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### **Review Article**

# Critical Review on Carbon Nanomaterial Based Electrochemical Sensing of Dopamine the Vital Neurotransmitter

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The clinical diagnosis of dopamine biomarkers plays a crucial role in classifying nervous system-related disorders, which are increasingly prevalent across all age groups worldwide. Accurate and thorough diagnosis is essential for administering appropriate drug therapies. However, it has been observed that there is a scarcity of diagnostic methods available in the market, highlighting a significant demand for such tools, particularly as the healthcare system transitions towards personalized medicine. This growing demand has garnered significant attention from researchers working in diagnostics. It is of great therapeutic and pharmacological significance to design and develop diagnostic instruments for the monitoring of dopamine levels both in vivo and in vitro. Extensive research efforts have been dedicated to devising realistic diagnostic techniques for assessing dopamine levels in bodily fluids, with a particular focus on electrochemical sensing methodologies. While studies related to electrochemical sensing of dopamine have shown promising advancements in terms of simplicity, speed, and sensitivity, there remains a notable gap in their application for clinical studies. Thus, this review aims to provide an overview of the latest progress in non-enzymatic (enzyme-free or direct electrochemical) electrochemical sensing of dopamine, specifically focusing on its integration with carbonaceous nanomaterials in electrodes. Additionally, the review discusses the potential for the commercialization of these laboratory-proven techniques soon, emphasizing their feasibility and practicality in real-world applications.

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## **Graphical Abstract**



### Highlights

- This review initially summarizes the properties of dopamine and the significance of dopamine sensing.
- It discusses the fundamental features of carbonaceous nanomaterials and their advantages in electrochemical sensing.
- This review presents the latest developments in quantitative dopamine sensing platforms based on carbonaceous nanomaterials.
- The authors critically evaluate various aspects of electrochemical dopamine detection and interferences.
- Finally, the review outlines critical challenges in dopamine sensors and provides prospects.

## 1. Introduction

Dopamine is an active endogenous organic molecule acting as a messenger, known as a neurotransmitter, within the

nervous system and various biological systems of both human and animal bodies. Extensively studied due to its significance in human physiology and psychology, dopamine (DA) is secreted by dopaminergic neurons in the brain's Substantia nigra (SNr) region, originating from the amino acid tyrosine. It circulates through the bloodstream, reaching every cell to regulate their function. Regulating various actions and behaviors throughout the body, dopamine plays a vital role in human physiology, and it signaling pathways, known as the dopaminergic system, are crucial for maintaining physiological processes<sup>[1][2][3][4][5][6]</sup> Dysfunctions in dopamine secretion from brain cells can lead to neurological disorders, including the neurodegenerative condition Parkinson's disease, characterized by uncontrolled brain activity due to the loss of dopamine-secreting neurons and decreased dopamine production levels<sup>[7][8][9][10]</sup>. Additionally, various disorders, such as depression, psychotic depression, ADHD (attention deficit hyperactivity disorder), bipolar disorder, and schizophrenia, are associated with imbalances in dopamine levels<sup>[11][12][13]</sup>. According to the World Health Organization (WHO), neurological disorders contribute significantly to mortality, accounting for 12% of total deaths globally, a figure projected to double by 2030 due to the aging population<sup>[14]</sup>. In the United States alone, more than half a million people are affected by Parkinson disease<sup>[15]</sup>. Factors such as drug abuse and diets high in sugar and saturated fat can suppress dopamine secretion, while a protein-deficient diet lacking in tyrosine can lead to lower dopamine synthesis. Medications are available to treat dopamine deficiency, including dopamine-stimulating and modulating drugs that regulate dopamine resupply to nerve cells<sup>[16]</sup>. Chemically, dopamine is an amino acid-derived hormone with a molecular weight of 183 Da, known as 3,4-Dihydroxytyramine  $(C_0H_{13}NO_3)$ . It comprises of an amine group connected to a benzene ring through an ethyl group, and two hydroxyl side groups, occurring as a large organic base and cationic under physiological conditions  $\frac{[17]}{}$ . Dopamine is hydrophilic and is approximately 50% bound to plasma proteins in circulation.

# 2. Dopamine diagnosis and clinical significance

Monitoring and diagnosing diseases are of critical importance for effective treatment and the prevention of long-term complications in patients<sup>[13]</sup>. Similarly, the monitoring of dopamine biomarker levels in bodily fluids has become crucial, as they are directly linked to the dysregulation of functions associated with the dopaminergic system in the brain. Recent studies suggest that major depressive mental disorders are increasingly common across all age groups, underscoring the need for early diagnosis and monitoring through dopamine-based diagnostic methods<sup>[18]</sup>. Various techniques have been developed to measure dopamine concentration and its analogs, such as poly (3-(3-4-dihydroxy phenyl)-L-alanine) (PL-DOPA), poly (5-hydroxy tryptophan) (PL-50HTP), and poly (Adrenalin) (PAdrenalin), in bodily antibody-based fluids. Commercial enzyme-linked immunosorbent assay (ELISA) kits are widely available in the market and are commonly used to measure dopamine concentrations in samples such as serum, plasma, urine, tissue homogenates, and other biological fluids<sup>[19]</sup>. These kits are highly specific for dopamine and show minimal crossreactivity with dopamine analogs, making them beneficial for patients undergoing dopamine-stimulating treatment for conditions such as Parkinson's disease. Dopamine concentration in bodily fluids generally varies across different age groups and disease states. Research reports indicate that in normal adults, the standard range of dopamine at the ventral tegmental area (VTA) of the brain is approximately  $4.8\pm1.5$  nm, while in the red nucleus, it should be around  $0.5\pm$ 1.5 nm<sup>[20]</sup>. In healthy individuals, the concentration of dopamine in urine ranges from 0 to 20 ng/ml (0-0.15 nM), and in blood plasma, it ranges from 0 to 28 ng/ml (0-0.1  $\mu$ M). Urine typically contains a higher concentration of dopamine compared to other bodily fluids, although there is no clear evidence of dopamine presence in sweat. Additionally, the standard dopamine level is lower in patients with renal or hepatic diseases<sup>[18][21]</sup>.

Commercially available ELISA diagnostic kits are efficient and accurate in detecting dopamine concentrations ranging between 1.56-100 ng/ml<sup>[22]</sup>. However, the sensitivity of these kits may vary after prolonged storage, and they may not be suitable for detecting below-average levels of dopamine in body fluids associated with certain neuronal diseases. The existing methods for dopamine detection are complex, requiring rigorous sample preparation, including bloodplasma separation, specialized laboratory equipment, skilled workers, and high reagent costs. Therefore, there is an ongoing need for advanced diagnostic platforms that offer earlier, rapid, simultaneous, and accurate detection of dopamine in physiological or biological samples for therapeutic purposes. Importantly, such diagnostic kits should be user-friendly, allowing operation by individuals at any time and location.

Numerous research papers have been published detailing advances in techniques for in vivo and ex vivo detection of dopamine, including enzyme assavs<sup>[23]</sup>. spectrophotometry<sup>[24]</sup>, high-performance liquid chromatography<sup>[25][26]</sup> mass spectrometry<sup>[26]</sup>, microdialysis<sup>[27]</sup>, microelectrodes<sup>[28]</sup>, capillary electrophoresis<sup>[29]</sup>, fluorescence<sup>[30]</sup>, chemiluminescence<sup>[31]</sup>, flow-injection<sup>[32]</sup>, colorimetric, electrochemical<sup>[33][34]</sup>, and photo electrochemistry<sup>[35][36]</sup>, detection methods. While these analytical sensing procedures offer various advantages, such as sensitivity and specificity, many are expensive, timeconsuming, involve complex pre-treatment steps, use hazardous substances, and do not provide continuous analysis. However, electrochemical sensing techniques stand out as the most straightforward, rapid, and cost-effective methods for detecting neurotransmitters, including dopamine<sup>[37]</sup>.

This critical review emphasizes the importance of dopamine sensing and outlines the latest advancements made by nonenzymatic-based electrochemical biosensors. The discussions primarily revolve around the utilization of different electrochemical detection methods incorporating carbonaceous nanomaterials (CNs), signal amplification strategies, and their benefits. Additionally, the review highlights the simplicity and accuracy of dopamine detection systems. Finally, the review suggests trials and potential solutions for integrating electrochemical biosensors into the healthcare market.

# 3. Outline of electrochemical sensing methods

The demand for sensing applications tailored to human ailments is currently surging, paralleling the success of glucose sensors in the market. Presently, healthcare is becoming increasingly personalized with the advent of advanced diagnostic sensors such as wearable sensors, enabling customized care to meet individual needs. The World Health Organization (WHO) anticipates a significant surge in demand for real-time healthcare sensors in the near future. Consequently, diagnostic sensor development stands out as one of the most active research areas in the healthcare sector. Electrochemical sensors represent a rapidly growing segment in the healthcare market, owing to their numerous advantages<sup>[38]</sup>. In the present global market estimation, electrochemical sensors were valued at USD 6.19 billion in 2019 and are projected to reach USD 11.83 billion by 2025, with a compound annual growth rate (CAGR) of 11.4% over the forecast period 2020 – 2025<sup>[39]</sup>.

