ACS APPLIED BIO MATERIALS

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Advancements in 2D Materials Based Biosensors for Oxidative Stress Biomarkers

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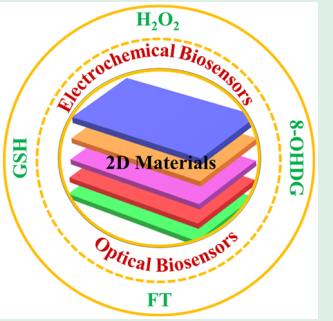
ABSTRACT: The imbalance in generation of reactive oxygen species and its depletion causes oxidative stress. Because of its importance, there is a need to explore the role of oxidative stress biomarkers. The limitations of the conventional methods cause the researchers look for other alternatives. Biosensors are highly promising candidates for the detection of trace quantities for various analytes with high specificity, selectivity, and quick response time. Nanomaterial based matrices are the most popular choice while fabricating a biosensor. Two-dimensional (2D) materials such as graphene, transitional metal dichalcogenides, and various metal oxides have been used for the biosensing of different oxidative stress analytes. High electron mobility, good optical properties, tunable properties, high yields, easy synthesis, and availability make these materials the first choice. In this review, we have comprehensively discussed various biomarkers associated with oxidative stress. The review will provide information related to different kinds and various synthesis procedures employed for 2D nanomaterials. The major focus of the review is to elaborate the role of 2D nanomaterial based structures for the optical and electrochemical methods for the detection of oxidative stress. This review is an effort to help the researchers better understand various 2D based transducers available for the detection of oxidative stress biomarkers.



KEYWORDS: *oxidative stress markers, biosensors, two-dimensional materials, graphene family, transitional metal dichalcogenide family, metal oxide family*

1. OXIDATIVE STRESS

An imbalance between generation of reactive oxygen species (ROS) and their counter antioxidants is termed oxidative stress.[1] ROS are formed in all aerobic organisms and are of physiological importance in a human body as their excessive production is associated with cell damage and imbalance in oxidative stress.[2] The amount of the oxidative stress can be determined from the level of various (bio)markers. Considering the importance of oxidative stress, researchers have started making efforts to understand it exhaustively, which is evident from the trend in publications in past few years (Figure 1).

1.1. Markers Associated with Oxidative Stress. Markers associated with oxidative stress play a significant role in cellular metabolism and cell functions. Basically, these markers can be classified into three main categories such as molecules modified by reactive oxygen species, lipids destroyed by oxidation, and based on antioxidants. Peroxides, superoxide, hydroxyl radicals, singlet oxygen, and alpha radical are the species that are formed from the interaction with ROS. Among various markers reacting with ROS, hydrogen peroxide is given emphasis here. The damage caused due to hydrogen peroxide includes cell membrane leakage, DNA damage, and senescence.[3,4] Markers emerging from the oxidation of DNA/RNA, lipids, and proteins include 8-hydroxydeoxyguanosine (8-OHdG), malondialdehyde, and isoprostanes.[5] 8-OHdG is the most studied marker

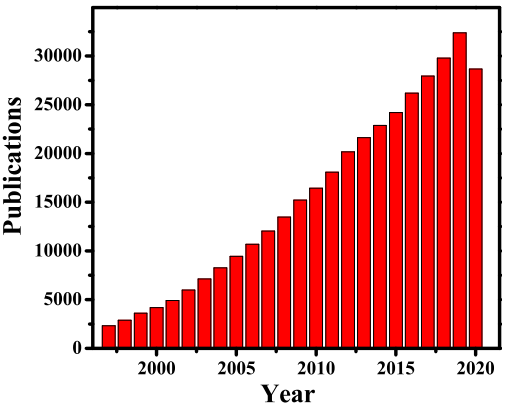


Figure 1. Figure shows the number of publications related to oxidative stress during 1997−2020 (Source: Web of knowledge search in Web of Science core collection with keyword: oxidative stress).

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among these. This can be further classified in the following categories: antioxidants based biomarkers include ferritin, glutathione, reduced glutathione, and superoxide dismutase. For a comprehensive understanding, various diseases associated with an imbalance in the oxidative stress (bio)markers are furnished in Table 1. Neurodegenerative diseases are conditions that lead to sensory and functional disruption due to loss of nerve cells from the spinal cord and brain. As the disease progresses, it results in death and degeneration of neuron cells, making it incurable. Various neurodegenerative diseases have been associated with oxidative stress such as Alzheimer's disease, Parkinson's disease, and ALS. Alzheimer's Disease (AD) is associated with increased levels of HNE (4-hydroxyl-2,3-noneal), acrolein, and F2-isoprostanes along with various other breakdown products of lipid peroxidation.[6]

Table 1. Diseases Due to Oxidative Stress

S. No.	Biomarkers	Ref
	Neurodegenerative Diseases	
1(a)	MDA, F2-IsoPs, GSH concentration	9, 10
1(b)	HNE	11
1(c)	HNE, GSH concentration	12
1(d)	MDA	13
1(e)	F2-IsoPs	14
	Cardiovascular Diseases	
2(a)	Acrolein, F2-IsoPs	15
2(b)	Acrolein, F2-IsoPs	16, 17
2(c)	Acrolein	18
2(d)	F2-IsoPs	17
	Kidney Diseases	
3(a)	F2-IsoPs	19
3(b)	Carbonylated proteins	20
	Lung Diseases	
4(a)	MDA, GSH concentration, F2-IsoPs, NO2-Tyr	17, 21−23
4(b)	GSH concentration, F2-IsoPs	24
4(c)	Carbonylated proteins, NO2-Tyr	22, 25−27
	Eye Diseases	
5(a)	GSH concentration	13
5(b)	GSH concentration	28
	Skin Diseases	
6(a)	F2-IsoPs	16
6(b)	F2-IsoPs	14
	Blood Disorders	
7(a)	Increase in superoxide dismutase	13
7(b)	Decrease in GSH levels	29, 30
	Bone Disorders	
8(a)	Cytokines, IL-1, TNF	31−33
8(b)	MDA, F2-IsoPs, GSH levels	14
	Liver and Pancreatic Disorders	
9(a)	MDA	34
9(b)	MDA	35
	Infectious Diseases and Immunology	
10	Carbonylated proteins	36

Risk factors such as older age, hyperglycemia, and obesity can be associated with increased oxidative stress. Though there is no direct correlation between severity of COVID-19 and oxidative stress level, we can assume that increased oxidative level can provoke the severity of COVID-19 infection and can be reduced by increased antioxidant supply.[7] The exact features that spike the macrophages during COVID-19 are not known. Various hypotheses have been proposed for its reason. One of the reasons can be being triggered by nonstructural viral proteins like coronavirus 3a proteins. Second, it may be due to changed glycosylation in the IgG Fc tail. Lastly, elevated mitochondrial ROS can promote monocyte activation as well as viral replication.[8]

Considering the role of various oxidative stress markers in many diseases, detection of these markers is very important. At present, oxidative stress markers are detected using techniques that involve use of sophisticated equipment which are expensive and laborious such as ELISA, chromatography, colorimetric and fluorometric methods, etc. The disadvantages and demerits of the conventional methods make biosensors the most suitable and convenient tool to explore. Biosensors have been used for quite a long time now. Many biosensors have found their way into the market as well.

Since biosensors rely on the interactions between the analyte and biorecognition elements, it becomes the key aspect to consider while determining the efficiency of the biosensor. The biosensor's efficiency is mainly governed by the immobilization efficiency, which can be achieved through various protocols and methods, namely adsorption, covalent bonding, encapsulation, entrapment, overlayer, and layer by layer. In the span of a decade, nanomaterials have emerged as one of the important components of the biosensing setup, either in the form of functionalization material or as a catalyst and transducers. Nanomaterials can potentially be classified into various types based on the dimensions that are discussed in the following sections.

