Application of MXene in the electrochemical detection of neurotransmitters: A Review

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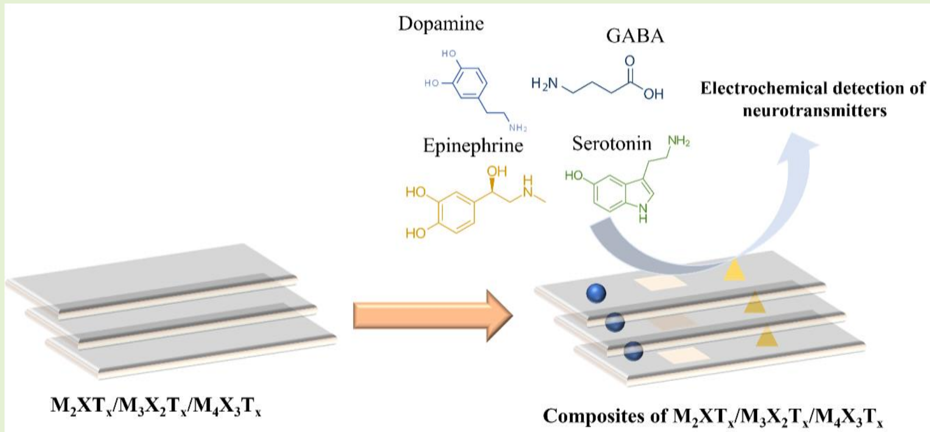
***Abstract*— Neurotransmitters are small chemical signaling molecules crucial for the proper function of the nervous system. The dysregulation of neurotransmitters results in several mental disorders like Parkinson's and Alzheimer's diseases, schizophrenia, and conditions such as depression and addiction. These signaling molecules are present at low concentrations, and obtaining information about these molecules' levels is vital. Moreover, neurotransmitter monitoring in the nervous system remains challenging due to its low concentrations and rapid response. Electrochemical detection continues to garner significant attention as an attractive technique due to its facile nature, high sensitivity, and cost-effectiveness. The electroactive materials of electrochemical sensors are at the heart of this sensing technology. Although multiple nanomaterials have been explored as active components in electrochemical sensors for detecting neurotransmitters, MXenes are gaining attention in the electrochemical sensing of neurotransmitters. This review aims to discuss the use of MXenes and their composites for the electrochemical detection of neurotransmitters, describe the various MXene composites based on the nature of the composite viz pristine and chemical functionalized, carbon nanomaterial, polymer, metal nanoparticle, and transition metal dichalcogenide composites, and define the future directions in leveraging the properties of MXene composites for early-stage electrochemical detection of neurological diseases originating from an imbalance in neurotransmitters.**



***Index Terms*— Sensing materials, MXene, 2D nanomaterials, neurotransmitters, biosensors**

I. Introduction

Neurotransmitters are small chemical signaling molecules that carry information between cells. They are involved in the activation of T-cells [1], the development of nervous systems [2], modulation of human behavior [3], and sensitization of pain response [4]. Due to these diverse roles, neurotransmitter dysregulation can indicate the onset of neurological disorders like schizophrenia, Parkinson's, and Alzheimer's conditions such as depression and addiction [5-7]. Dopamine (DA), acetylcholine, serotonin, gamma-aminobutyric acid (GABA), epinephrine (EP), norepinephrine (NEP), and glutamate are some of the most common neurotransmitters. Each of these signaling molecules has a unique purpose, and their detection can provide helpful information about the onset and progression of different neurological disorders.

T-cells are an important part of the immune system, which develop from stem cells in the bone marrow. They act as a line of defense from infections and help to fight cancer [8]— neurotransmitters, including DA, serotonin, glutamate, and acetylcholine, impact T-cells. For example, it was found by Bergquist et al. that 10 nM of catecholamine leads to decreased proliferation and differentiation of T-cells [9, 10]. Levite et al. observed that 10 nM of DA activates resting effector T-cells and is important for antigen-specific interactions between T-cells and dendritic cells [11]. These neurotransmitters have the potential to play an important role in activating T-cells, which can help in finding cures for dangerous diseases [12].

Dopamine and acetylcholine (ACh) play an important role in controlling motor activity. Dopamine is the most

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abundant catecholamine in the brain and regulates many physiological functions in the central nervous system (CNS) [13, 14]. Variation in DA levels has been linked to Parkinson's disease [15, 16], Tourette's syndrome [17], schizophrenia [18], and attentional deficit hyperactive disorder (ADHD) [19]. ACh plays a role in opening cation channels, polarizing and depolarizing the cell membranes, and the pre-and post-ganglionic neurons in the autonomic nervous systems [20, 21]. The imbalance of ACh has been known to induce brain disorders like dementia and Alzheimer's [22]. An increase in the ACh also produces adverse effects like muscarinic and nicotinic toxicity [23]. Serotonin, or 5-hydroxytryptamine (5-HT), is a 5-hydroxy derivative of tryptamine that is mainly present in the stomach and mediates essential functions like neurotransmission, gastrointestinal motility, hemostasis, and cardiovascular integrity [24]. An increase in serotonin levels has been shown to lead to confusion, increased reflexes, restlessness, increased heart rate, and seizures. Like DA, serotonin is associated with happiness, and its dysregulation has been linked to depression, anxiety, and poor sleep quality [25].

Gamma-Aminobutyric Acid (GABA), an amino acid, exhibits inhibitory effects and has been known to reduce stress and induce sleep [26]. A disturbance of GABAergic inhibition causes spasticity, stiff person syndrome, and psychiatric disease [27]. Another amino acid, glutamate, exhibits excitatory effects and has been linked to the excitotoxic effects in the central nervous system when elevated [28]. At the same time, lower glutamate levels may contribute to Alzheimer's [29]. Epinephrine produced in the adrenal medulla also plays a unique role in cognition, motivation, and intellect [30]. Like DA, its role in Parkinson's disease is gaining significant attention [31]. Norepinephrine or noradrenaline (NEP) is another neurotransmitter in the body's sympathetic nervous system. It is a first-line vasopressor and forms a part of the body's acute stress response [32]. These molecules also increase attention, constrict blood vessels, and affect the sleep-wake cycle, mood, and memory. Low levels of norepinephrine cause anxiety, depression, attention deficit hyperactivity disorder, and memory and sleep problems. More importantly, pheochromocytoma, an adrenal gland tumor, also causes high levels of norepinephrine.

