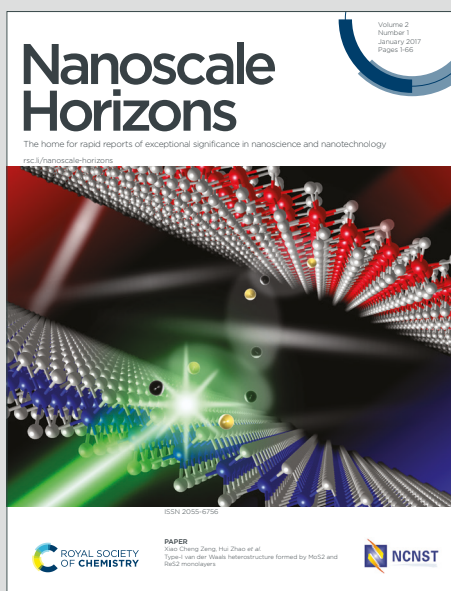


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Synergistic Integration of MXene Nanostructures into Electrospun Fibers for Advanced Biomedical Engineering Applications

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Abstract

MXene-based architectures have paved the way in various fields, particularly in the healthcare area, owing to remarkable physiochemical and electromagnetic characteristics. The modification of MXene structures, along with their combination with polymeric networks, have also gained considerable prominence to further progress their features. The combination of electrospun fibers with MXene faces would be promising in this era since electrospinning has been declared a mature technique that is now being spun out into commercial biomedical applications. The introduction of MXene into the electrospun fibrous frameworks has highlighted outcomes in various biomedical usages, including cancer therapy, controlled drug delivery, antimicrobial targets, sensors, and tissue engineering. Correspondingly, this review describes the employed strategies for the preparation of electrospun configurations in tandem with the MXene nanostructures with fabulous characteristics. Then, the advantages of MXene-decorated electrospun fibers for use in biomedical applications are comprehensively enlightened. According to the investigations, rich surface functional groups, hydrophilicity, large surface area, photothermal features, and antimicrobial and antibacterial activities of the MXene could synergize the performance of electrospun layers to engineer versatile biomedical targets. Also, the future of this path is clarified to combat the challenges related to the electrospun fibers decorated with MXene nanosheets.

Keywords: MXene; Electrospinning; Nanofiber; Biomedical application; Drug delivery; Tissue engineering.

1. Introduction

In recent decades, nanofibrous configurations have emerged as valuable constraints toward approaching a diverse range of biomedical applications, specifically biomedical targets [1, 2].



36 Electrospinning is a well-known and scalable technique extensively declared to fabricate
37 flexible fibers in the range of nano to micro diameters with tunable mechanical strength. The
38 electrospun fibers could be feasibly synthesized from numerous polymeric materials in
39 adjustable alignment ratios [3, 4]. Highly porous structure, tiny and interconnected pores, and
40 large surface-to-volume ratio are remarkable characteristics that make the electrospun carrier
41 media a promising candidate for biomedical and tissue engineering applications [5-7].
42 Meanwhile, several parameters have limited their practical usage, including the challenges
43 linked with the electrospinning procedure in tandem with the defects in the final deployed
44 structures. As an example, several polymers could not be easily fabricated due to improper
45 electric conductivity, low viscosity, or non-electrospinnability department. Additionally,
46 inhomogeneous structure, poor dimensional stability, inadequate cell infiltration, and
47 cytotoxicity are other unfavorable traits declared for some electrospun compositions [8-10].

48 As a representational strategy, the addition of nanoparticulate architectures into the
49 electrospun fibers could effectively combat these blocks [11, 12]. The size and distribution of
50 nanoparticles can be effectively modified by adopting appropriate methods of fabrication and
51 carefully adjusting key process parameters [13]. It's crucial to select the right additive with the
52 appropriate morphology and dimensions based on the influencing parameters. In this era,
53 MXene has been broadly investigated for assorted applications, resulting from remarkable
54 features such as electrical conductivity, hydrophilicity, mechanical strength, chemical stability,
55 and high surface-to-volume ratio [14-16]. Besides, photothermal activity, biological features,
56 antimicrobial and antibacterial properties, and formidable adhesiveness to natural organs have
57 caused outstanding outcomes for the MXene-decorated electrospun fibers in biomedical end-
58 users [17, 18].

59 **Fig. 1a** shows the timeline relating to applying MXene nanosheets in various forms and
60 configurations for tissue engineering targets in the biomedical era. As can be seen, MXene was
61 introduced in 2011 and modified through the years. In 2019, MXene-decorated film was
62 declared as an efficient nanocomposite for bone regeneration [19]. Additionally, loading
63 MXene into the hydrogel [20], 3D printed [21], cryogel [22], and nanofibrous [23]
64 architectures were reported to regenerate bone and heart tissues in 2020. **Fig. 1b** displays the
65 number of Scopus-indexed publications on employing the MXene configurations in various
66 fields, showing the increasing focus on the usage of MXene-loaded structures in different
67 applications. Among various integrated tissue configurations, the electrospun structures have
68 revealed favorable results benefiting the pros of both electrospun media, as well as MXene
69 nanosheets. According to the literature, the MXene nanosheets are commonly embedded into
70 the electrospinning solutions to decorate the electrospun fibers. Based on the polymer chain
71 groups, the MXene galleries could be located inside, on the surface, or in both regions,
72 changing characteristics of the electrospun fibers. **Fig. 1c** exhibits the visualization
73 bibliographic map of the Scopus-indexed papers relating to employing MXene in electrospun
74 structures, highlighting the application of MXene-loaded electrospun structures in a wide range
75 of biomedical usages.



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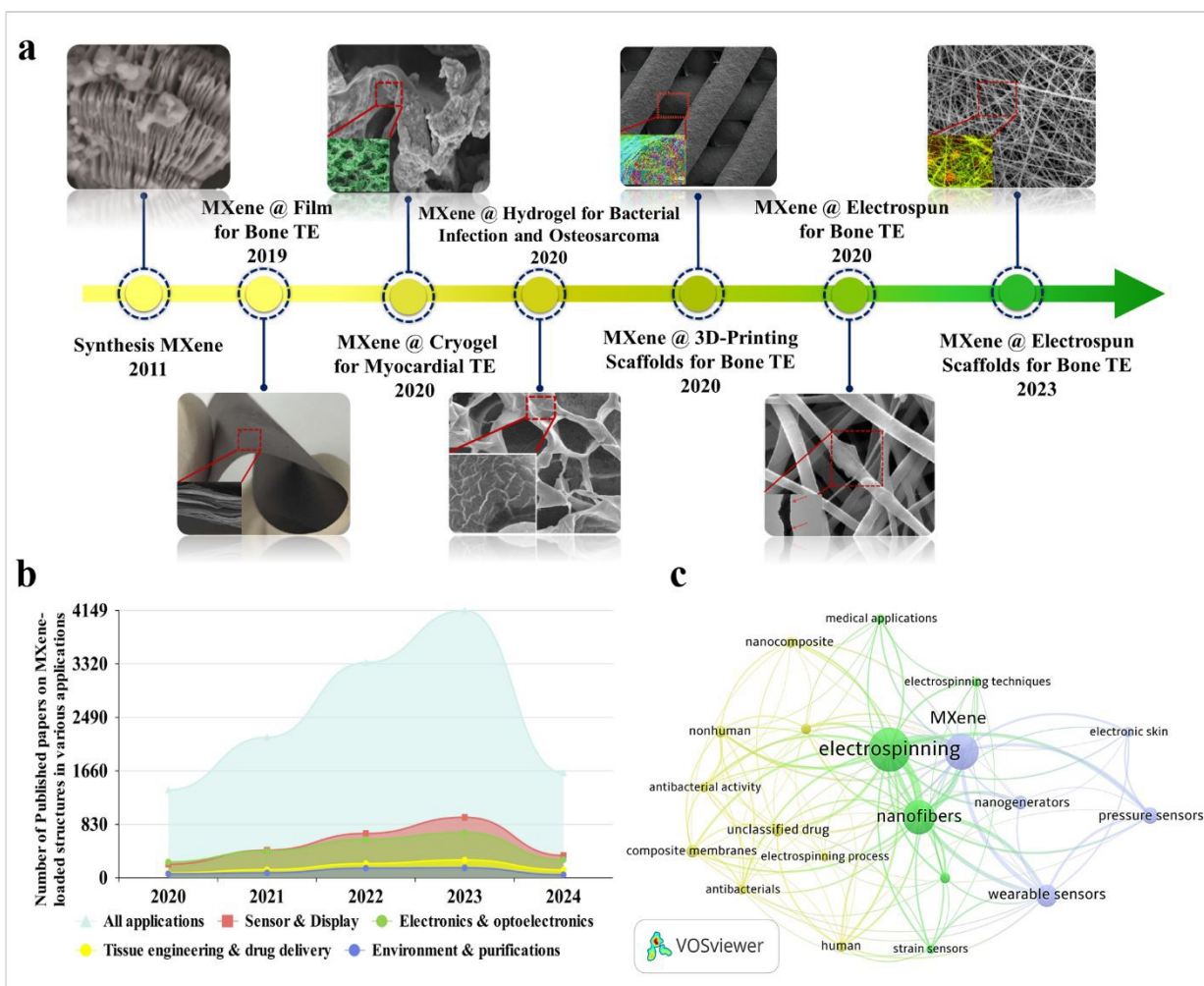


Figure 1. Evolution history of the MXene-decorated tissue scaffolds; (a) MXene structure: Reproduced from reference [24] with permission from Wiley, Copyright 2011, MXene-loaded film for bone tissue: Reproduced from reference [19] with permission from Dove press, Copyright 2019, cryogen containing MXene for heart tissue: Reproduced from reference [22] with permission from Ivyspring International Publisher, Copyright 2020, hydrogel-based tissue loaded with MXene: Reproduced from reference [20] with permission from the American Chemical Society, Copyright 2020, bone tissue developed by embedding MXene into a 3D-printed layer: Reproduced from reference [21] with permission from Wiley, Copyright 2020, and integrated electrospun fibers fabricated in 2020 and 2023: Reproduced from references [23, 25] with permissions from the American Chemical Society, Copyright 2020 and 2023. (b) the number of Scopus-indexed publications related to the MXene-loaded compositions for various end usages, and (c) visualization of a bibliographic map of the Scopus-indexed papers relating to the usage of MXene in electrospun architectures.

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93 As a two-in-one strategy, the electrospun architectures integrated with MXene nanosheets
94 have resulted in remarkable compositions applicable to medical-related usages. The synergetic
95 effect of integrating MXene in the electrospun nanofibers for biomedical applications has been
96 overviewed in some studies [26, 27]. Meanwhile, few papers have comprehensively
97 demystified the intriguing behavior of MXene nanosheets, bare electrospun fibers, and
98 MXene-loaded nanofibrous architectures in all biomedical sub-categories. Accordingly, this
99 review has provided an in-depth investigation of the synthesis and characterizing of the MXene
100 nanostructures. Then, the beneficial role of pristine electrospun fibers for biomedical targets is
101 remarked. Additionally, the electrospun scaffolds embedded with MXene nanosheets are
102 overviewed, throwing up many knowledge gaps and novel ideas for exploring versatile
103 electrospun composite networks applicable in cancer therapy, drug delivery, antimicrobial
104 activities, sensor devices, and tissues. Besides, the biomedical usages of the MXene-loaded
105 hybridized structures, obtained through combining the electrospun nanofibers with hydrogels,
106 films, and other polymeric architectures, are pointed out in this review.

