedicine (Huang *et al*., 2018). In most cases, these materials have a layered structure with (n + 1) layers of M (the early transition metal) interconnected by n layers of X (carbon and nitrogen). Given the comparatively few atomic layers, a single MXene stack typically has a thickness of less than 1 nm. Whereas the lateral dimensions of MXenes vary from nanometers to micrometers depending on how the materials were prepared.

Furthermore, transition metals exhibit metallic conductivity, which gives these compounds the ability to exhibit electronic, optical, and magnetic properties. One of the most recent discoveries about MXene is the application of these compounds in the bioengineering. Bioengineering is a discipline that applies engineering principles of design and analysis to biological systems and biomedical technologies. The nanoscale size of MXene not only makes it possible for them to have a longer circulation time in biological systems, it also endows them with novel properties, such as closer interactions with surrounding molecules and size effect-induced luminescence. As a novel type of nanomaterial, nano-sized MXenes may provide new solutions for ultrasensitive diagnosis and the efficient treatment of diseases (Huang *et al*., 2018). This review paper discusses the process of MXene synthesis and their application in bioengineering field. Usually top down or bottom up processes are followed in synthesis of MXene. Among the two, first one is more common. But there are some of the limitations that needs to be overcome. For example, use of HF in etching may be toxic for cell and both human safety and the environment. HF can cause systemic toxicity that can lead to fatality. For biological applications, the MXene nanosheets must be extremely small. Conventional top-down multi-layered MXene production results in huge sheet sizes, which could cause biosafety problems and poor therapeutic results. (Zamhuri *et al*., 2021). Again the CVD (Chemical vapour depositon) method in case of bottom up is also not suitable for cell and biomedical components. If these challenges can be overcome then MXene can be of great use in the field of bioengineering. For example, these nanoparticles can be used as biosensors, for bioimaging, tissue regeneration through bioengineering. Cancer therapy can get a wide spectrum of development through the use of MXene. Again the antibacterial activity of MXene against both Gram positive and Gram negative bacteria can be used to engineer new antibiotics. Application of these nanocomposites in agriculture is also possible. Till now, biosensors are developed using MXene those can sense CO_2, NH_3, various toxins like alfatxin, etc. Pesticide delivery system can also be prepared using them. Again detection of genetically modified crops and heavy metals for waste water treatment is also possible. The aim of this review is to highlight the key MXene synthesis technologies with top notch biomedical and agricultural applications. The current challenges and future outlooks of biocompatible MXenes are also discussed. This review will be useful as a guidance for upcoming new research of MXenes for more advanced and diverse applications. **Considering the facts, present study was undertaken with the following objectives**

1. To analyze the structural organization, properties and synthesis mechanism of MXene

2. To assess the potential of MXenes for use in cell and biomedical engineering

3. To evaluate the potential applications of MXenes in agricultural bioengineering

CHAPTER II

MATERIALS AND METHODS

This paper is mainly a review paper. Hence, with the goal of writing this paper, all the information was gathered from secondary sources. The choice of the title was made with the help of my major professor. The secondary sources used included journals, reports, internet searches. Most of the information are collected by internet browsing. The valuable suggestions and guidance from my major professor and the respected course instructors have helped me a lot in preparing the paper. After collecting the necessary information, I have compiled and arranged them chronologically for better understanding and clarification.

CHAPTER III

REVIEW OF FINDINGS

3.1 Concept of MXene

MXene has unique properties and adjustable chemical structures, "which has gained significant attention in the field of 2D nanomaterial research. Researchers from Drexel University in Philadelphia made the first ever discovery of MXene when they used hydrofluoric acid (HF) to exfoliate 3D titanium aluminium carbide (Ti_3AlC_2), also known as the MAX phase, to create 2D titanium-carbide (Ti_3C_2) layers (Naguib *et al.*, 2011). Because of being similar to graphene, MXenes are typically created by exfoliating their 3D precursors. The ternary carbides or nitrides that make up the MAX phases are the 3D precursors for MXenes. According to the general formula of MXene, $M_{n+1}AX_{n,}$ M indicates an early transition metal, A is an A-group element (mostly main group IIIA or IVA), X is either carbon or nitrogen, and n = 1, 2 or 3 (Figure 1) (Zamhuri *et al.*, 2021). The A layers can be selectively removed by a strong acid (such as hydrofluoric acid, HF) etching to generate M_{n+1}Xn layers that can be further separated by sonication. Strong acids are used because M-X bonds are much stronger than M-A bonds and the A layers are chemically more active than M-X layers (Cai *et al.*, 2020). Due to their high surface energy, MXenes generally have their surfaces terminated with fluorine (-F), hydroxide (-OH), and oxygen (-O) groups by this etching procedure (Zamhuri *et al.*, 2021). As a result, MXene's complete chemical formula is $M_{n+1}X_nT_x$, where Tx stands for the surface functional groups (Cai *et al.*, 2020). The Ti_3C_2 and Ti_2C families of MXenes have so far seen the most use in biomedicine and biotechnology. This creates the possibility of new elemental combinations from the M and A groups, aside from Ti and C (Zamhuri *et al.*, 2021).

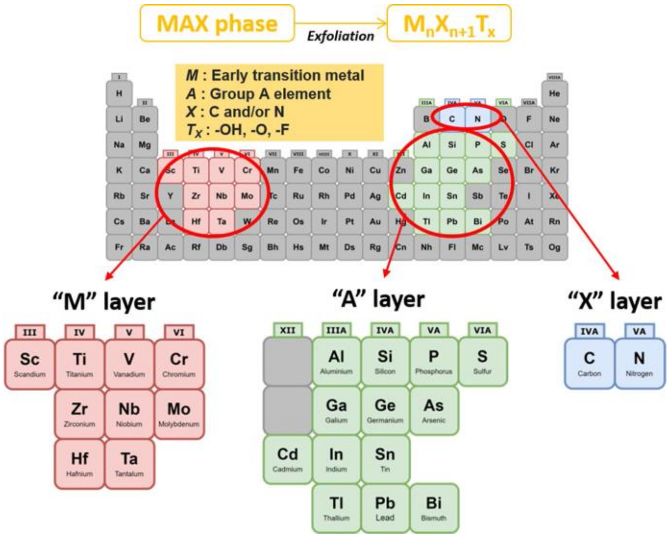


Figure 1. General element composition of MAX phase and MXene: M: early transition metal, A: Group A element, X: C and/or N, Tx: surface functional group (Zamhuri *et al*., 2021).

3.2 Properties of MXene

MXene has a number of special properties that help it to become one of the important biotechnological application tools. For example

3.2.1 Optical and electroactive properties: The dielectric response of MXenes is greatly influenced by their metallic nature and interband transitions. (Berdiyorov & Madjet, 2016) demonstrated that surface functionalization (or functional groups) significantly affects the optical properties of MXenes (Guo *et al*., 2017). The use of MXenes in transparent conductive electrodes, photocatalysis, and light-controlled anticancer therapies is made possible by their optical characteristics (Ran *et al*., 2017). The electroactive properties of the MXenes are still being investigated for their potential. These materials' primary distinguishing trait is their metallic-like behavior, which is made up of significant electron concentrations near to the Fermi level (The highest energy level that an electron can occupy at the absolute zero temperature) (Liang *et al*., 2017).