Electrochemical sensors are considered the most straightforward approach among analytical techniques. They are adept at measuring potential, charge, or current to determine the concentration of an analyte or characterize its reactivity<sup>[40]</sup>. chemical Electrochemical sensing is unparalleled compared to other sensing methods due to its capability to continuously monitor the level of a chemical substance. Essentially, electrochemical sensing involves a transfer of charge from an electrode into a liquid or solid sample phase. Chemical reactions occur at the electrodes as a result of this process, and charge is carried through the sample phase mass. The chemical modulation of both electrode reactions and charge transport is the foundation of the sensing process<sup>[41]</sup>. Several factors influence the sensing process, including electrode type, electrolyte choice, and the nature of the analyte. Additionally, the fabrication method and geometry of the electrode can significantly impact the voltammetric response of the system<sup>[42]</sup>.

The potential advantages of electrochemical sensing over other detection techniques include susceptibility to miniaturization, cost-effectiveness, delivery of both quantitative and qualitative results, low detection limits, an extensive linear response range, reliability, and reproducibility<sup>[43]</sup>. Due to these numerous advantages, electroanalytical methods find extensive application in sensing applications. The most common electroanalytical techniques include cyclic voltammetry (CV), differential pulse voltammetry (DPV), chronoamperometry (CA), linear sweep voltammetry (LSV), stripping voltammetry (SV), square wave voltammetry (SWV), and electrochemical impedance spectroscopy (EIS), among others<sup>[44]</sup>.

Among these techniques, cyclic voltammetry, fast-scan cyclic voltammetry (FSCV), and differential pulse voltammetry are particularly prevalent in dopamine sensing approaches. Each electroanalytical technique mentioned can be highly effective when optimized to achieve the best electrochemical response in each medium. Cyclic voltammetry, for instance, is a well-known and fundamental analytical tool used by electrochemists to study investigate the electrochemical characteristics of a molecule adsorbed onto an electrode or an analyte in solution<sup>[43]</sup>. Fast-scan cyclic voltammetry, on the other hand, is a variant of cyclic voltammetry characterized by very high scan rates (up to  $1 \times 10^6 \text{ Vs}^{-1}$ ), enabling the measurement of rapid changes in electroactive biomolecules in localized cells and tissues<sup>[45]</sup>.

Differential pulse voltammetry (DPV) is another widely used technique in dopamine sensing studies due to its ability to produce less charging current, resulting in lower detection limits, and its capability to differentiate between analytes<sup>[46]</sup>. Sophisticated electrochemical workstations equipped with modular programs facilitate various analytical studies simultaneously. Additionally, portable devices like microfluidics and customized electrochemical testing gadgets are available in the market for simultaneous detection at a reasonable  $cost^{[47]}$ .

### 3.1. Electrochemical sensing of dopamine

Electrochemistry is an effective analytical approach for monitoring electroactive species like dopamine in living organisms. With the rapid advancement in the application of various classes of nanomaterials in electrochemistry, it has become an invaluable tool, spanning from experiments in vitro to in vivo and in situ measurements of cell communications<sup>[17]</sup>. The electrochemical sensing of dopamine can be classified into two main types: biosensing and chemical sensing. Biosensors utilize enzymes as recognition elements that catalyze reduction-oxidation (redox) reactions. In dopamine sensing, the enzyme tyrosinase (Tyr), also known as polyphenol oxidase (PPO), has been utilized in several published biosensors as a recognition element<sup>[48]</sup>. Conversely, chemical sensors consist of nonbiologically active elements as transducers, offering greater selectivity and sensitivity in analyte detection. These are also known as non-enzymatic sensors<sup>[49]</sup>. Recently, nonenzymatic sensors have been perceived to overcome the limitations of enzymatic sensors, such as high cost, complex production procedures, and short shelf lives.

Electrochemical sensors with modified electrodes have been widely employed as selective sensing platforms for dopamine and other neurotransmitters. A variety of inorganic or organic materials with strong electrical conductivity and catalytic qualities are used to create these modified electrodes<sup>[49]</sup>. In this review, we gather information from the latest discoveries and comparatively examine them with earlier competitive publications in this field. Specifically, we focus on non-enzymatic electrochemical sensing methods of dopamine, particularly those based on carbon nanomaterials.

The inherent electroactive nature of dopamine facilitates its quantification through electrochemical detection methods. Under physiological conditions, dopamine undergoes electrochemical oxidation to form dopamine-quinone (DAQ). This irreversible two-electron process, accompanied by the transfer of two protons (2e/2H+), can be detected using electrochemical analytical techniques<sup>[50]</sup>. The faradaic current estimated from the oxidation of dopamine may exhibit linearity with its concentration in the extracellular medium. However, electrochemical detection of dopamine, both in vivo and in vitro, is often challenged by the presence of similar compounds, including electroactive monoamine neurotransmitters such as acetylcholine, histamine. norepinephrine, serotonin, octopamine, neuromodulators like enkephalins, endorphins, dynorphins, and metabolites such as uric acid and ascorbic acid, all of which are considered as interferences<sup>[51][52]</sup>. Notably, uric acid (UA) and ascorbic acid (AA), which are major interfering molecules, coexist constantly with biological fluid specimens. Despite being low molecular weight antioxidants abundant in the central nervous system and body fluids, the concentrations of UA and AA are several orders higher than those of dopamine and other neurotransmitters.

analysis, During electrochemical oxidation peaks corresponding to dopamine, UA, and AA observed at a bare electrode may overlap, resulting in voltammetric responses that complicate dopamine determination<sup>[53]</sup>. Several dopamine sensing studies have reported similar challenges. with bare electrodes failing to separate the signals of these electroactive compounds<sup>[35]</sup>. Additionally, bare electrodes are prone to fouling effects due to the accumulation of oxidized products on the surface, leading to poor selectivity and sensitivity<sup>[54]</sup>. To address these complex issues, researchers have advocated for the use of chemically modified electrodes as a diagnostic platform to enable the single detection of dopamine amidst interferences. In all dopamine sensing methods, charged materials are typically used in electrode modification due to the known charge properties of dopamine (pKa=8.87), UA (pKa=5.75), and AA (pKa=4.10). Consequently, the modification of carbon-electrode materials with specific functional groups offering negative charges (such as carbonyls, phenols, lactones, and carboxylic acids) facilitates the selective adsorption of cationic dopamine while repelling the anionic species such as ascorbate and uric acid at physiological pH<sup>[42]</sup>.

In recent years, researchers have observed significant progress in the chemical modification of electrode surfaces, particularly employing carbonaceous nanomaterials (CNs). These CNs have been implemented on electrodes to enhance catalytic affinity, expand reaction space, and mitigate the influence of interferences. Through the utilization of CNs-modified electrodes, researchers have achieved notable advancements and published numerous studies focusing on the selective sensing of dopamine amidst interfering compounds<sup>[35]</sup>.



Figure 1. Chemical properties of the common neurotransmitters and their metabolites

# 4. Carbonaceous nanomaterials in electrochemical sensing

Carbon remains an immensely versatile element and ranks as the sixth most abundant element in the universe. It serves as the foundation for at least 95 percent of known compounds, comprising approximately 10 million compounds to date<sup>[55]</sup>. Carbon exhibits a diverse array of properties owing to its various allotropes and structures, characterized by sp, sp2, or sp3 hybridization. The ability of carbon orbitals to hybridize in these configurations gives rise to numerous natural (such as diamond, amorphous carbon, and graphite) and synthetic allotropes (including graphene, carbon nanotubes, fullerenes, etc.). At the nanoscale level, these synthetic allotropes are referred to as carbonaceous nanomaterials. Carbonaceous nanomaterials have garnered extensive attention in the realm of electrochemical sensors for neurotransmitter analysis. This is owing to their interfacial properties, which facilitate efficient electron transfer and the ready adsorption of neurotransmitters through electrostatic interactions<sup>[42]</sup>. Numerous studies have underscored the remarkable sensing capabilities of electrodes modified with carbonaceous nanomaterials, particularly in the detection of dopamine, by enhancing electron transfer kinetics<sup>[56][57]</sup>.

Carbonaceous nanomaterials, ranging from 1 to 100 nm in size, are widely regarded as ideal electrode materials owing to their exceptional physicochemical properties at the nanoscale.

These nanomaterials hold immense appeal across various electrochemical sensing applications due to their enhanced interfacial adsorption properties, heightened electrocatalytic activity, biocompatibility, and rapid electron transfer kinetics[58][35]. Among the myriad carbonaceous nanomaterials utilized in electrochemical sensing, graphene (Gr) and its derivatives, such as graphene oxide (GO) and reduced graphene oxide (rGO), stand out prominently. Additionally, various types of carbon nanotubes (CNTs), including single-walled carbon nanotubes (SWCNTs), doublewalled carbon nanotubes (DWCNTs), and multi-walled carbon nanotubes (MWCNTs), each possessing distinct thicknesses and metallic/semiconducting properties, have found widespread use across diverse electrochemical applications<sup>[57]</sup>. Fullerenes (C60), another form of carbon allotrope, have also made significant contributions to electrochemical studies, akin to other carbon nanomaterials, within sensing platforms<sup>[59]</sup>.