In summary, these neurotransmitters function together in a careful chemical balance, and an imbalance in their levels leads to an over- or underproduction of one or more neurotransmitters, which can cause the physical and psychological symptoms described herein. Due to the crucial role of these neurotransmitters, it is essential to develop efficient sensor systems that can detect the levels of these signaling molecules.

Conventionally, these neurotransmitters are detected using neurotransmitter panel kits like ZRT 15 Neurotransmitter Urine Test Kit, NeuroBasic Neurotransmitter Test, and NeuroHormone Complete Panel Neurotransmitter and Hormone, Adrenal Test. All these test kits require sample collection followed by the sending of samples back to a lab for analysis. An inherent disadvantage of these methods is the cost and the time delay required for the results to be available. This demerit leads to a need for real-time sampling due to the rapid variations in the levels of neurotransmitters, in addition to the requirement of a shorter period for sampling. An example of such a technique was reported by Vandenryt et al., who reported on a single-shot detection of neurotransmitters in whole blood samples. This sensor features a capillary pumping unit and point-of-care sampling techniques such as a blood lancet device. Also, there is minimal sample pre-treatment, which is required, like the addition of an anticoagulant. Another sample that can be used is urine for non-invasive detection. In addition, neurotransmitters found in urine are stable and present in sufficient concentrations [33]. Another biofluid, which could be a potential source of the neurotransmitter, is saliva, which can be extracted from subjects in a non-invasive manner. However, the use of alternative biofluids requires further research [34].

Various techniques have been employed to address these limitations of detecting neurotransmitters. Some of these techniques include colorimetric [35], spectroscopic [36], magnetic [37], microdialysis [38], and electrochemical [39] detection methods. Among these techniques, electrochemical techniques possess advantages like high sensitivity, low limit of detection (LOD), rapid detection of analytes, facile operation, and cost-effectiveness [40]. The selectivity of the electrochemical method comes from the redox-active nature of neurotransmitters. The application of a potential at which the redox of the neurotransmitter takes place can lead to specificity in terms of neurotransmitter detection. This can be done by engineering composites of nanomaterials, which require a potential close to the ideal potential at which the redox of the neurotransmitter takes place. Another method to achieve specificity is to create sensing systems involving enzymes wherein the activity of the enzyme would lead to an increase or decrease in the levels of a particular neurotransmitter [41].

Discovered in 2011, MXenes are two-dimensional (2D) nanomaterials comprised of transition metal carbides, nitrides [42], and carbonitrides [43]. The general formula of the MAX phase is $M_{n+1}AX$, where M is an early transition metal (Ti, Nb, V, etc.), A is a group III element (Al, Si, Ga, etc.), and X is either C or N. MXenes are derived from MAX phases using selective etching of the "A" layer from the MAX phases using HF [44, 45]. In addition to etching using HF, other techniques such as electrochemical etching, alkali etching, Lewis acid molten salt etching, and polar organic solvent etching have been explored for synthesizing MXenes [46]. MXenes have garnered applications in charge storage [47], energy generation [48], wearable devices [49], photovoltaic [50], environmental remediation [51], and electrochemical sensors [51, 52]. Due to the high electron density near the fermi level, MXenes are predicted to have a metallic nature, which makes them an ideal candidate for electrochemical sensing applications [42, 53, 54]. In addition, MXenes have excellent mechanical properties, the ability to form stable films, and superior electrical conductivity. However, layers of MXenes have a strong tendency to aggregate with each other due to van der Waal's forces, which limits its use in various applications. These limitations are currently being addressed by the formation of composites of MXenes with other materials for electrochemical applications, as these composites are expected to possess more stability than their parent MXenes, in addition to retaining all the favorable characteristics of MXenes [55]. Despite their great potential for device-related applications, only a few reports exist on MXene-based platforms for detecting neurotransmitters.

Traditionally, carbon-based electrodes (e.g., carbon nanofibers, carbon nanotubes (CNTs), carbon, etc.) have received significant attention for the electrochemical detection of neurotransmitters over the past three decades due to their unique structural and electronic properties [56]. Novel electrode materials such as MXene exhibit superior electronic properties compared to traditional carbon electrode materials. Their catalytic surface can enhance neurotransmitter detection through surface adsorption, where the π-π interactions between the delocalized π-electron systems of MXene and the aromatic rings of the neurotransmitter facilitate the oxidation reaction and the transfer of electrons from the neurotransmitter molecules to the MXene surface [56]. Due to MXene's high surface area, electron-transfer capabilities, and ability to generate reactive species, they have begun to garner attention as an effective and highly sensitive catalyst for the oxidation of neurotransmitters.

Composites of MXene that typically incorporate metal nanoparticles or conductive polymers are known to enhance the sensitivity of the biosensor through several mechanisms, such as an increased surface area to enhance the number of interactions between the neurotransmitter and the sensing surface, selective functionalization allowing for discrimination of the target neurotransmitter from interfering species and to improve electron transfer kinetics by acting as mediators to facilitate electron transfer between the neurotransmitter and the electrode surface. Furthermore, MXene composites can exhibit synergistic effects by combining different materials' catalytic activity, electrochemical reactivity, and mechanical stability to improve sensor signal amplification, long-term performance, sensitivity, and detection limits, thereby improving the sensitivity and reliability of neurotransmitter detection [57,58].

This review analyzes the trends in using MXene-based composites to detect neurotransmitters. The various MXene composites based on the nature of the composite viz pristine and chemical functionalized, carbon nanomaterial, polymer, metal nanoparticle, and transition metal dichalcogenide composites are are discussed. We also discuss the future directions in leveraging the properties of this composite for early-stage electrochemical detection of neurological diseases originating from an imbalance in neurotransmitters.