3.2.2. Electronic properties: Comparing MXenes to other 2D materials, their electronic characteristics are the most unique. According to (Huang *et al*., 2018) the nature of M and X as well as their surface terminations have an impact on the electrical characteristics of MXenes. Theoretical investigations suggested that MXenes may exhibit metallic to semiconductor-like properties for specific compositions, and insulation may also be feasible for some heavy transition metal (such as Cr, Mo) containing MXenes. The electrical characteristics of a few varieties of MXenes, such as Ti_2C, Ti_3C_2, Mo_2C, Mo_2TiC_2, and $Mo_2T_2C_3$ with heterogeneous surface terminations, have been experimentally confirmed. For several forms of activations, such as bio-catalysis and the formation of reactive oxygen species, MXenes' semiconducting characteristic is crucial (ROS). Under specific stimuli, such as light stimulation, active electrons and vacancies may be developed in the semiconductor-like MXenes. These electrons respond to the environment and put themselves under oxidative stress, which is a crucial step in catalysis and the production of ROS (Huang *et al*., 2018). Still the knowledge on electronic properties of MXene is not sufficient and further research is needed.

3.2.3. Magnetic Properties: Physical characteristics like magnetic force are frequently used in a variety of biomedical applications. Experimental studies have rarely confirmed the magnetic properties of MXenes because it is challenging to prepare termination-free MXenes.Recently, two types of MXenes (Cr_2C and Cr_2N) were predicted to have a magnetic moment even with surface terminations, whose magnetic mechanism is however unclear(Singh *et al*., 2005). The present biomedical uses of MXenes that use magnetic stimuli, however, are based on hybrid materials made of MXenes and magnetic nanoparticles because magnetic MXenes have not yet been created (e.g. MnO_2 and iron oxide)(Huang *et al*., 2018).

3.3. Preparation of MXene

In general, top-down or bottom-up methods can be used to synthesize MXenes. Determining their general physical and chemical features, such as size, shape, and functioning of the material, requires careful consideration of the best method (Shao *et al*., 2020). More than twenty of the approximately seventy distinct MXene compositions that have been theoretically predicted have been empirically attained (Huang *et al*., 2018). The following provides a summary of the synthesis and surface modification of MXenes.

3.3.1.Top-down method: Top-down fabrication techniques typically draw from the cleavage of relatively large bulk precursors, which can be categorized by the categories of antecedents, the compositions of etchants, or the composition of delamination intercalants (Alhabeb *et al*., 2017). The precursors indicates MAX phase and non MAX phase precursors for manufacturing of MXene. The MAX phase precursors include Al-attaching or some other metal attaching like Ga and Si in $M_{n+1}AlX_n$, $M_{n+1}GaX_n$, and $M_{n+1}SiX_n$ precursors respectively. For instance, the MXene stacks (Ti_3C_2 or Ti_2C) were connected to one another through relatively weak ionic bonds via Al (or other ions like Si, Ga in other MAX-phase precursors). In a typical method, the precursors were firstly treated with etching reagents (HF or acid-fluorides) and were subsequently treated with shearing forces or sonication to generate a single-layer stack (Huang *et al*., 2018). For the selective etching of MXene precursors, HF is an effective and commonly used reagent. Lately, a number of substitution strategies are put out in an effort to avoid the toxic and harsh HF reagent. One strategy is that of taking use of the *in situ* production of HF by the reaction of acids with fluorides (typically HCl and LiF/NaF) to get selective etching of attaching ions (Al or Ga) (Ghidiu *et al*., 2016). There are two different kinds of delamination intercalants: intercalant-organic intercalant and metal ion intercalant.(Ghidiu *et al*., 2016). One of the problems of using HF as etchant is it is harmful for cell and causes cell death. So use of less harmful HCl/LiF etchant and fluorine-free etching process are more suitable for biomedical applications.

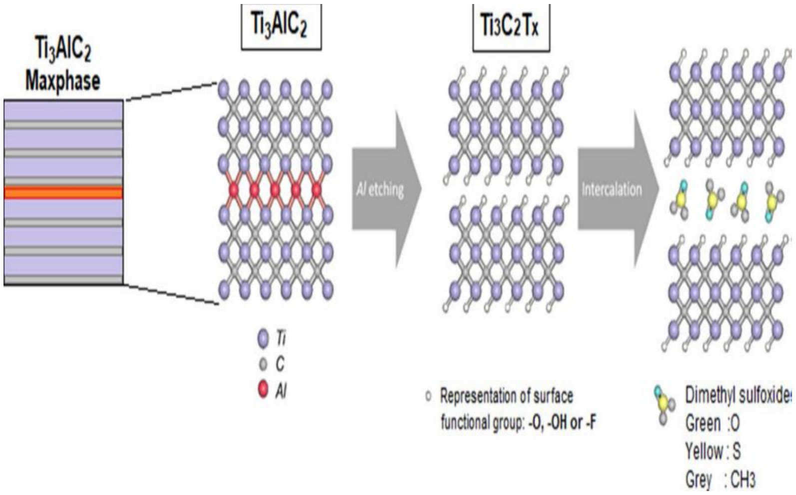


Figure 2. A schematic chemical representation of top-down approach: etching and intercalation procedure of MAX phase (Ti_3AlC_2) to form Ti_3C_2 MXene (Naguib *et al*., 2011).

3.3.2. Bottom-up method: The bottom-up synthesis method using atomic scale control is another less well-known MXene synthesis method. Tiny organic or inorganic molecules or atoms are typically the starting point for bottom-up synthesis, which is then followed by crystal formation that can be arranged to produce a 2D-ordered layer. The chemical vapour deposition (CVD) process, which can create high-quality thin films on a variety of substrates, is the most used technology for this strategy (C. Xu *et al*., 2015). Using methane gas (CH_4) as the carbon source and a Cu/Mo (copper/molybdenum) foil as the substrate, the first MXene synthesis by CVD technique produced high-quality ultrathin Mo_2C (molybdenum carbide) at temperatures above 1085 °C. A variety of films with lateral sizes between 10 and 100 m were made by optimizing the growth temperature and growth duration. Though the MXene produced in this process is defect free but not suitable for biomedical application for the size being too big for permeation of the cell.

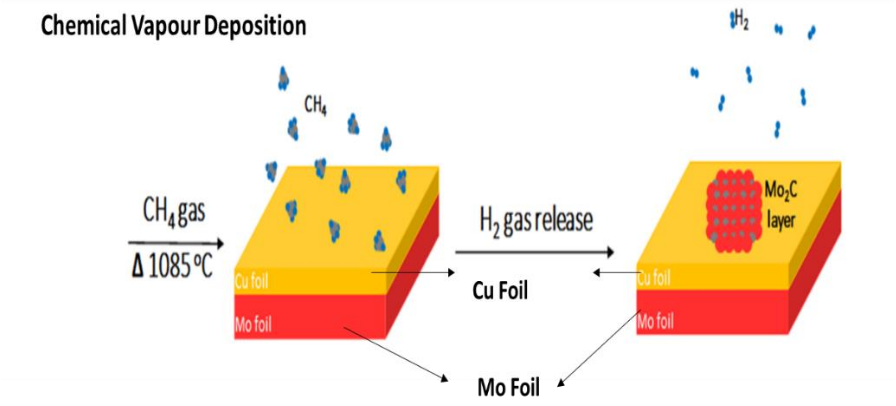


Figure 3. Schematic illustration of bottom-up methods (Chemical vapour deposition of Mo and C to form Mo_2C thin film in gas chamber) (C. Xu *et al*., 2015).

In addition to CVD, other techniques for MXene synthesis include included the template approach and plasma-enhanced pulsed laser deposition (PELPD) (Xiao *et al*., 2017). Though very little is known and so further experimentation is needed.