Graphene, a fundamental constituent of graphite, exhibits a crystalline structure composed of atoms arranged in hexagonal patterns. Remarkably, a one-millimeter-thick graphite sheet can yield up to 3 million layers of graphene nanosheets. Dubbed a "wonder material" upon its discovery, graphene owes its acclaim to its remarkable electrical conductivity stemming from its sp2 hybridization energy and its delicate atomic structure (0.345 nm). These distinctive properties render graphene an ideal candidate for various applications, including electrodes, batteries, and solar panels. Furthermore, graphene has emerged as a favored nanomaterial for electrochemical sensing applications due to its extensive 2-D electrical conductivity, expansive surface area, and relatively cost-effective manufacturing processes. Various forms of graphene, such as reduced graphene oxide, graphene quantum dots, carbon nanohorns, graphene nanofoams, graphene nanorods, graphene gels, and graphene nanoflowers, have gained increasing popularity in sensor fabrication. Graphene boasts several advantages over carbon nanotubes (CNTs), including the absence of metallic impurities and the potential for "bulk" production from graphite. Notably, graphene can be produced through methods like mechanical exfoliation of graphite, reduction of graphite oxide, epitaxial growth of silicon carbide, and unzipping of CNTs<sup>[55]</sup>. On the other hand, graphene with structural flaws and functional groups is produced by chemical reduction of graphite oxide, which is widely used in electrochemical sensors to improve the electrochemical detection of neurotransmitters<sup>[60]</sup>. Graphene-modified and graphenecomposite electrodes have been directly integrated and utilized in dopamine sensing<sup>[61]</sup>.

Once again, graphite serves as the primary source of carbon nanotubes (CNTs) and their structural configurations. CNTs represent unique nanoscale entities composed of one-atomthick sheets of sp2-hybridized graphene rolled into tubular structures. These structures can manifest as single-walled carbon nanotubes (SWCNTs), double-walled carbon nanotubes (DWCNTs), or multi-walled carbon nanotubes (MWCNTs) based on the number of concentric rings they possess. The diameter of SWCNTs typically ranges from 0.7 to 2 nm, while their lengths vary from a few hundred nanometers to micrometers<sup>[57]</sup>. Other types of CNTs exhibit diverse size ranges determined by the number of rings in their structure. The conductive and mechanical properties of CNTs are inherently structure-dependent, resulting in variations between different types of CNTs. MWCNTs, for instance, exhibit higher conductivity and mechanical stability compared to other types. These distinctive characteristics make CNTs suitable for a wide array of applications, particularly as platforms for composites requiring enhanced electrochemical and conductive properties. Consequently, carbon nanotubes hold significant potential due to their high surface-to-volume ratio and unique electron transport properties, which can be significantly influenced by minor surface modifications induced by the binding of macromolecules. Such one-dimensional materials offer the promise of rapid and sensitive non-enzymatic detection, particularly in real-time scenarios. Because of its quick electron transport, less electrode fouling, lower overpotential, and enhanced sensitivity and selectivity for neurotransmitter detection despite interferences, CNs-based electrodes have been utilised in numerous dopamine sensors<sup>[51][62][63]</sup>. Dopamine detection has been achieved with the use of carbon nanotubes (CNTs), graphene, and its derivatives, either alone or in combination with metal nanoparticles or polymers, according to a number of literary works<sup>[35][51][64][35]</sup>. Moreover, the capability to attach chemical species to the sidewalls of CNTs enables the introduction of unique catalytic functionalities. For example, doping graphene or CNTs with heteroatoms such as N, P, B, S, Cl, and Si can introduce defects in the ends and sidewalls, thereby tuning their electrocatalytic activity and enhancing their ability to sense dopamine<sup>[65][42]</sup> [66]

Carbonaceous nanomaterials find extensive use in modifying traditional carbon-based electrode surfaces for sensing applications. These materials include carbon paste electrode (CPE), glassy carbon electrode (GCE), glassy carbon paste electrode (GCPE), carbon fibers (CF), edge plane and basal plane pyrolytic graphite, boron-doped diamond electrodes (BDDE), carbon fiber microelectrodes (CFMEs), graphene and graphite-based electrodes, screen-printed electrodes (SPE), and flexible carbon electrodes (FCE). These electrodes can be readily modified to create chemically modified electrodes (CMEs) tailored to various electrochemical functions. Techniques for integrating carbonaceous nanomaterials into sensors encompass direct growth on substrates, drop-casting, incorporation into polymers, co-deposition with metal nanoparticles, and utilization in field-effect transistor (FET)based devices to enhance conductivity. The direct development of carbonaceous nanoparticles on electrodes provides a more uniform coating than traditional dip coating or drop-casting techniques, potentially facilitating future batch manufacturing of materials. Polymer coatings can modify the physical and chemical characteristics of carbon nanostructures and facilitate their dispersion for deposition. Most electrochemical dopamine sensors do not employ

specific molecular recognition elements<sup>[51][64][35]</sup>. From various demonstrations, it is evident that achieving optimal electrode performance relies on factors such as the synthesis method of carbonaceous materials, surface modification, electrode attachment method, and the incorporation of electron mediators<sup>[51][64]</sup>. The majority of electrochemical measurements of dopamine are conducted using a three-electrode system with a standard potentiostat/galvanostat instrument.

Characterization of synthesized carbon-based nanomaterials is essential for various applications, particularly in Understanding the physicochemical electrochemistry. properties and microstructural features of carbonaceous nanomaterials provides valuable insights into morphology, layering, chemical composition, uniformity, defects, population distribution, and stacking order. Various techniques are commonly employed to investigate these features, including X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FT-IR), atomic force microscopy (AFM), Raman spectroscopy, X-ray photoelectron spectroscopy (XPS), and energy-dispersive X-ray spectroscopy (EDX). Dopamine sensors have made extensive use of carbonaceous nanomaterial-based electrodes because of its capacity to promote quick electron transfer, lessen electrode fouling, limit over potential, and improve sensitivity and selectivity for neurotransmitter detection, even in the presence of interferences<sup>[51][62][63]</sup>. The use of graphene, carbon nanotubes (CNTs), and its derivatives for dopamine detection has been the subject of numerous investigations in the literature. These studies have used CNTs, graphene alone or in conjunction with metal nanoparticles or polymers<sup>[35][51]</sup> [64]

# 4.1. Graphene & CNTs based electrochemical sensors for dopamine

In this section, we delve deeply into the advancements made in CNs-based dopamine (DA) electrochemical sensing platforms from 2020 to 2017, complemented by earlier notable reports. Comprehensive data pertaining to electrode composition, electroanalytical techniques, sample sources, interferences, and the linear range of DA detection, sensitivity, detection limit, and response times are meticulously summarized and presented in Table 1. A prominent observation from multiple data points is the extensive utilization of graphene nanomaterials, which have played a pivotal role in real-time dopamine detection. Typically derived from graphite via the modified<sup>[67]</sup>, graphene and its derivatives have been instrumental in advancing DA sensing. Singh et al.[68] were pioneers in reporting graphene-modified electrodes for the selective determination of DA, utilizing chitosan for charge-based selective absorption of DA on the electrode surface. Despite their significant findings, challenges persisted, particularly regarding weak adhesion between sensitive films and electrodes, leading to compromised sensitivity and storage stability. Addressing this issue, X. Wang et al.<sup>[69]</sup> employed a CVD-based fabrication of graphene nanosheets directly on Ta wire, resulting in robust binding and improved stability, thereby enhancing sensitivity. et al.<sup>[70]</sup> Arumugasamy developed a ratiometric electrochemical biosensor to detect dopamine in serum samples, utilizing acid-functionalized MWCNTs incorporated with graphene quantum dots (GQDs) on a GCE surface. Their work underscored the importance of surface functionalization in enhancing sensitivity and selectivity for dopamine sensing. Similarly, Q. Huang et al.<sup>[71]</sup> reported an ultrasensitive sensor based on GQDs-MWCNTs composites, demonstrating superior sensitivity compared to other MWCNTs-based sensors, particularly in detecting dopamine secretion in live neuronal cells. Further innovations include Hsine et al.<sup>[72]</sup> development of GO-based nanohybrid materials for efficient dopamine sensing, showcasing a synergistic effect resulting in enhanced conductivity and catalytic properties. Additionally, Ikram et al. [73] introduced an ultrasensitive non-enzymatic electrochemical sensor for DA using a graphene oxide-nickel and gold nanoparticles nanocomposite, demonstrating high selectivity and sensitivity in detecting dopamine amidst interfering analytes.

Moreover, Demirkan et al.<sup>[74]</sup> presented a novel GCE coated with palladium nanoparticles supported on polypyrrole/reduced graphene oxide for simultaneous detection of AA, DA, and UA, highlighting the versatility and reproducibility of this sensing approach. Collectively, these advancements underscore the significant strides made in CNs-based DA sensing platforms, offering enhanced sensitivity, selectivity, and applicability across various sample matrices.