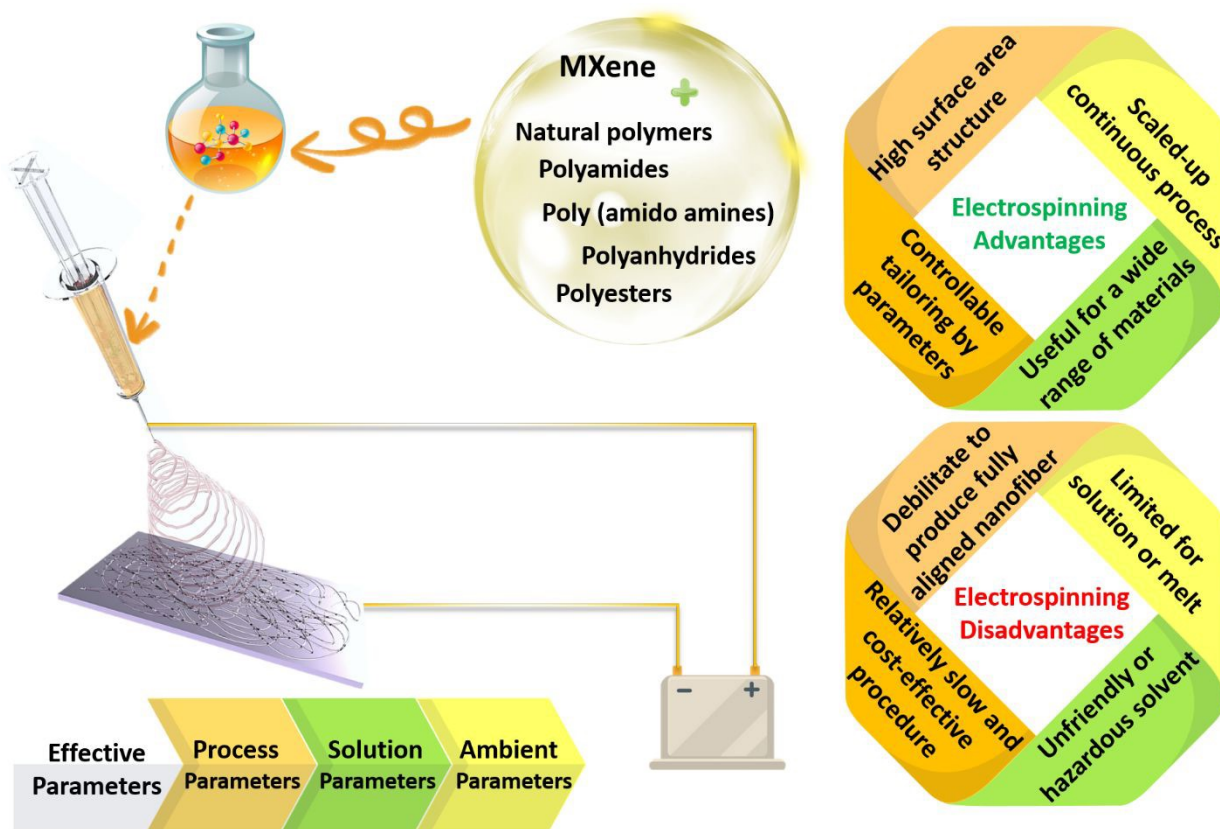
107 2. Electrospun fibers for biomedical targets

108 Polymeric architectures have been extensively declared for various targets in clinical
109 management. To design a fabulous polymeric structure for biomedical applications, the
110 physical features of the polymeric element, in tandem with the geometrical properties, play
111 crucial roles. Chemistry, composition, biodegradation rate, and biocompatibility are
112 categorized as well-documented physical characteristics, while shape and size are critical
113 morphological parameters. In this regard, the selection of polymer type is a significant factor
114 to be noticed. Based on the literature, biopolymers (collagen, gelatin, alginate, chitosan, etc.),
115 polyesters (e.g., polycaprolactone (PCL)), polyamides (e.g., silk and nylon), poly (ortho esters)
116 (e.g., polyglycolic acid (PGA) and poly-lactic acids (PLA)), poly (amido amines),
117 polyanhydrides, and poly (β -amino esters) could be appropriate choices, which are also called
118 bio- and smart-polymers. The polymers, as mentioned above, are hydrolytically degradable
119 and serve prompt physical and chemical changes. The degradability of the polymeric
120 compositions should be customized based on the final usage to prevent the accumulation of
121 materials and so toxicity. Additionally, such polymers are normally selected as they represent
122 proper compatibility with the body. Besides, solubility, thermal stability, mechanical strength,
123 and other inherent features are major properties which are considered depending on the end
124 usage of the designed product [28, 29].

125 Regarding the geometrical properties, the fabrication of polymeric compositions in the
126 form of thin nanofibers could endow remarkable properties for a wide range of biomedical
127 targets. So far, different mechanical, chemical, thermal, and electrostatic methods have been
128 introduced to generate fine and homogenous fibers in the nanoscale region. Among them,
129 electrospinning has been known as the most employed method as a result of the straightforward
130 setup, which is schematically shown in **Fig. 2**. Electrospinning involves electrohydrodynamic
131 force to form nanoscale threads from polymeric droplets using a high-voltage power supply, a
132



133 spinneret, a syringe pump, and a conductive collector. This procedure could be divided into
 134 several main steps. In the first phase, the liquid droplet is charged, generating a cone-shaped
 135 jet called a Taylor cone. The electric field applied to the droplet induces a charge separation,
 136 creating a positive charge at the surface and a negative charge at the center of the droplet.
 137 Afterwards, the charged jet is extended along a straight line, forming thin, continuous fibers.
 138 The speed and direction of the jet depend on the applied voltage, the distance between the
 139 spinneret and the collector, and the solution properties, such as viscosity and surface tension.
 140 Then, the jet thins out due to the presence of an electric field and grows the electrical bending
 141 instability, which arises from the competition between the electrostatic repulsion and the
 142 surface tension of the jet. As a result, the jet meanders and forms a series of loops and coils,
 143 leading to an increase in the surface area of the fibers. Finally, the jet solidifies and forms
 144 nanoscaled fibers, which are gathered on a collector. The collected fibers can be further
 145 processed by annealing, crosslinking, or functionalization to enhance their mechanical,
 146 chemical, and biological properties [30-32].



147
 148 **Figure 2.** Schematic illustration of the electrospinning setup, along with the pros and cons of
 149 the electrospinning method for the fabrication of nanofibrous structures.

150 The electrospinning process could be modified by playing with electrospinning parameters,
 151 such as the solution factors, in tandem with the electrospinning conditions, leading to
 152 fabricating fibrous structures with various morphologies. For example, the critical voltage
 153 employed during the electrospinning is identified based on the polymer solution. Changes in
 154 the critical voltage of a specific electrospinning solution could lead to fibers with different



155 morphological structures being obtained. In this era, a proper voltage range of 10-20 kV was
156 exhibited for electrospinning the PAN nanofibers. According to this study, a rise in the voltage
157 from 10 to 20 kV could cause the formation of finer fibers due to the amplified repulsive forces,
158 thereby inducing more stretching [33]. However, increasing the voltage might fabricate fibers
159 with larger diameters in some cases. For example, Matabola et al. [34] declared an increment
160 in the average PVDF fiber diameters from 100 to 180 nm by enhancing the voltage from 10 to
161 16 kV. There is also a critical flow rate for electrospinning the polymer solutions, varying
162 based on the polymer type, in tandem with solution concentration. Generally, the flow rate
163 differs from a hundred microliters to a thousand microliters per minute in standard polymer
164 solutions. A rise in the optimized range of the feeding rate could lead to generating thicker
165 fibers, resulting from the ejection of more solution. For example, a shift from 1 to 2 $\mu\text{l}\cdot\text{min}^{-1}$
166 in the feeding rate increased the fiber diameters from 18.9 to 36 μm . It is worth noting that an
167 asymmetrical Taylor cone is developed below the optimized threshold, causing instability of
168 the electrospinning jet and the fabrication of fibers in a wide-diameter distribution [35]. As
169 another variable, the working distance should be set based on the polymer system to attain
170 homogenous electrospun fibers. In short working distances, solvent evaporation is limited,
171 leading to defects and beading in the nanofibers. Also, the electrical field is weakened above
172 the threshold, increasing the jet instability. In a study conducted by Jabur et al. [36], it was
173 displayed that a rise in the working distance from 4 to 22 cm could lead to an increase in the
174 PVA fiber diameters from 875 to 600 nm. Therefore, it is vital to determine the optimized
175 parameters based on the required morphological factors of the electrospun fibers.

176
177 Electrospun fibers have shown several advantages, including a high surface-to-volume
178 ratio, consistent structure, tunable porosity, and malleability to conform to diverse sizes and
179 forms. These characteristics make electrospun fibrous membranes particularly attractive for
180 biomedical applications, such as cancer therapy, drug delivery, sensor devices, and tissue
181 engineering. In drug delivery systems, high surface area is beneficial as it allows for loading
182 diverse amounts of drugs. Additionally, loading larger therapeutic agents into the system
183 becomes more accessible with an expandable pore size. It is important to note that the specific
184 surface area of a drug delivery system has a significant impact on the rate of drug release. This
185 is because the surface area determines the amount of drug that is exposed to the surrounding
186 environment and thus controls the rate at which the drug is released [37, 38].

187 Also, electrospun membranes have established specific attention in generating biosensors
188 due to showing a high surface area, modification simplicity, and fabricability. Additionally,
189 nanosized structures have proven effective as membranes that immobilize bioanalytics. This
190 creates a favorable microenvironment for physiologically active molecules, enhancing
191 biosensing efficiency [39-42]. In the case of tissue engineering, the high surface-to-volume
192 ratio allows for increased cell attachment and proliferation, while the consistent structure
193 provides a uniform environment for tissue growth. Furthermore, electrospun fibers' tunable
194 porosity and malleability permit customization to match specific application requirements.



195 However, this technique still faces two main limitations: insufficient tiny pores and porosity
196 and poor mechanical properties, which are significant features that cover the requirements
197 essential for biomedical applications [31]. To overcome the challenges, researchers have come
198 up with some innovative solutions. One approach is to adjust the electrospinning parameters,
199 such as the solution concentration, flow rate, applied voltage, and the collector. Accordingly,
200 numerous attempts have been devoted to optimizing the fiber diameter, pore size, and porosity
201 of the electrospun fibers. As an example, McCann et al. [43] utilized a cryogenic liquid to
202 collect the fibers. In the proposed procedure, a phase separation was induced between the
203 solvent and the polymer, forming highly porous structures and revealing a promising
204 architecture for various biomedical applications. Another approach is to use a sacrificial
205 component during electrospinning, which can be removed to create a more open and
206 interconnected network for cell migration. Considering this strategy, Huang and Thomas
207 combine chloroform with ethanol and dimethyl sulphoxide as low and high boiling point
208 liquids to create surface and internal porosity in the electrospun PLA nanofibers, respectively
209 [44].

210 Poor mechanical strength is another challenge related to the electrospun networks for load-
211 bearing applications. Therefore, post-processing modification techniques, such as cross-
212 linking, annealing, or heat treatment, have enhanced the structural and mechanical strength of
213 electrospun fibers. These approaches could create fibrous membranes that are more suitable
214 for biomedical applications and tissue engineering targets [45-47]. For example, Lee et al. [48]
215 Utilized a simple freezing/thawing process to increase the crystallinity of the PVA electrospun
216 fibers from 23.5 to 43.6%, thereby raising the mechanical strength to 65% compared to the
217 untreated PVA nanofibers.

218 Additionally, integrating particulate fillers into the electrospun structures has been
219 extensively recommended as an efficient modification [49, 50]. For example, carbon nanotubes
220 (CNTs) and graphene are documented as appropriate fillers for the polymeric membranes,
221 which could be evenly distributed in the developed architectures. The high mechanical strength
222 of the CNT filler could provide incomparable superb specific strength for the electrospun fibers
223 [51]. The enhancement of mechanical strength in the CNT-loaded electrospun fibers could be
224 attributed to the increased interconnections between the polymer chains by the presence of
225 CNT filler. Also, the mediated CNT could decrease the contact angle and improve cell viability
226 in the electrospun tissues [52]. However, graphene has been known as a more interesting filler
227 for promoting the characteristics of electrospun fibers due to its abundance and lower cost [53].
228 Reduced graphene oxide (rGO), a substantial graphene derivative, has been widely employed
229 to engineer potential bioactive electrospun architectures. While GO possesses frequent
230 functional groups, and so proper hydrophilicity, rGO provides superior electrical conductivity
231 [54]. Accordingly, Ivanoska-Dacicj et al. [55] declared that the incorporation of 20 wt. % rGO
232 into the PEO-based nanofibers could effectively reduce the electrical resistance, leading to an
233 approach of 96% cell viability. In another attempt, Gozutok et al. [56] displayed that the
234 incorporation of 1 wt.% rGO into the PVA nanofibers could serve 23 and 30% higher elastic



235 modulus and tensile strength values than those of the neat PVA nanofibers, resulting from the
236 created strong interaction between the PVA polymer chains and rGO nanogalleries. Moreover,
237 TGA analysis confirmed the thermal degradation of rGO-filled PVA structure at 450°C, while
238 the pure PVA fibers degraded at 345°C. Furthermore, the filler incorporation led to an
239 increment in the electrical conductivity from 0.1 to 11 $\mu\text{S}\cdot\text{cm}^{-1}$.

240 As a new emerging filler, MXene nanosheets have also reaped much attention by boosting
241 the mechanical properties, along with enhancing the physiological and biological features,
242 widening their applications in various biomedical fields. MXene nanosheets could be easily
243 embedded into the electrospinning solutions and form thin nanofibers, benefiting from their
244 outstanding rheological characteristics. These structures endow excellent electrical
245 conductivity with no need to perform reduction procedures. MXene-loaded solutions could be
246 generated in various cylindrical, ribbon, aerogel, or core-shell structures, depending on the
247 polymer matrix. The defects and loose stacking states of the MXene-integrated electrospun
248 fibers could be enhanced by the axial MXene orientation in the electrospun networks. By
249 tuning the spinning condition, MXene size, and filler concentration, different physical,
250 chemical, mechanical, and electrical conductivity could be tailored depending on the
251 considered application. Correspondingly, the MXene-polymer nanofibers composite has
252 convincingly shown tremendous potential in promising areas, such as antibacterial treatments,
253 wound healing, cellular differentiation, bone tissue regeneration, neural tissue guidance, and
254 health monitoring systems. In the following section, the role of MXene in biomedical
255 applications is described based on its noteworthy properties.

