

*Mini Review*

## **Electrochemical detection of neurotransmitter dopamine: a review**

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Neurotransmitters monitoring with newly developed tools is a challenge. The quantification and identification of neurotransmitters by electrochemical sensors attracted the attention last years due to the need to provide high sensitivity and selectivity, real-time measurements, and quick response. This review focuses on current advances of different modified sensors used for dopamine (DA) detection. These advances are challenging due to similar redox potentials in real biological samples of high concentration and co-existing interfering species. The different materials description and their role in DA electrochemical detection were evaluated. Therefore, this review opens the door for researchers in neurobiomedical applications.

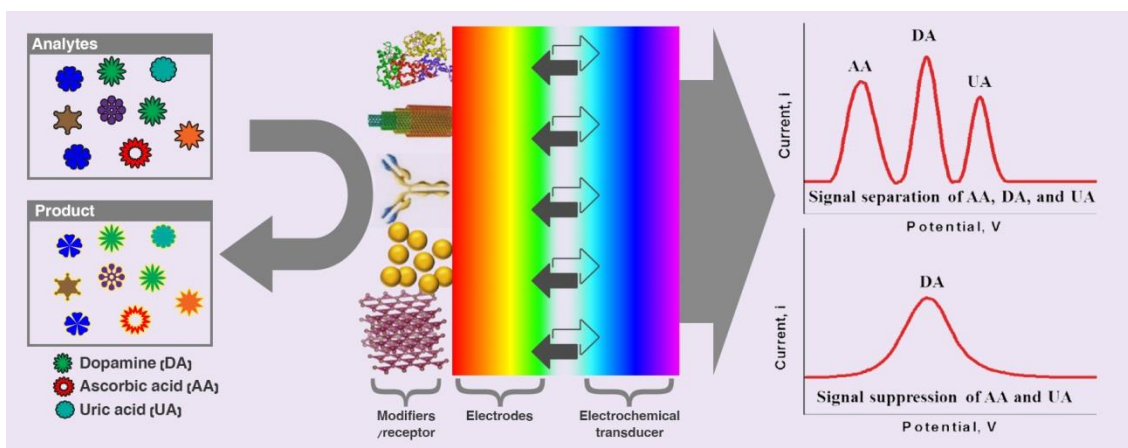
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### **1. INTRODUCTION**

Dopamine (DA) represent essential catecholamines that present in the central nervous system of mammals and regulates human cognition and emotions. In addition, it plays a significant role in cardiovascular, memory and hormonal systems [1, 2]. The normal level of DA in human serum and blood is  $10^{-6}$ - $10^{-9}$  mol/L. However, medical disorders were associated with its abnormal levels such as Alzheimer, schizophrenia, Parkinson and senile dementia diseases [3-5]. Therefore, the DA determination is important inside biological systems for proper diagnosis and treatment of associated disorders. The precise determination of DA levels with simple, low cost, sensitive and selective methods is highly required [6]. Other than all analytical methods, electrochemical studies provide highly sensitive and selective methods for DA inside biological samples. Electrochemical sensors are the most appropriate method for the detection of neurotransmitters. This suitability is due to its potential appears at the potential window of metal surfaces. Small biomolecules (e.g. ascorbic acid and uric acid) that

present together inside blood, urine and extracellular fluids exist a similar potential on the bare electrodes with a significant interference during the detection of DA. Many efforts have been made to modify bare electrodes to separate the ascorbic acid, uric acid and DA signals for high resolution [7-13]. By electrodes modification, the surface of the electrode become has electrocatalytic activity toward the DA biomolecule [14, 15]. The surface modifiers include inorganic complexes, nanomaterials, composite materials, ionic liquids and conducting polymers. The modification process includes a combination between different materials like metal oxide or metal nanoparticles, carbon, ionic liquids and conducting polymers. Schematic diagram of DA electrochemical detection by sensors is shown in Scheme 1. Hundreds of researchers publish articles for DA detection by electrochemical sensors in absence and presence of interfering biomolecules uric acid and ascorbic acid, but most of these methods can not be used in life application due to the cost and complex of modification. Among used sensors, graphene-based sensors are of great promise due to unusual graphene properties like high mechanical properties, excellent electrical and thermal conduction, and high mobility of charge. Therefore, these unique properties of graphene and its based biosensors enhance its effective use for the detection of DA. The electrochemical detection of DA is also includes the use of other materials electrodes such as carbon nanotubes, molecular imprinted polymers, boron-doped ultrananocrystalline diamond, modified electrodes with gold nanoparticles and ZnO nanoparticles. From the previous examples, it is observed that nanomaterials were broadly used for the fabrication of biosensors to detect neurotransmitter DA. Thus, this review is an attempt to summarize the DA electrochemical biosensors for the real-life applications.