In<sup>[75]</sup> introduced a novel three-dimensional (3D) nanostructured composite, synthesized via a one-pot hydrothermal process, merging MoS2 nanospheres and polyaniline (PANI) loaded on reduced graphene oxide (rGO) (3D MoS2-PANI/rGO). Leveraging the unique properties of MoS2 as a 2D layered nanomaterial and PANI as a conductive polymer, the authors aimed to enhance electrochemical activity and conductivity for selective and sensitive dopamine (DA) detection. The resulting composite, applied on a glassy carbon electrode (GCE), exhibited promising performance for the simultaneous detection of ascorbic acid (AA), DA, and uric acid (UA). Dynamic peak currents observed through differential pulse voltammetry (DPV) demonstrated excellent linearity over a wide concentration range for each analyte, with low detection limits of 0.70 µM for DA, 22.20 µM for AA, and 0.36 µM for UA. This innovative sensing platform based on 3D MoS2-PANI/rGO showcased high reliability and replicability in detecting DA in serum and urine sample. Another notable DA sensing approach was presented by<sup>[76]</sup> Combining zinc oxide–copper oxide p–n junction heterostructures (3DCuxO-ZnO NPs/PPy/rGO) and reduced graphene oxide (rGO) adorned with polypyrrole nanofibers in a three-dimensional porous nanocomposite. By leveraging conductive polymer polypyrrole (PPy) to protect rGO and enhance stability and sensitivity, along with AA, paracetamol

(PAR), and tryptophan (TRP), the modified electrode demonstrated significant selectivity for DA detection. The sensor successfully determined the quantities of DA and AA in serum samples, exhibiting linear responses for DA values ranging from 0.04 to 420 mM with a low detection limit of 0.012 mM.

In<sup>[77]</sup> a modified graphene-multiwalled carbon nanotubegold nanoparticle nanocomposite (PTCA-RGO-MWCNTs-Au NPs/GCE) comprising 3,4,9,10-perylene tetracarboxylic acidfunctionalized graphene. The sensor demonstrated superior electrochemical performance for DA detection by taking use of PTCA to distribute RGO-MWCNTs-Au NPs and stabilize the electrode. The negatively charged -COOH groups of PTCA-RGO-MWCNTs-Au NPs facilitated electrostatic adsorption of cationic DA, eliminating interference from anionic species like AA and UA. The sensor displayed a sensitivity of 0.124  $\mu A$ mM-1, a wide linear range of 1–100  $\mu$ M, and a low detection limit of 0.07 µM for DA, with negligible interference from various inorganic compounds. This novel sensor demonstrated exceptional selectivity towards DA amidst multiple interferences, setting a precedent in electrochemical sensing. Similarly, [69] introduced an Au@NAC-MWCNTs/GCE complex, comprising carboxylated MWCNTs functionalized with N-acetyl-l-cysteine (NAC) stabilized Au clusters. This complex-modified GCE enabled simultaneous electrochemical sensing of DA and UA, exhibiting linear detection ranges of 0.1–250 µM for DA and 0.1–300 µM for UA, with low detection limits of 30 nM for DA and 40 nM for UA. The sensor demonstrated high sensing performance and recovery rates in human serum and urine samples, highlighting its potential for practical applications in biomedical and clinical settings.

In 2018,<sup>[78]</sup> introduced a novel nanohybrid material composed of Au-Pt bimetallic nanoparticles (AuPtNPs) decorated on sulfonated nitrogen sulfur co-doped graphene (S-NS-GR), termed AuPtNPs/S-NS-GR. Bimetallic nanoparticles are known for their enhanced catalytic performance and improved electron transfer capabilities due to synergistic effects compared to monometallic counterparts. The modified glassy carbon electrode (GCE) with AuPtNPs/S-NS-GR exhibited excellent electrocatalytic activity towards dopamine (DA) and uric acid (UA), as confirmed by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) [79]. Under optimized conditions, the linear detection ranges for DA and UA were determined to be 0.01-400 µM and 1-1000 µM, respectively, with low limits of detection (LOD, S/N = 3) of 0.006 µM for DA and 0.038 µM for UA. Moreover, when applied to real samples such as DA injections and human serum and AuPtNPs/S-NS-GR/GCE demonstrated urine, excellent recovery percentages for DA and UA, ranging from 99.8% to 101.9% and 98.2% to 100.5%, respectively, with a relative standard deviation (RSD) of less than 3.67% (n = 5). Additionally, the modified electrode exhibited outstanding repeatability with an RSD of about 2.49% for DA and 3.36% for UA over 20 repeated measurements. The sensing approach also showcased remarkable reproducibility and long-term stability, making it a promising candidate for practical applications.

In<sup>[80]</sup> developed an amperometric dopamine sensor based on a modified screen-printed carbon electrode (SPCE) incorporating reduced graphene oxide (RGO), polyneutral red (PNR), and gold nanoparticles (AuNP). This sensor exhibited a high electrocatalytic effect on the oxidation of dopamine, with a sensitivity of 2.14% (n = 10) as determined by the relative standard deviation (RSD) under optimized working conditions. The sensor demonstrated a linear range between 0.57 and 500  $\mu$ M, with a detection limit of 0.17  $\mu$ M, excellent reproducibility, and storage stability. Interference studies with electroactive species such as ascorbic acid (AA) and uric acid (UA) were conducted, followed by testing in artificial blood serum samples, further validating the reliability and practical utility of this sensing approach. In 2013,<sup>[81]</sup> reported a highly selective dopamine electrochemical sensor built upon a modified screen-printed carbon electrode (SPCE) modified by electrochemical pretreatment of graphite/Nafion composite. After the electrode was electrochemically activated, its sensitivity was greatly increased. This resulted in good dopamine electrocatalytic oxidation, with a linear response range of 0.5 to 70  $\mu M$  and a detection limit of 0.023  $\mu M$  to studies demonstrated negligible interference from other substances, confirming the sensor's robust selectivity. In 2017, [82] presented the innovative N-doped graphene quantum dots-chitosan nanocomposite-modified nanostructured screen-printed carbon electrode for dopamine detection. Graphene quantum dots (GQDs), recognized for their distinctive structural and electrical characteristics, were generated using a microwave-assisted hydrothermal reaction of glucose, with nitrogen doping accomplished by incorporating ammonia into the reaction mixture. The demonstrated resultant nanocomposite favorable characteristics for chemical stability, electrical conductivity, and electrocatalytic activity, establishing a basis for prospective applications in dopamine detection.

In 2018,<sup>[78]</sup> introduced a new sensor utilizing a nanohybrid material consisting of Au-Pt bimetallic nanoparticles (AuPtNPs) affixed to sulfonated nitrogen and sulfur co-doped graphene (S-NS-GR), termed AuPtNPs/S-NS-GR. Chitosan was incorporated into the sensor, playing a significant role in enhancing selectivity by hindering interference from ascorbic acid and increasing peak potential separation between dopamine and uric acid. By using cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS), the resulting CS/N, GQDs@SPCE sensor demonstrated low limits of detection (LOD =  $0.145 \mu$ M) and quantification (LOQ = 0.482 $\mu$ M), a wide linear range (1–100  $\mu$ M and 100–200  $\mu$ M), and high sensitivity (418 µA mM cm<sup>-2</sup>). The sensor efficiency was validated by analyzing dopamine in human urine, showing 100% recovery with an RSD < 2%, confirming its practicality and reliability. Additionally, the sensor demonstrated high reproducibility (RSD  $\approx$  3.61%).

In<sup>[83]</sup> explored a flexible, unmodified thin-film carbon electrode (TFCE) as a potential low-cost solution for detecting low concentrations of dopamine (DA). The TFCE, with a diameter of 1.09 mm, exhibited superior sensitivity compared to a standard screen-printed electrode (SPE), capable of detecting dopamine concentrations ranging from 50 pM to 1 mM. The TFCE showed excellent differentiation between dopamine and ascorbic acid (AA) at physiologically relevant concentrations, unlike the SPE. This represents a significant advancement in dopamine detection without electrode modification, with potential applications in both in vivo and ex vivo settings. In 2020, <sup>[84]</sup> developed a needle-type solution-gated field-effect transistor (FET) based on reduced graphene oxide (rGO) for ultra-low-level dopamine detection. The FET exhibited high sensitivity towards dopamine, with a linear response ranging from 1 nM to 1 µM and a rapid response time of 2.60 ± 0.19 s for ultra-low detection (1 nM). Despite being sensitive to dopamine, the FET showed equal performance in the presence of interfering species such as AA. However, FET-based sensors typically require longer equilibration times, limiting their real-time application for in vivo measurements. In 2018,<sup>[85]</sup> demonstrated the electrophoretic deposition (EPD) of reduced graphene oxide/polyethyleneimine (rGO/PEI) on a gold (Au) microelectrode for dopamine detection. The functionalized microsystem (rGO/PEI/Au microelectrode) showed the ability to detect 50 nM of dopamine in solution, with minimal interference from uric acid (UA) and ascorbic acid (AA) even at higher concentrations (5 µM). The sensor was successfully applied for dopamine detection in meat samples, demonstrating its potential for real-world applications.