2. NANOMATERIALS

Zero-dimensional (0D), one-dimensional (1D), two-dimensional (2D), and three-dimensional (3D) are the dimensionality based classification of nanomaterials[37] as also shown in Figure 2.

As the name suggests, 0D materials do not possess any finite dimension, for example, quantum dots (QDs).[38] One-dimensional materials have finite length, for example, nanotubes and nanofibers. Two-dimensional materials possess both length and breadth, for example, nanosheets. Three-dimensional materials

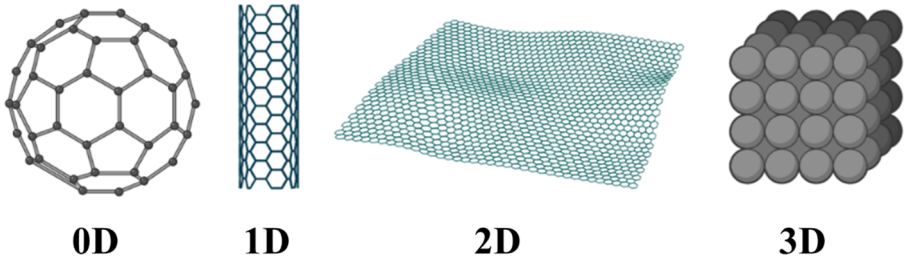

Figure 2. Nanomaterial classifications based on the dimensionality.

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are complex materials having 0D, 1D, and 2D in close proximity to each other interacting in specified manner. These materials exhibit electronic, physical, optical, thermal, and mechanical properties that are very helpful for various applications. These properties, however, can be modulated by varying synthesis protocols, which are discussed later in the coming sections. In this review, emphasis has been given on 2D materials, which make up the most researched and highly sought out topic in today's time.

2.1. 2D Materials. Since the discovery of graphene at The University of Manchester, in 2004, many 2D materials have been discovered and studied.[39] Consequently, the number of publications related to this topic has grown exponentially as can be seen in Figure 3, with Republic of China leading the

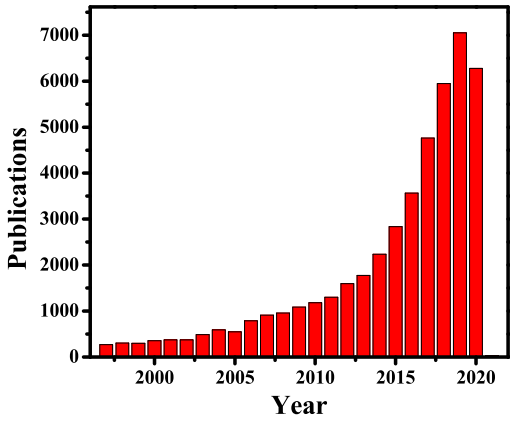

Figure 3. Number of publications related to 2D materials from 1997–2020 (Source: Web of knowledge search in Web of Science core collection with keyword: 2D materials).

research community in this subject area (data not shown, gathered from Web of Science analysis). The typical applications of 2D material include catalysis, energy generation and storage, photonics, optics, electronic devices, and diagnostics.[40−42] Figure 4 summarizes the general applications of 2D materials.

2.2. Synthesis of 2D Materials. Like any other nanomaterial, the synthesis of 2D layered materials can also be achieved through either top-down or bottom-up methods, as summarized in Figure 5. Top-down approach converts the bulk state of the material to a single or few layered materials. Few examples of top-down methods include liquid-phase exfoliation, electrochemical exfoliation, etc. When single atoms are arranged one by one to create few layers of the material, it is referred as bottom-up approach.

2.3. Synthesis Methods. *2.3.1. Top-down Approach.* The process of breaking the bulk form of the material into simpler structures comes under material exfoliation. This is usually the preferred form of material synthesis as this gives high yield and the synthesis protocols are also simple. With application of physical or chemical forces, the bulk materials can be exfoliated easily.

2.3.1.1. Liquid-Phase Exfoliation. This method uses dispersion in chemical solutions, which weakens the bonds between layers and is later sonicated to cause exfoliation.[47] Although this method is effective and could be up-scaled, still the oxidization of materials during process and extensive purification requirements necessitate the need to combine it with other reduction/oxidation or purification methods.[48]

2.3.1.2. Electrochemical Exfoliation. In this method, potential is applied to cause exfoliation of the bulk material. The exfoliated structure is then dispersed into the electrolyte solution, which is further separated and purified.[49,50]

2.3.1.3. Chemical Reduction. This method is commonly used for graphene based nanostructures and involves reaction with strong oxidizing agents like sulfuric acid, nitric acid, and potassium permanganate for the oxidation of graphite.[51] The method is referred as Hummer's method, named after "William S. Hummers Jr.". However, this method has been modified to various extents to reduce the use of toxic and harsh chemicals.[52]

2.3.2. Bottom-up Approach. This approach includes methods where smaller molecules are used to create bigger structures. Some examples include CVD, epitaxy, and hydrothermal among many others.

2.3.2.1. Chemical Vapor Deposition (CVD). CVD is a common method used for deposition of different precursor molecules to grow thin films, amorphous or crystalline structures, etc. This method uses conducting metals as substrates where the intended structures deposit forming single to multilayer structures. The method, however, suffers from complexities like precise control of synthesis parameters and high operation cost.

2.3.2.2. Epitaxial Growth. The method involves the generation of well oriented layers of material onto a substrate surface. Precise control of parameters will result in self-assembling of materials in the desired structure. Again, the major drawback of this technique is control of parameter, which results in uncontrolled number of layer deposition, defects, and structural disorders in sheets.

2.3.2.3. Hydrothermal Treatment. This method can be included both in the top-down as well as the bottom-up approach. Hydrothermal treatment is given to the material to further exfoliate it;[58] whereas, in case of bottom-up approach, the constituents of the intended 2D material to be fabricated are mixed together and then subjected to the hydrothermal treatment.[59]

2.4. Types of 2D Materials. All the 2D materials are fundamentally similar in structure, that is, stacked layers of atoms, held by various forces and can be broadly classified into four families as shown in Figure 6.

2.4.1. 2D Oxides. Because of their unique physicochemical properties, 2D oxides have been gaining wide popularity. They consist of stacked atomic layers (<10) or sheets in which metal ion (X) is bound to an oxygen atom, (where X can be Ti, Co, Zn, W). Because of the unique synergisic combination of metal and 2-dimensionality, performances in energy applications are widely increased.[60] These materials[61] find many applications in electronic devices such as batteries and FETs.[62−64] Researchers have been synthesizing these 2D oxides using the self-assembly method. In this, the constituents of the 2D oxide react together in the presence of some chemical agents and assemble themselves in the form of sheets.[65] Other methods of synthesis includes ion layer adsorption and reactions,[66] using lasers[67] or using molten salts method.[68]

2.4.2. Graphene Family. The most commonly studied materials in the graphene family are graphene and hexagonal boron nitride. Graphene is a 2D, one carbon atom thick, hexagonal structured material, is the most studied material of carbon family.[69] It has high electron mobility and high conductivity making it useful for many applications.[70] Graphene is further modified as GO and RGO having nanodimensions and various forms like nanosheets and quantum dots. Hexagonal