**Scheme 1.** Electrochemical dopamine sensors presentation.

## 2. SCOPE OF THE REVIEW

The main goal of the current review is to summarize the developments in the DA electrochemical sensors by different methods. The study includes the electrochemical sensors based on carbon nanotubes, graphene, metal and metal oxides nanoparticles, polymeric materials, ionic liquids and inorganic modifiers. This review focuses on research articles in the period 2000-2019 that describes the

electrochemical detection of DA neurotransmitter via sensors. Therefore, it will offer assistant to the researchers in the field of neurobiological sciences and electrochemical devices.

### 3. OVERVIEW OF MATERIALS USED IN DA ELECTROCHEMICAL DETECTION

#### 3.1. Metal and metal oxide nanoparticles

As a result of metal nanoparticles high reactivity and surface area, it exhibits electronic, physical and chemical properties better than that of bulk materials. The precursor materials of metal nanoparticles are significantly determining the properties of metal nanoparticles. In addition, the stability, shape, size, and charge of metal nanoparticles can be controlled by using stabilizers. Many properties are qualified using metal nanoparticles in electrochemical sensors, such as the ability to convert any small redox activity to a signal. This property, which is because of the high sensitivity of metal nanoparticles to any surface changes, shows fast electron transfer with the analyte due to high surface area. However, the bare electrodes show slow electron transfer and thus affect the ability of modified electrodes with metal nanoparticles to resolve overlapped potentials of mixed compounds. Recent developments in metal and metal oxides-based electrochemical sensors for dopamine are summarized in Table 1. From many reports, it is noticed that the enhancement of analytes electrochemical detection is reached by the combination of different materials with metal nanoparticles.

Electrodes modified with Pd nanoparticles were reported to exhibit high oxidative activity to DA at low potentials but these electrodes fail in high UA and AA concentration systems. So, Pd nanoparticles can be loaded on the surface of graphene oxide (GO) in order to resolve the overlapped peaks by the attraction between DA positive charge and GO negative charge. So, a good support material like cellulose microfibrils supported with Pd nanoparticles was loaded over a semiconductive GO to select DA with LOD = 23 nM [16].

Fe<sub>2</sub>O<sub>3</sub> nanoparticles have several properties such as electrocatalytic properties, stability, natural abundance, and satisfactory bandgap that enhance its use in electrochemical applications. Fe<sub>2</sub>O<sub>3</sub> nanoparticles inside glassy carbon electrode modified with graphene nanosheets speed up the electron transfer between analyte and electrode surface producing a good LOD = 0.001 μM (DPV) and 0.004 mM (amperometric) [17].

Cu<sub>2</sub>O-RGO/GCE modified electrode was prepared by mix Cu<sub>2</sub>O and GO nanoparticles and its drops were loaded over GC surface followed by electrochemical reduction. The fabricated sensor gives excellent electrocatalytic response due to high surface area and adsorption ability [18].

A solvothermal method was used for the preparation of Porous Cu<sub>2</sub>O nanoparticles/graphene composite in the presence of a reducing agent, and then this composite was used to modify GCE. The LOD = 0.015 μM for the fabricated electrode with the absence of AA peak and completely separated DA and UA peaks [19]. Thus, Cu<sub>2</sub>O nanoparticles were used in electrochemical applications due to its low cost, narrow band gap, and high surface area.

The preparation of Au/m-Ni(OH)<sub>2</sub>/GCE by the distribution of gold nanoparticles on Ni(OH)<sub>2</sub> support without surfactant. After that, the composite was used to modify GCE to give excellent peak separations for DA without interference with DA and UA due to the presence of m-Ni(OH)<sub>2</sub> nanowires

that enhance electron transfer process by allowing a good dispersion for gold nanoparticles. The LOD= 0.09  $\mu\text{M}$  for the electrode with peak separation = 260 mV (UA and DA) and 280 mV (DA and AA) [20].