3.4. MXene in cell and bioengineering

Bioengineering is a discipline that applies engineering principles of design and analysis to biological systems and biomedical technologies. Whereas, cell is the structural and functional unit of body. So, bioengineering or biomedical engineering is the use of artificial tissues, organs, or organ components to replace damaged or absent body parts. With the advent of 2D materials, advances in illness therapy and biomedicine bloomed once more. These nanoparticles like MXene, were superior to a single element of graphene in terms of their performance, flexibility, and compatibility (Maleki *et al*., 2022). The surfaces of MXenes can be tailored with a variety of materials useful for biosensors, cancer theranostics (therapeutics and diagnostics), medication transport, and antibacterial activities in biomedical research studies (Zamhuri *et al*., 2021). A pictorial view of MXene in biomedical engineering is given below

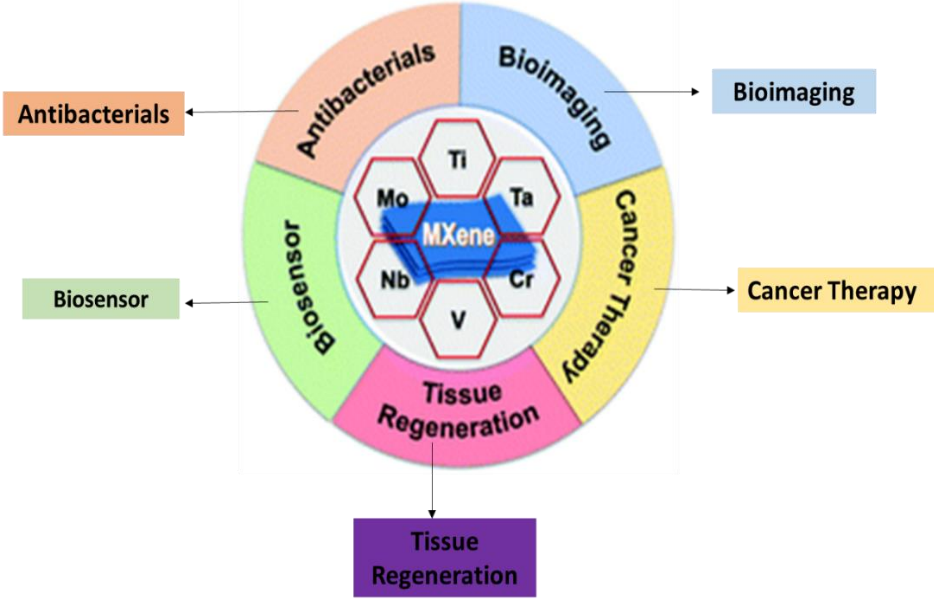


Figure 4. Application of MXene in Biomedical engineering (Huang *et al*., 2018).

Some examples of different MXene composite and its application in biomedical engineering is given in the table below.

Table 1. Types of MXenes, their syntheses methods, surface functionalization and biomedical applications

Type of MXene/MXene composite	**Synthesis method of MXene**	**Functionalization(s)**	**Application**
TiO_2–Ti_3C_2	Hydrothermal synthesis	Hemoglobin (Hb), Nafion	Detection of hydrogen peroxide and nitrite via amperometry changes(detection of ions in a solution based on electric current or changes in electric current)
Ti_3C_2	HF etching	Glucose oxidase (GOx)	Detection of H_2O_2 through oxidation of glucose

Type of MXene/MXene composite	**Synthesis method of MXene**	**Functionalization(s)**	**Application**
Ti_3C_2	LiF + HCl etching	Poly-L-lysine (PLL), GOx	Detection of H_2O_2 through oxidation of glucose
Ti_3C_2	HF etching	Tyrosinase, chitosan	Detection of phenol in real water samples
Ti_3C_2	HF etching, TMAOH intercalation	AuNPs, staphylococcal protein A, anti-CEA	Detection of CEA via surface plasmon resonance (SPR)
Ta_4C_3	HF etching	Manganese oxide (MnOx), soybean phospholipid (SP)	Cancer theranostics,Multi-imaging guided (MRI, CTscan and PAI) PTT
Nb_2C	HF etching, TPAOH intercalation	Polyvinylpyrrolidone (PVP)	PAI-guided PTT
Nb_2C	HF etching, TPAOH intercalation	Cetanecyl trimethyl ammonium chloride (CTAC), polyethylene glycol (PEG)	PAI-guided PTT
Ti_3C_2 (QDs)	Hydrothermal synthesis	-	Multicolour cellular imaging
Ti_2N (QDs)	KF + HCl etching, sonication in NMP	-	PAI-guided PTT
Ti_3C_2	HF etching, TPAOH intercalation	SP, doxorubicin (Dox)	Drug delivery, Chemotherapeutic agent, synergistic chemotherapy and PTT
Ti_3C_2	LiF + HCl etching	-	Antimicrobial activity

(Source: (Zamhuri *et al*., 2021)

3.4.1 Biosensor and wearable electronics

MXenes are widely recognized for their high surface area to volume ratio, outstanding ion transport behavior, high electrical conductivity (Ti_3C_2Tx monolayer: 4600 1100 S/cm), strong biocompatibility, and ease of functionalization. As a result, these characteristics make MXenes an extremely sophisticated biosensing tool that can identify a variety of tiny chemicals, large macromolecules, and even cancer cells (Huang *et al*., 2018). Any alteration in the surface termination significantly changes the properties of MXene. Usually when a specific gas gets attached with MXene, the change in conductivity occurs. This helps to identify the specific gas. According to (Huang *et al*., 2018) a Ti_2C monolayer with oxygen terminations was extremely selective to NH_3 versus other gas molecules like H_2, CH_4, CO, CO_2, N_2, NO_2, and O_2 based on the density functional theory (DFT) calculation. Using first-principles simulation, the interaction between NH_3 and semiconductor-like MXenes M_2C with oxygen terminals and various charge states was studied. Here the M of M_2C indicates Sc, Ti, Zr,etc. In accordance with their findings, NH_3 molecules could be strongly adsorbed on oxygen-terminated M_2C with apparent charge transfer, and the release of NH_3 could be achieved simply by adjusting the electrons injected into M_2C (Figure 5).

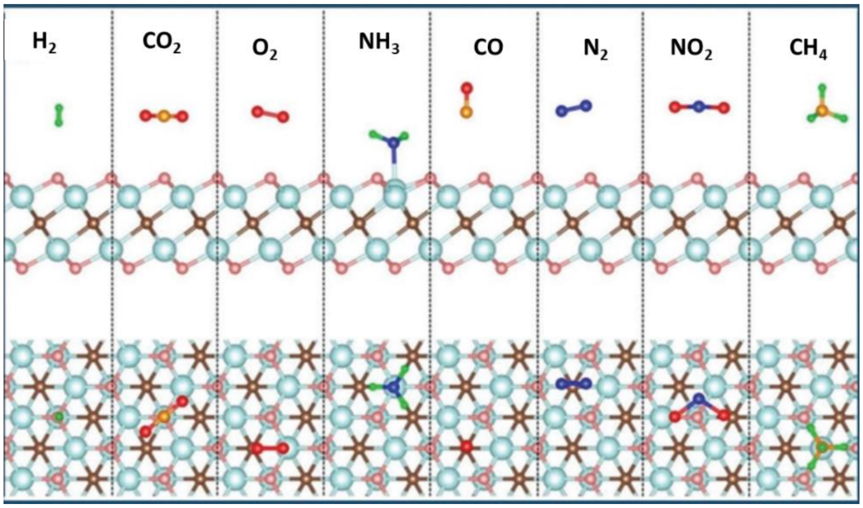


Figure 5. Application of MXenes as biosensor for the detection of NH_3 (Huang *et al*., 2018).

In addition to NH_3, the MXene-based H_2O_2 sensor has also been theoretically and empirically studied. Ti_3C_2 MXene (TiO_2-Ti_3C_2) nanocomposite with modified TiO_2 nanoparticles that resembles an organ was created by (Wang *et al*., 2015). They immobilized hemoglobin (Hb) on this technology to create a biosensor without the use of mediators. The TiO_2-Ti_3C_2 nanocomposite was a biocompatible and superior matrix for immobilizing redox proteins, ensuring strong protein bioactivity and stability, according to spectroscopic and electrochemical data (Huang *et al*., 2018). MXenes have been created for the detection of many other small molecules, including glucose and phenol, in addition to NH_3 and H_2O_2. For the sensitive detection of glucose, researchers created a glucose oxidase (GOx) enzyme immobilized Au/MXene nanocomposite. Besides, MXene integrated biosensors have some other functions too. List of some of the important MXene-integrated biosensors is given below.