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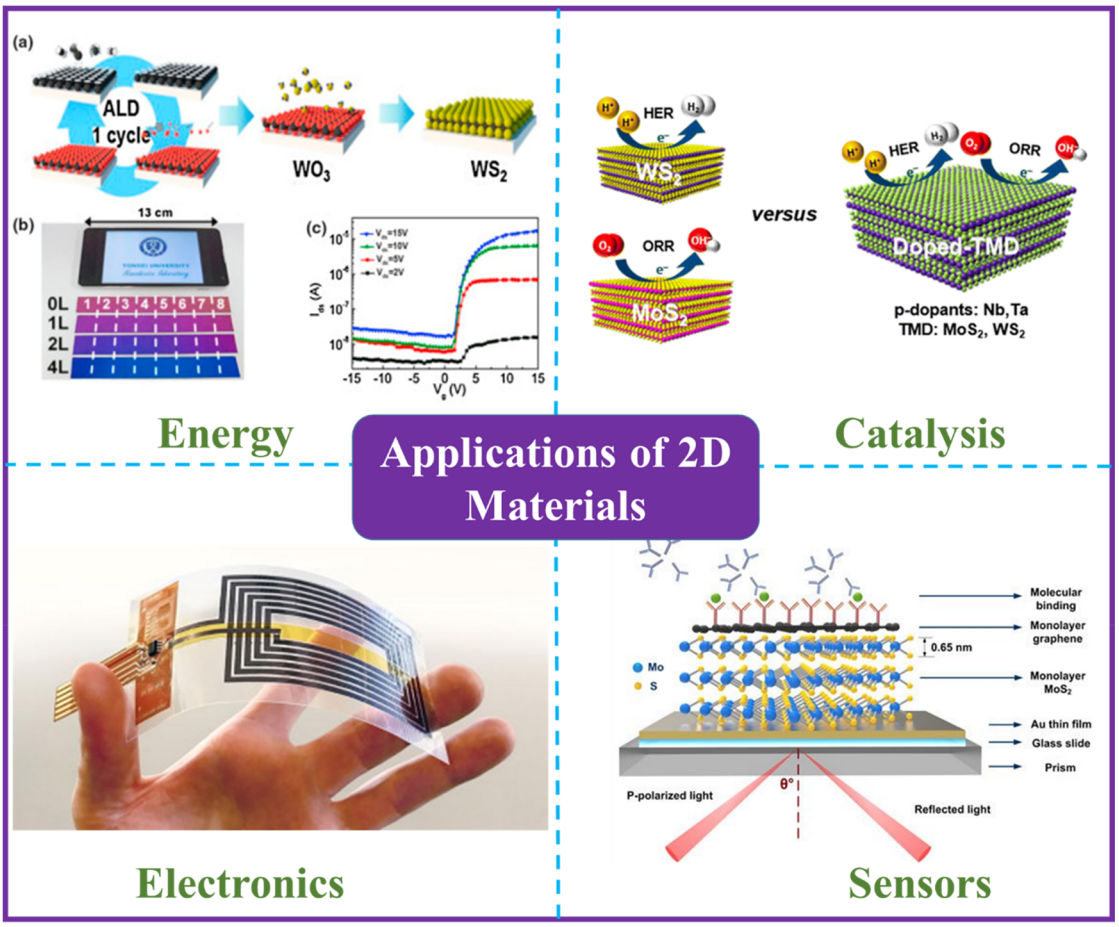

Figure 4. Various application areas of the 2D materials (Reproduced with permission from ref 43. Copyright 2013 American Chemical Society. Reproduced with permission from ref 44. Copyright 2016 American Chemical Society. Reproduced with permission from ref 45. Copyright 2018 Elsevier. Reproduced with permission from ref 46. Copyright 2015 Elsevier.).

boron nitride, analogous to graphene is useful in dielectrics, coatings, and devices.[71] Graphene coated on hBN has been used as FET devices as hBN allows graphene to achieve high electron mobility.[72]

2.4.3. 2D Chalcogenides. 2D chalcogenide material is made from the layers of materials in which a transition metal (M) is bound covalently to two chalcogens (X). The inter lyers have weak Vander Waal forces. These materials are represented as MX_2, and some examples are molybdenum disulfide, tungsten disulfide, tungsten ditelluride, and many more.[73−75] The crystal structure of TMDs changes from a metallic state (1T) to a semiconducting state (2H) when they are converted from bulk form to a monolayer form.[76] The properties of these materials are almost similar to the other 2D materials discussed in above sections.

2.4.4. MXenes. This is the recent addition to the 2D material family. In a typical MXene structure, layers of a transition metal are sandwiched between carbon or nitrogen atoms. This material also has terminal groups, which can be oxides, hydroxides, fluorides, etc.[77] MXenes consist of a mixture of metallic and covalent bonds giving it unique properties. Majorly, this class of material has been employed in energy related applications.[78] Recently, wearable sensors based on MXenes, have also been developed.[79]

2.5. Applications of 2D Materials. The excellent multifaceted properties of the 2D materials make them the first choice for any potential applications. Researchers across the globe have exploited the electrical, electronic, and optical properties of these materials for almost all the possible applications ranging from catalysis, photocatalysis, batteries, transistors, supercapacitors, fuel cells, and adsorbents to sensors to name a few.[63,80−84]

Among many of these above-mentioned applications, (bio)sensing application of 2D materials is exhaustively covered in recent past for (bio)sensing of diverse analytes ranging from nitrogen dioxide, acetone, ethanol, formaldehyde, etc. to many diagnostic relevant biomarkers.[85−91] This booming trend is represented in Figure 7a and b. It is interesting to note that though 2D materials were being used as sensors, their use as biosensors started in the year 2002. It was in the year 2019 that first time the number of publications crossed 50 on the use of 2D materials as biosensors. This clearly highlights the tremendous potential of these materials as biosensing platforms. The number of publications grew rapidly after 2015, and hence, studying publications for the past 5 years (2015 onward) makes sense for the literature review.

Graphene and its derivatives, owing to their multifaceted properties, ease of synthesis and functionalization, and high yields, are exhaustively explored for sensor-like applications such as chemo-sensors and biosensors for the detection of various environmental and clinical relevant analytes.[92,93] Coming to the TMDs, after graphene and its derivatives, these are emerging materials being explored for various applications like catalysis, photocatalysis, energy generation, and as electronic devices.[94]

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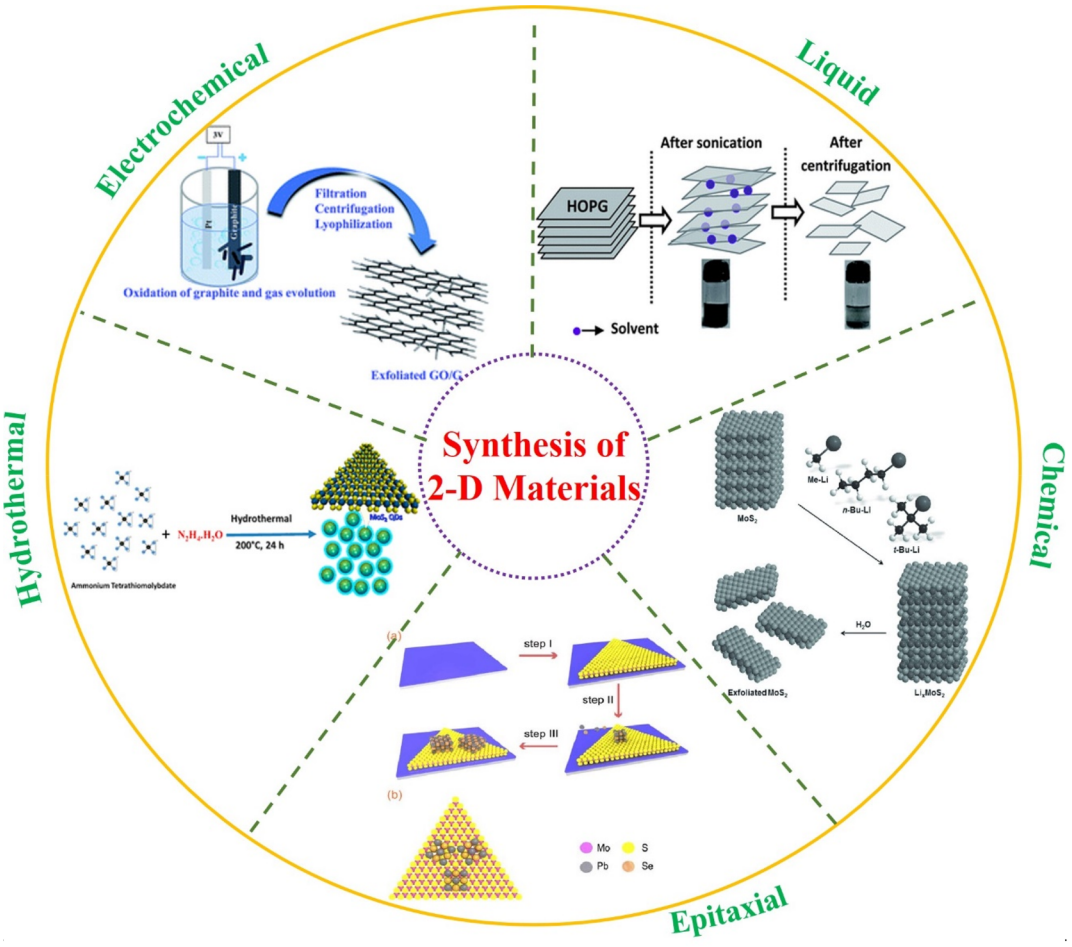