II. SENSING PLATFORMS USING MXENE, NANOMATERIALS, AND POLYMER COMPOSITES

The metallic nature of MXenes makes them ideal for use in electrochemical sensors. Multiple reports have focused on leveraging the use of MXenes for sensing various physiologically and environmentally relevant molecules. Most of these reports have extensively explored $Ti_3C_2T_x$, while only a few works exist on using the other members of the MXene family for electrochemical sensing applications [59-62]. Although pristine MXenes have aggregation-related demerits, chemical functionalization minimizes the aggregation in those cases where the MXene is used alone [63,64]. Amara et al. successfully prevented the agglomeration of MXenes using ionic liquids, offering many advantages [59]. Using ionic liquids resulted in superior electronic conductivity, thermal and redox stability, and biocompatibility. In this work, MXene was efficiently deposited on a conductive graphitic pencil electrode (GPE) to tailor the MXene interface [59]. It was tailored to exhibit a specific binding site for biomolecules using a task-specific ionic liquid (IL) (1-methyl imidazolium acetate) as a multiplex host material. Because MXene and IL interacted well, the composite material prevented leaching and enhanced electron transport at the electrode-electrolyte interface. The IL-MXene/GPE interface depicted in **Figure 1A** resulted in a highly stable electrode with a low detection limit of 702 nM and a wide linear range of 10 μM − 2000 μM DA. The electron-deficient imidazolate group in ionic liquids served as a binding site for DA and its oxidation. A similar strategy was utilized to sense DA, wherein the graphite pencil electrode was modified by perylene diimide (PDI) $Ti_3C_2T_x$ composite [65]. By leveraging the rigid backbone of PDI, the composite's charge transport and redox properties were improved over a linear range of 100 – 1000 μM with a LOD of 240 nM. In human serum, PDI functionalization led to enhanced sensing outcomes with insignificant biofouling. The imide functionalization improved the hydrophilicity and thermal, photochemical, and overall electrode stability. Murugan et al. reported the use of Ti-C-T_x MXenes for the simultaneous detection of DA, uric acid (UA), and ascorbic acid (AA) [66]. Owing to the superior electrochemical properties of MXenes, the material exhibited a linear response toward the detection of AA, DA, and UA in the range of 100 − 1000 μM, 0.5 − 50 μM, and 0.5 − 1500 μM, respectively. The Ti-C-T_x MXenes also detected molecules in urine samples spiked with known AA, DA, and UA concentrations. The complex nature of the urine sample had an insignificant impact on the sensor's performance.

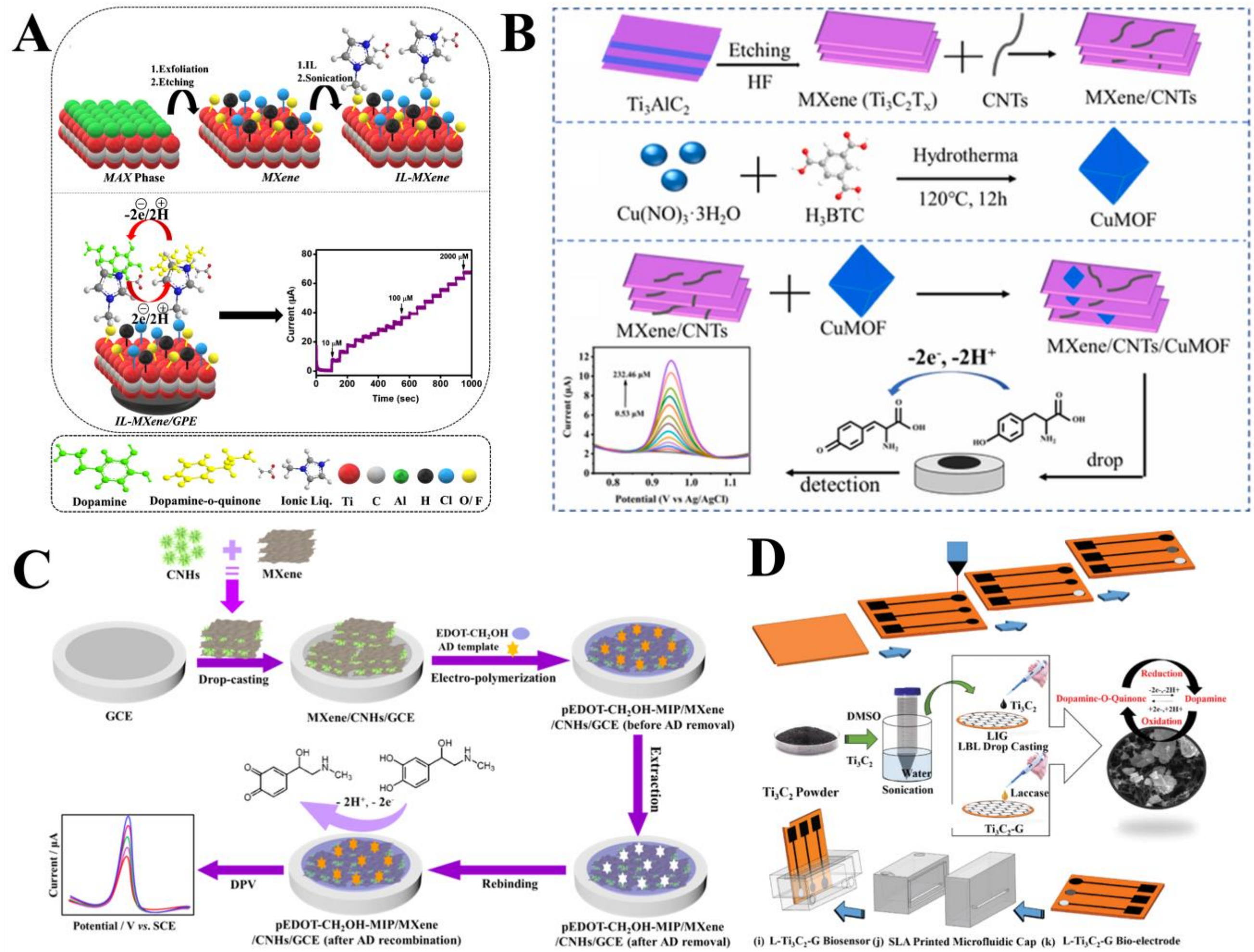

Figure 1 (A) $Ti_3C_2T_x$ MXene IL based composite reported by Amara et al. for the electrochemical sensing of DA [59], (B) MXene Cu MOF composites were used by Chen et al. for the detection of tyrosine [60], (C) MXene-PEDOT-CH_2OH-MIP carbon nano horns for the electrochemical determination of EP as reported by Chen et al. [61], and (D) Microfluidic biosensor for the detection of DA employing Ti_3C_2 MXene reported by Wagh et al. [55].