Table 2. List of MXene integrated biosensors with analyte, sensing range, LOD and main achievements

Formulation	**Analyte**	**Sensing range**	**Limit of detection (LOD)**	**Main achievements/diagnostics performance**
Prussian blue/Ti_3C_2 MXene	Exosomes	$5 \times 102^{-5} \times 105$ particles μL^{-1}	229 particles μL^{-1}	Detection of exosomes secreted by various cancer cells (i.e., the breast cancer) cervical cancer cell line (Hela cells), and human ovarian cancer line (OVCAR cells) with high specificity in serum samples.
MXene–MoS_2	MicroRNA	100 fm to 100 nm	26 fm	Satisfactory selectivity, reproducibility, and stability were achieved by the MXene biosensors.
Ti_3C_2–MoS_2 MXene	Toxic gases	10–100 ppm	-	The composite showed reaction signals to some hazardous gases (i.e., NO_2 ammonia and methane) and suggested multigas-detecting sensors that are very sensitive in the air.
MXene–Au	Gram(-ve)and (+)bacteria	$3 \times 105^{-3} \times 108$ CFU mL^{-1}	3×105 CFU mL^{-1}	Could detect bacteria sensitively and showed antibacterial and photothermal sterilization effects.

Formulation	**Analyte**	**Sensing range**	**Limit of detection (LOD)**	**Main achievements/diagnostics performance**
Ti_3C_2Tx MXene–Au NPs@ polyimide thin film	Carcinoembryonic antigen	0.1–100 ng mL^{-1}	0.001 ng mL^{-1}	The biosensor illustrated high selectivity compared with other common tumor markers.
MXene N-Ti_3C_2 quantum dot/Fe^{3+}	Glutathione	0.5–100 µm	0.17 µm	It could be considered a promising probe for detecting/showing cellular imaging of glutathione in MCF-7 cells.
MXene-based cytosensor	HER2-positive cancer cells	102–106 cells mL^{-1}	47 cells mL^{-1}	The MXene-based cytosensor might be extended for detecting other tumor cells and used in targeted drug delivery
MXene-derived quantum dot@Au	Triple-negative breast cancer	5 fm to 10 nm	1.7 fm	It could be applied as an idea for the green synthesis of MXene and a guide for applying in the field of electrochemi luminescence sensing.
MXene @Au NPs@ methylene blue	Prostate-specific antigen	5 pg mL^{-1} to 10 ng mL^{-1}	0.83 pg mL^{-1}	This biosensing system has been proved to be a universal antifouling detection strategy by changing the recognition sequence of the peptides.

(Source: (Maleki *et al*., 2022)

Again, according to (Zamhuri *et al*., 2021), the detection of hydroxyburate (β -HBA) is made possible by the modification of Ti_3C_2 nanosheets with hydroxyburate dehydrogenase. So, the use of MXene as biosensor or enzyme based biosensor has promising impact on bioengineering or biomedical engineering.

3.4.2. Cancer diagnosis and therapy

Another important application of MXene nanosheets is in cancer diagnosis and therapy. Rich surface functional groups on MXenes make it easy to combine them with other substances, such as surface-super paramagnetic iron oxide, g-C_3N_4, MnOx, zinc oxide, mesoporous silica nanoparticles, Au nanoclusters, or polymers, to create advanced functional nanocomposites with advanced therapeutic functionality. These materials can then be used to realize additional functionalities, such as a combination of photodynamic therapy and multimodal imaging (Maleki *et al*., 2022). PDT (Photodynamic Therapy) and PTT (Photo thermal Therapy) combined with a nano sonosensitizer could achieve excellent tumor-therapeutic efficacy. The addition of Ti_3C_2 to g-C_3N_4 may greatly boost the material's NIR absorption, which will then boost the photocatalytic activity of the resulting nanocomposites to produce more ROS. An ROS-augmented and mitochondria-targeted nanomedicine was created after further altering triphenyl phosphonium bromide on Ti_3C_2/g-C_3N_4 (Ti_3C_2/g-C_3N_4-TPP) to fight cancer in conjunction with PTT. The study confirmed that because of application of NIR irradiation synergistic Type I and II PDT were activated. A lot of O_2 could be generated in the type II PDT and under low illumination by Ti_3C_2/g-C_3N_4 NSs breaking endogenous water. The electrons in g- C_3N_4's valence band (VB) energized its conduction band (CB) through the type I PDT to produce photo activated electrons and holes. Water molecules and the excited holes interacted to form the -OH species. Under 808 nm laser illumination, Ti_3C_2/g-C_3N_4 nano composites at various concentrations showed a good photo thermal effect. Their comdined potential was higher than the normal Ti_3C_2 nanosheets. The tumor-bearing nude mice used in the in vivo multimode PTT and PDT experiments were used to demonstrate the Ti_3C_2/g-C_3N_4-TPP nanocomposites' potent anticancer activity. The Ti_3C_2/g-C_3N_4-TPP-treated group did not exhibit any abnormal blood biochemical indicators, indicating that the composite did not significantly cause renal and hepatic cytotoxicity. The H&E staining assay of the major organs, including the liver, kidney, lung, heart, and spleen, showed no substantial inflammation or chronic pathological damage following intravenous administration of the nanosheets for two weeks. These results validated that Ti_3C_2/g-C_3N_4-TPP nanocomposites are biocompatible (Maleki *et al*., 2022).

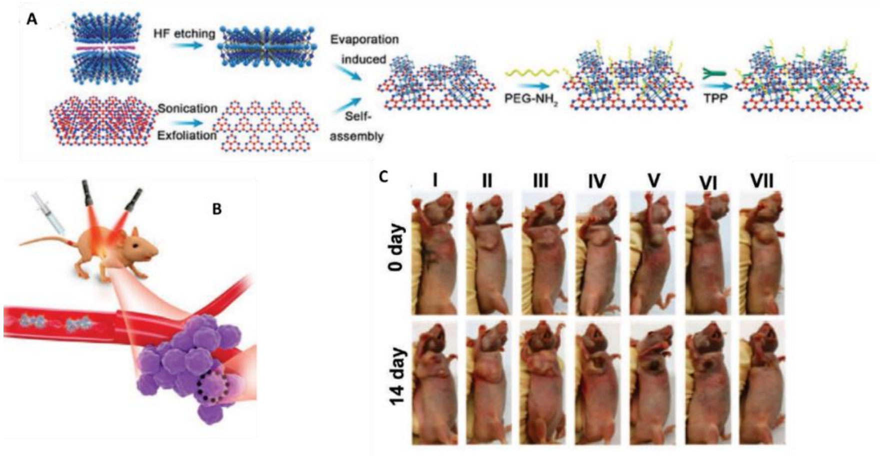


Figure 6. (A) Preparation of Ti_3C_2/g-C_3N_4-TPP nanocomposites; (B) Using nanocomposites for mitochondrial-targeted PDT and PTT; (C) Digital images of MCF-7 tumor-bearing mice after different treatments during two weeks (Maleki *et al*., 2022).

Again, MXene-based CEA (Carcinoembryonic antigen) detectors are used as cancer biomarkers. In MXene-based CEA detectors, carcinoembryonic monoclonal antibodies are covalently immobilized on single- or few-layered Ti_3C_2 MXene coated with an amino group of the receptor (Zamhuri *et al*., 2021). Some important examples of MXene-integrated nanocomposites for cancer therapy are mentioned in the table below.