256 3. Synthesis methods and biomedical applications of MXene

257 3.1 Synthesis and Characteristics of MXene

260 Over the last two decades, two-dimensional (2D) nanomaterials have been an attractive
261 field of study due to their outstanding physical and chemical properties. Carbides and nitrides
262 of early transition metals are considered significant materials, resulting from their unique
263 features consisting of superior chemical stability, excellent hardness, and high metallic
264 electrical conductivity [57]. MXenes are 2D inorganic compounds with few atoms thickness,
265 comprising nitrides, carbides, and carbonitrides layers of early transition metals [58]. MXenes
266 are usually obtained by chemical etching of a MAX phase with a general formula of $\text{M}_{n+1}\text{AX}_n$,
267 where M represents an early transition d-metal (Mo, Ti, Zr, Cr, etc.), A is mostly referred to as
268 an element of group 13 to 16 (e.g., Al, Ga, Ge, Si, etc.), X represents carbon and/or nitrogen,
269 and n is equal to 1 to 3 (see **Fig. 3a**). The MAX phase possesses a layered hexagonal structure,
270 including densely packed M layers and X atoms occupied octahedral positions. After selective
271 etching of A layers in the MAX phase, the chemical formula of resulting MXene would be
272 $\text{M}_{n+1}\text{X}_n\text{T}_z$, where T_z is the surface terminations group ($-\text{F}$, $-\text{O}$, $-\text{OH}$, etc.) bonded to M, and z
273 is the number of the interfacial functional groups [59].



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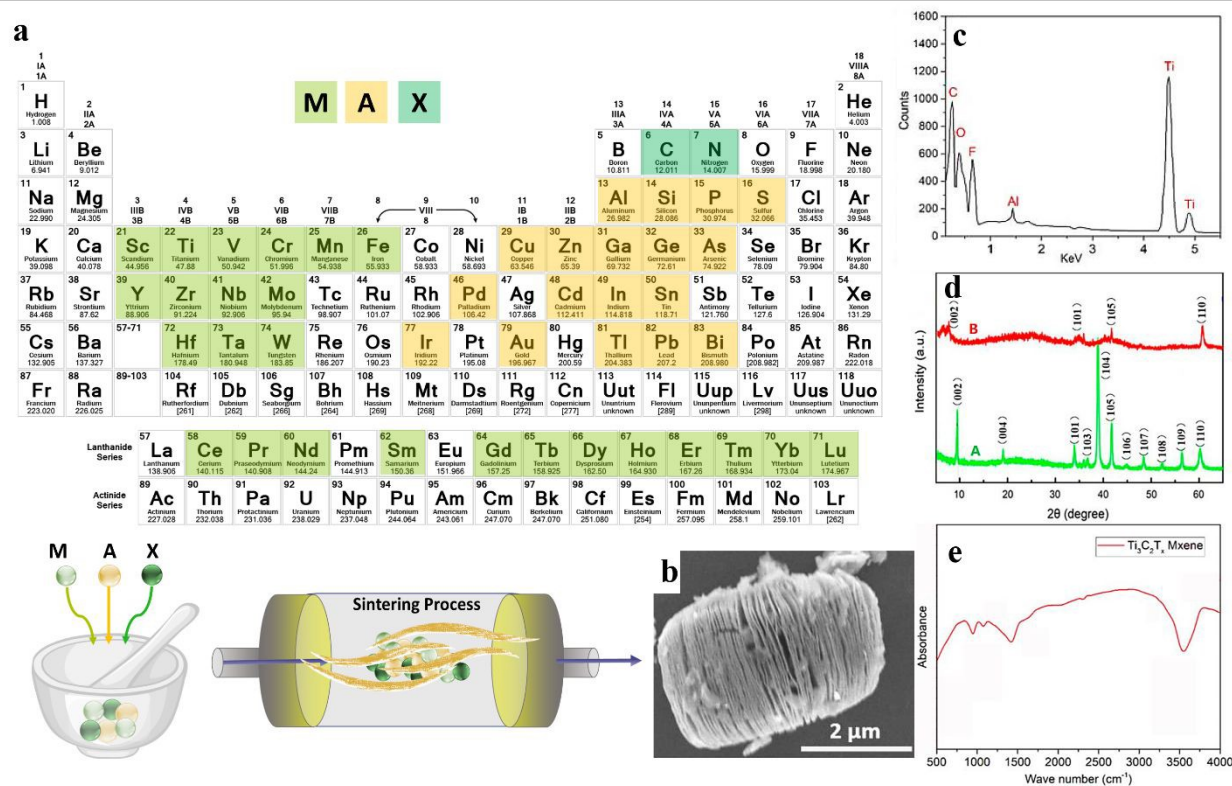


Figure 3. The structure and synthesis of the MXene nanosheets; (a) schematic illustration of the MXene structure and synthesis procedure. (b) SEM, (c) EDX, (d) XRD, and (e) FTIR results of the Ti_3AlC_2 and $Ti_3C_2T_x$ powders, Reproduced from reference [60] with permission from MDPI, Copyright 2020.

To date, several attempts have been devoted to developing the etching methods. In general, these approaches could be divided into three different methods, including wet chemical, molten salt, and electrochemical methods [61]. Among them, the wet chemical etching route is the most conventional and mature etching technique, consisting of HF-containing and HF-free approaches. Although it is reported that HF-containing methods possess high-risk operation conditions and require extra caution, it is still the most efficient etching technique [62]. Accordingly, studies over wet chemical routes to minimize or even avoid using HF resulted in valuable outcomes. As an example, Dirscoll's group reported using a small portion of HF along with other acids. They successfully fabricated Ti_3C_2 MXene using a volumetric ratio of 6:3:1 of HCl: water: HF [63]. Comparing the conventional use of HF as the etchant, the proposed method reduced the usage of this hazardous acid by 90%. Additionally, the authors reported fewer structural defects, large lateral sizes, and high yield for the developed MXene nanosheets. In another approach, $Ti_3C_2T_x$ was synthesized by immersing the Ti_3AlC_2 powders in a LiF/HCL solution. SEM illustration of the synthesized nanosheet is displayed in **Fig. 3b**. Additionally, the elemental mapping of the generated nanostructure is represented in **Fig. 3c**, showing strong peaks of C, Ti, O, and F components, along with a weak peak regarding the Al



297 element. Accordingly, the etching procedure was almost completed in the obtained MXene
298 nanostructures. Also, the presence of $-F$, $-OH$, and $-COOH$ functional groups could be
299 corroborated by the appeared peaks. **Fig. 3d** examines the XRD patterns of the Ti_3AlC_2 and
300 $Ti_3C_2T_x$ powders. As can be seen, the Ti_3AlC_2 revealed about eleven peaks, showing its
301 crystalline structure. Meanwhile, the crystalline regions were reduced to 4 phases after the
302 etching procedure, which could be linked to the removal of Al layers. The 002 crystalline plane
303 was also shifted to a lower value in a broadened peak, proving a rise in c-spacing by replacing
304 the Al atoms with $-F$ and $-OH$ functional groups. **Fig. 3e** shows the FTIR spectrum of the
305 $Ti_3C_2T_x$ nanosheets, displaying the $-OH$ and $C-F$ vibrations at 3490 and 1216 cm^{-1} ,
306 respectively [60].

307 The molten salt etching is based on the selective removal of A elements through a redox
308 reaction of molten salts and A elements. Consequently, it can be used to install and remove
309 surface functional groups. Moreover, applying molten salts as etchant enables synthesizing
310 MXenes with $-O$, $-S$, $-NH$, $-Se$, $-Cl$, and $-Br$ termination, as well as bare MXenes with no
311 surface group [64]. As an example, Urbankowski et al. [65] employed this method to
312 synthesize the first nitride MXene $Ti_4N_3T_z$. Additionally, Huang et al. [66] applied molten
313 $ZnCl_2$ for the etching of new Zn-MAX phases, such as Ti_2ZnN , Ti_2ZnC , Ti_3ZnC_2 , and V_2ZnC ,
314 reporting the substitution of Zn and resulting Cl-terminated MXenes.

315 The electrochemical etching method has also been used as an effective route to fabricate
316 MXenes in an HF-free way [64]. Ti_2CT_z and $Ti_3C_3T_z$ can be obtained through electrochemical
317 etching of A elements from Ti_2AlC and Ti_3AlC_2 MAX phases using HCl, NH_4Cl , and
318 tetramethylammonium hydroxide as an electrolyte. However, extreme etching would change
319 the MAX phase to carbon as a result of the simultaneous dissolution of A and M fundamentals
320 [67]. Apart from the aforementioned etching methods, some other infrequent approaches have
321 been used. A promising study by Yang et al. [68] reported the anodic corrosion of Ti_3AlC_2 as
322 a fluoride-free etching process. The authors claimed that the method successfully transforms
323 Ti_3AlC_2 to $Ti_3C_2T_x$ with a sufficient yield.

324 In the generated multilayered MXene structures, the layers are held together through van
325 der Waals and hydrogen bonding. Nevertheless, these secondary bonds make the intercalation
326 between layers possible to produce delaminated MXene [69]. Generally, inorganic cations and
327 organic or ionic compounds are utilized for the intercalation and, thereafter, an ultrasonication
328 step. Due to the negatively charged surface of the as-obtained flakes, they are able to make a
329 stable suspension in organic solvents or water without any surfactant addition. Based on the
330 literature, several cations, such as $Na(1+)$, $K(1+)$, $Mg(2+)$, and $Al(3+)$, have been successfully
331 applied to intercalate the MXenes [70]. As a result, MXenes can be obtained in different forms
332 of multilayer powders to delaminated flakes, which can be employed in several applications
333 via various techniques, including printing, spraying, fiber forming, electrospinning, and many
334 more [58].

335 MXene structures could be feasibly functionalized with covalent and non-covalent bond
336 interactions to combat the MXene weak points, such as poor oxidation stability. Non-covalent



337 functionalization is commonly carried out through weak intermolecular or interatomic bonding,
338 such as van der Waals forces, hydrogen bondings, or electrostatic interactions in a fast and
339 mild procedure. Meanwhile, the covalent functionalization method creates strong interactions
340 via equal sharing of electron pairs, offering surface modification with superior stability. Unlike
341 the non-covalent modification method, covalent functionalization requires a complex synthetic
342 procedure, lasts long, and might lead to oxidative degradation [71, 72]. Overall, far from
343 synthesizing other 2D materials with similar applications that yield small amounts under
344 challenging conditions, MXenes can be produced on a large scale through a straightforward
345 procedure, making it more potential to meet industry measurements. MXenes have become
346 one of the most favorable groups of 2D nanomaterials because of their outstanding properties.
347 The easy functionalization of MXenes renders them extremely auspicious material for
348 laboratory studies, as well as practical usage in various industries.

349 **3.2 The role of MXene and MXene-loaded nanofibers in biomedical applications**

350 According to the literature, the MXene family is a promising candidate to boost versatile
351 structures for a wide range of applications, such as environment and purification, electronics,
352 sensors and displays, and biomedical targets. In the biomedicine category, MXene has been
353 utilized to optimize the efficiency of cancer treatment, drug delivery, bioimaging, and
354 biosensors in the developed architectures. The highlighted potentials could be referred to as
355 proven fascinating features of the MXene-based configurations, such as proper elastic
356 mechanical strength, electronic conductivity, hydrophilicity, chemical stability, and many
357 more [73]. Incorporating MXene nanosheets into the electrospun fibers creates a synergetic
358 effect for biomedical applications due to their complementary features. The combination of
359 MXene layered structure and high porosity of electrospun fibers endow a large surface area.
360 The mechanical strength of the electrospun fibers could be reinforced by embedding the
361 MXene nanosheets into the nanoarchitecture, attesting to better performance in various
362 biomedical applications. The layered structure of the MXene, in tandem with appropriate
363 morphological characteristics of the electrospun fibers, serves great capacity for loading drugs,
364 providing sustained and controlled drug release. The electrical conductivity could also be
365 escalated by incorporating the MXene into the conductive electrospun fibers, which is
366 favorable for tissue engineering and sensors.