The doping of Nb_2C MXenes with nitrogen and sulfur is known to improve electron mobility and hydrophilicity of MXene, thus leading to superior electrochemical activity. The doping can be achieved by exposing MXene to high temperatures in an argon atmosphere in the presence of thiourea. Such doped MXene has been utilized to coat the surface of GCE via Nafion to generate a wide linear dynamic range of 0.4 – 90 µM DA along with a LOD of 0.12 µM under acidic conditions [67]. Nafion was used to prevent the agglomeration of the MXene sheets and protect the underlying layers from deterioration in the presence of acidic gastric juice and resulting in more stable MXene sheets that selectively accumulate positively charged species. Shahzad et al. reported this composite material for the electrochemical sensing of DA with an excellent linear range of 0.015 µM – 10 µM with a low LOD of 3 nM. Although Nafion has been indicated to block active sites [48], these reports reveal the contrary, where using Nafion resulted in the superior electrochemical activity of MXene towards DA.

Tyrosine acts as a precursor of some neurotransmitters, such as DA and thyroxine, and it also regulates emotions and stimulates the nervous system. To monitor this vital molecule, Chen et al. reported a composite of $Ti_3C_2T_x$ MXene, multiwalled carbon nanotube (MWCNT), and metal-organic framework (MOF) for the detection of tyrosine, as shown in **Figure 1B** [60]. The composite of Ti_3C_2Tx with MWCNT resulted in the elimination of aggregation of the MXenes. In addition, using MOFs resulted in increased material porosity and improved catalytically active sites in the material. It is reported that the compositing of $Ti_3C_2T_x$ with MWCNT resulted in the avoidance of aggregation of the MXenes. The composite material detected tyrosine with a linearity of 0.53 µM – 232.46 µM and a LOD of 0.19 µM. Chen et al. reported using MXene/ carbon nano horn with many accessible sites and superior electric conductivity to detect EP [61]. **Figure 1C** shows the composite material coated with hydroxymethyl-3,4-ethylene dioxythiophene using an EP template. Differential pulse voltammetry (DPV) was used for the electrochemical characterization of EP. The sensor displayed a wide linear range from 1 nM – 60 µM EP with a low LOD of 0.3 nM. The hydroxymethyl-3,4-

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ethylenedioxythiophene enhanced the hydrophilicity and conductivity of the MXene-coated electrode to improve electrochemical performance. Navid et al. reported modifying screen-printed electrodes with Ti_3C_2 MXene to determine DA and tyrosine simultaneously [68]. The simultaneous determination was achieved by monitoring the two well-defined anodic peaks of DA and tyrosine at 200 and 700 mV, respectively. The modified sensor detected DA linearly from 0.5 µM – 600 µM with a LOD of 0.15 µM. Rasheed et al. investigated the use of $Nb_4C_3T_x$ for the electrochemical determination of DA [69]. The large d spacing of Nb4C3Tx facilitates more efficient electron transport, which resulted in higher electrocatalytic activity when coated on a glassy carbon electrode and used for DA detection [70]. Two linear ranges of 50 nM – 1 µM and 1 µM – 10 µM were observed for DA. The LOD of the biosensor was calculated to be 29 nM. Shahzad et al. and Rasheed et al. were the first group to report biosensors capable of detecting low concentrations of DA using MXene [69, 71].

Carbon nanomaterials have been used extensively for electrochemical sensing of biomolecules and have been reported to show superior performance. MXenes, in combination with these carbon nanomaterials, are expected to improve material and device-related sensing characteristics. Using laser-induced graphene (LIG) electrodes with microfluidic platforms introduces a new avenue for detecting neurotransmitters. More recently, Wagh et al. investigated the incorporation of laccase/MXene/LIG (L- Ti_3C_2-G) composite designed for selective detection of DA and other biomolecules with applicability in human blood serum and synthetic urine [55]. The fabricated biosensor is shown in **Figure 1D**. The laccase enzyme catalyzed the oxidation of DA to dopamine-o-quinone in the presence of oxygen. The incorporation of MXene enhances the conductivity, volumetric capacity, surface hydrophilicity, and stability of the sensors, leading to its use in various applications. A linearity of 1 nM to 10 µM with a LOD of 0.47 nM DA was obtained. This fabricated biosensor was the first to use laccase enzyme in combination with MXene to achieve high stability and reproducibility with exceptional selectivity and negligible response to multiple interfering biomolecules. The enhanced performance can be attributed to the use of laccase.

Lignocellulosic biomass is a promising avenue for the upgradation of lignin into advanced carbon materials such as graphene. Mahmood et al. reported kraft lignin (KL) and cellulose nanofibers (CNFs) to create a biomass-based film from which laser-induced graphene (LIG) was produced [72]. The surface for the laser writing was initially developed by casting a homogenous suspension of KL and CNF onto a plastic petri dish and then peeling the dried film from the petri dish. Utilizing cyclic voltammetry and DPV, the LIG-based electrode was used to quantify DA with a concentration range of 5 – 40 mM and a LOD of 3.4 µM. This method offers multiple advantages such as cost effectiveness, ease of fabrication, and production of environmentally friendly electrodes for detecting DA. Wang et al. also explored LIG-based electrodes modified with $Ti_3C_2T_x$ to detect DA, UA, and AA simultaneously. The $Ti_3C_2T_x$ was modified with Au and Pd nanoparticles using a facile self-reduction strategy [73]. This composite reacted with the carboxyl and hydroxyl groups of the LIG at room temperature to promote the adhesion of the material on the surface. The in-situ reduction was possible owing to negatively charged terminal groups on the MXenes. In addition, the material offers the possibility of developing a flexible sensor for the simultaneous detection of DA, UA, and AA. The addition of the MXenes also helped to alleviate the drawbacks of 3D microporous structures by introducing interfacial interactions and multiple bonding, thereby making the electrode more responsive to the target analyte. The composite material detected DA simultaneously along with UA and AA with the linearity of 10 – 1600 µM, 8 – 800 µM, and 12 – 240 µM, respectively. The LODs exhibited by this sensor were 3 µM, 0.13 µM, and 1.47 µM for AA, DA, and UA, respectively.