By using one-pot wet reflux method bimetallic Pt-Ni nanoparticles/ RGO was synthesized and loaded over GCE to give a modified electrode with low LOD = 0.0026  $\mu\text{M}$  for DA and good response in the presence of etilefrine hydrochloride and acetaminophen [26]. GCE has modified also with graphene/ferrocene derivative composite (Au/C NC) to give excellent resolved peaks for acetaminophen, DA, AA, and UA with LOD= 0.05  $\mu\text{M}$  for DA [21].

At room temperature with a one-pot approach, GO was reduced over a slice of Zn to form RGO-ZnO composite that used to cover Zn slice. Subsequently, RGO-ZnO composite cover Zn slice was used to modify GCE to fabricate electrode with high sensitivity and good separation for AA, DA, and UA [22].

### 3.2. Polymeric materials

The overlap of p-bonding carbon atom orbitals leads to the delocalization of the electrons inside conducting polymers (CPs). This situation gives it exceptional properties other than polymers like low ionization energy, high electron affinity, electrical conductivity, and low energy optical transition. Across the polymeric chain, CPs have alternating double and single bonds (p-conjugated system). CPs are called synthetic metals as a result of high electrical conductivity [23]. Recent developments in CPs-based electrochemical sensors for dopamine are summarized in Table 1.

From their monomer solutions, the modifier CPs can be electrochemically deposited over the surfaces of bare electrodes. Cyclic voltammetry was used to polymerize a film of poly (2-naphthol) orange on the surface of paraffin wax electrochemically. Thus the graphite electrode is impregnated to show a selective electrocatalytic activity to DA with LOD= 0.13  $\mu\text{M}$  by using DPV as sensing technique. This behavior of the electrode is due to the electrostatic attraction between ammonium and hydroxyl groups of DA with the sulfite group of poly (2-naphthol) orange. This electrode has 60 days of stability, while the peak current may be decreased due to DA oxidation. The buffer solution can be used to regenerate its original current by cycling for 40 segments. From human, rat blood serum and pharmaceutical formulation, DA can be recovered by this electrode [24].

Another method is performing cyclic voltammetry in a solution of phosphate buffer to deposit a film of cinnamic acid polymer on the surface of carbon paste electrode to give excellent electrocatalytic activity with LOD= 3.5  $\mu\text{M}$  and well-separated potentials of AA, and UA. From pharmaceutical drugs and serum, DA can be recovered by this method [25].

Laser-scribed graphene is the formation of graphene layers over the substrate by using laser scribing that has the advantages of graphene plus good mechanical stability, excellent conductivity, flexibility, and high surface area to form implantable arrays/electrodes. Poly(3,4-ethylenedioxythiophene) conducting polymer with its fast electron transfers ability, superior biocompatibility and stability, and low oxidation potential can be functionalized over Laser-scribed graphene to give excellent electrocatalytic activity toward DA with LOD= 0.33  $\mu\text{M}$  and well-separated potentials for AA, UA, and DA. This electrode shows high roughness and surface area compared to other electrodes [26].

4-aminobenzene sulfonic acid can be electro-grafting over graphene paste electrode to show excellent sensing for DA with LOD= 0.09  $\mu\text{M}$  in the presence of 1000 fold AA [27].

Poly(3,4-ethylenedioxythiophene) (PEDOT) can be used to modify GCE to form excellent antifouling electrode in the serum samples with non-specific adsorption of protein as a result of uncharged surface and hydrophilicity that is approved by different techniques such as confocal fluorescence images, EIS, and SEM. LOD=33 nM for this electrode in the presence of concentrated protein [28].

Also, Poly(3,4-ethylenedioxythiophene) can be embedded with another material to fabricate electrodes such as GCE/MWCNTs/CeO<sub>2</sub>-PEDOT in which GCE firstly modified by MWCNTs, and secondly by a chemically polymerized composite CeO<sub>2</sub>-PEDOT. The prepared electrode with excellent electrocatalytic activity and LOD=0.03 due to fast electron transfer process, high active surface area (0.24 cm<sup>2</sup>). From urine samples and pharmaceutical injections, this electrode can recover DA. However, the presence of organic and inorganic impurities, this electrode shows high DA selectivity [29].