367 **3.2.1 Cancer Therapy**

368 In recent years, the MXene family has been introduced to achieve therapeutic, imaging, and
369 drug delivery precise abilities in photothermal tumor treatments (PTT) and photodynamic therapy
370 (PDT). High light-to-heat conversion efficiency and strong absorption in both the first and second
371 NIR bio windows in comparison with conventional photosensitizers, have remarked the
372 advantages of MXene nanostructures toward PTT and PDT. Also, the highlighted capabilities of
373 MXenes in anti-cancer therapy could be linked with the proper atomic number, paramagnetic
374 behavior, and high surface-to-volume ratio. Common cancer therapies lead to unwanted side
375 effects and drawbacks, resulting in direct biological targeting for the local cancer treatment
376 requiring signal transduction and actuation, which could be carried out via radical oxygen, heat,
377 and irradiation. Among the introduced methods, PTT is assumed to be a fresh and efficient



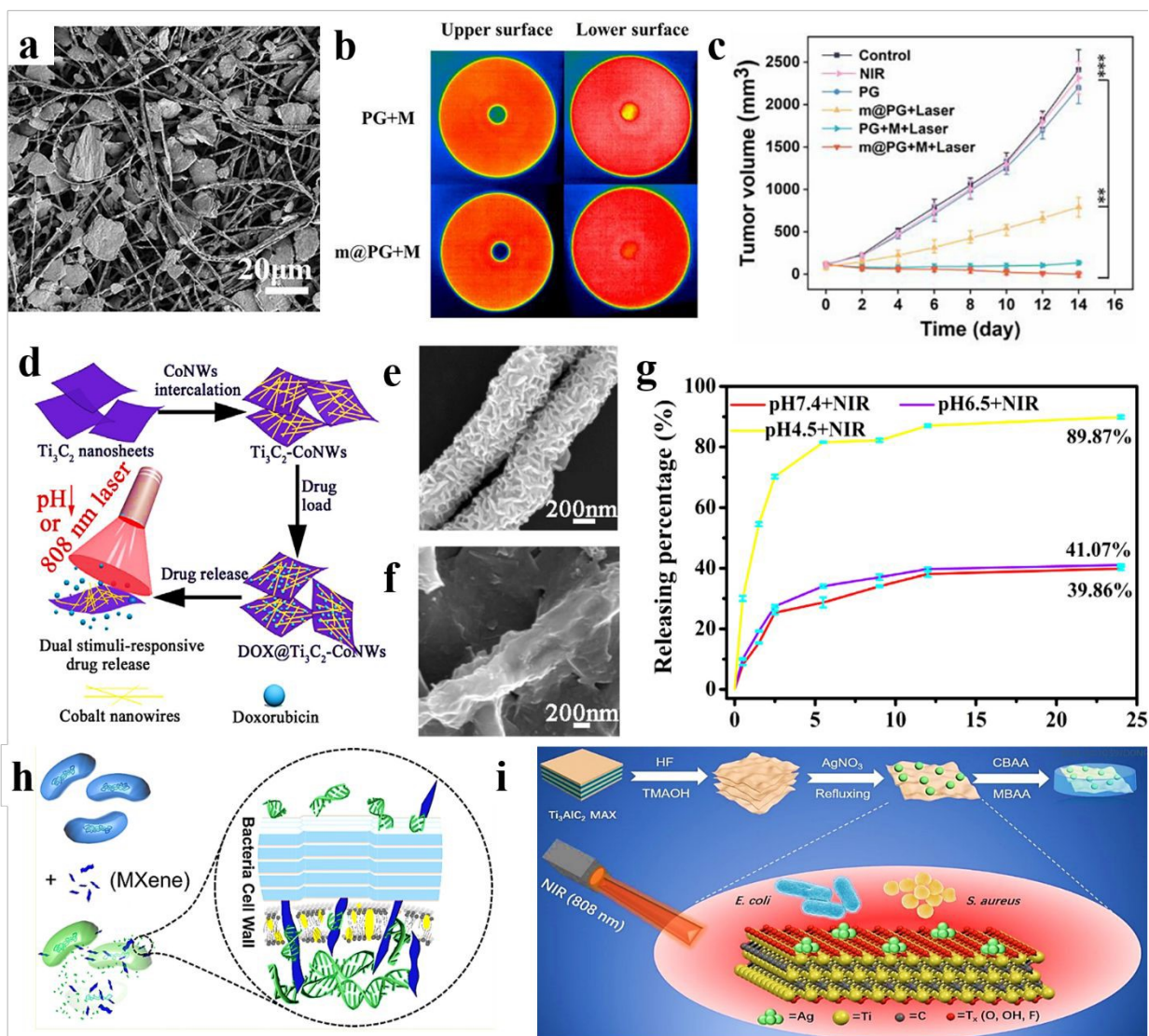
378 treatment for cancer curing. In this technique, the light is converted to heat, causing cell death
379 without influencing the surrounding tissues. Also, the precise location of the cancer cells could
380 be detected and monitored through the PTT agent inflation in tumors in a remotely controlled
381 manner.

382 Li et al. [74] utilized a droplet light heating system to estimate the light-to-heat photothermal
383 activity of the Ti_3C_2 MXene nanostructure. A wide spectrum laser beam was irradiated to the
384 droplets containing Ti_3C_2 and CNT, implying a higher temperature for the Ti_3C_2 than that of the
385 CNT, possibly due to the superior light absorption of the MXene. According to the obtained data,
386 excellent light absorption capability was represented by the employed Ti_3C_2 compared to that of
387 the carbon nanotubes. Accordingly, the CNT structure did not reveal any absorption peak from
388 300 to 1300 nm, while Ti_3C_2 showed a higher absorption and an observable peak around 800 nm.
389 In addition, the internal light-to-heat conversion efficiency of 100% was approached. Despite the
390 great advantages of MXene, its non-stable structure in buffer saline, poor oxidation stability, and
391 agglomeration behavior have motivated researchers toward modifying the MXene family through
392 combination with other structures. Gao et al. [75] designed a 3D honeycomb structure comprising
393 Ti_3C_2 /CNT to approach the anti-aggregation property, displaying proper photothermal activity
394 and stability in the NIR region.

395 It is also worth noting that among various 2D materials, MXene nanosheets are ideal for use
396 in PDT as photosensitizers. PDT is a safer and more targeted cancer treatment than chemotherapy
397 and radiotherapy, reducing the risk of side effects [76]. This is because photosensitizer drugs only
398 become toxic when activated by external light. In this era, Liu et al. [77] confirmed the excellent
399 drug release profile of MXene-based structure, due to its efficient NIR laser-induced and pH-
400 responsive behavior. The attempts in the area of MXene modification in cancer therapy have
401 resulted in the evaluation of MXene photothermal activity in different configurations, including
402 Ti_3C_2 quantum dots [78], Ti_2C nanosheets [79], Ti_3C_2 /Co nanowires [80], MXene/Doxjade
403 platform [81], Au/ Fe_3O_4 / Ti_3C_2 nanocomposite [82], MXene/PVA hydrogel [83],
404 collagen/silk/hydroxyapatite/MXene 3Dprinted scaffold [84], MXene/borneol-poly(N,N-
405 dimethyl ethyl methacrylate) [85], and many more. Furthermore, MXene-based
406 nano/microarchitectures could be employed in targeted anti-cancer drug delivery systems or
407 therapeutic agents after modifying with biocompatible activated agents. Considering the
408 beneficial characteristics of the electrospun fibers in biomedical engineering, as well as the
409 prominent role of MXene in designing versatile architectures, several studies have been devoted
410 to analyzing the properties of the MXene-loaded electrospun compositions. For example, Ding et
411 al. [86] declared that simultaneous $Ti_3C_2T_x$ electrospay on the $Ti_3C_2T_x$ -loaded PLA nanofibers
412 could generate a highly efficient membrane with the ability to kill tumor cells, in tandem with
413 bacteria after surgical melanoma excision, decreasing the tumor recurrence. **Fig. 4a** shows the
414 SEM image of the electrospun fibers decorated with MXene nanocoating. **Fig. 4b** exhibits the
415 upper and lower surfaces of the provided films attached to the hot plate. When the hot plate was
416 applied to the upper surface, the lower surface of the sample containing MXene nanosheets
417 represented higher temperature compared with that of the free-filler film, corroborating the better



418 conductivity of the MXene-loaded film. Resulting from the $Ti_3C_2T_x$ presence both inside and on
 419 the surface of the electrospun fibers, and so an excellent unidirectional thermal conductivity, a
 420 high temperature of about $70^\circ C$, could be achieved in 1 min with proper photothermal cycling
 421 stability. As a result, reaching a certain temperature in the developed structures could result in
 422 killing the B16F10 cancer cells. **Fig. 4c** shows the tumor growth curve relating to the application
 423 of various films. Based on the results, the tumor recurrence was effectively prevented from
 424 MXene-loaded structure. Additionally, an antimicrobial ring diameter of 1.3 cm was approached
 425 in the mentioned membrane under 808 nm laser NIR light, mighty resulting from the enhanced
 426 thermal distribution in the lower surface of the fibrous structure.



427
 428 **Figure 4.** Characteristics of the PLA nanofibers decorated with electrospayed MXene for cancer
 429 treatment; (a) SEM image of the film, (b) temperature distribution in the MXene-free and MXene-
 430 loaded films, and (c) the growth curve of tumor volume in different provided films. Reproduced
 431 from reference [86] with permission from Elsevier, Copyright 2023. Properties of the
 432 Ti_3C_2 /cobalt nanowire heterostructure; (d) the designed procedure, (e&f) SEM images of the



433 *Ti₃C₂ and Ti₃C₂/cobalt nanostructures, and (g) drug delivery rate. Reproduced from reference*
434 *[80] with permission from Elsevier, Copyright 2020. (h) Mechanism of the MXene antimicrobial*
435 *activity. Reproduced from reference [87] with permission from the American Chemical Society,*
436 *Copyright 2018. (i) Simultaneous use of antimicrobial and NIR photothermal activities of*
437 *MXene/Ag nanocomposite. Reproduced from reference [88] with permission from the Royal*
438 *Society of Chemistry, Copyright 2020.*

439

440 3.2.2 Drug delivery

441 Ultra-thin 2D planar structure, NIR responsiveness, photothermal conversion capability,
442 and chemically adjustable surface functionalities of the MXene family caught the interest of
443 researchers for developing efficient controlled drug release systems. MXene structures could more
444 freely migrate through the body than the large particles. In addition, a lower drug amount is
445 required to be loaded on the MXene due to its outstanding surface area. Notably, the pH sensitivity
446 and photothermal activity of MXene structures have made them a great candidate in cancer therapy.
447 Therefore, these unique materials could reveal a dual-stimuli response for drug release, as well as
448 ablation of malignant cells.

449 Although the MXene family has revealed remarkable characteristics, their inadequate
450 control ability and poor drug loading capability lead to continuous drug detaching and injuring
451 normal tissues. In addition, non-stable structure in the physiological conditions causes the
452 limitation toward efficient treatment of cancer diseases. To address the highlighted downsides,
453 adding magnetic nanoparticles to the MXene structure has been considered a prominent strategy
454 [89, 90]. Accordingly, the drug could be effectively confined to the targeted tissue by applying an
455 external magnetic field. For example, Liu et al. [80] designed a heterostructure Ti₃C₂
456 MXene/cobalt nanowire, noticing the ferromagnetic properties of the cobalt. In this study, the
457 cobalt is intercalated on the Ti₃C₂ nanosheets, and the doxorubicin was loaded on the prepared
458 structure. Then, the loaded drug was released under an 808 nm laser beam in three pH levels, which
459 is schematically summarized in **Fig. 4d**. SEM images of Ti₃C₂ and Ti₃C₂/cobalt nanocarriers are
460 illustrated in **Figs. 4e&f**, respectively. The provided structure showed excellent photothermal
461 conversion activity at the wavelength of 808 nm. The doxorubicin loading increased up to 225%,
462 corresponding to the electrostatic interaction between the negative surface of the Ti₃C₂-cobalt
463 nanocarriers and the positive charge of the employed drug. In addition, the drug release of the
464 prepared material in various pHs is shown in **Fig. 4g**, declaring 89.3% release at a pH of 4.5 after
465 illuminating NIR for 24h. Overall, chemo photothermal therapy could be enhanced resulting from
466 the synergetic effects of the composite elements, which is beneficial in cancer therapy.

467 MXene properties could also be modified by various polymers. For example, hydrophobic
468 biocompatible polymers, such as PLGA, can tune the hydrophilicity inherent feature of the
469 MXene and ease its interaction with hydrophobic drugs [91]. In addition, the combination of
470 photothermal polymers, such as polypyrrole and polydopamine, can cause a synergetic effect and



471 boost the MXene performance. Moreover, polymer matrixes could provide a desirable
472 accommodation for the MXene nanoparticles, impeding the leakage in the body [92]. In this era,
473 the enhanced drug delivery performance of MXene combined with nanoscaled polyacrylamide
474 [89], polyethylene glycol (PEG) [93], Chitosan/hyaluronic acid/gold [94], agarose [95],
475 polydopamine/gold [96], and PEG/gold [97] compositions are reported.

476 To escalate the efficiency of drug delivery systems, temperature-responsive MXene nanobelt
477 fibers were generated through electrospinning the PAN/PVP/MXene solution, followed by
478 coating with polyacrylonitrile and polyvinylpyrrolidone composition. In a 3 min time, the
479 developed structure could reach from 23 to 39°C under NIR exposure. Accordingly, the coating
480 layer could be opened and the loaded vitamin E could be released in a favorable profile over a
481 longer period, resulting in good wound healing. According to the obtained data, proper surface
482 area, high mass loading, and the mass production capability of the suggested structure could
483 facilitate the application of this architecture in a diverse range of biomedical applications, from
484 drug delivery and wound dressing to biosensors and tissue engineering [98]. In another research
485 study, a hybrid system was designed comprising MXene nanofibers and hydrogel components
486 embedded with deferoxamine mesylate (DFOM) and acetylsalicylic acid (AC) to develop a highly
487 efficient wound dressing. Based on the results, the photothermal activity of the MXene nanofibers
488 could regulate the release of DFOM to prevent excessive angiogenesis. The immune micro-
489 environment around the wound region could be controlled by favorable release of AC, assisting
490 in approaching appropriate anti-inflammatory activity [99].