In<sup>[86]</sup> introduced carbon fiber (CF) microelectrodes modified with electrochemically reduced graphene oxide nanosheets decorated with carbon dots (CD) for dopamine sensing in the presence of AA and UA. This novel modification enhanced the electrode's surface area, resulting in improved dopamine-electrode interaction. The CF microelectrodes exhibited an excellent linear relationship for dopamine sensing over a range of 0.1–100  $\mu$ M, with a detection limit of 0.02  $\mu$ M and a sensitivity of about 6.5 nA/ $\mu$ M, surpassing previous reports with CF microelectrodes.

[47] pioneered the development of an electrochemical microfluidic paper-based analytical nanosensor (EµPAN) for dopamine sensing. The sensor utilized a graphite-chitosanpolyethylene glycol (PEG) mixture as a working electrode for electrochemical detection of dopamine on microfluidic paperbased analytical devices (µPADs) with blood and urine samples. The microfluidic structure was created on chromatography paper using a wax-based stamping method, incorporating a three-electrode system within the hydrophilic detection zone, with a working electrode diameter of 0.5 mm. Various nanomaterials (MWCNT, graphene, and Fe3O4) were tested on the electrode for selective dopamine sensing, with graphene combined with sodium dodecyl sulfate (SDS) surfactant proving to selectively detect dopamine in blood and urine samples. The SDS surfactant conferred negative charges on the electrode, repelling negatively charged interferents such as ascorbic acid and uric acid, thereby enhancing dopamine adsorption on the electrode. This setup achieved linear ranges of 0.5–120  $\mu$ M and a detection limit of 0.01  $\mu$ M. [87] synthesized a novel hybrid material combining hexagonal boron carbon nitride (h-BCN), also known as "white graphite,"

with graphene. The h-BCN hybrid material was developed via an in situ high-temperature solid-state reaction followed by chemical reduction with hydrazine. The synthesized h-BCN exhibited interlayered structures with characteristic dspacing values of 0.33 and 0.21 nm, as confirmed by XRD and TEM analyses. The working electrode was equipped with carbon cloth as the current collector, and h-BCN-carbon cloth electrodes (hBCN/carbon cloth) were made by pasting h-BCN powders onto the carbon cloth using an inactive carbon colloid binder. The resulting h-BCN showed excellent performance in detecting dopamine (DA) and uric acid (UA), with CV and amperometric experiments demonstrating a linear relationship between current densities and concentrations for DA (10-300  $\mu$ M) and UA (10-500  $\mu$ M). The sensitivity for DA reached 0.14  $\mu$ M, with detection limits of 5 μМ.

Although graphene is known for its high performance as an electrode material, a drawback is its instability due to the lack of interfacial forces between graphene and conductive substrates. To address this issue,<sup>[88]</sup> introduced highly durable graphene electrodes for dopamine sensing. Using the diamond as a carbon source, they created few-layer graphene directly on an HPHT diamond substrate by converting sp3 to sp2 using catalytic heat treatment. This allowed them to create electrodes. In the concentration range of 5 µM to 2 mM, the resultant hybrid electrode showed a linear electrochemical response to dopamine and a high conductivity, with a low detection limit of 200 nM. Although the modified electrode showed fouling effects after prolonged exposure to dopamine, the authors overcame this issue through a 5-minute ultrasonic cleaning process, suggesting its suitability for long-term dopamine detection.

<sup>[89]</sup>endeavored to create a sensitive and label-free aptamerbased ratiometric electrochemical sensing method for dopamine (DA). Aptamers, akin to oligonucleotide or peptide probe molecules, exhibit binding affinity to specific target molecules. In this study, a glassy carbon electrode (GCE) was modified by drop-coating with graphene oxide (GO) and Nile blue (NB) to form GO/NB/GCE. Subsequently, gold nanoparticles (AuNPs) were electrodeposited onto the GO/NB/GCE surface through a one-step co-reduction treatment under cyclic voltammetry (CV), simultaneously generating reduced graphene oxide (rGO). A 50-SHterminated aptamer specific to dopamine was then attached via Au-S coupling to the AuNPs, resulting in an aptamerrGO/NB/AuNPs/GCE system. Upon the presence of dopamine in the sample, high-specificity hybridization/affinity occurred between dopamine and the aptamer, leading to complex formation on the electrode surface. Consequently, the electron transfer channel was partially obstructed by the newly formed dopamine-aptamer complex, resulting in a reduction of the electrochemical signal responses of the inner Nile blue. The experimental setup employed a 0.1 M phosphate-buffered saline (PBS) solution (pH 7.0) with a 1 mM [Fe(CN)6]3-/4electrolyte solution (volume ratio 1/1). As the dopamine concentration (CDA) increased, the electrochemical signal responses of the inner Nile blue decreased regularly, while those of extrinsic dopamine increased. Various techniques, including cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS), and square wave voltammetry (SWV), were utilized to measure the responses of this working electrode system. Excellent linear relationships were observed in the concentration range of 10 nM to 0.2 mM, with a low detection limit of 1 nM. Experimental findings confirmed that this aptamer-based sensing approach exhibited high stability, selectivity, and sensitivity towards dopamine detection, even in the presence of potential interferences.

<sup>[90]</sup>pioneered a DNA-based dopamine (DA) detection method using a glassy carbon electrode (GCE) modified with fullerene C60 nanotubes (FNTs) and sequence-specific single-stranded DNA (ssDNA) (FNT@DNA). This modified electrode displayed an irreversible two-step six-electron transfer reduction reaction in a Britton–Robinson buffer solution of pH ≥7.0. The reduced FNT@DNA-modified GCE exhibited a wide electrochemical window and demonstrated good enrichment capability for positively charged molecules, particularly dopamine. Despite the presence of high amounts of ascorbic acid, selective detection of dopamine was achieved with a detection limit of 0.6 µM in a neutral buffer solution. In<sup>[91]</sup>reported a double-strand DNA-based multi-walled carbon nanotube (MWCNT) nanocomposite sensor for the detection of dopamine (DA) and uric acid (UA). Their biosensor consisted of a bio-composite film fabricated with (Chit)/poly(amidoamine) MWCNT-chitosan (PAMAM) nanocomposite along with DNA-modified gold electrode. Double-stranded DNA served as the recognition element for DA, leveraging its efficient electroconductivity and ability to create a thin conductive layer of nanostructures on the electrode surface. The negative charge of the DNA's phosphate backbone facilitated the absorption of positively charged target species while repelling undesired adsorption on the same surface. The biosensor exhibited strong catalytic activity toward the oxidation of DA and UA, with well-defined oxidation peaks and satisfactory peak separations from interfering species. The detection limits for DA and UA were 0.03  $\mu$ M and 0.07  $\mu$ M, respectively, with high sensitivity and surface reproducibility demonstrated.

<sup>[92]</sup> introduced an ITO-based sensing platform comprising a 3D porous graphene oxide (pGO)/gold nanoparticle (GNP)/pGO composite-modified ITO electrode. The synthesis involved ultrasonication and centrifugation to produce pGO, which was then deposited onto the surface of GNP-immobilized ITO glass. Compared to pGO- or GNP-modified ITO electrodes, the 3D pGO-GNP-pGO-modified ITO electrode exhibited superior performance in dopamine (DA) detection, offering a linear range from 0.1  $\mu$ M to 30  $\mu$ M with a limit of detection (LOD) of 1.28  $\mu$ M. The platform's specificity for dopamine detection was not explicitly stated, but the authors suggested that the presence of hydroxyl groups on the pGO plane could facilitate hydrogen bonding with DA, while nanoholes on the pGO plane supported electron transfer to GNP surfaces, enhancing electrochemical-redox signals.

<sup>[93]</sup> explored the use of phosphorus-doped graphene (P-G) as both a metal-free catalyst and a support for metal catalysts in

electrochemical dopamine sensing. As a metal-free catalyst, P-G exhibited notable performance in dopamine sensing due to the enhanced electrocatalytic activity resulting from phosphorus doping. Additionally, P-G served as an effective support for gold nanoparticles (AuNPs), forming an Au/P-G hybrid with excellent electrocatalytic activity and sensing performance, featuring a wide linear range of 0.1-180 µM and a LOD of  $0.002 \ \mu$ M. The heteroatom doping not only improved the catalytic activity of graphene but also provided sites for anchoring metal and metal compound nanoparticles (NPs). The Au/P-G/GCE demonstrated exceptional selectivity, maintaining consistent amperometric responses even after successive addition of various compounds. Furthermore, it exhibited excellent performance after 10 days of storage and achieved a high recovery rate in human serum samples ranging from 99% to 102.5%.