Thus, the use of conductive polymers in electrochemical sensors shows a number of advantages such as the avoiding of interfering species that provide selectivity toward the analyte, avoiding surface fouling as it is a protective layer, excellent biocompatibility, providing oppositely charged species against the analytes, and having the properties of both organic polymers and metals.

### 3.3. Carbon materials

Graphene, carbon nanotubes and their derivatives are the most common electrochemical used materials alone or by combination with other materials because of their compatibility, fast electron transfer ability, low cost, modified easily, and availability. Recent advances in carbon-based electrochemical sensors for dopamine are shown in Table 1.

As coming next, many advanced materials were used to modify different shapes of carbon materials to use in electrochemical sensing.

The properties of graphene, such as fast electron transfer, high tensile strength, functionalization easily, high electrical conductivity, and low cost, allow using it for DA electrochemical sensing. The reduction of graphene oxide leads to the formation of graphene with high purity and wide potential window compared to carbon nanotubes and glassy carbon. Some disadvantages of graphene overcome by combination with other materials as discussed next.

Accessible surface areas of graphene were negatively affected as discussed due to reordering of its sheets by van der Waals and p-p interactions. Different morphologies of 3D graphene can be synthesized to overcome the problem that characterized to have higher availability space and larger surface area due to porosity. There are various methods for the preparation of porous 3D graphene such as chemical vapor deposition, chemical etching, and template methods. Due to the ability to control the size of 3D graphene, template method is the convention method.

In a typical template method, microspheres of polystyrene with positive charge were distributed ultrasonically over graphene oxide. To get polystyrene/reduced graphene oxide (PS/rGO), the reducing agent hydroiodic acid was added to the mixture. To remove the template, PS/rGO was submerged in

tetrahydrofuran. Finally, the prepared porous 3D graphene was used to modify GCE by drop 1 mg/mL on its surface. The fabricated electrode gives a linear working range 0.2-0.8  $\mu\text{M}$ , and LOD=0.2  $\mu\text{M}$  for DA in the presence of UA, and AA [30].

The composites of reduced graphene oxide show excellent electrocatalytic activity. So, it can combine with Pd nanoparticles of low cost compared to Au and Pt to form an improved electrochemical activity toward DA. The GCE was modified by the ternary composite Pd/ poly (2-anilinoethanol)/rGO to detect DA with LOD=0.024 $\mu\text{M}$  and a linear range 0.08-250 $\mu\text{M}$  [31].

Also, GCE can be modified by another composite Pd/Poly(3,4-ethylenedioxythiophene)/rGO to give excellent electrocatalytic activity toward DA with a linear range 1-200  $\mu\text{M}$  and LOD=0.14 $\mu\text{M}$  [32].

Carbon nanotubes with its different shapes (MWCNTs and SWCNTs) are widely used in electrochemical applications. Heteroatoms like B, N, and P can be used in the doping process of MWCNTs to enhance its chemical and electrical properties. By the chemical vapor deposition technique, silicon/silicon oxide substrate can be covered by B doped MWCNTs. In this complex, boric acid is the source of B, ethanol is the source of C, and the catalyst is ferrocene. The fabricated electrode shows excellent electrocatalytic activity toward DA with LOD=0.11 $\mu\text{M}$  [33].

### 3.4. Ionic liquids

Ionic liquids (IL) are a new class of purely ionic, salt-like materials that are liquid at unusually low temperatures. These liquid salts with a low vapor pressure at room temperature can be used instead of usual used solvents during chemical reactions. Ionic liquids contain anions and cations with distorted crystal in which physical and chemical properties mainly depend on the present anion and cation. The unusual properties of IL, such as large potential window, less toxicity, high conductivity, high solvation ability, electrochemical stability, and thermal stability, enhance using it in electrochemical applications. ILs exhibit higher conductivity compared to organic electrolytes while its conductivity is lower than aqueous electrolytes because of pairing of ions and slow mobility of large ions. The co-solvent can be used to overcome the high ILs viscosity and enhance the transport of mass [34]. Latest progress in ILs-based electrochemical sensors for dopamine are summarized in Table 1. ILs as a modification process to improve the electrocatalytic activity can replace nonconductive liquids, such as paraffin, and mineral oil. The length of cation alkyl chain and the nature of ions can be used to change hydrophobicity of ILs. Many materials can be dissolved in ILs due to its solvation power and form uniform electrode compositions [35]. The simplicity and sensitivity can be achieved by a combination of ILs and single-walled carbon nanotubes. SWCNT can modify the GCE and screen-printed carbon electrode (SPCE) in BMIMBF<sub>4</sub> and chitosan. Modified SPCE gives better results due to its ease modification. The electrode has LOD= 0.16  $\mu\text{M}$  for DA [36]. BMIMBF<sub>4</sub> achieves the better response of ILs than that of BMIMPF<sub>6</sub>.