Biofouling is a limitation of many electrochemical sensors for detecting physiologically relevant biomolecules. To address the issue of biofouling, Zhang et al. employed $Ti_3C_2T_x$ MXene electrochemically reduced holey graphene composite for DA biosensing [74]. The material provided an abundance of active sites and imparted stability to the modified surface, thus hindering agglomeration and oxidation of MXenes. A linearly of 0.2 µM–125 µM with a LOD of 0.044 µM was achieved, and the sensor successfully detected DA in serum and cerebrospinal fluids.

Graphitized MWCNT, $Ti_3C_2T_x$, and ZnO nanospheres were synthesized as a composite material by Ni et al., as shown in **Figure 2A**, for the detection of DA [75]. The obtained composite was used to modify a GCE to detect DA in the range of 0.01 µM – 30 µM with a LOD of 3.2 nM. The compatibility of ZnO provided excellent adsorption capacity and chemical stability. As variations in the level of serotonin are known to cause various diseases, including depression, irritable bowel syndrome, and Alzheimer's disease, Su et al. reported an electrochemical sensor for serotonin in human blood plasma [76]. The composite was prepared by physically mixing rGO with $Ti_3C_2T_x$. This physical mixing minimized the recombination of individual MXene sheets. The composite oxidized serotonin with a linear range of 0.025 µM – 147 µM, a LOD of 10 nM, in addition to exhibiting high sensitivity, specificity, and stability for serotonin. Chen et al. used a $Ti_3C_2T_x$ MXene/N doped reduced graphene oxide (N-rGO) composite on GCE for the sensing of EP [77]. The oxidation of EP took place on the MXene particles bound by N-rGO to achieve a linearly of 10 nM – 90 µM with a LOD of 3 nM of EP. The high electronic conductivity of the electrodes was attributed to the tight linking of the MXene and N-rGO networks as shown in **Figure 2B**.

To improve the electrocatalytic activity towards EP, Li et al. reported a mixed dispersion of $Ti_3C_2T_x$ and rGO (GMA) as shown in **Figure 2C**. The composite was coated on indium tin oxide (ITO) electrodes and achieved a linearly of 1 µM – 50 µM with a LOD of 3.5 nM [78]. A $Ti_3C_2T_x$ graphite composite paste electrode was reported to detect EP by Shankar et al. [57]. Incorporating MXenes was found to increase the electronic conductivity and improve the electron transfer process. The porous structure enabled the oxidation of EP to adrenoquinone. The sensor achieved a low LOD of 9.5 nM in addition to two linear ranges of 0.02 µM – 10 µM and 10 µM – 100 µM. The same composite material was also able to simultaneously detect 5-HT,

III. SENSING PLATFORMS USING MXENE-METAL NANOPARTICLE AND TRANSITION METAL DICHALCOGENIDE

Using the catalytic activity of metal and metal oxide nanoparticles in developing electrochemical sensors can improve the surface area, conductivity, and thermal stability where storing electrochemical sensors in low temperatures is impossible. MXenes as support material for these nanoparticles resolves both the aggregation problems of MXenes and helps to improve the loading of these nanoparticles on sheet-like MXenes [57].