Table 3. List of examples of MXene integrated nanocomposites for cancer therapy

Formulation	**Cancer**	**Combined therapy**	**Main achievements and therapeutic performance**
Ti_3C_2–polyvinyl pyrrolidone@ doxorubicin jade	Colorectal carcinoma	Iron chelation/ chemotherapy/ PTT	The apoptotic cell death has occurred, and the iron depletion-induced iron transferrin receptor (TfR) was down regulated.
Carbon dot@$Ti_3C_2T_x$ heterojunctions	Breast	SDT/PTT	The complete tumor ablation was occurred due to the enhancement of ROS generation efficiency
The assembly of	Cervical carcinoma	Chemotherapy/PTT	The blood perfusion and drug extravasation were enhanced due to the

Formulation	**Cancer**	**Combined therapy**	**Main achievements and therapeutic performance**
Nb_2C plasmon (MXene), Pt nanozymes, and DOX			dilating tumor vessels by the photothermal properties of the composite.
Ti_3C_2@chitosan–$MnFe_2O_4$ (TC@Ch–MFO)	Pancreatic	CDT/PTT/magnetic resonance imaging	The tumors were effectively inactivated due to the photothermal and CDT efficacy
Hydroxyapatite/chitosan/hyaluronic acid/ MXene/ gold nanorods	Breast	Chemotherapy/PTT	The superior pH/NIR dual-responsive drug delivery characteristics were exhibited.
MXene@hydrogel	Melanoma	Chemotherapy/PTT	The high photothermal conversion efficiency, as well as good photothermal stability, was exhibited.
MXene@agarose/TNF-α	Colorectal carcinoma	Chemotherapy/PTT	The programmed cell deaths (PCD) of tumor spheroids were induced by an NIR light due to the promoting proapoptotic signaling pathway by the integrated TNF-α.

(Source: (Maleki *et al*., 2022)

3.4.3. Regenerative medicine

Disease or trauma may cause organ failure or tissue damage, which leads to millions of deaths worldwide each year. Due to their versatility, biocompatibility, and biodegradability, as well as their capacity to create a biomimetic 3D microenvironment to support cell activity, hydrogels have attracted the most interest among the various scaffold biomaterials that have been utilized in tissue engineering. It is possible to incorporate conductive particles like MXenes into wound dressing materials (such hydrogels) to enhance their electrophysiological properties. The anti-inflammatory and immunomodulatory qualities of MXene-based biomaterials have been demonstrated in studies, and this makes them ideal for tissue engineering applications (Maleki *et al*., 2022).

Examples of regenerative medicine using nanocomposites of MXene has been enlisted by (Maleki *et al*., 2022) in tabular form. The table is given below:

Table 4. List of MXene-integrated nanocomposites for regenerative medicine

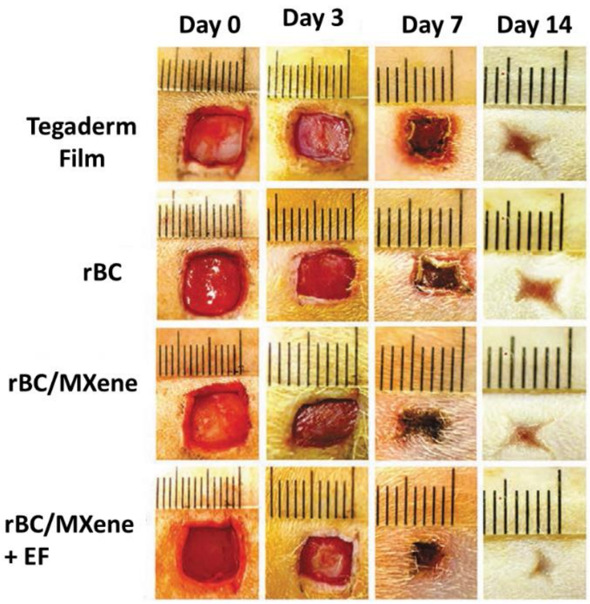
Formulation	**Targeted tissue**	**Combined therapy**	**Main achievements**
Bioglass@NbSiR	Bone	PTT-IT	The BG@NbSiR scaffold could eradicate primary tumors, boost the immune response, and suppress metastases by synergizing with checkpoint blockade Immune therapy, and accelerate osteogenesis *in vivo.*
MXene–amoxicillin–PVA nanofibrous membrane	Skin	-	Functioned as a physical barrier to colloid the amoxicillin and MXene, exhibited a high antibacterial and accelerated wound healing capacity, which will advance the design of novel wound healing dressings and antibacterial strategies.
Muscle-inspired MXene	Skin	PTT	The MXene-based hydrogel suppressed bacterial infections without developing drug resistance
Ti_3C_2Tx MXene nanosheets	Skin	-	Efficient anti-inflammation effects, promoting cell proliferation and the angiogenic process, stimulating granulation tissue formation, collagen deposition, vascular endothelial differentiation, and angiogenesis.
Nb_2C MXene-integrated 3D-printed	Bone	PTT	Niobium carbide MXene could promote the neogenesis and migration of blood vessels in the defect site, which could transport more oxygen, vitamins,

Formulation	**Targeted tissue**	**Combined therapy**	**Main achievements**
bone-mimetic scaffold			and energy around the bone defect for the reparative process
MXene/hydroxyapatite nanoparticle	Bone	PTT	Using the MXene/hydroxyapatite-based composite nanofiber, synergistic effect of photothermal performance and osteogenic properties was deduced.
Nb_2C MXene titanium plate	Skin	-	Promote angiogenesis and tissue remodeling

(Source: (Maleki *et al.*, 2022)

Some of the important aspects of regenerative medicine is discussed below:

3.4.3.1. Wound healing: The biggest surface area on the outside of our bodies is the skin, which shields the interior organs from injury, infection, ultraviolet radiation, and extreme heat. Hence, any skin flaws might cause a number of illnesses, like wound infection, which can harm people's health. A good dressing for wound healing ought to maintain a steady temperature, guard against cell migration and proliferation, and be antibacterial. These reasons led Yang and colleagues (Maleki *et al.*, 2022) to create a hydrogel dressing that, when exposed to external electrical stimulation, might hasten wound healing since it was comprised of regenerated bacterial cellulose and MXene. The outcomes of an in vivo rat trial showed that the addition of external electrical stimulation to cellulose/MXene hydrogels had a substantial impact on cell activity. The MXene-integrated hydrogels with or without electric field caused the formation of new blood vessels, normal epithelium, less inflammation, higher density of fibroblasts, and better wound healing effect than a commercial film and cellulose hydrogel, according to histological analysis of healed tissues by H&E and Masson trichrome staining as well as the immunofluorescent staining for CD31 (Maleki *et al.*, 2022).



(Source: Maleki *et al.*, 2022)

Figure 7. Wound healing process on days 0, 3, 7, and 14 in the different treated groups.

3.4.3.2. Cardiac tissue engineering: Cardiac failure is a disorder that can happen in a variety of circumstances and affects around 64 million individuals globally. The design and creation of conductive cardiac patches to support the cardiac patch's electrical coupling with the host tissue is one of the potential methods for enhancing heart tissue regeneration. To improve electro physiological properties for cardiac tissue engineering applications, many conductive polymers and particles have been included into hydrogels and cryogels, including carbon nanotubes, graphene, gold nanorods, and MXenes (Maleki *et al*., 2022). Because of its exceptional resolution and versatility in printing on both hard and soft tissues, aerosol jet printing (AJP) is a good method for producing printed patterns at the cell scale. The AJP approach was used in a study to prepare MXene-integrated composites for use as a human cardiac patch. The alignment of the human induced pluripotent stem cell-derived cardiomyocyte (iCMs) on the constructed electroconductive cardiac patches was examined. The conductive Ti_3C_2Tx MXene was printed on polyethylene glycol (PEG) hydrogel in predesigned patterns. Immunostaining, qRT-PCR, and western blotting methods were used to determine the effects of MXene and patterning on the iCM phenotype and maturity. The immunostaining results on day 7 of incubation revealed some expression of striated and aligned sarcomeric alpha-actinin and intercellular junction protein (the cytoskeletal actin-binding protein).