### 3.5. Metal organic frameworks

Due to many reasons such as exposed metal sites, significant available surface areas, well-organized crystalline designs, and tunable pores sizes, coordination polymers or Metalorganic frameworks (MOFs) have widely used in different applications including catalysis, adsorption, and

sensing [37]. The electrochemical applications are the most critical use of MOFs, primarily when used to modify electrodes surfaces by combination with other materials such as graphene, and CNTs. Many trials have been performed to use it in DA detection [38]. Current investigations in MOFs-based electrochemical sensors for dopamine are summarized in Table 1. DA can react with the composite UiO-67-DQ, UiO-67- MQ (MOFs), and bipyridinium moieties to improve the sensitivity. Detection of limit can be enhanced using MWCNTs as a modifier [38].

GCE can be modified using the nanocomposite of copper terephthalate MOF/GO in which the reduced GO was obtained by the electrochemical treatment of GO in order to enhance its electrocatalytic activity toward DA. The LOD= 0.21 $\mu$ M for the modified electrode [37].

In another research, GCE was modified using frameworks zeolitic imidazolate (ZIF-8) by the growth of its nanocrystals on graphene to prevent its restacking. The LOD=1  $\mu$ M for this electrode [39].

Likewise, RGO/ZIF-8 nanocomposite can be synthesized by using RGO as a template [124]. XRD and SEM techniques were used to characterize GO, ZIF-8, RGO/ ZIF-8, and RGO. The fabricated sensor has high sensitivity toward DA that investigated according to this research by CV and DPV with LOD= 0.03 $\mu$ M [40].

The MWCNTs can be added to Mn-BDC MOFs to provide a sensor with high sensitivity toward DA, UA, and AA. The LOD= 0.02 $\mu$ M for DA with a linear range of detection 0.01-500  $\mu$ M [41].

The researchers try to study the electrochemical behavior of AA and DA by using the vanadium-substituted phosphomolybdate and MIL-101 (PMo<sub>10</sub>V<sub>2</sub>@MIL-101 (Cr)) composite over pyrolytic graphite electrodes that provide linear ranges 0-0.03 and 0-0.09 $\mu$ M for DA and AA, respectively [42].

DA was also detected over GCE modified by Nafion/C/Al-MIL-53-(OH)<sub>2</sub>. DMF solvent was used to suspend C/Al-MIL-53-(OH)<sub>2</sub> then agitated for 1h. The GCE was modified by using the suspension, and then the solvent kept to evaporate. Finally, (0.5%, 5 mL) Nafion solution was used to coat the electrode. The LOD=8.0 $\mu$ M for DA with a linear range of 0.03-10 $\mu$ M [43].

### 3.6. Inorganic modifiers

Due to their unique properties, the inorganic modifiers were used for the DA electrochemical detection. Recent developments in inorganic modifiers-based electrochemical sensors for dopamine are summarized in Table 1.

For example, the modification of GCE by the nanocomposite of rGO/Bi<sub>2</sub>S<sub>3</sub> that synthesized by a one-pot hydrothermal method in which thioacetamide was used as sulfur source and reducing agent. The amount of GO was used to control the morphology of rGO/Bi<sub>2</sub>S<sub>3</sub> nanocomposite. The LOD=12.3 nM toward DA with a linear range of 0.01-40  $\mu$ M [44].

Another study was used nickel foam (NF) as a substrate for the growth of nanoneedles of hollow-core-shell NiCo<sub>2</sub>S<sub>4</sub> array by using the hydrothermal process. The LOD=0.2 $\mu$ M toward DA detection by using DPV technique [45].