Figure 5. Various synthesis approaches for the 2D materials (Reproduced from ref 53 with permission from The Royal Society of Chemistry. Reproduced from ref 54 with permission from The Royal Society of Chemistry. Reproduced from ref 55 with permission from The Royal Society of Chemistry. Reproduced with permission from ref 56. Reproduced with permission from ref 57. Copyright 2018 American Chemical Society.).

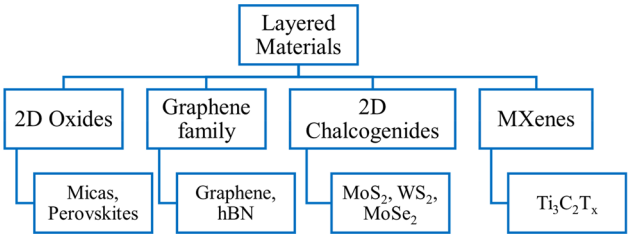

Figure 6. Various families of the 2D layered materials [hBN, hexagonal boron nitride; MoS_2, molybdenum disulfide; WS_2, tungsten disulfide; $MoSe_2$, molybdenum diselenide; $Ti_3C_2T_x$, titanium carbide based].

There is ample literature on the applications of these materials.[95,96] Biomedical applications of these materials have also not remained untouched where these materials have been used for photothermal therapy, biosensors, cellular imaging, etc. The photothermal therapy is a targeted killing of tumor cells in the presence of light, as anticancer agents, as antimicrobial agents, bioimaging, and use as biosensors.[97−99] For biosensing applications, TMDs have been used for optical and electrochemical detection of various markers like nucleic acids, small molecules such as glucose, hydrogen peroxide, cholesterol, various disease biomarkers, and many more.[100]

A number of reviews are available covering various dimensions and aspects of 2D materials.[101−104] Hence, this review has been restricted to application of 2D materials for biosensing of oxidative stress markers, which is yet not documented.

3. 2D LAYERED MATERIALS BASED (BIO)SENSORS FOR OXIDATIVE STRESS MARKERS

Conventionally, oxidative stress markers have been reported to be detected using sophisticated and specialized analytical techniques using high end instrumentations. Recently, Marrocco et al. and Katerji et al. comprehensively reported the techniques used for the marker detection, concluding that flow cytometry, gas chromatography−mass spectroscopy, enzyme linked immunosorbent assay, and high performance liquid chromatography have been employed until now commonly.[105,106] Gasparovic A et al. also showed the use of High Performance Liquid Chromatography (HPLC) and Enzyme-Linked Immunosorbent Assay (ELISA) based method for the detection of oxidative and nitro-oxidative stress.[107] The various oxidative markers related to systemic lupus erythematosus were discussed in work by Shah et al. in which methods such as electron spin resonance, ion electrode method, ELISA, HPLC, Liquid Chromatography (LC), flow cytometry, flame photometry, and colorimetric and fluorometric methods were discussed in relevance to the stress markers.[108] Although these methods of detection are highly sensitive and selective, they still are not a viable option because of the involvement of huge costs of the instruments and labor-intensive tests. This gives the need

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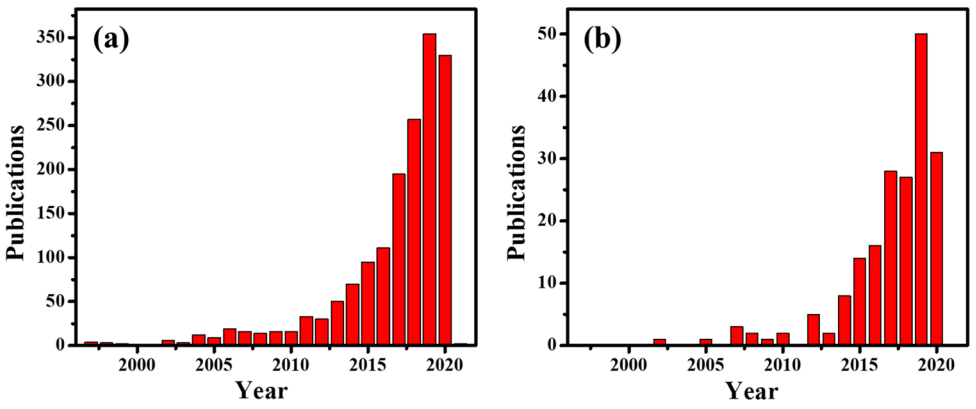

Figure 7. (a) Number of publications related to 2D materials as sensors from 1997−2020 (Source: Web of knowledge search in Web of Science core collection with keyword: 2D materials as sensors); (b) number of publications related to 2D materials as biosensors from 1956−2020 (Source: Web of knowledge search in Web of Science core collection with keyword: 2D materials as biosensors).

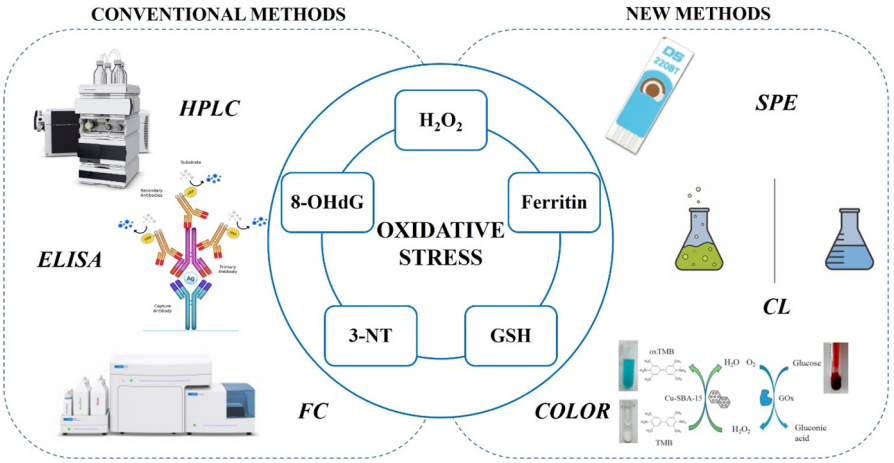

Figure 8. Comparison of conventional versus new methods for the detection of various oxidative stress markers (The colorimetric sensor has been reproduced with permission from ref 109. Copyright 2016 Elsevier.).

for systems that are selective, sensitive, and cost efficient as compared to the conventional methods (Figure 8).