In another study, (Maleki *et al*., 2022) revealed for tissue engineering applications, chitosan-based hydrogels containing Ti_3C_2 MXene, honey, and fluorescent carbon dots were created. These hydrogels demonstrated favorable compatibility with various stem cell types as well as anti-inflammatory and antibacterial qualities. Besides, some other modifications using MXene nanosheets can be used for cardiac tissue engineering.

3.4.3.3. Infection therapy: By conjugating AuNCs to Ti_3C_2Tx MXene nanosheets, a synergistic antibacterial agent was introduced in 2020. This led to the synthesis of amine-modified Ti_3C_2Tx (MXene-NH_2) using Ti_3C_2Tx and (3-aminopropyl) triethoxysilane. The bacterial membrane is physically damaged by the pointy MXene nanosheets, which enables the nanocomposites to integrate within bacteria. It was also reported that Au conjugation had increased the efficiency of 2D MXene. These nanomaterials increased the production of ROS (Figure 7 (A) in bacterial body. Thus the cell membrane and bacterial DNA (Figure 7B) were hampered and finally the bacteria degenerated. They also inhibited biofilm formation (Figure 7D, E). Despite the lack of an in vivo research, the synergistic action of the Au-conjugated MXenes holds considerable potential for the development of new, bacterial infection-fighting MXene-based nanocomposites (Maleki et al., 2022). Despite the lack of an in vivo research, the synergistic action of the Au-conjugated MXenes holds considerable potential for the development of new, bacterial infection-fighting MXene-based nanocomposites.

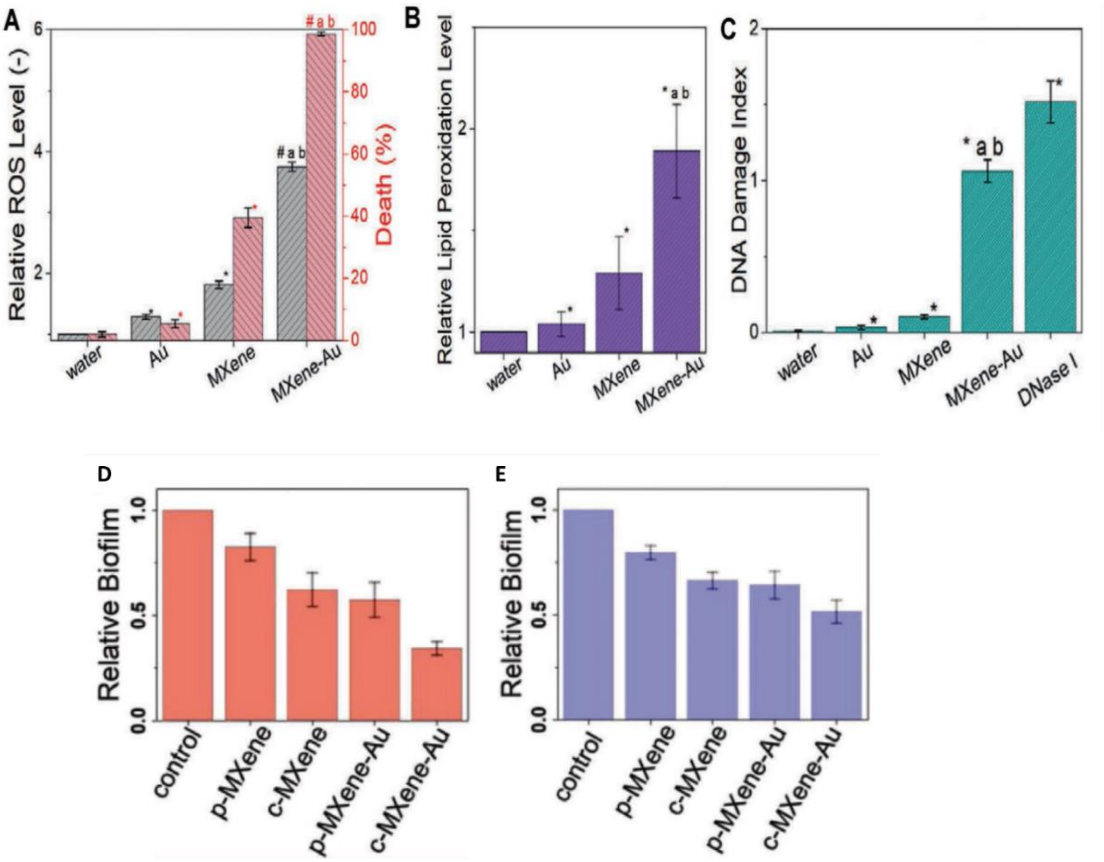


Figure 8. (A) Increase in ROS level and death in *Staphylococcus aureus*; (B) Relative lipid peroxidation level of *S. aureus*; (C) DNA damage index; (D) *S. aureus* and (E) *Escherichia coli* biofilm formation condition on the four structures (Maleki *et al.*, 2022).

3.4.4. Antimicrobial activity of MXene

Prior to the development of MXenes, the mode of action of nanomaterials based on graphene used in antibacterial applications relied on the generation of reactive oxygen species (ROS) and direct interaction with bacterial membranes. The first Ti_3C_2 MXene colloidal solution requires a high concentration dose of 200 g mL $^{-1}$ to give positive inhibition for its antibacterial capabilities. But modified Ti_3C_2 that has been treated with poly vinylidene fluoride (PVDF) significantly enhances the antibacterial properties (Zamhuri *et al.*, 2021).

The destruction of bacterial cells may be possible using MXenes' semiconducting characteristic. MXenes could exploit the reactive metal-F couples to move the reactive electrons to the surrounding cell membranes upon light excitation, analogous to semiconductors that produce negative electrons and positive holes, to produce cell death akin to type-I photodynamic treatment

(PDT). (Rasool *et al*., 2016) looked into the use of Ti_3C_2 in the application of antibacterial killing of *Bacillus subtilis* and *Escherichia coli* cells. To test the Ti_3C_2 MXenes' capacity to prevent bacterial development, bacteria were cultivated with them for 4 hours. The potential of MXenes to considerably limit bacterial growth was validated by counting the number of colonies on the culture plate following treatment with various concentrations (0-200 mg ml^{-1} of Ti_3C_2). Their findings suggested that MXenes subjected bacterial cell membranes to oxidative stress.

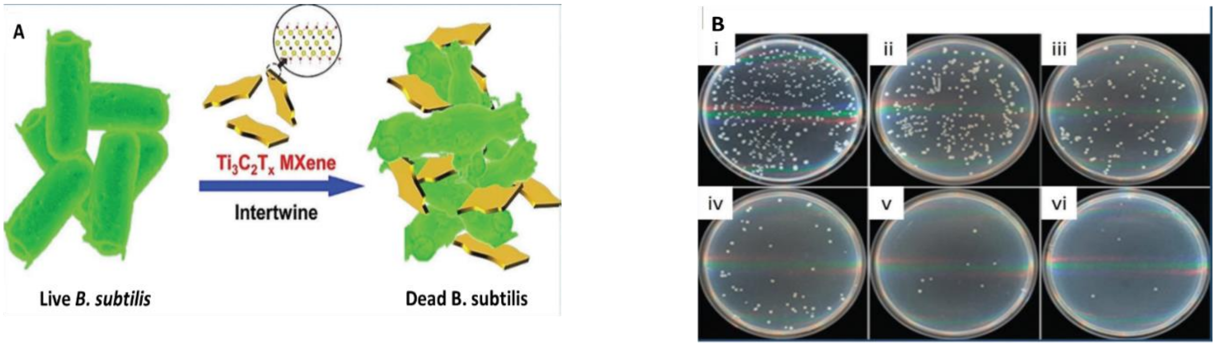


Figure 9. (A) MXenes for antibacterial activity; (B) *E. coli* bacterial cells were recultivated after treatment for 4 h with 0 mgml^{-1} (i), 10 mgml^{-1} (ii), 20 mgml^{-1} (iii), 50 mgml^{-1} (iv), 100 mgml^{-1} (v), and 200 mgml^{-1} (vi) of Ti_3C_2, respectively (Huang *et al*., 2018).