Perovskite complex oxides (ABO<sub>3</sub>), in which the rare earth metal represents by (A) and transition metal represents by (B) have unique chemical and physical properties that qualify it to be used in DA electrochemical sensing. The hydrothermal approach, which allows the growth and shape control of

nanostructures, was used for the preparation of  $\text{LaCoO}_3$  nanostructures with the employment of different surfactants as CTAB, citric acid, and urea.  $\text{LaCoO}_3$  nanostructures that prepared in the presence of urea as surfactant have higher surface area due to porous structure. So, the porous  $\text{LaCoO}_3$  nanostructures show the highest electrocatalytic activity toward DA. The prepared  $\text{LaCoO}_3$  nanostructures were used to modify GCE to improve its ability to DA detection; however, in the presence of AA and UA 100-fold concentrations [46].

The surfaces of a boron-doped diamond (BDD), screen-printed electrodes (SPEs), and GCE were modified by using 2D Boron Nitride (2D-hBN) with different amounts. One  $\mu\text{M}$  of DA was detected over unmodified electrodes by using CV inside phosphate buffer. Higher peak current was provided by SPE, while the best peak potential was provided by GCE with low detection of DA. As the amount of boron nitride increased from 108 ng to 324 ng, the oxidation potential decreases and the peak current increases for 2D-hBN/SPE toward DA with  $\text{LOD}=0.65 \mu\text{M}$ . For hBN/GCE and hBN/BDD electrodes, the peak current decreases and oxidation potential increases, meaning that the electrocatalytic activity depends on the roughness and smoothness of the surfaces of the electrodes [47].

Due to a low cost, wide electrochemical window, and high thermal stability of fluorine-doped tin oxide (FTO), it was used for the electrochemical detection of DA. Well-separated signals of DA, AA, and UA can be obtained with high sensitivity by using graphene nanoplatelet (GNP)-modified FTO electrodes. The obtained results is due to the mixing of FTO unique properties with functional group enrichment of graphene nanoplatelet. High sensitivity was detected toward DA and UA as a result of interaction between GNPs and analytes by p-p and H-bonding interactions. However, a lower sensitivity was observed for AA as a result of the repulsion with negative GNPs functional groups. The  $\text{LOD}=0.28 \mu\text{M}$  for UA and  $0.22 \mu\text{M}$  for DA in the occurrence of AA high concentrations [48].

DA selective determination has been performed using nitrogen-doped graphene (N-G)/nickel tetrasulfonated phthalocyanine ( $\text{NiTsPc}$ ) nanocomposites in which the available sites of nitrogen-doped graphene allow the interaction with DA that would enable fast electron transfer between the analyte and the modified electrode. The  $\text{LOD}=0.1 \mu\text{M}$  for N-G/ $\text{NiTsPc}$ /GCE toward DA [49].

DA potentials can be shifted to lower values and the electron transfer can be accelerated by using metal complexes in the electrochemical sensing. Octahedral metal ions can coordinate with benzimidazole-scaffolded ligand in a dinuclear manner to form self-assembled monolayers over the surface of gold metal. So, the DA was detected in the presence of AA and UA over the sensor Au-Mn(II) Schiff-base complexes to provide 6.8 nM of LOD [50].

In another literature, the graphite electrode was modified using Copper (II) complexes with bis(3,5-dimethylpyrazol-1-yl) methane and acetate. By poly(sodium 4-styrenesulfonate) addition, the activity toward DA was improved due to the interaction between DA and sulfonate anion, which accelerate the electron transfer. The  $\text{LOD}=0.5 \mu\text{M}$  toward DA in the existence of UA and AA [51].

DA electrochemical sensing can be improved by the combination of different materials with metal complexes such as the association between Nafion and  $[(\text{Co}(\text{bdmpzm})_2(\text{NCS})_2)]$  cobalt complex to modify SPE (screen printed electrode). Quasi-reversible redox behavior was showed for modified electrode with a great recovery in samples of urine [52].