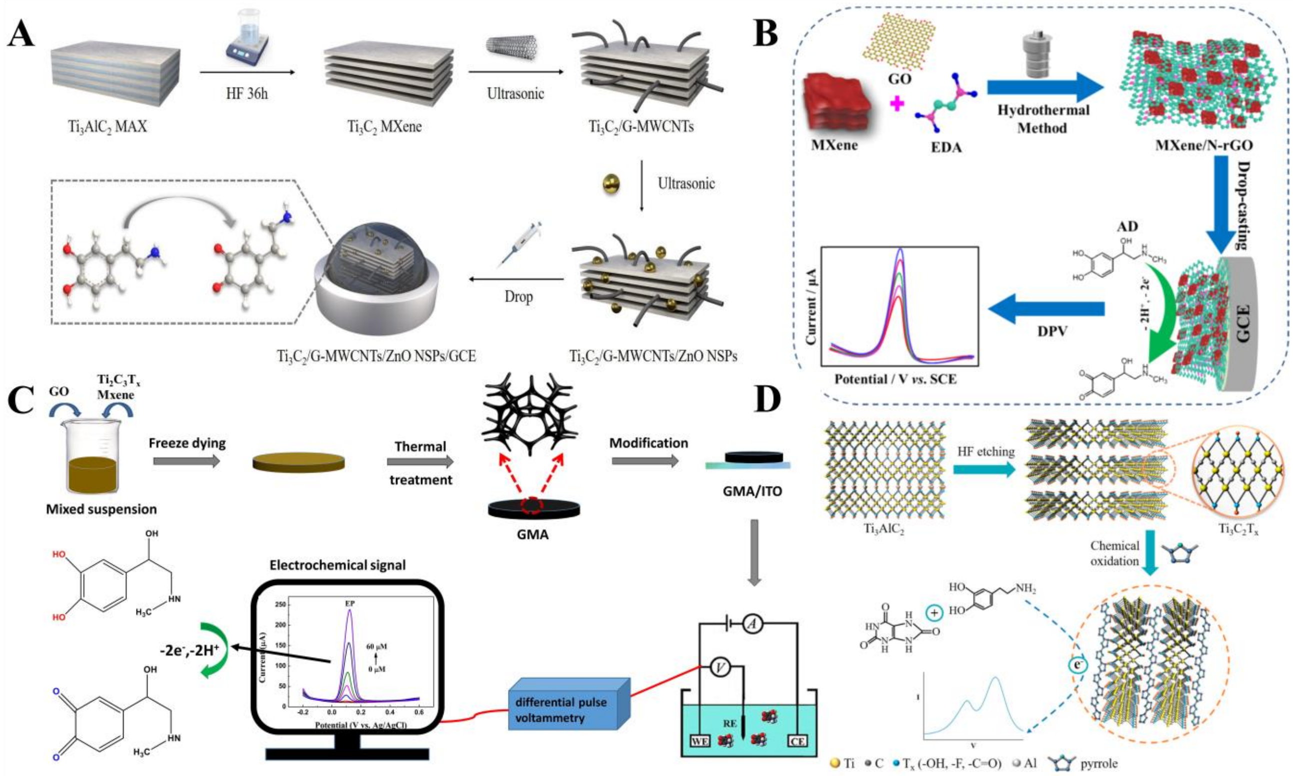

Figure 2 (A) The DA sensor reported by Ni et al incorporating Ti_3C_2 MXene, graphitized multiwalled carbon nanotubes and ZnO spheres [75], (B) $Ti_3C_2T_x$ MXene nitrogen dope reduced graphene oxide composite as an electrochemical sensing platform for EP detection reported by Chen et al.[80], (C) ITO surface modified with $Ti_3C_2T_x$ reduced graphene oxide for the determination of EP reported by Li et al. [81], (D) Intercalated $Ti_3C_2T_x$ polypyrrole composite for the electrochemical determination of DA as reported by You et al [82].

serotonin, and AA, thus exhibiting significant potential for application in wearable neurotransmitter sensing. You et al. synthesized a $Ti_3C_2T_x$ polypyrrole composite for the sensitive detection of DA [79]. By taking advantage of the delamination of single-layer sheets of MXenes from their MAX phases, they proposed an in-situ growth of polypyrrole nanowires. This approach further prevented MXene agglomeration and resulted in excellent electrocatalytic activity towards DA as illustrated in **Figure 2D**. The composite material produced a linear response of 12.5 µM – 125 µM DA and showed simultaneous detection of AA and UA. The LOD achieved was 0.37 µM in addition to exhibiting superior electrochemical stability.

Lorencova et al. reported a $Ti_3C_2T_x$ Pt composite to detect DA simultaneously with UA and AA [83]. They used Pt on the MXene to improve the stability and the electrochemical signal. This composite material detected DA with a linearity of up to 750 µM and a LOD of 250 nM. This combination resulted in increased conductivity and electrochemical surface area. In a report by Chen et al., 5-HT was detected using an L-cysteine (L-Cys)-terminated triangular silver nanoplate mounted on MXene [84]. L-cysteine is an electrically active amino acid with a sulfhydryl group used in this work to replace trisodium citrate (TSC) in TSC-capped triangular silver nanoplates (Tri-Ag-NP/TSC). This led to the formation of a more stable Ag-S bond with silver nanoparticles, as shown in **Figure 3A**. In this scenario, MXenes offer a suitable loading platform for Tri-AgNP/L-Cys because of their high conductivity, compatibility, and large surface area, which resulted in an enhanced electrochemical

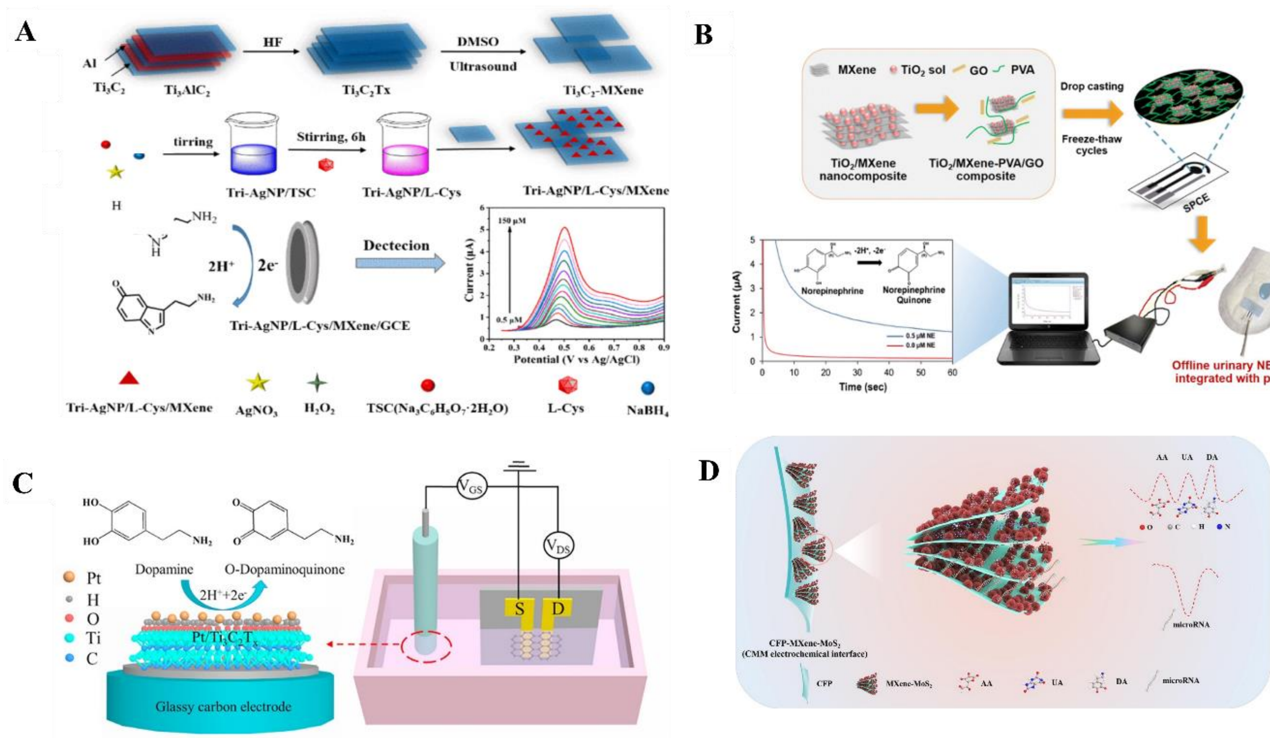

Figure 3. (A) 5-HT sensor using MXene modified with cysteine and silver nanoparticle reported by Chen et al. [84], (B) TiO_2/MXene-PVA/Go hydrogel based sensor for the detection of urinary EP [86], (C) Pt/$Ti_3C_2T_x$ graphene electrochemical transistor for the detection of DA [88], and (D) The 3D CFP modified MXene MoS_2 composite applied to the electrochemical sensing of DA reported by Zhao et al. [89].

signal. The LOD for detecting 5-HT was 80 nM under optimal conditions, while the linear range was 0.5–150 µM 5-HT. The sensor also displayed a high recovery rate of approximately 95.38 – 102.3% for detecting 5-HT in serum samples.