3.4.5. Bioimaging

MXenes can function as imaging contrast agents for bioimaging in addition to biosensing and antibacterial activities. PAI and luminescence imaging are two of the highly developed imaging modalities of MXenes. MXenes are extremely desirable for PAI because of their higher photothermal conversion capacity. Due to the semimetal-like LSPR action of MXene nanosheets, broad spectral light is strongly absorbed and converted efficiently. It has been shown that different kinds of MXenes may absorb excitation light, transform photon energy into crystal vibrations, and then release the energy as heat on a macroscale. Several MXene compounds have demonstrated the photothermal effect (e.g. Ti_3C_2, Nb_2C, and Ta4C3). MXenes have been used for luminescence cell imaging by utilizing the recently produced luminous MXene QDs. These MXene dots were useful for cell imaging after suitable surface modifications (Huang *et al*., 2018).

MXenes can be utilized as contrast agents for X-ray and computed tomography (CT) in addition to PAI and luminescence imaging. Moreover, MXene conductivity can be used for bioimaging by monitoring changes in the electrical signal under specific conditions. For instance, MXenes were incorporated by (Xu *et al*., 2016) into a patterned scaffold for neuron cell culture. As MXenes' conductivity is sensitive to its environment, it is possible to monitor cellular activity by observing variations in the field-effect of these materials. This technology can keep track of brain activity.

3.5. Application of MXene in Agricultural Bioengineering

3.5.1. MXene based pesticide delivery system in agriculture

Moern agriculture cannot help using chemical pesticides. It causes both environmental pollution and increase in cost of production as pesticide loss is more than 90% in our country. Therefore, it is urgently necessary to establish a smart pesticide delivery system (PDS) and create high-efficiency, environmentally friendly pesticide formulations. (Song *et al*., 2021) has developed a new composite using Avermectin and MXene Ti_3C_2. Avermectin (AV) is a low toxic biological pesticide. However, the substantial disadvantages of standard AV formulations, such as poor water solubility, quick photo-degradation, burst release, limited efficiency, and environmental unfriendliness, have made it extremely difficult to use them in the field. On the other hand, according to (Liu *et al*., 2017) excellent adsorption capacity and a high drug loading rate of 84.2% are both characteristics of Ti_3C_2. So, (Song *et al*., 2021) formulated AV@Ti_3C_2 pesticide delivery system. Fast adsorption efficiently loaded AV onto Ti_3C_2, resulting in the uniform and stable AV@Ti_3C_2 nanoformulation (Figure 10).

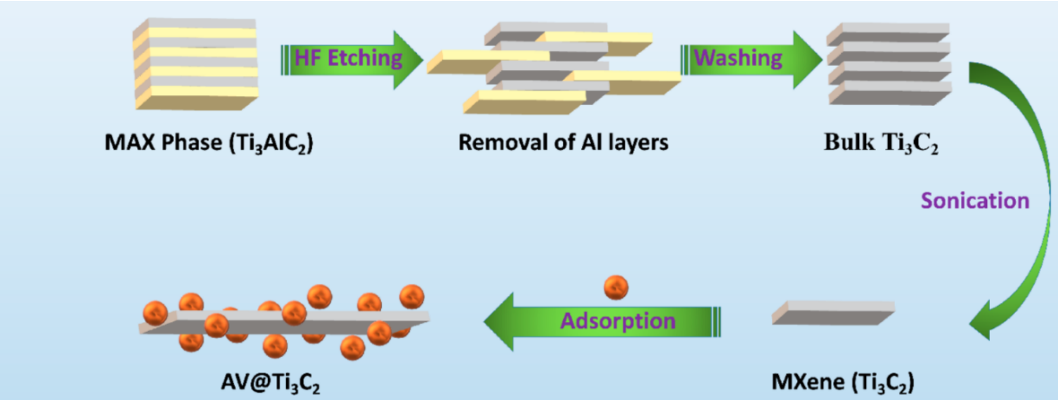


Figure 10. Synthesis of AV@Ti_3C_2 for development of new pesticide delivery system (Song *et al*., 2021).

The pH-response release behavior of AV@ Ti_3C_2 was different from the rapid loss of AV. Also, the significantly increased stability of AV@Ti_3C_2 under UV light added to the assurance of its long-lasting activity. As a result, during the 14 days following spraying, AV@Ti_3C_2 shown increased antipest activity. Also, our research demonstrated that Ti_3C_2 is a secure pesticide delivery vehicle that has no detrimental effects on crop germination or growth. Only three ingredients make up the AV@Ti_3C_2 nanoformulation in this study: water (solvent), AV (pesticide active ingredient), and Ti_3C_2 (carrier). As a result, it is less harmful to the environment than conventional formulations, which frequently contain a significant amount of hazardous organic solvents or additives.

3.5.2. MXene based biosensors in the field of agriculture

1. Biosensor for detection of Alfatoxin in food and agricultural products: The deadly mycotoxins known as aflatoxins (AFs) are produced by the molds *Aspergillus flavus* and *Aspergillus parasiticus*, which are typically found in soil, hay, decaying plants, and grains. Cereals (wheat, rice, and corn), spices (coriander, turmeric, ginger, and black peppercorns), oilseeds (cotton, sunflower, and soybeans), and tree nuts (coconut, walnut, and almonds) are crops that are frequently impacted by *Aspergillus* species. Aflatoxicosis is a serious poisoning brought on by consuming too many aflatoxins, which are dangerous and frequently result in death (Parihar *et al.*, 2023). The biosensor-based detection of aflatoxin overcomes the drawbacks of traditional methods including LC/MS-MS, HPLC, and ELISA assays since it is rapid, less expensive, and requires less qualified workers. Because to their excellent mechanical strength, favorable biocompatibility, simplicity of surface functionalization, and tuneable optical and electrical properties, 2D MXenes prove to be an effective material for biosensing. Aptamers, in contrast, have higher selectivity, sensitivity, and ease of synthesis when used as biorecognition elements (BREs) than traditional BREs. Examples of some recently used aptamers for detection of alfatoxin is given below

Table 5. List of recently used aptasensor for detection of aflatoxins

Biosensors	**Nanocomposites**	**Detection method**
Electrochemiluminescence (ECL)	PANI/TiO_2 NPs	Electrochemiluminescence (ECL) signal
Electrochemical	MXene/$NiCo_2O_4$	Differential pulse voltammetry (DPV)
Ratiometric SERS	MXenes SERS	Raman spectroscopy

(Source: (Parihar *et al.*, 2023)

Till now the knowledge about preparing an aptasensor using MXene is at introductory level. Researchers may be able to develop and create aptasensors with fast binding kinetics for the detection of target molecules and short receptor-analyte interaction times by observing the existing information about the binding kinetics of receptors with target analytes.