Biosensors and chemo-sensors are low-cost, portable, sensitive, and selective systems. Their performance, however, depends upon many factors such as immobilization material, immobilization technique, and transducer employed. Nanomaterials such as gold, platinum, carbon, TMDs, MXenes, etc. are now emerging as potential materials and platforms for biosensing applications due to their ease of synthesis, high surface to volume ratio, biocompatibility, ease of functionalization, and so on. The 2D layered materials have shown tremendous potential for being used as immobilization matrices in biosensors and have been employed for the detection of various oxidative stress markers. In their role as immobilization matrix, these materials play dual role of providing a surface for biochemical reaction as well as act as catalysts. Apart from being used as immobilization matrices, these materials have been exploited as transducing systems also by encashing their optical and electrochemical properties.

The nanomaterials provide a surface over which the biorecognitions take place. In case of an electrochemical sensor, biointeractions causes change in the current or resistance, which can be further used for signal detection. In optical sensors, change detected may be in the form of color, absorbance, or fluorescence intensity.

Transducers are the platforms that convert one form of signal into another readable and interpretable form. In terms of biosensors, these convert the biological signal into a signal that can be easily measured/comprehended. Depending on the type of change, these can be classified into electrochemical, optical, thermal, and piezoelectric based.[110,111]

All the literature to date reports the use of various electrochemical and optical platforms only. This can be easily explained considering the advantages of these methods. Both these methods allow for sensing of very trace levels of the biomarkers, have quick response time, are highly selective, are able to work in extreme environmental conditions, are low-cost, are user-friendly, and can be miniaturized, which are the key parameters while considering a point of care device.

3.1. Electrochemical Based Detection. Electrochemical based transducers work on the principle of electrochemistry where redox reactions take place to generate the signal. The signal can be detected or monitored using various electrochemical techniques: voltammetry, amperometry, or conduction/conductometric and impedance spectroscopy.[112−115] Owing to the sensitivity and selectivity of electrochemical technique, many oxidative stress markers like 8-OHdG, 3-nitrotyrosine, and hydrogen peroxide have been detected as depicted in Figure 9.

8-oHdG has been shown to be detected using various allotropes of carbon, be it used alone or in tandem with some

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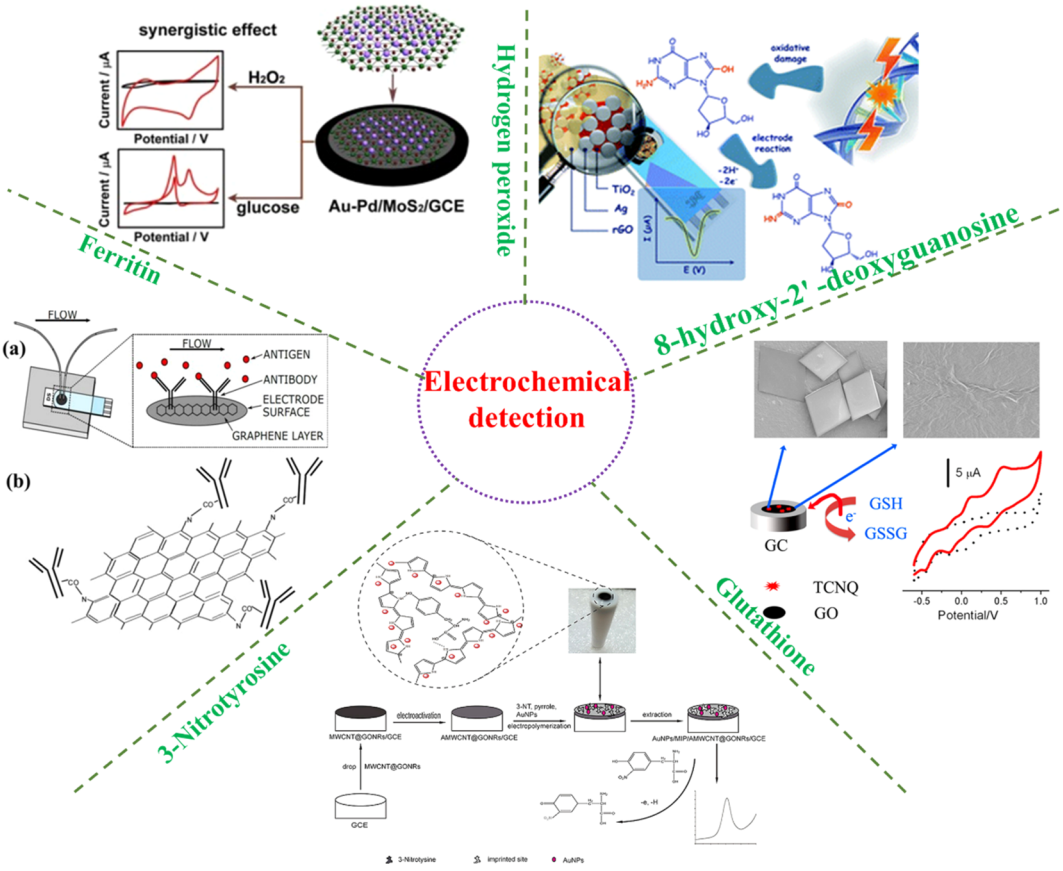

Figure 9. Electrochemical method for the detection of various oxidative stress markers (Reproduced with permission from ref 132. Copyright 2017 Elsevier; Reproduced from ref 134. Reproduced with permission from ref 135. Copyright 2017 Elsevier. Reproduced from permission from ref 123 with permission from The Royal Society of Chemistry. Reproduced with permission from ref 124. Copyright 2018 Elsevier.).

Table 2. Detection of 8-OHdG Using Various Electrochemical Methods[a]

S. No.	Sensing Platform	Detection Range	LOD	Technique Used	Real Sample	Ref
1.	dysprosium oxide NPs@ reduced graphene oxide	0.05−135.3 μM	1.02 nM	amperometry	human urine and blood serum	119
2.	ZnO NRs: RGO composites	1 pg mL^{-1}−5 ng mL^{-1}	100 fg mL^{-1}	CV	urine	120
3.	carboxyl-functionalized carbon-allotropic nanomaterials wrapped AuNPs	0.014−14.12 μM	7.06 nM	DPV	human urine	121
4.	graphene	300 nM−100 μM	90 nM	LSV	human saliva	122
5.	Ag-TiO_2−RGO hybrid nanomaterial	0.05−25 μM	10 nM	DPV	human urine	123

[a][NPs, Nanoparticles; RGO, reduced graphene oxide; ZnO, zinc oxide; CV, cyclic voltammetry; DPV, differential pulse voltammetry; LSV, linear sweep voltammetry; Ag, silver; TiO_2, titanium dioxide; AuNPs, gold nanoparticles].

heterostructures. Single wall carbon nanotubes-Nafion composite film modified electrode was able to detect this analyte in nanomolar concentrations.[116] Gupta et al. used square wave voltammetry for the electrochemical detection of this analytical on a pyrolytic graphite electrode, which had a limit of detection in nanomolar range.[117] Hemin/G-quadruplex on the carbon nitride nanosheets were used for the electrochiluminescent detection of 8-OHdG in atomolar concentrations by Lv et al.[118] More examples for the use of 2D layered material based sensors for this analyte are given in Table 2.