491 3.2.3 Antimicrobial activity

492 Today, medication overuse has caused microorganism resistance against drugs' antimicrobial
493 activity, requiring the development of materials with superior efficiency. MXene family possess a
494 remarkable antibacterial property, linked with appropriate semiconductor features, hydrophilicity,
495 electrical conductivity, functional groups on the surface, the thickness of the atomic layer, and
496 optical behavior (see **Fig. 4h**). Based on the literature, these materials are able to inhibit Gram-
497 negative (*E. coli*) and Gram-positive (*B. subtilis*) growth, depending on the employed MXene
498 concentration. This could be attributed to the interfacial interaction between the MXene-based
499 structures and the cells. In fact, this direct contact destroys the cell membranes, followed by cell
500 death. The active surface, as well as the small size of the MXene nanosheets, ease their penetration
501 into the cells, resulting in their significant interaction with the specific molecules placed in the
502 microbial cell walls and cytoplasm, and eventually, cell disruption and death. Moreover, a
503 conductive bridge could be created on the lipid layers due to the anionic surface of the MXene
504 nanostructures, boosting the electron transduction from bacteria to the environment and so the cell
505 death [100, 101]. Furthermore, the hydrogen bonding between MXene's surface functional groups
506 lipopolysaccharide string in the cells might hinder bacterial growth. As an example, better
507 antimicrobial behavior was reported by reducing $Ti_3C_2T_x$ nanosheet size against both *E. coli* and
508 *B. subtilis* [102]. In another attempt, the application of $Ti_3C_2T_x$ was proposed to attain both
509 photothermal and antibacterial activities, which is schematically depicted in **Fig. 4i**. [103].
510



511 Benefitting the favorable characteristics of the electrospun fibers, a core-shell structure was
512 generated comprising PCL/Ti₃C₂T_x and PCL/gelatin/Ti₃C₂T_x, respectively, as the core and shell
513 to develop an antibacterial and electroactive wound dressing. Based on the results, the presence of
514 Ti₃C₂T_x led to an increment in the mechanical stability, antibacterial behavior, proliferation
515 activity, and wound healing procedure. Additionally, the electrospun matrix acted as a barrier
516 against bacterial infiltration through the formation of a dense structure, revealing a promising
517 architecture applicable in bioactive dressings for cutaneous wound healing [104].

518 3.2.4 Smart sensors

519 The large surface area and easy surface modification ability of the MXene groups potentiate them
520 for application in the design of various sensors, such as gas, humidity, stress-strain, and optical
521 devices. In addition, the ideal MXene properties, such as biocompatibility, conductivity, surface
522 chemistry, and shaping, have made it an exceptional platform for electrochemical sensors [41, 105].
523 Besides, MXene nanosheets have illustrated a wide band gap. For instance, the band gap of some
524 MXenes Oxides, such as Zr₂CO₂ and Ti₂CO₂ is found to be 2.13 and 1.15 eV, respectively.
525 Moreover, when compared to other established 2D nanomaterials like graphene, MXenes propose
526 superior hydrophilicity and superior electrical conductivity [106, 107]. Furthermore, studies have
527 shown higher electrical conductivity of MXene nanosheets compared with CNTs and reduced
528 graphene oxide (rGO) materials, which could be attributed to their layered structure, allowing for
529 efficient electron transport along the layers [74, 108]. Accordingly, such structures could be
530 employed in chronoamperometric biosensors due to its unique characteristics, including
531 electrocatalytic activity and fast response in the 50 to 750 μm region, which is beneficial for
532 glucose detection. Meanwhile, van der Waals bondings between the MXene sheets cause the
533 synthesis of thin layers and nanosheet aggregations, requiring further modification methods to
534 address the block as mentioned above [109-111]. As an example, Rakhi et al. [112] developed a
535 Ti₃C₂T_x/Au composite for glucose biosensors, showing proper stability and reproducibility
536 behaviors. MXene-based materials have also illustrated a prominent role in fabricating wearable
537 electrochemical sensors, applicable in health- and sport-related devices. Accordingly, a porous
538 sandwiched structure was fabricated comprising Ti₃C₂T_x and PLA to produce a pressure-flexible
539 and degradable sensor, representing a great sensitivity even in a wide range from 10.2 Pa to 30
540 kPa and great cyclability over 10000 cycles. So, it could be utilized in monitoring the patient's
541 health effectually and in real-time clinical diagnosis [113]. In an attempt carried out by Sohel Rana
542 [114], it was declared that loading Ti₃C₂T_x nanosheets into the PVDF-TrFE nanofibers could
543 generate a sensor motion with outstanding low-pressure performance (power 4.02 W/m²) as well
544 as proper mechanical response sensitivity (1.1 V/kPa). According to the results, embedding
545 Ti₃C₂T_x could cause a rise in the electronegativity, dielectric property, and biocompatibility of the
546 provided architecture, resulting from the formation of microscopic dipoles and microscopic
547 networks. Hence, the integration of electrospun fibers with MXene-based galleries could open a
548 viable new avenue to tackle challenges in sensor fabrication and approach the desirable
549 performances.



550 3.2.5 Tissue engineering

551 The organs' injuries and fractures could result in traumas, diseases, paralysis, and mortality of
552 many people every year. The multifaceted tissue engineering field has utilized biomaterials,
553 biological molecules, cells, and scaffolds to efficiently recover and reconstruct damaged organs.
554 Accordingly, numerous attempts have been made to design tissues with the ability to mimic natural
555 matrixes. Therefore, novel composite scaffolds have been developed, comprising synthetic and
556 natural polymers, as well as ceramics and 2D materials. MXene is a considered 2D geometry
557 substance, endowing notable characteristics to the scaffolds due to its large surface area, proper
558 hydrophilicity, 2D structure, conductivity, and particle size regulation. The hydrophilic surfaces
559 of MXenes, with high metallic conductivities, distinguish them from most 2D materials such as
560 graphene. Moreover, their high metallic conductivity allows them to efficiently transport electrical
561 signals, which is crucial for many tissue engineering applications [115]. Meanwhile, more attempts
562 are required to optimize and adjust the prepared composite according to the targeted native matrix,
563 such as oxidative stability, biodegradability, biocompatibility, physiological condition stability,
564 etc. Correspondingly, surface functionalizing of the MXene by organic and inorganic materials
565 has been extensively suggested as a result of its high surface area. Also, the formation of MXene
566 in various composite architectures, such as membranes, layers, porous structures, particles, 3D
567 printed composites, and specifically nanofibrous configurations, could integrate its features.

568 MXene-based structures have been employed to boost the regrowth and reconstruction of
569 various tissues. For example, it is a good choice for designing and regeneration of bone defects.
570 The MXene-based materials easily interact with water and oxygen, causing their degradation and
571 subsequent release of Ti-based materials. Such species are appropriate for the promotion of bone
572 cell growth. Therefore, they could be applied in bone cancers to simultaneously ablate the tumor
573 cells and reconstruct the bone. Pan et al. [17] synthesized a 3D-printed Ti_3C_2 /bioactive glass bone
574 scaffold (TBGS) and compared it with a bioactive glass 3D-printed membrane (BGS), which is a
575 common and beneficial material for bone scaffolds. The fabrication route of both BGS and TBGS
576 layers are schematically provided in **Fig. 5a**. A desirable element distribution was also shown by
577 the element-mapping analysis (See **Fig. 5b**). As is depicted in **Fig. 5c**, triggering photothermal
578 ablation was examined by irradiating the osteosarcoma cells by 808 nm laser. **Fig. 5d** confirmed
579 much fewer living cells with increasing the laser-irradiation duration. 3D reconstruction of the
580 tissue was analyzed after 24 weeks of implantation of the composite scaffolds, representing more
581 calcified tissues and better regeneration outcome with the presence of TBGS, compared with that
582 of applying BGS (**Figs. 5e**). The values of BV/TV, BMD, and TOT in newborn osseous tissues
583 collectively exhibited a superior osteogenic performance of TBGS than the BGS layer, displaying
584 in **Figs. 5f-h**.

585



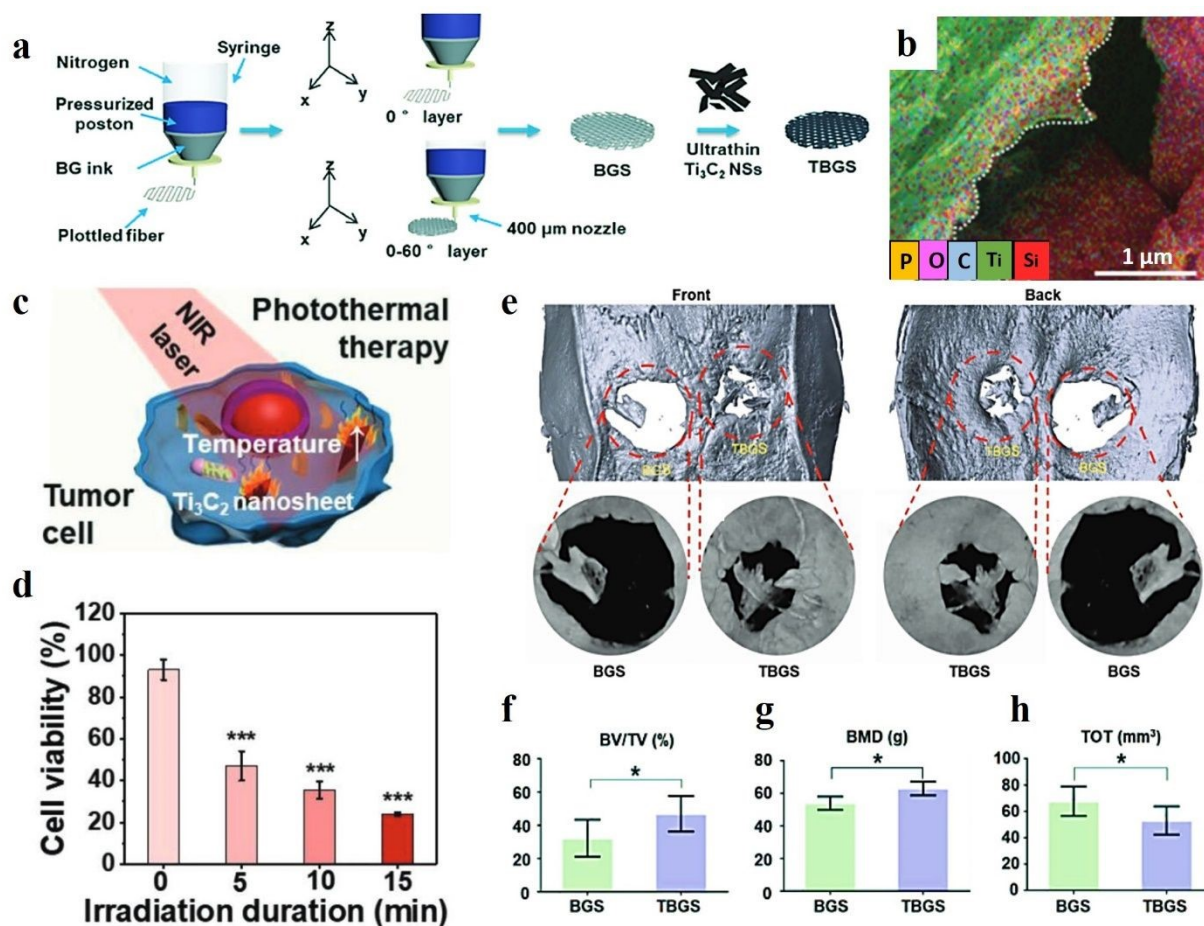


Figure 5. Characteristics of a 3D-printed Ti_3C_2 /bioactive glass bone scaffold; (a) schematic design of the synthesis methods, (b) EDS mapping, (c&d) schematic illustration of the photothermal therapy and its outcome, (e) evaluating the 3D reconstruction of the tissue after 24 weeks implantation of the composite tissues, and the value of (f) BV/TV, (g) BMD, and (h) TOT in newborn osseous tissues. Reproduced from reference [17] with permission from Wiley, Copyright 2020.

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594 MXene films have also illustrated promising features, such as planar structure for regenerating
595 the skin tissue. In a study, a multifunctional crumpled $Ti_3C_2T_x$ MXene-based membrane was
596 designed as a skin tissue scaffold. In this research, various MXene ratios were coated on the
597 polycarbonate membrane using a vacuum filtration technique. According to the results, the
598 mechanical features were enhanced to 30.48% strain, 28.63 MPa tensile strength, and 77.0 dB
599 shielding performance for the membrane containing 70 mg $Ti_3C_2T_x$. This could be attributed to
600 the interfacial interaction between the MXene nanosheets and the 3D fibrous network. So,
601 increasing the MXene ratio up to 70 mg provides more hydrogen bonds and higher mechanical
602 features. The fracture morphology of the MT70 membrane also revealed the tighter attachment of
603 the fibers inside the layer, which could be the reason for attaining superior mechanical properties.
604 Moreover, thermal conductivity was improved by loading more MXene ratio in the membrane.