2. MXene biosensor for detecting CO_2: Constant carbon dioxide gas (CO2) emissions have a negative impact on crop yield, the environment, and human health. Due to crops' simultaneous respiration and photosynthesis, the dynamic concentration of emitted CO_2 in agriculture, particularly in restricted greenhouses, swings dramatically. CO_2 enrichment beyond 300 ppm prevents nitrate absorption into organic nitrogen molecules, which lowers crop productivity.So, detection of CO_2 at low concentration is very important. Till now the biosensors developed for detection of CO_2 are not that effective. As they detect CO_2 at very high concentration. The temperature requirement is also very high. According to (Zhou *et al.*, 2020), a nitrogen-doped MXene Ti_3C_2Tx (N-MXene)/polyethyleneimine (PEI) composite film adorned with reduced graphene oxide (rGO) nanosheets was creatively used to detect 8–3000 ppm CO_2 gas, overcoming the challenges of high operation temperatures and faint response experienced by conventional CO_2-sensitive materials such as metal oxides. They can detect CO_2 at 20^oC room temperature and at 8 ppm concentration.If we observe the following table the result will be clear

Table 6. List of sensing performance of various biosensors for detection of CO_2

Materials	**Temperature(°C)**	**Detection limit (ppm)**	**Carrier gas**
$LaFeO_3$	300	2000	dry air
ZnO	250	200	wet air
CeO_2	100	150	wet air
rGO/N-MXene	20	8	wet air

(Source: (Zhou *et al.,* 2020)

3.5.3. Waste treatment using MXene

The vast quantities of wastewater that are released into the aquatic system are a growing threat to the ecosystem. Heavy metal ions and other harmful pollutants found in wastewater that are the result of various industrial processes can have a negative impact on human health, vegetation, and marine life. As solitary or nanocomposite adsorbents, the nanoscale materials have been extensively utilized for a variety of wastewater treatment applications. The economy has benefited from these products' accessibility, low price, and promising capacity to remove a variety of impurities. Using MXene as nanocomposite to remove waste and heavy metals is gaining interest. For the purpose of separating heavy metal cations (Pb^{2+}, Cd^{2+}, and Cu^{2+}) and co-existing anions (Cl and/or NO3) from wastewater, Wang *et al*. (2021) used a laminar hydroxylated MXene membrane (Naji *et al*., 2023). A new nanocomposite membrane made of a separation layer of chitosan-coated MXene nanosheets was created by Lin *et al*. in 2022 and placed over a support layer of a PVDF mixed-matrix membrane that had undergone g-C_3N_4 photocatalyst modification (Naji *et al*., 2023). But still a lot of work on using these nanocomposites is necessary. MXene should go through thorough, extended examination, just like any metal-based nanoscale materials, to determine its stability within the polymeric membrane and ultimate placement in water streams. MXene stability is a serious issue since MXene breakdown could result in harmful metabolites that could affect the ecosystem. Also, MXene is susceptible to oxidation, while it is unknown how this problem would limit the MXene's potential.

3.5.4. GMO crops detection using MXene biosensors

With the help of transgenic technology, which alters organisms' genetic makeup using contemporary molecular biology techniques, crops can be genetically engineered to be highly nutritious, ideal for storage, and resistant to pests and herbicides. The safety concerns surrounding genetically modified food and crops, as well as some possible effects on the environment and society, have drawn considerable attention worldwide as commercialisation continues to rise. Thus, there is an urgent need for the development of precise, sensitive, and practical detection technologies for genetically modified crops and food. According to the detection targets, there are now two primary categories for detecting genetically modified crops and food: protein-based immunoassay and DNA-based polymerase chain reaction (PCR) technologies. But they have their own shortcomings. A new technique for detection of GMO crops can be use of MXene based biosensors. According to (Chen *et al*., 2021) for the purpose of identifying the transgenic protein Cry1Ab in genetically modified (GM) crops, an MXene-catalyzed Faraday cage-type electrochemiluminescence (ECL) immunosensor was created. With limit of detections (LODs) of 0.001 ng mL^{-1} and 0.001%, respectively, Cry1Ab protein and GM maize MON810 could both be quantitatively detected under the most favorable experimental circumstances. All of the criteria selectivity, stability, repeatability, precision, and accuracy—were met. The effective detection of genuine samples demonstrates the potential of these biosensors for use in agricultural and food safety.

3.6. Future outlook

MXenes are a fascinating class of 2D nanomaterials that are attracting attention in biomedical engineering applications, such as biosensors, cancer therapy, infection treatment, and regenerative medicine and in agricultural aspects. These nanomaterials have remarkable promise for tissue engineering, drug delivery, antibacterial characteristics, and high surface area to volume ratio, and broad-spectrum near-infrared absorptionBecause of their outstanding antibacterial action, MXenes' chemistry makes it possible for them to be used in traditionally unexplored areas, such as the surface coating of medical devices including catheters, masks, and gloves. It has also been noted that MXenes are elastic and flexible (Zamhuri *et al*., 2021). Moreover, MXenes can be coupled with other materials to greatly improve their performance in biomedical applications above that of their solo equivalents. Although MXenes have distinct features and have shown a lot of promise for biomedical applications, there are still a lot of obstacles in the way of their clinical implementation. MXenes' long-term biosafety hasn't been systematically evaluated. The majority of these investigations were focused on cell experiments or short-term hematological assays, despite the fact that numerous studies have shown that the MXenes currently available for biomedical purposes are typically biocompatible and some of them are even biodegradable in vivo. Further biological uses will require systematic research on the biosafety of MXenes. Though in a very recent finding, (Xu *et al*., 2016) has confirmed that Ti_3C_2 coated soybean phospholipid inserted into the nude mice was completely excreted through the body. Another showed nontoxic to fish.

The absence of guidelines for safety testing that all researchers must follow creates another obstacle to employing these composites for cancer therapy and tissue regeneration. Moreover, tests for toxicity must be carried out using models of both health and disease. Comprehensive studies are also required to establish links between the properties of composites, the experimental parameters, and their toxicity because different composites are created utilizing diverse MXenes exposed to various chemicals and with varying sizes and compositions. Collaboration with molecular biologist is essential for complete understanding the function. There are currently no reports on how MXene affects the human physiological system. Another area of research that has received less attention to date but requires more attention is the potential impact of MXene composites on stem-cell engineering via thermo modulation and electrical signaling. This area of research has the potential to support the creation of a new generation of hydrogel-based 3D-cell cultures and regenerative tools. To ensure there is no environmental risk after discharge, it is also necessary to investigate more ecologically friendly processing methods. With the recent increase in scientific confidence in MXenes, hopefully, the aforementioned difficulties will soon be overcome and the ongoing research in MXene composites will result in outstanding biological advancements.

CHAPTER IV

CONCLUSION

MXene is newly emerged 2D material made of a layer of early transition metal and n numbers of layers of either carbon or nitrogen with a general formula of $M_{n+1}X_n$. The conversion of MAX phase to MXene follows either top down or bottom up technique to remove the A layer (an A group element mostly main group IIIA or IVA). Among the two methods top down is more popular and frequently used. Although both the methods have some drawbacks that needs to be overcome for nontoxic application of MXene in cell and bioengineering. Electrochemical, optical, magnetic properties are some of the important properties of MXene. Using these properties alteration in MXene composition is possible for using them in bioengineering.

Application of MXene in biomedical engineering is gaining popularity day by day. The high surface area for drug loading and distribution, the good hydrophilicity for biocompatibility, and other electronic features for computed tomography (CT) scans and magnetic resonance imaging make MXenes also exhibit favorable biological characteristics (MRI).Some of the application of these nanocomposites in biomedical engineering includes biosensors, cancer therapy, bioimaging, tissue regeneration and antibacterial approaches. The application will be broaden in the future with proper research and experimentation.

Application of MXene in agricultural sector may be considered as the most recent approach. Researchers are moving with caution for applying this nanocomposite in agriculture as it may directly affect human health. Till now, application of MXene is confined to manufacturing biosensors for sensing various gases like CO_2, NH_3, some toxins like alfatoxin and formulation of pesticide delivery system. Their application in sensing genetically modified crops is also seen. Waste water treatment and detection of heavy materials using this nanoparticle is gaining popularity. Though this sector also needs extensive research and experimentation.

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