# 4.2. Carbon nanotube-based electrochemical sensors for dopamine with interferences

Table 2 provides a summary of carbon nanotube-based electrochemical sensors for dopamine, comparing electrode composition, electrochemical technique, sample source, interferences, linear range of detection, sensitivity, detection limit. and response times.<sup>[94]</sup> introduced an electrochemical sensing platform using gold nanobipyramid/multi-walled carbon nanotube hybrids (AuNBP/MWCNTs) for detecting dopamine in serum samples containing ascorbic acid (AA) and uric acid (UA). The hybrids were prepared by self-assembling AuNBP onto MWCNTs, forming hybrids confirmed by various characterization techniques. The modified electrode showed distinct oxidation peaks for dopamine in the presence of interference in both differential pulse voltammetry (DPV) and chronoamperometry (CA) measurements. The sensor exhibited a wide linear range from 50 nM to 2.7 mM and a low detection limit of 15 nM (at S/N = 3). The authors elucidated the sensing mechanism, attributing the effective separation of dopamine, AA, and UA to interactions based on pH sensitivity and  $\pi$ - $\pi$  interactions between DA and MWCNTs. However, the sensing system demonstrated unrealistic performance with human serum samples.<sup>[95]</sup> also reported similar work using MWCNTs/GNPs for dopamine detection. They synthesized the nanocomposite via a modified biphasic route and tested its dopamine sensing properties using square wave voltammetry. The modified electrode exhibited distinct oxidation peaks for dopamine, ascorbic acid, and uric acid, with a linear range of 0.4–5.7  $\mu$ M and a detection limit of 0.07  $\mu$ M. The recovery rate was reported to be 86-107% with synthetic cerebrospinal fluid samples.

(B. Zhang et al.<sup>[96]</sup>) devised a cost-effective, disposable filter paper-based diagnostic platform for quantifying dopamine (DA) concentration in animal tissue extracts. They modified indium tin oxide (ITO) electrodes with carboxylic multiwalled carbon nanotubes (MWCNTs) to enable selective and sensitive DA detection in rat brain tissue extracts, alongside noradrenaline (NE) and 5-hydroxytryptamine (5-HT). The three-electrode system comprised an ITO glass electrode modified with MWCNTs as the working electrode, an Ag/AgCl reference electrode, and a platinum wire auxiliary electrode, all embedded within a paper-based analytical device. The amperometric response to DA was observed at a low potential (0.43 V vs. Ag/AgCl) and remained unaffected by NE or 5-HT. The sensor exhibited linearity over a concentration range of  $2.5 \times 10^{-8}$  M to  $1 \times 10^{-5}$  M, with a detection limit of 5 nM. (B. Zhang et al.<sup>[96]</sup>) also explored the correlation between the analytical signals and the amount of assembled MWCNTs in the electrode area, demonstrating the applicability of their methodology for quantifying DA in rat brain and tendon tissues. This technique offers a simple, rapid, and cost-effective alternative to conventional methods.

(Durairaj et al.<sup>[97]</sup>) presented a composite membrane for selective dopamine (DA) sensing that included carbon MWCNTs distributed in a sulfated nanofibrillar cellulose (SNFC) and Nafion matrix. They utilized tetrahedral amorphous carbon (ta-C) thin-film electrodes for modification and attributed the DA selectivity to the high density of negative functional groups present in both SNFC and Nafion ionomers. The electrodes modified with MWCNT, SNFC, and Nafion demonstrated notable DA selectivity and sensitivity, even when ascorbic acid (AA) and uric acid (UA) were present. They demonstrated a linear detection range of 0.05–100  $\mu$ M with detection limits of 65 nM in 0.1 M PBS (pH 7.0) and 107 nM in AA solution (Palomäki et al.<sup>[98]</sup>) demonstrated the potential of ta-C films modified with MWCNTs for DA sensing, achieving excellent detection sensitivity and biocompatibility in in vitro cell cultures. (Keerthi et al.<sup>[99]</sup>) employed molybdenum nanoparticles entrapped via functionalized MWCNTs (Mo NPs@f-MWCNTs) to modify screen-printed carbon electrodes (SPCEs) for electrochemical DA detection. The hybrid nanomaterial exhibited robust electrostatic interaction, serving as an excellent electrocatalytic material for DA detection in both buffer and biological samples. The modified SPCE with Mo NPs@f-MWCNTs displayed a low detection limit of 1.26 nM, excellent linear response, and good sensitivity in real samples like rat brain, human blood serum, and DA hydrochloride injection. Additionally, the sensor demonstrated high selectivity against interfering compounds and showed longterm stability, repeatability, and reproducibility.

[100] pioneered the use of carbon nanotube-grown metal microelectrodes, specifically niobium-based (CNT-Nb), for enhanced neurotransmitter detection in vivo rat models. These microelectrodes were designed to minimize tissue damage and enhance spatial resolution for in vivo dopamine detection. The CNT-Nb microelectrodes demonstrated high sensitivity and rapid measurements in detecting stimulated dopamine release in anesthetized rats. CNT-Nb had superior sensitivity and decreased ∆Ep value in contrast to CNTs grown on carbon fibers or other metal wires. Its dopamine detection limit was  $11 \pm 1$  nM, which is roughly two times lower than that of bare carbon fiber microelectrodes. The stability of CNT-Nb microelectrodes over four hours of continuous measurement further confirmed their potential for measuring stimulated dopamine release in live models, suggesting potential clinical applications in neurotransmitter detection<sup>[101]</sup> using polypyrrole (PPy) as a molecularly imprinted polymer (MIP) and multi-walled carbon nanotubes spaced graphene aerogels (MWCNTs/GAs) as the sensing substrate, this new molecularly imprinted electrochemical sensor for dopamine (DA) works. Graphene aerogels were synthesized through a process involving the addition of graphene oxide (GO) into distilled water followed by ultrasonication, heating, and freeze-drying. Scanning electron microscopy (SEM) analysis revealed well-dispersed MWCNTs a porous structure with a large active surface area is produced by the graphene walls of the aerogels. Dopamine detection became possible when MWCNTs were added because they improved the composite aerogel's electrical conductivity and electrochemical performance. Incorporating MIPs as a recognition element further improved the sensor's selectivity for dopamine. In serum samples, the final composite of MIP/MWCNTs/GAs on a glassy carbon electrode (GCE) showed a broad linear detection range from 5 nM to 20.0  $\mu$ M and a low detection limit of 1.67 nM (S/N= 3).

[94] discovered the ability of a flexible membrane-based sensor based on poly (styrene-butadiene) fiber to withstand interference when modified with multi-walled carbon nanotubes (MWCNTs). XPS was used to describe this flexible fiber membrane that was created via electrospinning technology. The resulting MWCNT-sulfonated poly (styrenebutadiene) flexible fiber membrane (MWCNT/PEI/SSB)-GCEelectrochemical sensor successfully reduced based interference during the detection of dopamine (DA) in human serum and dopamine injection from ascorbic acid (AA) and uric acid (UA). Dopamine showed a linear response in the 1-650 μM range under ideal experimental conditions with DPV, with a detection limit of 0.062  $\mu$ M (S/N=3). The greatest oxidation current peak was found to be at pH 7.0 after research into the impact of pH on the electrochemical response of DA at the MWCNT/PEI/SSB electrode. The anodic peak potentials of DA shifted negatively as the electrolyte pH increased from 5.5 to 7.5.

[102] a composite of nitrogen-doped carbon nanotubes (NCNTs), polyoxometalate (POM) Na12[WCo3(H2O)2(CoW9O34)2], and poly(vinyl imidazolium) cation [PVIM<sup>+</sup>] was utilized to develop an ultrasensitive carbon nanotube (CNT)-based sensing technique. By eliminating ascorbic acid (AA) interference at physiological pH (7.4), this new composite promoted effective electron transport at the electrode/electrolyte interface. Even with 500 µM AA present, the tailored electrode demonstrated excellent DA selectivity and sensitivity, with a detection limit of 500 pM  $(0.0005 \ \mu M)$  and a broad linear detection range of 0.0005-600 $\mu$ M.<sup>[103]</sup> AA, DA, acetaminophen, nitrite, and xanthine are the five electroactive chemicals that can be detected simultaneously using a modified electrode built on a copper polydopamine complex and multiwalled carbon nanotubes. For every molecule in the potential range of 0.1 to 1.1 V, the modified electrode showed distinct oxidized peaks by CV and DPV in PBS at pH 2.0. With detection limits of 0.82, 0.45, 0.87, 0.92, and 0.67  $\mu$ M, the responses were linear up to 175, 125, 75, 150, and 115 µM for AA, DA, acetaminophen, nitrite, and xanthine, respectively. Tests using actual serum and urine samples revealed exceptional recovery levels.

## 5. Future challenges and perspective

In recent years, the clinical market has seen a surge in pointof-care (POC) sensors designed to monitor social wellness indicators, a trend driven by advancements originating from research laboratories worldwide. As healthcare increasingly shifts toward personalized medicine, aiming to provide care closer to patients' homes, the concept of the hospital is evolving<sup>[18]</sup>. Presently, researchers are focusing on developing smarter disease-diagnosing sensors that are more affordable, portable, user-friendly, and environmentally friendly than existing ones. Dopamine levels in body fluids serve as a crucial indicator of nervous system-related diseases and stress, creating a high demand for smart sensors capable of simultaneously monitoring dopamine levels. While enzymebased diagnostic kits and other sensing methods for dopamine are available in the market, they have drawbacks, particularly in terms of accessibility for economically disadvantaged populations. These demands can be addressed by numerous electrochemical sensing methods published in the literature, which have been refined to meet real-time challenges.