Similar to 8-OHdG, 3-nitrotyrosine has also been detected using allotropes of carbon, which include graphene and carbon nanotubes. Wang et al. fabricated an electrode modified with molecularly imprinted polymer-coated AuNPs, which was further modified with activated multiwall carbon nanotube at graphene oxide nanoribbons for the electrochemical detection of 3-nitrotyrosine. The fabricated sensor showed limit of detection in the nanomolar range.[124] Composite of porous RGO nanosheets/$CuFe_2O_4$ nanodots was used successfully for the electrochemical sensing of this analyte and the sensor system was able to detect the analyte even in picomolar concentrations.[125] $CdWO_4$ nanodots decorated reduced graphene oxide has also been shown as the sensing platform for this analyte. The sensor system was able to work in the nanomolar concentration range.[126]

Glutathione is another major oxidative stress marker that has been shown to be detected using various electrochemical techniques. Rawat et al. used MoS_2 surface that was modified with glutathione-S-transferase enzyme for the detection of glutathione. The sensor had a very broad linear range, which

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Table 3. Detection of Glutathione Using Various Electrochemical Methods[a]

S. No.	Sensing Platform	Detection Range	LOD	Technique Used	Real Samples	Ref
1.	graphite-phase carbon nitride/silica	0.1−500 μM	20 nM	ECL		129
2.	manganese oxide nanosheets	10−2000 nM	3.7 nM	ECL	human serum	130
3.	single-walled carbon nanotubes	1−500 μM	0.5 μM	CV		131
4.	7,7,8,8-tetracyanoquinodimethane and GO	0.25−124.3 μM and 124.3 μM−1.67 mM	0.15 μM	amperometry	eye drop solution	132
5.	graphene		8.01 μM	CV		133

[a][GO, Graphene oxide; ECL, electrochemiluminescence; CV, cyclic voltammetry].

Table 4. Detection of Hydrogen Peroxide Using Various Electrochemical Methods[a]

S. No.	Sensing Platform	Detection Range	LOD	Technique	Real Samples	Ref
1.	Ag functionalized MoS_2 hybrid nanostructures	0.025−135.2 mM	3.5 μM	amperometry	tap water	153
2.	Ag NP− RGO−polyaniline	0.01−1000 μM	50 nM	amperometry		154
3.	Prussian Blue−polythiophene−GO membrane	1.0−100.0 μM	0.32 nM	amperometry	milk and fruit juice	155
4.	Pt NPs @ graphene−CNT hybrid	up to 25 μM	10 nM	amperometry	live cells macrophage	156
5.	Pd NPs/porous graphene	2−1672 μM	0.9 μM	amperometry		157
6.	MoS_2 flowers grown on graphene/CNT	5−145 μM	0.83 μM	amperometry	human serum	158
7.	MoS_2 nanoflowers decorated with Pt NPs	0.02−4.72 mM	0.345 μM	amperometry		159
8.	RGO nanocomposites decorated with Au, Fe_3O_4, and Pt NPs	0.5 μM−11.5 mM	0.1 μM	amperometry	living cells	160
9.	MoS_2−CNT hybrid	10 nM−100 μM	5 nM	amperometry	spiked sterilized milk	161
10.	GO supported tin oxide nanoclusters	0.5−800 μM	0.478 μM	CV		162
11.	Pd NPs@ N-doped GQDs @N-doped carbon hollow nanospheres	up to 1.4 mM		amperometry	cancer cells	163
12.	layered MoS_2/ graphene composites	6.25−225 μM	1.25 μM	CV		164
13.	Au−Pt bimetallic NPs on MoS_2 nanoflowers	10 μM−19.07 mM	0.39 μM	amperometry	serum	165
14.	MoS_2−Prussian Blue nanocube nanohybrid	0.01−300 μM	4.1 nM	amperometry		166
15.	AuNPs@MoS_2 nanocomposite	10−300 μM	4 μM	CV		167
16.	Pt nanoparticle-decorated rGO−CNT nanocomposite	25−1000 μM	4.3 μM	amperometry	cancer cells	112

[a][MoS_2, Molybdenum disulfide; Ag, silver; NPs, nanoparticles; RGO, reduced graphene oxide; GO, graphene oxide; Pt, platinum; Pd, palladium; CNT, carbon nanotube; Au, gold; Fe_3O_4, iron oxide; GQDs, graphene quantum dots; CV, cyclic voltammetry].

spanned from micromolar to millimolar with the detection limit in nanomolar.[127] A composite of cobalt phthalocyanine and functionalized multiwalled carbon nanotubes was fabricated for detection of glutathione. The LOD value was found to be 100 μM and 8.3 μM for reduced glutathione and oxidized glutathione respectively.[128] Several sensing platforms for electrochemical detection of glutathione are compiled in Table 3.

Hydrogen peroxide, another important oxidative stress marker, has also been detected using electrochemical techniques where 2D materials have been used either as immobilization surface or as catalysts. Magyar et al. used indium tin oxide (ITO) functionalized with multiwalled carbon nanotubes (MWCNTs) and horseradish peroxidase (HRP) for the real time measurements of hydrogen peroxide.[136] In yet another study, HRP-AP/rGO (AP: 1-aminopyrene as a linker between HRP and rGO) modified glassy carbon electrode was used for intracellular hydrogen peroxide detection.[137] Though bioreceptor based (bio)sensors are famous for their inherent specific activity, they suffer from disadvantages like high cost of bioreceptors, loss in their activity with time, and other physiological parameters. Consequently, these are not quite successful for field applications, which limits their usage. To overcome these disadvantages, many alternate approaches have been proposed wherein the 2D materials like molybdenum disulfide,[138] cobalt oxyhydroxide nanosheets,[139] graphene,[140] etc. have been utilized for hydrogen peroxide detection.[141,142] In one such example, the platinum containing carbon nanofibers have been used for the detection of hydrogen peroxide with quick response times.[143] Similarly, reduced graphene oxide/gold nanoparticles and platinum nanoparticles embedded porous graphene were fabricated by Patella et al. and Liu et al., respectively, for the detection of hydrogen peroxide.[144,145] Many composites of gold nanoparticles-graphene oxide have also been reported for the detection of H_2O_2.[146−151]

In yet another approach, MoS_2 interconnected porous carbon heterostructures were used. This material was synthesized using hydrothermal treatment method. The resulting sensor had a detection limit of 11.8 μM and was found to be highly selective and sensitive.[152] A configuration of gold−palladium nanoparticles supported on MoS_2 nanosheets has been fabricated by Li et al. for hydrogen peroxide detection. The electrochemical system displayed a LOD of 0.16 μM.[135] For compilation, a table is appended as Table 4 summarizing the use of various 2D material based electrochemical sensing platforms for the detection of hydrogen peroxide as an oxidative stress marker.

The following points can be concluded from the Table 4:

- The sensitivity of amperometry makes it a preferred electrochemical technique.
- The high electron mobility in graphene and transition metal dichalcogenide (especially molybdenum disulfide) based nanostructures allows for the development of electrochemical biosensor.
- The electrochemical methods are robust enough to detect minute changes in the complex sample matrices as well. Hence, these have been abundantly used for real sample analysis.