Zheng et al. designed a composite material of Ti_3C_2 MXenes using DNA, Pd, and Pt nanoparticles for DA sensing [85]. The MXene was combined with the single-stranded DNA through π- π stacking interaction followed by the reduction of Pd and Pt on the surface of the MXenes. The affinity between the components was the result of the electrostatic interactions between the negatively charged phosphate backbone of the DNA and the metal ions. The constructed sensor was characterized using amperometry with linearity in the range 0.2 µM–1000 µM DA and a LOD of 30 nM. MXene TiO_2 nanocomposite has been reported to help prevent agglomeration in MXenes. Boobphahom et al. synthesized a composite using TiO2 and Ti_3C_2 MXenes [86]—such a composite aids in detecting DA with superior performance. Also, using hydrogels of Polyvinyl alcohol (PVA) and graphene oxide could help improve the biocompatibility and water absorption ability of the resulting composite. **Figure 3B** shows the composite TiO2/MXene-PVA/GO material used for the urinary detection of NEP. It is incorporated into textiles for offline determination of NEP, thus showcasing commercial viability. This sensing electrode catalyzes the oxidation of NEP to NEP quinone. The linearities that were achieved in NEP detection were 0.01 µM –1 µM and 1 µM – 60 µM with a LOD of 8 nM. This is within the cutoff limit of 16 µM for distinguishing between patients with or without neurological disorders.

Adding nonnoble metal with MXenes has been explored as an attractive avenue for detecting DA [87]. ZnS exhibits enlarged surface area, large biocompatibility, extraordinary catalytic efficiency, and excellent stability. Compositing ZnS with MXene can prevent the agglomeration of the MXenes and helps in the selective detection of DA. Nb_2C MXenes were prepared by milling the MAX phase of this material, and the ZnS was prepared by hydrothermal methods. Subsequently, these materials were mixed physically to evenly distribute ZnS in the final composite. The composite was used to modify the GCE and detect DA in the range of 0.09 mM – 0.82 mM with a detection limit of 1.39 µM. The material was also reported to be selective towards determining DA in the presence of multiple interferents. Zhou et al. used a $Ti_3C_2T_x$ MXene Pt composite to modify a glassy carbon electrode as the gate electrode of a transistor device [88]. The device leverages the amplification effect of transistors, the electrical conductivity of MXenes, and the catalytic property of Pt nanoparticles, as depicted in **Figure 3C**. This strategy differs from previously reported electrochemical sensors, employing a combination of electrochemical and electronic techniques to detect DA. The sensor achieved a wide linear range of 50 nM – 9 mM and a low LOD of 50 nM. The composite material exhibited an overall negative charge that electrostatically absorbs DA and repels other negatively charged interfering molecules. In addition, compositing MXenes with TMDCs presents the latest trend in MXene-based electrochemical detection of neurotransmitters. TMDCs-MXenes composites present an enhanced surface area with more active sites for binding molecules, excellent electrical conductivity, and the additional benefit of structural stability. These composites can easily be integrated into wearable applications using flexible substrates like carbon fiber paper.

Zhao et al. have used a $Ti_3C_2T_x$ MoS_2 composite-modified carbon fiber paper to electrochemically detect DA [89]. The heterostructure integrated with MoS_2 nanosheets is shown in **Figure 3D.** This composite material demonstrated to improve the analyte collisions with the active binding sites on the electrode surface, thus resulting in excellent sensor performance. This composite detected DA simultaneously with UA and AA with a linearity of 0.5 µM – 1000 µM DA with a LOD of 0.27 µM.

Ankitha et al. recently reported detecting DA from human serum using Nb_2CT_x-MoS_2. Owing to the better electrochemical stability of Nb_2CT_x, this composite exhibited better sensitivity towards DA detection. Optimization of the ideal material composition was carried out, and it was reported that the composite containing 12.5% MoS_2 compared to Nb_2CT_x showed better sensitivity compared to 6.25% and 25%. The composite material was able to detect DA linearly from 1 fM to 100 µM with a LOD of 0.23 fM. This is the lowest concentration of DA that has been detected to date [90].

Paul et al. reported a Ti_3C_2 MOF composite for the voltammetric detection of DA [91]. This composite improved the stability of MXene in PBS and atmospheric conditions. This composite also possesses excellent resistance to fouling in addition to enhancing the activity of the electrode. This method was used to detect DA in the presence of AA and 5-aminovaleric acid (VA) in PBS. The physically abounded MOF around the MXene sheets enhance the electrical conductivity due to unidirectional charge mobility. The material detected DA in the range of 90 – 300 nM with a LOD of 110 nM. Zhang et al. also detailed a MXene-based porous film constructed using a simple self-assembly process. Such a self-assembled film possesses improved electrochemical activity combined with good accuracy for the detection of DA in biological samples. In addition to this, the porous structure was tailored to bring about varying electrochemical performances. This material was able to detect DA with an LOD of 36.8 nM [92].

IV. FUTURE PERSPECTIVES

Most recent reports have successfully elaborated on detecting neurotransmitters from media like human serum, urine, and blood plasma by the standard addition method. This method entails the collection of samples from subjects followed by the dilution of these samples with buffers. Such a technique presents solutions for the lab-based analysis of neurotransmitters due to the buffer-dominant nature of the used samples. Real-time analysis of samples like urine, plasma, and blood would require understanding the behavior of the developed sensors in complex media containing different analytes like glucose, urea, lactate, bacteria, components of blood, and other physiologically important chemicals. The media containing such complex molecules may be detrimental to such sensors' working. Biofouling of neurotransmitter sensors in complex environment is a future direction that could be investigated. This direction can be explored using a microfluidic device. The complex media's flow can be regulated, and its interaction with the modified electrode can be investigated as a function of time. This will help researchers understand multiple aspects like biofouling, erosion of modifying material, and changes in the potential for detection of the relevant analytes.