Electrochemical sensing methods, developed over the past decades, represent the most promising approach for the qualitative and quantitative detection of neurotransmitters. These methods offer rapid response times, selective detection of dopamine amid interferences, and eliminate the need for pre-treatment or purification of biological fluid samplescritical characteristics for point-of-care sensing applications. Furthermore, the incorporation of various forms of engineered carbon nanomaterials into electrochemical sensors has significantly improved their analytical performance due to their unique catalytic and conductive properties. Laboratories involved in sensing applications must transition to the next level by developing point-of-care devices for real-time applications. Numerous electrochemical diagnostic techniques documented in the literature exhibit significant compatibility with microfabrication technologies, facilitating the development of miniaturized electrochemical sensors and sensor arrays. Microfabrication methods, including thick and thin-film technology, silicon-based techniques, and photolithography, provide cost-effective, disposable electrochemical devices such as flexible electrodes, screen-printed electrodes, thin-film transistors, microfluidics, microelectrodes, and nanoelectrodes. These electrochemical analytical tools are applicable in portable peripheral instruments already available in the market<sup>[104][105][106]</sup>. However, the high production cost of sensors remains a hurdle in commercial and clinical sectors, leading to economic burdens for patients in need. Low-cost sensors have higher market potential, and researchers have explored paper-based platforms as a cost-effective alternative. Paper-based sensing platforms have been integrated into various devices, with inkjet printing being used to create electrochemical sensing platforms on paper. Additionally, reusable sensors help reduce costs, and non-enzymatic electrochemical sensing platforms tend to be regenerated after use. These developments, along with the fabrication of miniaturized sensing and processing prototypes, support researchers aiming to bring their products to commercialization.

Emerging sensing techniques such as micro-total analysis systems (µTAS) integrate different analytical operations into a single microfabricated device, showing excellent compatibility with electrochemical studies. Wearable sensors represent the next generation of sensing technology, monitoring biological parameters non-invasively in everyday life. In the case of dopamine sensing, wearable electrochemical sensors have not been thoroughly studied, but their integration into commercial point-of-care testing sensors has begun. Organon-chip methods, another clinically emerging sensing approach, enable in vivo measurement of biomarker concentrations in cells, offering promise for direct dopamine quantification. Nanosensors fabricated with nanoelectrodes, including carbon nanotubes, detect ultra-low concentrations, making them suitable for lab-on-a-chip systems at the nanoscale. Microelectrodes based on carbon nanotubes have been used for in vivo analysis of dopamine, providing high sensitivity and rapid measurements with less tissue damage than conventional techniques.

In summary, the future of dopamine sensors lies in adopting point-of-care device methods and focusing on implantable organ-on-chip-based electrochemical sensing devices. These advancements should be evaluated based on clinical norms and commercial viability, ensuring their compatibility with existing market players and large-scale production.

## 6. Summary

At this juncture, we aim to summarize key features of nonenzymatic electrochemical or direct electrochemical methods developed for dopamine sensing, as reported in recent literature studies. Firstly, non-enzymatic electrochemical sensing methods emerge as the most straightforward, simple, cost-effective compared to enzymatic rapid, and electrochemical sensing methods. The primary advantage lies in their ability to simultaneously determine biological electroactive compounds in complex matrices. Numerous research studies have demonstrated highly efficient nonenzymatic electrochemical methods for dopamine sensing despite interferences. Modified electrodes, particularly those employing various carbonaceous nanomaterials and their composites, play a crucial role in enhancing selectivity and sensitivity in dopamine biosensing. Carbonaceous nanomaterials, with their diverse compositions, exhibit significant electrochemical activity due to rapid electron transfer kinetics and superior electrocatalytic activity. Functionalized in a wide range of materials, such as monometallic. bi-metallic, metal oxides, polymers, and semiconductors, they provide excellent support in terms of electrical conductivity. Additionally, carbonaceous materials naturally offer a porous structure, enhancing surface area, reducing charge transfer resistance, and increasing electrocatalytic performance, ultimately proving costeffective. Graphene-based materials are widely used in dopamine sensors due to their ease of functionalization and high surface area to mass ratio, surpassing the usage of carbon nanotubes. Carbon nanomaterials consistently demonstrate promising performance in sensing systems for dopamine and other neurotransmitter detection, suggesting their potential in future advanced point-of-care sensing devices. Various issues associated with dopamine sensing, such as response time, detection range, and interferences, have been addressed by many studies, resulting in rapid and accurate detection of dopamine in real samples, even at the nanomolar and picomolar levels. However, some research studies have misconceptions regarding standard dopamine concentrations, leading to suboptimal sensing levels. Additionally, attention has been drawn to the simultaneous detection of dopamine, ascorbic acid (AA), and uric acid (UA) without overlapping peaks in real samples, considering AA and UA as deficiency and disease biomarkers. Overall, electrochemical dopamine sensing methods employing carbonaceous nanomaterials, as reported by several researchers, exhibit high selectivity, good reproducibility, long-term stability, portability, and reusability, highlighting their potential for commercialization viability and meeting current demands. In conclusion, this review provides a comprehensive discussion on the technical advances of electrochemical methods in dopamine detection, addressing recent demands, including commercialization viability.

### Tables

Electrode/ Materials/catalyst	Fabrication method	Detection Method	Interference	Sample source	Linearity (mol L <sup>-1</sup> )	Detection Limit (mol L <sup>-1</sup> )	Electrolyte/ PBS Buffer pH/	Reference
CRGO/Fc-ac-PPP/Au	Ultrasonication	CV, EIS	AA,UA	Urine	0.0001– 1000 μM	0.2 nM	7.0	[72]
GQDs-MWCNTs/GCE	Ultrasonication	CV, DPV, EIS	AA	Serum	250 nM – 250 μM	95.0 nM	7.0	[70]
GQDs-MWCNTs/GCE	Ultrasonication	CV, DPV	AA,UA	Serum, live cells	0.005 – 100.0 μM	0.87 nM	7.0	<u>[71]</u>
EG/Ni-Au/GCE	Electrodeposition	CV, SWV	UA, AA and Glu	Serum	0.2–100 μM	0.1 μΜ	6.0	<u>[79]</u>
thin-film carbon electrode	Microfabrication	DPV, SWV	AA	Pure chemical	50 pM – 1 mM	50.0 pM	7.0	<u>[83]</u>
rGo/pd@ppy nps	CS/US	DPV	UA, AA	Human Serum	38–1647 μM	0.056 μΜ	3.0	<u>[74]</u>
rGO-based FET	Electrochemical pulse deposition technique	CA	AA	Pure chemical	1nM to 1 μM	1.0 nM	7.4	[84]
MIP/MWCNTs/GAs/GCE	Ultrasonication	DPV, EIS	None	Pure chemical	5 nM –20 μM	1.67 nM	6.0	[101]
SPCE/ RGO/PNR/AuNP/SPCE	Ultrasonication	CA	AA,UA	Artificial blood	0.57- 500 μM	0.17 μM	7.0	<u>[80]</u>
hBCN/CCE	chemical reduction	CA	UA	Pure chemical	10-300 μM	0.14 μΜ	6.8	[87]
Graphene/SDS	Microfluidics	DPV	UA, AA	blood and urine	0.5–120 μM	0.01 μΜ	7.0	<u>[68]</u>
3D MoS <sub>2</sub> -PANI/rGO/GCE	One-pot hydrothermal	DPV	UA, AA	human serum and urine	5.0 to 500 μM	0.70 μΜ	7.0	[75]
Mo NPs@f- MWCNTs/SPCE	acid condensation	CA	AA, UA, AP, EP and NEP	rat brain, human serum, and DA injection	0.01 to 1609 μΜ	1.26 nM	7.0	<u>[99]</u>
3DCuxO–ZnO NPs/PPy/RGO/GCE	Electrochemical deposition	DPV	AA, TRP, PAR	Human Serum	0.04 to 420 mM	0.012 mM	7.0	[76]
rGO/PEI/Au microelectrode	Electrochemical deposition	DPV	UA, AA	Meat sample	0.05-1 μM	50nM	7.4	[85]
AuPtNPs/S-NS-GR/GCE	one-step thermal annealing method electrochemical deposition	CV, DPV	AA	DA injection, Human Serum & urine	0.01–400 μM	0.006 µM	5.0	<u>[78]</u>
Aptamer-rGO /NB /AuNPs/GCE	Co-reduction and Electrodeposition	CV,EIS, SWV	AA, UA, GL, EP, NP	serum	10 nM to 0.2 mM	1 nM	7.0 Fe(CN)6] <sup>3-/4-</sup>	[89]