**Table 1.** Electrochemical sensors for dopamine detection

Sensor	Detection method	LOD ( $\mu\text{M}$ )	Ref.
PPyNW/PtNP	DPV	0.6	[53]
Au/RME	CV	0.05	[54]
NiO/CNTs/PEDOT	DVP	0.026	[55]
Nafion-SWCNT	SWV	0.095	[52]
CuNP	CV	$5 \times 10^{-5}$	[56]
TiO <sub>2</sub>	PEC	$0.15 \times 10^{-3}$	[57]
Nano-MnOOH	SWV	0.1	[58]
Tyrosinase/NiO/ITO	CV	1.04	[59]
AuNP-DNS/MWCNT	DPV	0.05	[60]
AuNP@MIES	DPV	0.0078	[61]
BSA-Au NC	PL	0.06	[62]
luminoleH <sub>2</sub> O <sub>2</sub> eHKUST-1	CL	0.0023	[63]
Fe <sub>3</sub> O <sub>4</sub> @ZIF-8/RGO	DVP	0.00067	[64]
UiO-66-NO <sub>2</sub> @XC-72	DVP	0.005	[65]
Mn-MOF/MWCNT	DVP	0.002	[41]
Fe-MIL-88 MOF	ECL	$2.9 \times 10^{-7}$	[66]
ZIF-8	CV	0.195	[67]
RGO/ZIF-8	DPV	0.03	[40]
Nafion/C/Al-MIL-53-(OH) <sub>2</sub>	DPV	0.008	[43]

**Table 2.** Metaleorganic frameworks (MOFs) sensors for dopamine detection

Sensor	Detection method	LOD ( $\mu\text{M}$ )	Ref.
Fe-MIL-88eH <sub>2</sub> O <sub>2</sub> -OPD	FS	0.046	[68]
G-ZIF8	CV	1.0	[39]
POMOF/RGO	CV	0.0804	[69]
CNT-CS-SDS	DPV	6.32	[70]
GR/GLN/SPCE	DPV	0.0045	[71]
FTO/SiO <sub>2</sub> /AgNPs/TiO <sub>2</sub>	DPV	0.03	[72]
GCE-nsAu	SWV	0.85	[73]
PG/GPE	CV	0.04	[74]
PEDOT-LSG	DPV	0.33	[26]
GCE/PGE	DPV	0.2	[30]
PNEDA/AGCE	DPV	0.070	[75]
P2NO/PIGE	DPV	0.13	[24]
Graphite/[Cu(CH <sub>3</sub> COO) <sub>2</sub> (L)]	DPV	0.5	[51]
RGOe ZnO/GCE	DPV	1.08	[22]
Cs-SWCNT-IL/SPCE	LSW	0.16	[36]
Au/HBMs	SWV	$0.41 \times 10^{-6}$	[76]
RGO-P2AE-Pd/GCE	DPV	0.024	[31]
GCE	CV	5	[77]
Cu <sub>2</sub> O-RGO/GCE	SDSLV	0.006	[18]
Pd/PEDOT/rGO/GCE	DPV	0.14	[32]
NF-NiCo <sub>2</sub> S <sub>4</sub>	DPV	0.2	[45]
PTB/AGCE	DPV	0.36	[78]
GCE/IL/PEDOT	CV	0.033	[28]
CA/MWCNTs/GCE	DPV	0.0042	[79]
Nafion-SWCNT-[Co(bdmpzm) <sub>2</sub> (NCS) <sub>2</sub> ]/SPCE	SWV	0.095	[36]
Au/m-Ni(OH) <sub>2</sub> /GCE	Amperometry	0.09	[20]
LaCoO <sub>3</sub> /GCE	DPV	3.53	[46]
GNP/FTO	DPV	0.22	[48]
GQDse Nafion/GCE	DPV	0.00045	[80]

Fe <sub>2</sub> O <sub>3</sub> NP/GRS/GCE	DPV	0.004	[17]
SDBS-EGPE	DPV	0.027	[81]
Au-Mn(II) Schiff base complex	DPV	0.0068	[50]
LaMnO <sub>3</sub> /GCE	DPV	6.22	[82]
pCu <sub>2</sub> O NS-rGO/GCE	DPV	0.015	[18]
GCE/MWCNTs/CeO <sub>2</sub> -PEDOT	DPV	0.03	[29]
N-G/NiTsPc/GCE	Amperometry	0.1	[49]
rGO/Bi <sub>2</sub> S <sub>3</sub> -1/GCE	DPV	0.012	[44]
Pte Ni/rGO/GCE	DPV	0.0026	[83]

#### 4. COMPARISON BETWEEN DIFFERENT METHODS OF SENSING

Results reproducibility, sensitivity, and miniaturization easily are properties of electrochemical sensors that made these sensors used in analytical methods, efficient, and cost-effective. High surface area and porosity of metallic NPs allowing using it in the fabrication of the electrochemical sensors for the detection of DA neurotransmitter with good LOD and linear range of detection using DPV technique.