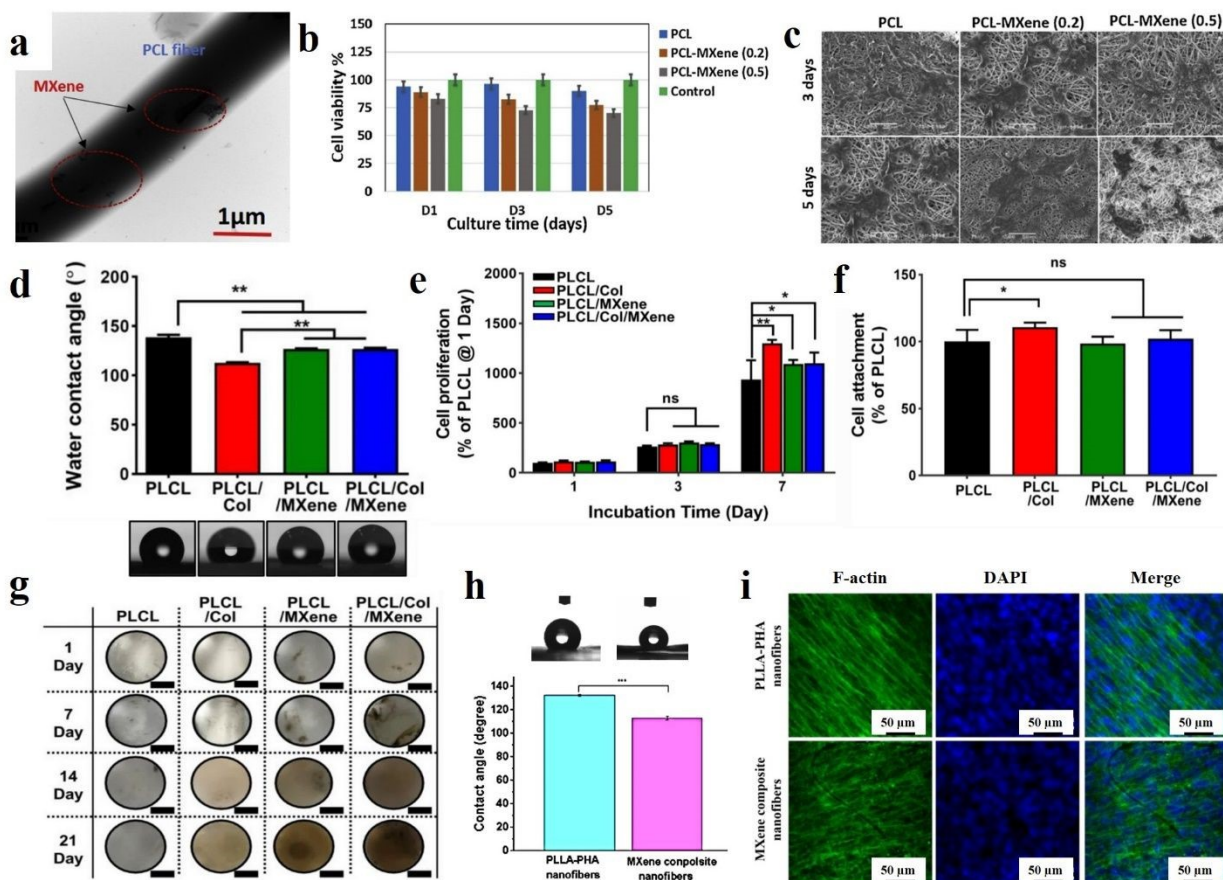
605 The through-plane conductivity enhancement refers to the vertical arrangement of the MXene
606 nanosheet on both sides of wrinkles [15].

607 MXene has also exhibited a fabulous structure as a cardiac patch by mimicking the native tissue
608 regarding its excellent electrical conductivity and topography cues. As an example, Basara et al.
609 [116] designed a 3D-printed $Ti_3C_3T_x$ MXene/PEG composite for cardiac tissue engineering. They
610 confirmed the non-cytotoxicity of the prepared tissue for the human-induced cardiomyocytes. Also,
611 the 3D-printed layer provided a great condition for cell alignment, resulting in the improvement
612 of the synchronous beating and conduction velocity. A similar outcome was also obtained by using
613 Ti_2C cryogel as a conductive bifunctional cardiac patch. The results illustrated the formation of a
614 3D vessel network after culturing the aortic endothelial cells. Moreover, this membrane
615 represented rapid calcium transient, enhanced cardiac function, and great synchronous heart-like
616 beating. Although the biocompatibility of the MXene-based compositions has been declared by
617 many attempts, long-term biocompatibility assessments seem to be scarce in this era. Accordingly,
618 incorporating systemic toxicity evaluations, immunogenicity assessments, and detailed
619 histopathological analyses of major organs following implantation could substantiate the safety
620 profile of these materials [117].

621 With the emerging nanotechnology science and the outstanding aptitudes of nanomaterials,
622 they caught a huge interest in tissue regenerating and biomedical applications. These arrays could
623 assist in approaching minimal side effects, passive and active targeting of damaged tissues, time-
624 dependent drug release, and controllable degradation. Considering the vital role of MXene and
625 various electrospun fibers in the progress of tissues, their combination could lead to eliminating
626 their downsides and obtaining a synergetic effect. Accordingly, Awasthi et al. [118] fabricated an
627 electrospun PCL/ $Ti_3C_2T_x$ composite and verified its potential for tissue engineering applications.
628 To prepare the specimens, $Ti_3C_2T_x$ with various concentrations of 0.2, 0.5, 1, and 2 wt.% was
629 added into the electrospinning solutions. The electrospinning procedure was carried out using a
630 12 ml syringe with a nozzle diameter of 0.51 mm under a spinning distance of 15 cm, voltage of
631 15 kV, and feeding rate of 1 ml/h. **Fig. 6a** shows the TEM illustration of the $Ti_3C_2T_x$ -loaded
632 nanofibers. The presence of MXene in the electrospun scaffolds was confirmed by XPS data. The
633 electrospun fibers containing 0.2, 0.5, 1, and 2 wt.% MXene showed average diameters of 0.69,
634 0.83, 1.32, 1.35, and 1.6 μm , respectively. The increment in the diameter could be due to the
635 presence of interconnected pieces of MXene. The mentioned membranes also exhibited a rise in
636 the contact angle from 100.7 to 37.2^o with increasing the MXene concentration, which is
637 fascinating for improving the cell adhesion and proliferation on the surface of scaffolds (see **Fig.**
638 **6b&c**). A laboratory biomineralization test was used to evaluate the hydroxyapatite nucleation
639 performance of the generated fibers. The EDS results obtained from the treatment of MXene-
640 reinforced scaffolds with SBF confirmed the sufficient deposition of calcium and phosphorus on
641 the surface of fibers for osseointegration according to the standard values reported for the HA
642 crystals, which could be assigned to the proper wettability of the MXene nanosheets.
643 Biocompatibility was investigated by fibroblast (NIH-3T3) and pre-osteoblast (MC3T3-E1) cells.



644 According to the results, PCL nanofibers loaded by MXene (up to 0.5 wt.%) represented more
 645 biocompatibility compared to the structures embedded with higher MXene ratios. This could be
 646 related to incrementing the fibers' diameter, leading to a reduction in protein adsorption, cell
 647 viability, and cell adhesion. Therefore, the biological activity of scaffold or bone graft could be
 648 boosted resulting from the MXene presence in the electrospun fibers due to its osteogenic
 649 properties.
 650



651
 652 **Figure 6.** Various characteristics of the MXene-decorated electrospun scaffolds; (a) TEM, (b)
 653 cell viability, and (c) cell attachment of the PCL nanofibers loaded by 0.2 and 0.5% MXene.
 654 Reproduced from reference [118] with permission from Elsevier, Copyright 2020. (d) water
 655 contact angle, (e) cell proliferation, (f) cell attachment, and (g) digital photographs of von
 656 Kossa-stained scaffolds of MXene-loaded PCL/Col nanofibers. Reproduced from reference [119]
 657 with permission from Springer, Copyright 2022. (h) water contact angle and (i) fluorescent
 658 images of the cultured BMSCs after 5 days of the PLLA-based nanocomposite. Reproduced from
 659 reference [23] with permission from the American Chemical Society, Copyright 2020.

660 Considering hybrid techniques of film casting and electrospinning, Yan et al. [120] fabricated a
 661 highly sensitive bionic MXene-based pressure sensor using the microstructure of the ginkgo leaf.
 662 The core deformation part of the sensor possessed microscopic shapes imprinted from the ginkgo



663 leaves. MXene was sprayed onto a PDMS model film with the ginkgo leaf structure. Also, the
664 PVA nanofibers were synthesized by the electrospinning technique between the MXene
665 component to approach a high-pressure sensitivity of up to 03.46 kPa^{-1} . The proposed pressure
666 sensor was durable and displayed a short response time of 99.3 ms, representing the promising
667 potential for application in physiological signal testing and human-computer interaction. Focusing
668 on combining the structures, a triboelectric nanogenerator (TENG) was developed using Ti_3C_2
669 MXene supported by cotton fabric as an electrode layer for self-powered flexible sensors. The
670 MXene was mixed with cellulose nanofibers to create the electrode layer, providing electrical
671 conductivity and negativity, while the cotton fabric boosted strength and flexibility. The generated
672 TENG could produce open-circuit voltage up to 400 V in single-electrode mode and sense the
673 mass of touched steel objects ranging from 2 to 200 g with good repeatability and a linear
674 relationship. The proposed TENG was highly flexible and could be stretched up to 100% of its
675 original length, producing different voltage signals depending on the bending and folding angles.
676 Therefore, the designed structure could be used as a self-powered flexible sensor to monitor
677 various physiological movements of the human body [121].

678 In 2022, Lee et al. [119] developed nanofibrous matrices of poly(L-lactide-co- ϵ -
679 caprolactone)/collagen (PLCL/Col) nanofibers loaded by Ti_3C_2 nanosheets for bone tissue
680 engineering. First, PLCL (75:25) and Col with concentrations of 5 and 0.5% (w/v) were dissolved
681 in 1, 1, 1, 3, 3, 3-hexafluoroisopropanol. Ti_3C_2 was dispersed in deionized water and mixed with
682 PLCL/Col solution to approach the final solution concentration of $400 \mu\text{g/ml}$. The electrospinning
683 distance was adjusted to 9 cm. The electrospinning process was carried out with a feeding rate of
684 0.2 ml/h under a voltage of 16 kV. According to FESEM images, the mean diameter of PLCL,
685 PLCL/Col, PLCL/ Ti_3C_2 , and PLCL/Col/ Ti_3C_2 nanofibers were 908 ± 68 , 449 ± 44 , 368 ± 22 , and
686 $357 \pm 3 \text{ nm}$, respectively. The observed reduction in fiber diameters could be related to the changes
687 in the viscosity of the solutions. Additionally, the surface roughness of the scaffolds also showed
688 a downward trend, possibly due to the formation of finer fibers. As is displayed in **Fig. 6d**, the
689 hydrophilicity of the PLCL scaffold increased with the addition of Col, Ti_3C_2 , and Col/ Ti_3C_2
690 combination. Cell attachment and proliferation of MC3T3-E1 preosteoblasts on the scaffolds were
691 also investigated, implying a significant increase in the cell attachment through the addition of Col
692 into the PLCL matrix compared with that of the PLCL (**Figs. 6e&f**). Meanwhile, there was no
693 significant difference in the cell attachment between the PLCL/ Ti_3C_2 or PLCL/Col/ Ti_3C_2 and
694 PLCL. At 7 days of incubation, PLCL/Col and PLCL/Col/ Ti_3C_2 nanofibrous matrices showed
695 significantly increased cell proliferation, $p < 0.01$ and $p < 0.05$, respectively. The obtained data
696 suggested the synergistic impact of increased initial attachment, as well as hydrophilicity
697 enhancement, in the improvement of cell proliferation. The results of exposure of the scaffolds to
698 cells stained with von Kossa exhibited that the MXene-loaded scaffolds exceptionally increased
699 osteogenesis activity and caused spontaneous differentiation from pre-osteoblasts (see **Fig. 6g**).
700 After cell incubation for 14 days, the mineralized bone nodules appeared on the provided MXene
701 loaded scaffolds, which are stained in a dark-brown color, while the MXene-free membranes did
702 not show any color changes. Therefore, the MXene presence in the structure could lead to stronger