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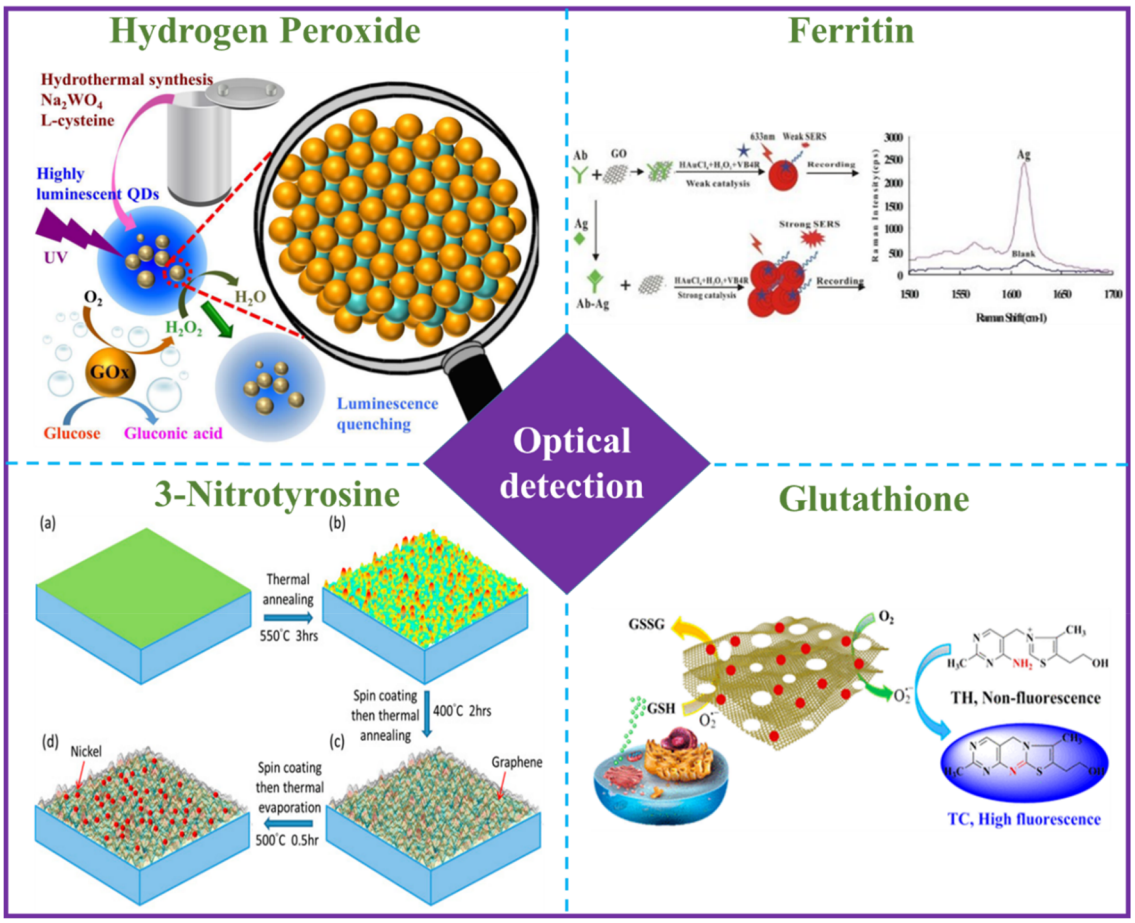

Figure 10. Detection of various oxidative stress markers using optical means (Reproduced with permission from ref 179. Copyright 2017 Elsevier. Reproduced from ref 187. Copyright 2019 Springer Nature. Reproduced with permission from ref 188. Copyright 2018 Elsevier. Reproduced with permission from ref 184. Copyright 2019 American Chemical Society.).

Ferritin, an antioxidant based oxidative stress marker, has also attracted dedicated research on its detection in recent years, though initial studies started much earlier. Covering the electrochemical based transduction systems, Garg et al. reported the use of quantum dots for the electrochemical detection of ferritin. The quantum dots of tungsten disulfide were synthesized using a biosurfactant, which provided a clean alternative to the chemicals that are usually used for the synthesis of these quantum dots. Though the sensor covered the clinical range for ferritin and was able to detect ferritin in spiked serum samples, the LOD achieved was not that high.[168] An improvement to both linear range and LOD was done by using quantum dots of white graphene. The LOD obtained in this case was 1.306 ng mL^{-1}. However, the method could not be validated using any real samples.[169] Boonkaew et al. reported the use of graphene based electrochemical platform for ferritin sensing. Graphene was further modified with EDC/NHS chemistry for antibodies. Though the sensor displayed quite a long linear range with good limit of detection, the multiple electrode preparation steps for immobilization of the antibodies added to its drawback.[170] Use of field effect transistor (FET) sensor by Oshin et al., based on graphene for ferritin detection, was shown. This method also involved multiple electrode preparation steps. 1-pyrenebutanoic acid, and succinimidyl ester were used for graphene modification.[171] Garg et al. reported the use of a microfluidic chip that can house a commercially available electrode. The electrode was modified with amine functionalized graphene oxide, which provided one step antibody immobilization to take place. The chip was designed in such a way that the fluid flowed over the working area of the electrode in a helical motion. The chip design also allowed for a swappable electrode system. This was demonstrated for the electrochemical immunosensing of ferritin. The sensor was able to cover the clinical range of ferritin and showed an LOD of 0.413 ng mL^{-1} and was also to demonstrate the sensing capabilities in spiked serum samples.[134] On the basis of the literature survey on electrochemical based detection on oxidative stress markers, it is concluded that

- 8-OHdG and hydrogen peroxide are the most studied and researched oxidative stress markers in terms of electrochemical sensors.
- Research related to 3-nitrotyrosine and ferritin is not at all sufficient and a lot of work needs to be done for the study of these markers.
- In terms of 2D materials, graphene family and transition metal dichalcogenide (especially molybdenum disulfide) are the most preferred materials.
- Other member of graphene family such as hBN should be employed as electrochemical sensors.
- Tungsten disulfide and other materials from TMD family should be employed as electrochemical sensors.

3.2. Optical Based Detection. Optical based detection systems involve generation of signal in the form of light. This

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Table 5. Various Nanostructures for Optical Hydrogen Peroxide Detection[a]

S. No.	Sensing Platform	Detection Range	LOD	Platform	Real Samples	Ref
1.	$MoSe_2$ QDs	10−100 μM	4 μM	colorimetric		196
2.	MoS_2 QDs @ MoS_2NS	2−94 μM	2 μM	fluorescent	green tea, blood	197
3.	Cerium(III)-doped MoS_2 NS	1−50 μM	0.47 μM	colorimetric	real milk samples	198
4.	MoS_2 QDs @ g-C_3N_4 NS	2−50 μM	0.02 μM	colorimetric		199
5.	MoS_2 QDs	2−20 μM		fluorescent		200
6.	SDS−MoS_2 NPs	2−100 μM	0.32 μM	colorimetric		201
7.	FePt @ MoS_2 NS NC	8−300 μM	2.24 μM	colorimetric	cancer cells	202
8.	MoS_2 layers	0.125−1.75 μM	0.08 μM	colorimetric	lake water	203
9.	WS_2 QDs	0−1000 nM	2.4 nM	CL		204
10.	brominated graphene	0.50−5.00 mM	0.417 mM	colorimetric		205

[a][$MoSe_2$, Molybdenum diselenide; QDs, quantum dots; NS, nanosheets; MoS_2, molybdenum disulfide; g-C_3N_4, graphitic carbon nitride; SDS, sodium dodecyl sulfate; NC, nanocomposite; FePt, iron−platinum; WS_2, tungsten disulfide; CL, chemiluminescence].

light change can be in the form of absorbance, fluorescence, luminescence, or a change in the refractive index.[172−175] The more advanced and recently developed optical transducers include surface plasmon resonance (SPR), optical waveguides, ellipsometry, reflectometric interference spectroscopy, and surface enhanced Raman scattering (SERS).[176] Optical methods have been extensively used for the sensing of oxidative stress markers as shown in Figure 10.[177,178] 3-Nitro-L-tyrosine has been reported to be detected using localized surface plasmon resonance biosensor, where the signal was generated from the surface of nickel doped graphene. This method provided a label free and direct determination of the analyte in the range of 0.5 pg mL^{-1} to 1 ng mL^{-1} of analyte concentration.[179]

A few reports also exist for the 2D materials based optical detection of glutathione. Manganese oxide paired with copper nanoclusters,[180] carbon dots[181] and graphene quantum dots[182] have been used for fluorescence based detection of glutathione. All these platforms demonstrated μM detection of glutathione. A combination of resonance Rayleigh scattering and colorimetry has been used for the detection of glutathione using the optical signal generated from manganese oxide nanoflakes. Glutathione caused reduction of manganese oxide to Mn^{2+}, which resulted in decreased scattering as well as absorbance signal.[183] Magnetic nanoporous graphene nanocomposites have also been shown as detection platform for glutathione.[184] Wong and co-workers developed a turn-off fluorescence sensor for glutathione detection. The work involved synthesis of folic acid-functionalized reduced graphene oxide-modified BSA gold nanoclusters as the fluorescent molecule. The addition of glutathione linearly quenched the fluorescence of the above nanomaterial. The sensor had a linear range from 0 to 1.75 μM. Real sample analysis using this sensor was however not demonstrated.[185]

Ye and co-workers developed a FRET based system for the optical detection of 8-OHdG. The work reported the use of carbon dots modified nanoporous membrane as the fluorophore and Au@ZIF-8 nanoparticles as the quencher probe. The sensor had a LOD of 0.31 nM and was able to detect the analyte molecule in human urine samples.[186]

On a similar track, reports are available on detection of hydrogen peroxide as oxidative stress marker using optical transduction. Most commonly reported transduction systems are either color based or fluorescence based, with only a single report on SPR based optical technique for hydrogen peroxide detection.