Overall NMs graphene and CNTs have mechanical strength and thermal/electrical conductivity, which allow using in the fabrication of DA sensing electrodes as summarized in Table 1. Graphene-based sensors are less sensitive than CNTs based sensors, as shown from the value of LOD. Consequently, the most proper material to detect DA in biological samples is CNTs.

MOFs based sensors for DA detection are listed in Table 2. Each MOFs based sensor has its structure and exceptional composition. These sensors provide excellent LOD and linear range value according to ECL technique. These advantages because these sensors reveal high-grade stability, low LOD, high sensitivity, good results reproducibility and wide linear range of measuring for DA in different samples (hydrochloride injection, urine, buffer solution, and serum). Thus, a wide range of MOFs based electrochemical sensors has been constructed due to MOFs unique properties. MOFs show a broad range of applications such as using as diagnostic materials or new therapeutic in biomedical application.

Inorganic modifiers, such as inorganic support materials, perovskite-type complex, NiCo<sub>2</sub>S<sub>4</sub>, 2D-Hbn, metal-ligand complexes, have shown DA excellent sensors like a good LOD and linear range of detection provided by Au-Mn(II) Schiff base complex based sensor. However, the using of Perovskite-type complex oxides in electrochemical applications still in its initial steps, its electrodes provide a good LOD comparing to other electrodes. Different types of DA sensors with their long-term stability are presented in Table 3.

**Table 3.** DA selected electrochemical sensors with their long-term stability

Sensor	DA (μM)	Technique	Conditions	Interferences	Response retained (%)	Ref.
PG/GCE		CV	2 weeks, 4°C	UA	94	[74]
PNEDA/AGCE	1		2 weeks		95	[75]
PTB/AGCE	10	DPV	1 week, 4°C		97	[78]
SDBS-EGPE	500		30 days, 25 °C		85.3	[81]

GNP/FTO	1000	CV	1 weeks, 4°C, PBS	UA and AA	92.8	[48]
N-G/NiTsPc/GCE		CV	30 days		93.2	[49]
RGOeZnO/GCE	150	DPV	1 week, room temperature and air	UA and AA	97	[22]
pCu <sub>2</sub> O NS-rGO/GCE			30 days, 4°C		94.3	[19]
Au/m-Ni(OH) <sub>2</sub> /GCE	2000		2 weeks		85	[20]
GCE/MWCNTs/CeO <sub>2</sub> - PEDOT	100	DPV	30 days	UA and AA	89.5	[29]
PEDOT-LSG	0.001	CV	30 days, 4°C, PBS		93.8	[26]
P2NO/PIGE	30	CV	5°C for 60 days		100	[24]
RGO-P2AE-Pd/GCE	5	DPV	2 weeks		88.4	[31]
GCE/PGE		DPV	1 week		95	[30]

## 5. CONCLUSION

The detection of DA in real-life applications as indicated by hundreds of publications is a promising area of research. Therefore, the possible electrochemical methods of DA detection must be reviewed. Nature of modifier is responsible for the sensitivity of modified electrode toward analytes. Better moving of the analytes and high surface area, conductance lead to the acceleration of electron transfer kinetics which achieved by using the modifiers such as CPs, NMs, redox mediators and IL. More specificity and selectivity were provided by the modification and led to better peak potential separation, which originates from unique properties of the modifier. DA is a positive charge biomolecule, so it is required that the modifier be a negative charged species for more selectivity. Thus, when the modification leads to electrostatic interactions or hydrogen bonding, this will enhance specificity and selectivity. In addition, the modification process must prevent the interference process for promoting the selectivity. Herein, a discussion of the possible modified electrodes for DA detection, which provide high electrocatalytic activity, excellent figures of merit, the potential of mass-production, high abundance, low-cost, simplicity of modification has been highlighted.

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