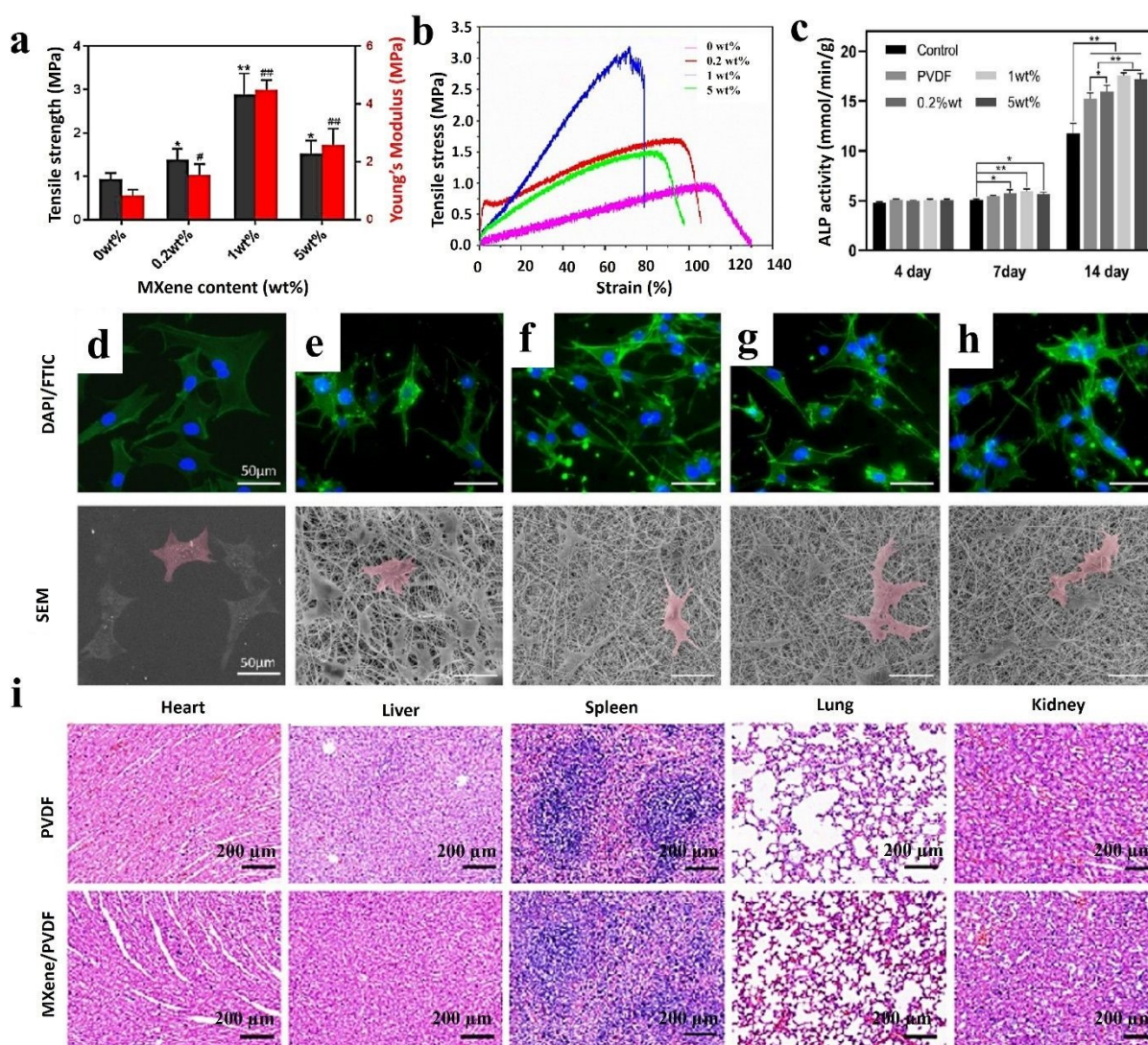
703 attractive cell interactions, accelerating the Ca^{2+} ions adsorption and so boosting the late-stage
704 osteogenic differentiation.

705 Huang et al. [23] also fabricated poly-l-lactic acid/Polyhydroxyalkanoates (PLLA/PHA)
706 nanofibers filled with Ti_3C_2 for bone tissue engineering. First, 40 mg of Ti_3C_2 was added to 4 ml
707 dichloromethane/dimethylformamide (DCM/DMF) and sonicated for 2 hours in an ice bath. Then,
708 0.16 mg of PLLA and 0.16 g of PHA were introduced into the mixture and stirred for 24h. The
709 electrospinning process was conducted using a 1 ml syringe under a voltage of 15 kV and a feeding
710 rate of 0.6 ml/h. According to the obtained data, fine and homogenous fibers with an average
711 diameter of 850 nm ranging from 600 nm to 1.5 μm . were obtained. The XPS data revealed the
712 creation of a large number of -OH and -O- terminal groups on the nanofibers' surfaces. The contact
713 angle of the electrospun composites decreased from 132.27 to 112.76° after the incorporation of
714 Ti_3C_2 into the PLLA/PHA nanofibers, resulting from the MXene functional groups (see **Fig. 6h**).
715 Bone marrow-derived mesenchymal stem cells (BMSCs) were seeded on the scaffolds for 1, 3, 7,
716 and 14 days. The results confirmed the cell adhesion enhancement on the MXene-loaded scaffolds
717 after day 1, which could be attributed to the rise in the hydrophilicity ratio. On day 3, a similar
718 trend was observed in the cell adhesion between the samples with and without MXene nanosheets.
719 Meanwhile, it was again enhanced in the filled membrane after day 7, which could be linked with
720 the formation of a desirable microenvironment for cell adhesion and proliferation. SEM images of
721 cell culture on the scaffolds showed the spreading of the BMSCs cells along the nanofibrous
722 pattern and the formation of a fiber-cell network (see **Fig. 6i**). The results of the PCR test displayed
723 that the scaffolds reinforced with MXene had better osteogenesis functions than the filler-free
724 scaffold after 14 days.

725 In 2023, Fu et al. [25] produced $\text{Ti}_3\text{C}_2\text{T}_x$ /PVDF nanofibers through a standard electrospinning
726 process for bone scaffolds. PVDF was first dissolved in a mixture of N, N-dimethylformamide/
727 acetone (3:2), and the solution with a concentration of 20 wt./v% was obtained after 2h stirring at
728 50°C. Then, 0.2, 1, and 5% $\text{Ti}_3\text{C}_2\text{T}_x$ were sonicated in the obtained polymer solution at 4°C for 30
729 min, followed by a stirring step of 8h at ambient temperature. The prepared solution was
730 transferred to a syringe with a 20-gauge nozzle and electrospun with a feeding rate of 0.8 ml/min
731 under a voltage of 13 kV and a spinning distance of 15 cm. The filler-free PVDF, as well as the
732 loaded samples with 0.2, 1, and 5% $\text{Ti}_3\text{C}_2\text{T}_x$, represented average diameters of 854.6 ± 300.4 , 803.4
733 ± 245.9 , 648.9 ± 215.5 , and 538.8 ± 171.1 nm, respectively. The destruction examination
734 confirmed the high stability of the provided scaffold structures and corroborated the role of the
735 PVDF shell in hindering MXene oxidation. According to the results, the PVDF scaffold is a
736 hydrophobic layer ($116.47 \pm 0.99^\circ$), and its contact angle and hydrophobicity was increased to
737 125.45 ± 1.88 , 123.72 ± 2.20 , and $124.85 \pm 1.87^\circ$ by adding 0.2, 1, and 5 wt % MXene, respectively.
738 These results are in contrast with previous studies, which can be stated that the PVDF leaf layer
739 prevents the contact of MXene with water droplets, and it is also speculated that the addition of
740 MXene increases the hydrophobicity of the structure due to the reduction of the surface free energy
741 and the increase of the pore structure. The pure PVDF scaffold showed a tensile strength of 0.94



742 ± 0.12 MPa and Young's modulus of 0.82 ± 0.22 MPa. Embedding up to 1% MXene into the PVDF
 743 structure caused an increase in the tensile strength (4.49 ± 0.33 MPa), while loading 5% led to a
 744 reduction in the tensile value (1.52 ± 0.29 MPa) (see **Figs. 7a&b**). Accordingly, a small amount
 745 of MXene could raise the modulus, possibly due to the strong interaction force between PVDF
 746 molecular chains and MXene functional groups. However, exceeding a specific loading ratio led
 747 to filler agglomeration and so a reduction in the scaffold modulus.



748
 749 **Figure 7.** Features of the MXene/PVDF nanofibrous bone scaffolds; (a&b) mechanical
 750 properties, (c) ALP activity, morphology, and adhesion of MC3T3-E1 cells on (d) glass, (e)
 751 pristine PVDF, (f) 0.2 wt % MXene/PVDF, (g) 1 wt. % MXene/PVDF, and (h) 5 wt %
 752 MXene/PVDF, and (i) H&E staining images after employing different treatments for 8 weeks in
 753 various organs, including heart, liver, spleen, lung, and kidney stained with hematoxylin–eosin.
 754 Reproduced from reference [25] with permission from the American Chemical Society, Copyright
 755 2023.



756 Staining of dead cells was performed by inoculating MC3T3-E1 on the scaffolds for 24h, showing
 757 acceptable cell viability by incorporating up to 1% MXene while increasing the dead cells through
 758 loading 5% MXene (see **Figs. 7c-h**). The fluorescence microscope proved the spreading of the
 759 MC3T3-E1 cells after 3 days on the surface of the scaffolds, which could be attributed to the 3D
 760 topographical structure of the electrospun fibers. To investigate the effective substances on the
 761 biological behavior of cells, a scratch test was conducted, showing similar migration of cells into
 762 the gaps in all samples after 24 and 48h. This phenomenon confirms the hypothesis of MXene
 763 placement in the PVDF shell, which does not affect the external cellular environment. The cell
 764 viability assay confirmed the suitability of the scaffolds for cell growth. The results of cell culture
 765 after 4 days were the same in all samples, but after 7 days scaffolds, containing 0.2% and 1%
 766 MXene showed the highest cell viability. This could be attributed to the difference in surface
 767 potential and topography of fibers, resulting from loading various amounts of MXene. The ALP
 768 activity of cells after 14 days in samples containing MXene was higher than that in the pristine
 769 PVDF, linking with the increase in surface potential and the fibers' topography. To evaluate the
 770 osteogenic activity of camels, the relative expression of the MC3T3-E1 bone gene, including OCN,
 771 OPN, ALP, Runx2, and Col I, was cultured and investigated. Accordingly, incorporating 1%
 772 MXene mainly regulates the expression level of osteogenic genes in both early and late periods,
 773 representing the great ability to improve osteogenic differentiation with a potential of 69.34 ± 2.64
 774 mV.

775 Finally, animal tests exhibited the appearance of normal branched muscle fibers in heart tissue,
 776 radially scattered cells in liver tissue, ideal splenic nodules in the spleen, proper alveoli and
 777 epithelial lining of bronchioles in lung tissue, and glomeruli and tubules for 8 weeks (see **Fig. 7i**).
 778 No significant difference was observed in the pathological results of the PVDF and PDF/MXene
 779 scaffolds on different organs, which indicates their outstanding biocompatibility. Also, new tissues
 780 were formed at the site of the bone defect after 4 and 8 weeks of treatment. The surface potential
 781 of the scaffold enhanced the differentiation of bone-forming cells and the absorption of osteogenic
 782 cells on the surface of the scaffold, allowing the bone defect to be filled after 8 weeks. Other recent
 783 attempts toward integrating the nanofibers via embedding MXene nanosheets toward approaching
 784 efficient tissues, as well as versatile healthcare devices, are summarized in Table 1.

785 **Table 1.** MXene-loaded electrospun fibers applicable as various biomedical devices and tissue
 786 engineering membranes.

Material contents	Application	Mechanism and Results	Ref.
MXene/Amoxicillin/PVA	Antimicrobial and photothermal platform for wound infection	-PVA matrix could control the Amoxicillin release. -MXene presented local Hyperthermia due to transforming the NIR laser into heat in battling bacterial infection.	Xu et al. [122]



		-The nanomembrane exhibited an antibacterial and accelerated wound healing capacity in the in vivo and in vitro models.	
TiC/zeolite imidazole framework-8 (MZ-8)/PLA	Wound healing	-MZ-8 could show hyperthermia PPT activity with a bactericidal rate of more than 99.0% and remarkable antitumor efficiency relying on photodynamic/photothermal therapy. -MXene/zeolite/PLA could boost infected wound healing without any bacteria resistance.	Zhang et al. [123]
Ti ₃ C ₂ T _x /chitosan	Antibacterial wound dressing	-In vitro, antibacterial activity was depicted via crosslinked chitosan nanofibers integrated with MXene. -Direct bacterial membrane destruction was observed by contacting and penetrating bacteria in MXene flakes, with a 95% to 62% reduction in colony-forming units. -The features were synergized with intrinsic chitosan antimicrobial activity.	Mayerberger et al. [124]
Ti ₃ AlC ₂ MAX phase/PLA	Curcumin delivery system with antibacterial behavior	-PLA electrospun membranes decorated with MAX phase exhibited significantly higher toughness than the plasticized PLA membrane with low cytotoxicity, supporting the proliferation of mouse fibroblast L929 cells, as well as higher antibacterial properties against E. coli and S. aureus. -Due to the curcumin diffusion from the polymer fibers and the MAX phase surface contributing to the overall increased curcumin adsorption and release sites, 7-day curcumin release was increased from 45 to 67%.	Krasian et al. [125]
PVA/ Ti ₃ C ₂ T _x / Molybdenum Diselenide (MoSe ₂)/ polyethylene terephthalate	Human skin moisture/Energy harvesting sensor	-Self-powered sensing device was fabricated by PVA/MXene nanolayer and integrated with a single layer of MoSe ₂ to decipher humidity by commuting mechanical energy to electric energy. -The excellent metallic conductivity and hydrophilicity of PVA/MXene, concomitant with the piezoelectric properties of MoSe ₂ generated the flexible, fast response humidity sensor (0.9/6.3 s, about 40-fold higher than pure MXene).	Wang et al. [126]
Ti ₃ C ₂ T _x /PVDF	Aptasensors	-The designed nanocomposite detected secondary fungal metabolite mycotoxin due to their electroactive sites and covalent biofunctionalization of the redox probe with aptamer. -The designed sensor was useful for OTA trace determination in the food safety analysis in the concentration range from 1 fg.mL ⁻¹ to 1 ng.mL ⁻¹ .	Al-Dhahebi et al. [127]
Ti ₃ C ₂ T _x /dopamine/polyurethane	Wearable sensor	-The inclusion of thermoplastic polyurethane in the composition offered enhanced flexibility and breathability.	Zhang et al. [128]