For optical detection of hydrogen peroxide as oxidative stress marker, different combinations of 2D materials have been explored. The 2D materials like MoS_2, WS_2, graphene oxide, etc. exhibited enzyme mimicking behavior, which makes the system quite robust and user-friendly.[189−191] Such behavior also helps in excluding the use of bioreceptors, which need multiple steps during immobilization and final usage. In this direction, mostly MoS_2, WS_2, and their composites have been reported. Yu et al. used different modifications of the MoS_2 and studied their peroxidase activities for the detection of hydrogen peroxide using 3,3′,5,5′-tetramethylbenzidine (TMB) and (2,2′-azinobis-[3-ethylbenzothiazoline-6-sulfonic acid]-diammonium salt) (ABTS) as substrate.[192] The peroxidase activity of lysine functionalized tungsten disulfide quantum dots was used for the opto-electrochemical detection of hydrogen peroxide by Garg and co-workers. The robustness of the method was checked using urine samples as well.[193]

Tungsten disulfide quantum dots were used by Hang et al. for the fluorescent detection of hydrogen peroxide and glucose. The presence of hydrogen peroxide resulted in the quenching of WS_2 QDs fluorescence, proportional to the analyte concentration.[194] The quenched fluorescence of Rhodamine-B by sulfur doped graphene oxide was used as the sensing signal for the detection of hydrogen peroxide. The limit of detection for this system was as low as 100 pM.[195]

Table 5 shows consolidated information on different types of 2D materials used for H_2O_2 detection and the following conclusions are drawn:

- Colorimetry is the most preferred platform for the detection of hydrogen peroxide majorly because of the peroxidase mimicking activity of the various nanostructures.
- The easy synthesis of transition metal dichalcogenide (especially molybdenum disulfide) makes it the most suitable candidate for the detection of hydrogen peroxide.
- Recording an optical signal from the complex sample matrix limits the use of optical based sensors, and hence, not many methods have been validated with real samples.

Regarding ferritin, not much work is documented on optical detection using 2D materials to date. In a SERS based approach, the catalytic activity of graphene oxide between chloroauric acid and hydrogen peroxide was utilized for ferritin estimation. Ferritin antibody inhibited the catalytic activity of graphene oxide, which was restored when the ferritin formed the immunocomplex with the antibody. This method had a linear range of only 0.017−1.02 ng mL^{-1}, which did not cover the prescribed limits.[188] Recently, Garg and co-workers developed an immunosensor for the fluorescent based ferritin detection. The sensing platform utilized amine functionalized graphene

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quantum dots conjugated with antiferritin antibodies. The fluorescence quenching was observed with methyl orange, which was restored with the interactions of the antigen−antibody@amine functionalized graphene quantum dot probe. The sensors robustness was evaluated with human serum samples and the method displayed a wide linear range.[206]

The following points can be concluded from optical based detection:

- Hydrogen peroxide is the most studied and researched oxidative stress markers in terms of optical sensors.
- Research related to glutathione, 8-OHdG, 3-nitrotyrosine, and ferritin are not at all sufficient, and much work needs to be done for the study of these markers.
- In terms of 2D materials, transition metal dichalcogenide (especially molybdenum disulfide) is the most preferred material.
- Graphene family should be employed as optical sensors for oxidative stress markers.
- Tungsten disulfide and other materials from TMD family should be employed as optical sensors.

4. CONCLUSION AND PERSPECTIVES

Oxidative stress is the underlying phenomenon behind most of the diseases, and extensive research has also proved this correlation. Level of oxidative stress can be judged through the associated biomarkers or footprints. The gold standard methods for the detection of these biomarkers involve the use of chromatography (generally HPLC, UPLC, or GC-MS), enzymatic methods, and nonenzymatic methods. Though these methods have sufficiently low detection limits and are highly sensitive, there are some drawbacks also. For instance, tedious sample preparations, requirement of bulky equipment, and being time-consuming. This encourages us to find and develop new rapid, cheap, and sensitive methods.

In this regard, the use of 2D layered derived material for sensing application is very unique and interesting. These possess high surface area and are electrically and optically active. These properties can also be tuned to match the intended application.

It is highly interesting to note that while fabricating an electrochemical based biosensor for the various markers, nanostructures in the form of sheets, cubes, or tubes are generally employed. This is quite understandable since these morphologies provide high surface area for the biochemical reactions to take place. Also due to presence of edges, high electron mobility is also observed. Both these parameters aid in highly sensitive measurement of the analytes. For the optical based platforms, generally quantum dots or nanoclusters are used due to their fluorescent properties. This allows for the development of fluorescence quenching based systems. Also, quantum dots of some materials possess peroxidase mimicking properties, which are exploited for the colorimetric based sensors.

Though these materials have been used for the detection of many biological and nonbiological analytes, their application for oxidative stress biomarker detection is less explored. The current review tried to highlight the researchers' efforts of using 2D materials as biosensing platforms for these oxidative stress (OS) markers. Our extensive literature survey has shown that most of the research has been focused on the detection of hydrogen peroxide and 8-OHdG; other markers have not gained significant attention. Among other biomarkers, research related to ferritin has picked up pace very recently. This can be attributed to the multifaceted nature of ferritin as it is widely involved in several diseases. The materials used for ferritin detection include use of nanostructures of graphene and transition metal dichalcogenides.

Having said this, much research is still required further. The scalability of the material synthesis is a major bottleneck. The hydrothermal method for the synthesis of the quantum dots and nanoparticles is the simplest method for the material synthesis. However, the yield obtained is low. Hummers method for the synthesis of graphene provides a relatively large yield, but the use of harsh and toxic chemicals is highly discouraging. These necessitate the development of environment-friendly, cost-effective and high yielding methods for 2D materials synthesis.

Another aspect while developing biosensor is the cost. The traditional methods provide high throughput of sample analysis, thereby reducing the cost of each sample. Research and analysis are required to reduce the cost of 2D material based biosensors. The authors feel that this can be achieved by partnering with industries to further exploit this field.

The ultimate goal is the development of multiplexed detection platform enabling detection of many disease markers simultaneously. This can be achieved by combining many electrodes into a single system. If we consider the specific detection of OS markers using 2D materials, there are many unexplored areas that have not been touched yet. For instance, work related to optical detection of glutathione, 8-OHdG, 3-nitrotyrosine, and ferritin using 2D materials is insufficient and presents a hot area of research. As mentioned in the review, many 2D materials possess peroxidase mimicking activity. This presents a wonderful chance for the development of color based biosensors, which are highly desirable. The 2D oxides and the newest 2D material (MXenes) have not been touched for the detection of OS markers. The 2D oxides due to their oxygen vacancies have been primarily been explored for catalytic activity. These are not among the first choice while considering a nanomaterial based platform for the detection of oxidative stress markers. MXenes, though possess extremely high electrical properties, have not gained much attention. This can be due to tedious synthesis methodology (compared with other 2D materials of other families) and also high cost of the starting material limiting its acceptability. All these perspectives present many opportunities for future research.

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Notes

The authors declare no competing financial interest.

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