Cost-effectiveness is another aspect that governs multiple factors, including readiness for translation, where various reports have focused on using LIG for direct patterning of free-standing Ti_3C_2–MXene [93], screen printing MXene [94], and 3D printing MXene [95] for wearable biosensors. Especially 3D printing and LIG are attractive avenues considering their potential for mass production. In addition, using flexible substrates like CC and CFP electrodes open attractive avenues for developing robust sensors more suited for the real-time detection of neurotransmitters [68]. Although the concept of minimally invasive sensors incorporating microneedles has been introduced to detect various molecules, neurotransmitters are yet to be detected using this technique. Recently MXene based microneedles were reported by Yang et al. for-monitoring muscle contraction [96]. This proves the effectiveness of this method for the wearable detection of neurotransmitters from interstitial fluids. However, this is a challenging avenue due to the transient nature of the levels of these molecules in the body. For this purpose, methods like fast scan voltammetry may be used where the sub-second resolution will help monitor the transient changes in the levels of these molecules [97]. There have been multiple reports of using MXene-based electrodes for sensing DA. Such reports are a positive step towards higher technology readiness [55, 72]. **Table 1** depicts the most recent reports on successfully detecting neurotransmitters in PBS and physiological media such as serum, urine, and blood plasma by the standard addition method. Sample biological fluids from human subjects are typically collected and diluted with buffers. Such a technique presents solutions for the lab-based analysis of neurotransmitters due to the buffer-dominant nature of the used samples. Real-time analysis of samples like urine, plasma, and blood would require understanding the behavior of the developed sensors in complex media containing different analytes like glucose, urea, lactate, bacteria, components of blood, and other physiologically essential chemicals. Therefore, more work is needed to minimize biofouling and the erosion of modifying material, ultimately impacting the detection of the relevant analytes.

Table 1. Performance of MXene-based neurotransmitter biosensors.

Material	Electrode	Molecule	Real Sample	LOD	Linear range	Ref
1-methyl imidazolium acetate-MXene composite	GPE	DA	Serum	702 nM	10 µM−2 mM	[55]
Laccase/ $Ti_3C_2T_x$	LIG	DA	Urine & human blood serum	0.47 nM	1 nM−10 µM	[36]
Nb_2CT_x/EDA	CC	DA	Serum	300 pM	1 nM–100 µM	[94]
rGO/$Ti_3C_2T_x$	ITO	EP	Urine	3.5 nM	1 µM− 60 µM	[78]
TiO_2/ $Ti_3C_2T_x$ -PVA/GO	SPCE	NE	Urine	8 nM	0.01–1.0 µM 1.0–60.0 µM	[86]
Pt/$Ti_3C_2T_x$	GCE	DA	-	50 nM	50 nM–9 mM	[88]
MoS_2/$Ti_3C_2T_x$	CFP	DA	Urine	27 µM	0.5–1000 µM	[89]

V. CONCLUSION

Although the use of MXenes for detecting neurotransmitters is currently being investigated, more avenues remain to be explored regarding various neurotransmitters, nanomaterials, and transduction mechanisms. Most work focuses on detecting essential neurotransmitters like DA, EP, and 5-HT. Reports on detecting other neurotransmitters, such as ACh, GABA, and glutamate, must also be extensively explored using MXene and MXene-based composites because of their excellent electronic properties. The family of MXenes is extensive and consists of more than 30 materials that have been reported experimentally and dozens more that are being computationally studied. Exploring these MXenes for detecting neurotransmitters would be an exciting pursuit, wherein the permutation and combination of MXenes termed as a solid solution, ordered double transition, and ordered divacancy MXenes can be envisaged [44]. Each MXene has its own physical and chemical characteristics, thus, exhibiting a unique affinity and selectivity toward biomolecules. Its composites could provide more opportunities for commercializing enzyme-based neurotransmitter sensors [98].

Various techniques have been reported for the synthesis of MXenes from their MAX phases, with significant attention devoted to the acid-based synthesis of MXenes, which would involve strong acids like HF and HCl. Future synthesis approaches could include other techniques that involve mild conditions. Using varied morphologies of MXenes like nanoribbons [85, 87] and nanospheres [99] could provide an exciting perspective for developing neurotransmitter sensors. MXenes with carbon-based nanostructures, polymers, metal, and metal oxide nanoparticles have garnered significant attention for neurotransmitter sensing. However, more reports need to be on compositing MXenes with transition metal dichalcogenides and other 2D materials like phosphorene. Exploring transition metal dichalcogenides and other 2D materials compositing with MXene would present a unique path from both the materials and neurotransmitter detection perspectives.

The unique 2-D structure of MXene is beginning to gain attention in developing wearable devices [98]. Specifically, integrating MXenes with textiles carried out by Seyedin et al. could serve as an exciting starting point for wearable sensing of neurotransmitters from sweat [100]. In addition, MXenes can be used to form very stable inks for inkjet printing and ink for tattoo-based sensors. Such sensors have been explored using other materials like carbon-based conductive inks, and MXenes in this domain have begun to gain some attention [90]. The mechanical stability of MXenes makes them an attractive option in commercial sensors, as they conform to the curvature of the skin. There have been increasing reviews and reports on using MXenes for chemotherapy [101, 102]. However, an in vivo application of MXene is yet to be seen despite promising reports of its applicability in chemotherapy. When in vivo applications of this material are realized, MXenes could also be used in developing microneedles for the real-time sensing of analytes in interstitial fluids.

In conclusion, multiple compositing pathways are yet to be explored for MXenes. Many of these avenues are at the developmental stages, and this presents opportunities for researchers to explore the applications of MXenes toward detecting neurotransmitters. The future of MXenes in the electrochemical detection of neurotransmitters is bright.

VI. References

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