		<p>-The presence of a poly-dopamine coating facilitated adhesion between MXene and thermoplastic polyurethane.</p> <p>-The incorporation of MXene resulted in strain-sensing capabilities and effective electromagnetic interference shielding performance.</p> <p>-The strain sensor design exhibited remarkable sensing functionality, demonstrating an exceptional recognition threshold.</p>	
$Ti_3C_2T_x/PCL$	Neurite regeneration and angiogenesis	<p>-The PCL layer was covered with MXene, and figured out the excellent cell adhesion and biocompatibility during cell culturing.</p> <p>-MXene-PCL composite for nerve guidance conduits showed similar results with the autograft in angiogenesis, electrophysiological examination, and nerve regeneration morphology in both in vivo and in vitro studies.</p>	Nan et al. [129]
$Ti_3C_2T_x/PLA$	Nerve guidance conduits	<p>-The functionalized layer exhibited biocompatibility and non-toxicity through the Cell culturing test and gram-positive bacterial adhesion assay.</p> <p>-MXene directly influences cellular membranes and damages the cell morphology.</p> <p>-Fabulous electroconductivity properties were confirmed with an electrical conductivity assay due to the MXene involved in PLA membranes.</p>	Kyrylenko et al. [130]
$Ti_3C_2T_x/PCL$	Tissue engineering	<p>-The effect of MXene layer thickness was evaluated, showing the most appropriate results of cell attachment, adhesion, and proliferation, as well as antibacterial behavior through repeating the immersing process 2 and 3 times.</p> <p>-These samples exhibited samples illustrated the least bacteria adhesion due to the inhibitory effect of the MXene thin layers on the membrane surface through physical damaging of the cell walls.</p>	Diedkova et al. [131]
$Ti_3C_2T_x/PLGA$	Nerve tissue regeneration	<p>-The formation of a more brittle structure via exceeding the MXene ratio from 0.1 g.</p> <p>- Antibacterial property of the produced scaffolds against <i>E. coli</i>, <i>S. aureus</i>, and <i>C. albicans</i>, due to high hydrophilicity and the bacteria absorption by surface anions of MXene nanosheets.</p> <p>- The results of the biocompatibility test were performed with the cultivation of Schwann cells on the scaffolds, illustrating the cell survival on the scaffolds containing 0.3 and 0.6 MXene, which is due to the increased hydrophilicity and conductivity.</p>	Zhang et al. [132]



788 Overall, flexible nanofibrous networks with tunable morphological features, as well as
789 mechanical strength, could be feasibly synthesized through the electrospinning method. The highly
790 porous structure of the electrospun fibers with interconnected pores could offer favorable features
791 for biomedical targets and mimic the native extracellular matrix, integrating cell adhesion, growth,
792 and proliferation in various organs. Although electrospun nanofibers embedded with MXene
793 nanostructures have showcased promising configurations for biomedical targets, a lack of long-
794 term evaluation is sensed in the performed analysis. As an example, mechanical properties are
795 considered as one of the main features, requiring to be optimized considering each application. For
796 example, in the context of tissue engineering, the designed structure must possess mechanical
797 properties that are appropriate for the desired vein. Failure to do so may result in the degradation
798 of the original tissue or the collapse of the new structure when subjected to load [2]. The analysis
799 of the mechanical stability in bodily fluids or under cyclic loadings mimicking bodily movements
800 could provide valuable insights into their long-term durability in biomedical applications. To
801 assess the mechanical properties of the designed structures, it is recommended that they be tested
802 under conditions that are similar to those found in vivo. For instance, the samples should be
803 immersed in a buffer solution or subjected to cell culture. Furthermore, it is advisable to test the
804 samples under both unidirectional and multidirectional conditions, depending on the intended
805 application. Consequently, the mechanical properties of the designed structures must be carefully
806 evaluated to ensure that they are fit for purpose [133].

807 Moreover, long-term cytotoxicity analysis is assumed to be a critical issue in biomedical
808 applications. Therefore, verifying the long-term compatibility and non-toxicity of materials is of
809 utmost importance. While various case studies have investigated the acute toxicological effects of
810 MXene-based compositions in vitro and in vivo, few studies have been dedicated to highlighting
811 its long-term toxicology behavior [134]. To address this, in vitro studies utilizing long-term cell
812 cultures and monthly observations are recommended. Additionally, the degradation of samples
813 under physiological conditions should be investigated over an extended period to ascertain if any
814 toxic substances are released or if the pH and other environmental factors are altered over time [2,
815 133].

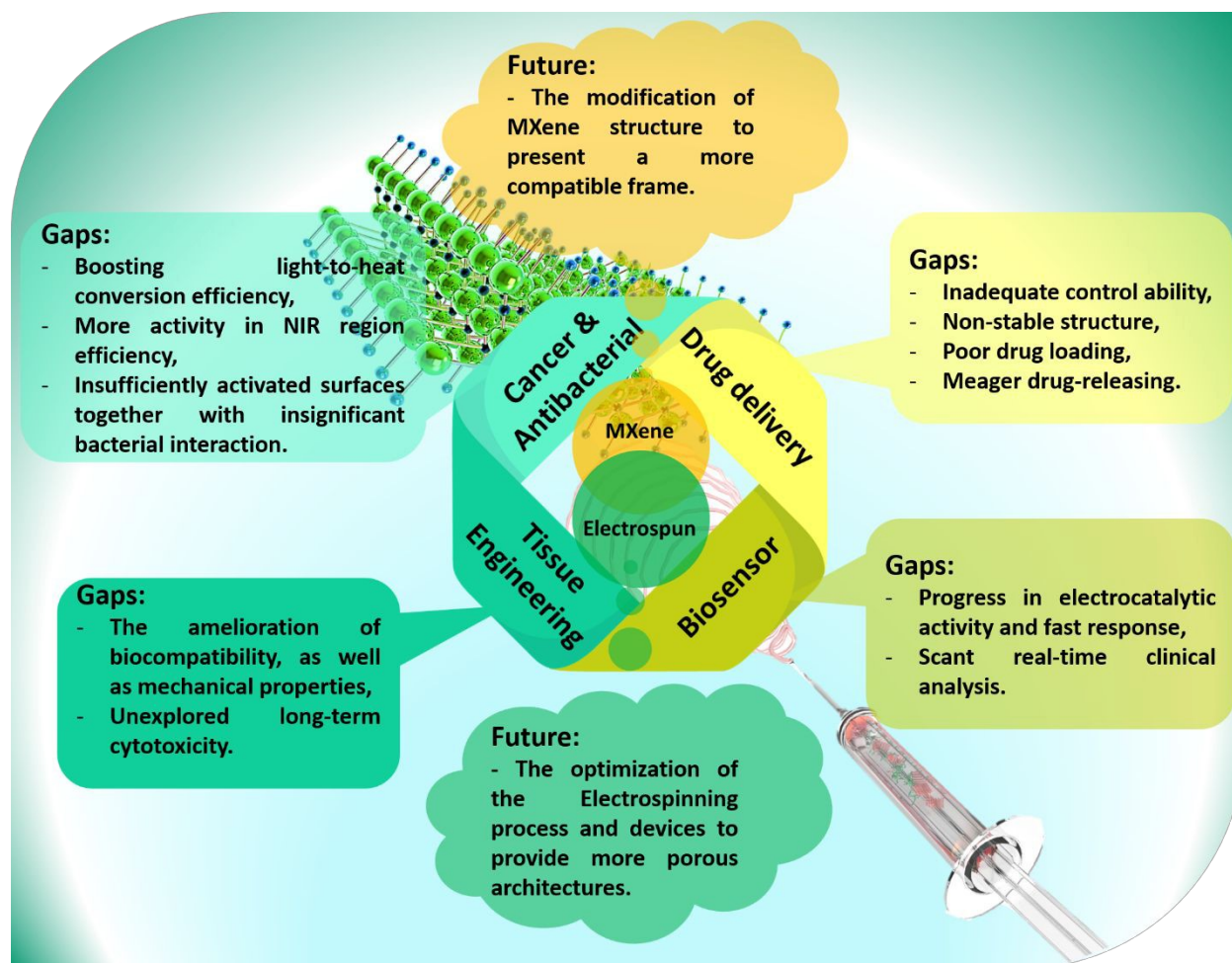
816 **Conclusion and perspectives**

817 As a very promising emerging material, the MXene family has shown outstanding features for a
818 wide range of applications. Several inherent MXene characteristics, including frequent functional
819 groups on the surface, biocompatibility, large surface-to-volume ratio, physiochemical properties,
820 and many more, have caused a plethora of benefits for biomedical usages and tissue engineering
821 targets. Among various MXene-loaded compositions, the electrospun fibrous architectures have
822 represented promising features resulting from the large surface area, highly porous networks, tiny
823 and interconnected pores, etc. The integration of electrospun fibers with MXene nanosheets could
824 boost hydrophilicity and enhance dimensional and mechanical stability. Additionally,
825 biocompatibility, antibacterial activity, as well as cell adhesion, growth, and proliferation could be
826 integrated into these platforms, leading to approaching ideal bone, nerve, skin, and heart tissues.



827 Accordingly, the electrospun tissues embedded with MXene nanosheets could alleviate the
828 challenges faced by individual components, benefiting from their synergetic effects.

829



830

831 **Figure 8.** Prospects for the future and gaps in biomedical applications; the developed path of
832 MXene and electrospun frameworks.

833

834 Despite the great consequences observed for the MXene-loaded nanocomposites, few researches
835 have been conducted in this era, leading to several remaining challenges (**Fig. 8**). First, in
836 competition with the present strategies, synthesis modification, surface functionalizing, and
837 morphology altering are proposed to be investigated more, since they could be influential on the
838 cytotoxicity and biocompatibility. Also, MXene is nonstable in the atmosphere and physiological
839 environments. The employed synthesis method should be progressed to achieve an eco-friendly,
840 long-term stable, adjustable, and cost-effective technique with least-hazard byproducts. In addition,
841 the biological behavior of the MXene-loaded materials should be focused more to further evaluate
842 long-term toxicity, the reaction of MXene with cells, drugs, blood, and organs, biodegradability,
843 biosafety, and histopathological properties. It is important to consider that the use of toxic and



844 corrosive liquids in the synthesis of MXene could result in negative effects. Also, most of the
845 research in this era is focused on the use and development of titanium carbide-based additives,
846 while the MXene family is very broad, and the lack of suitable explorations is deeply felt. This
847 route could also be continued through the design and analysis of the MXene combination or
848 coating with other organic and inorganic compounds in the electrospun configurations. It is
849 worthwhile to manipulate the electrospinning fabrication procedure to obtain more monotonous
850 fibrous networks comprising tunable pore sizes and porosity rates.

851 In the biomedical path, the physiological, biological, and mechanical features of nanofibrous
852 membranes play a critical role in the final success of designed architectures. In this regard, it is
853 proposed to amend the surface of nanofibrous layers through direct electrospinning of polymers
854 with organic-based components, as well as applying surface modification techniques, such as
855 plasma treatment, surface polishing, and others. The electrospun membranes could be integrated
856 with other MXene-loaded arrays, such as hydrogel, 3D-printed, or electro-written layers. Moreover,
857 in vitro and in vivo analyses are suggested to be carried out on various tissues generated with the
858 MXene and MXene derivatives-loaded materials. Furthermore, comprehensive studies along with
859 the simulation and modeling are offered for the prediction of MXene-loaded nanofibrous tissues'
860 behavior without the need for animal studies. However, it is also understandable that most studies
861 are currently limited to lab scale, which can create skepticism towards MXene-embedded
862 electrospun structures. Accordingly, a need is recognized for more comprehensive studies in order
863 to alleviate these concerns and ensure a safer and more sustainable approach. MXene-embedded
864 electrospun structures have the potential to revolutionize various fields by offering unique
865 combinations of properties and functionalities. Ongoing research and development efforts will
866 further advance this material system and unlock its full potential for next-generation technologies.

867

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873 **Contributions.**

874 X. Li: Collecting data, Writing the paper, and Validating data.

875 S. Wang: Collecting data, Writing the paper, and Designing the figures.

876 M. Zheng: Writing the paper and Approved data

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885

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