Electrode/ Materials/catalyst	Fabrication method	Detection Method	Interference	Sample source	Linearity (mol L <sup>-1</sup> )	Detection Limit (mol L <sup>-1</sup> )	Electrolyte/ PBS Buffer pH/	Reference
Graphene–diamond hybrid electrode	Catalytic thermal treatment	DPV	AA, UA, GL	Pure chemical	5.0- 2000 μM	0.20 μΜ		[88]
CS/N,GQDs@SPCE	Microwave assisted hydrothermal reaction	CV, EIS	AA	human urine	1–200 µM	0.145 μΜ	7.0	<u>[82]</u>
Gr/Ta wire	CVD fabrication	DPV	AA,UA, Trp, NO2	Serum	0.25–75 μM	0.06 µM	7.0	<u>[69]</u>
Graphite/nafion/SPCE	Electrochemical pretreatment/US	LSV	UA, AA and glucose	DA, DA injections	0.5 to 70 μM	0.023 μΜ	7.0	[ <u>81]</u>
MWNT- Chit/PAMAM/DNA/Au	Ultrasonication	DPV, EIS	UA	Pure chemical	0.2 –100 μM	0.03 µM	7.4	<u>[91]</u>
FNT/DNA/ GCE	Ultrasonication	DPV	UA	Pure chemical	2–160 μM	0.6 μΜ	7.0	<u>[90]</u>
GR-CS/GCE	Ultrasonication	CV, DPV	AA	Pure chemical	5 – 200μm	5.0 µm	7.0	(Wang, et al., 2019).
CD/rGO/CFM	Electrochemical reduction	CV, DPV	UA, AA	Pure chemical	0.1–100 μM	0.02 µM	7.0	<u>[86]</u>
3DpGO-GNP-pGO/ITO	ultrasonication	CV, CA	AA, Glu	Pure chemical	0.1 to 30 μM	1.28 μM	7.4	[92]
P-Gr/GCE	Thermal heating/CR	DPV	Glu, Lac, Fru,	Urine	0.1– 180μM	0.002µM	7.0	[93]

Table 1. Summary of Graphene-based electrochemical sensors for dopamine

Electrode/ Materials/catalyst	Fabrication method	Detection Method	Interference	Sample source	Linearity (mol L <sup>-1</sup> )	Detection Limit (mol L <sup>-1</sup> )	Electrolyte/ PBS Buffer pH/	Reference
AuNBP/MWCNT/GCE	CR/US	DPV, DA	AA, UA	DA injection	50 nM to 2.7mM	15.0 nM	7.0	<u>[94]</u>
MWCNT/ITO	Microfabrication	DPV	NE, 5- hydroxytryptamine (5-HT	brain tissues of rats	2.5×10 <sup>-8</sup> M to 1×10 <sup>-5</sup> M	5.0 nM	6.0	<u>[96]</u>
MWCNT/PEI/SSB/GCE	Electrospinning, ultrasonication	DPV	AA, UA	serum, DA injection	1-650 µM	0.062 μΜ	7.0	<u>[94]</u>
MWCNT/SNFC/Nafion/ta- C		CV	AA, UA	DA injection	0.05-100 μM	65 nM	7.0	<u>[97]</u>
PVIM-Co5POM/ NCNT/GE	Chemical synthesis	CV, DPV, EIS	AA	Pure chemical	0.0005– 600 μM	500 pM	7.4	(Thakur et al., 2019)
Ta-C/MWCNT	chemical vapor deposition	CV	AA, UA	Pure chemical	0.01–5 μM	30.6 nM	7.4	<u>[98]</u>
PTCA-RGO-MWCNT-Au NP/GCE	Chemical co- reduction	CA	AA, UA, Glu	DA injection	1–100 µM	0.07 μM	6.5	[ <u>77]</u>
Cu2+@PDA-MWCNTs/ GCE/	Chemical synthesis	CV , EIS, DPV	AA,acetaminophen, nitrite, and xanthine	real serum and urine	0.45- 125 μM	0.45μΜ	2.0	[103]
Au@NAC- MWCNTs/GCE	facile one-step method	CV, DPV	UA	real serum and urine	0.1–250 μM	30 nM	7.0	(Z. Wang 2015)
MWCNTs/GNPs/GCE	biphasic (Brust- Schiffin) route	SWV	AA, UA	synthetic cerebrospinal fluid	0.4–5.7 μM	0.07 μM	4.5	[95]
CNT-Nb/CFME	CVD fabrication	FSCV	AA, DOPAC serotonin, adenosine, and histamine	In vivo rat model	_	11 ± 1 nM	7.4	[100]

 Table 2. Summary of CNTs-based electrochemical sensors for dopamine

#### Abbreviations

Dopamine (DA); ascorbic acid (AA); uric acid (UA); acetaminophen (AP); epinephrine (EP); norepinephrine (NEP); paracetamol (PAR), and tryptophan (TRP); Noradrenalin (NE); 5-hydroxytryptamine (5-HT); Glucose (Glu); Lactose (Lac); Fructose (Fru); GCE- glassy carbon electrode; DOPAC (3,4-dihydroxyphenylacetic acid, a dopamine metabolite); CV- cyclic voltammetry; DPVdifferential pulse voltammetry CA-Chrono amperometry; FSCV-fast scan cyclic voltammetry; SWVsquare wave voltammetry; CVD-Chemical vapour deposition; µM-micro molar; nM-nano molar; SPCE- screenprinted carbon electrode; GE- Graphite electrode, CFMEscarbon fiber microelectrodes. GR-CS/GCE- graphene/ chitosan modified; Gr/Ta wire- graphene-modified Tantalum wire electrode; GQDs@MWCNTs/GCE- graphene quantum dots (GQDs)/multiwalled carbon nanotubes modified; CRGO/Fc-ac-PPP/Au- Combination of reduced graphene oxide/ redox poly (para-phenylene) (Fc-ac-PP) lateral position with ferrocenyl group modified gold electrode; EG/Ni-Au (NPs)/GCE- graphene oxide- Nickel and Gold Nanoparticles modified; rGo/pd@ppy nps/GCE- Reduced graphene oxide coated with palladium nanoparticles supported on polypyrrole modified; 3D MoS2-PANI/rGO: MoS2 nanospheres and polyaniline (PANI) loaded on reduced graphene oxide; 3DCuxO-ZnO NPs/PPy/RGO: 3D porous nanocomposite of reduced graphene oxide decorated with polypyrrole nanofibers and zinc oxide-copper oxide p-n junction heterostructures; PTCA-RGO-MWCNTs-Au NPs/GCE-3, 4, 9, 10-perylene tetracarboxylic acid-functionalized graphene-MWCNT-gold nanoparticle nanocomposite modified GCE;

Au@NAC- MWCNTs/GCE- MWCNTs functionalized with Nacetyl-l-cysteine (NAC) stabilized Au clusters; AuPtNPs/S-NS-GR/SPCE: gold-platinum bimetallic nanoparticles decorated on sulfonated nitrogen sulfur co-doped graphene (S-NS-GR) CS/N, modified screen-printed carbon electrode; GQDs@SPCE: N-doped graphene quantum dots-chitosan nanocomposite modified screen-printed carbon electrode; TFCE- thin-film carbon electrode; rGO/ FET- reduced graphene oxide -based solution gated field-effect transistors; rGO/PEI/Au microelectrode- reduced graphene oxide/polyethyleneimine on the gold microelectrode; CD/rGO/CF- Carbon fibre microelectrodes deposited with electrochemically reduced GO nanosheets decorated Carbon dots; ΕμΡΑΝmicrofluidic paper-based analytical nanosensor; h-BCN/ CCE - hexagonal boron carbon nitride/carbon cloth electrode, High-pressure high temperature (HPHT); Aptamer-rGO/NB/AuNPs/GCE: aptamer-graphene oxide/ Nile blue /gold nanoparticles modified; FNT@DNA: fullerene C60 nanotubes @ singlestranded DNA; MWNT-Chit/PAMAM/DNA/Au: multiwalled nanotubes/chitosan (Chit)/poly(amidoamine) carbon (PAMAM) nanocomposite along with the incorporation of DNA modified Au electrode; 3DpGO-GNP-pGO- ITO: 3 dimensional porous graphene oxide /gold nanoparticle/ porous graphene oxide modified Indium Tin oxide electrode; Au/P-G: -Gold nanoparticle/Phosphorous doped AuNBP/MWCNTsgraphene modified; gold nanobipyramid/multi-walled carbon nanotube hybrids; MWCNTs/GNPs- multi-walled carbon nanotubes/ Gold nanoparticle hybrids; MWCNT/SNFC/Nafion /ta-C: s multiwalled carbon nanotube /sulfated nanofibrillar cellulose/ Nafion/ tetrahedral amorphous carbon (ta-C) thin-film electrodes; ta-C/CNT: tetrahedral amorphous carbon/carbon nanotubes; Mo NPs@f-MWCNTs: Molybdenum nanoparticles entrapped via functionalized MWCNTs; CNT-Nb/ CFMEs: carbon nanotubes /Niobium/ modified carbon fibre microelectrodes; MIP/MWCNTs/ GAs/ GCE: molecularly imprinted polymer/multi-walled carbon nanotubes spaced graphene aerogels modified GCE; MWCNT/PEI/SSB: MWCNTsulfonated poly (styrene-butadiene) flexible fiber membrane; PVIM-Co5POM/NCNT: polyoxometalate (POM) Na12 [WCo3(H2O)2(CoW9O34)2] and poly(vinyl imidazolium) cation [PVIM<sup>+</sup>] in combination with nitrogen-doped carbon Cu<sup>2+</sup>@PDA-MWCNTs/GCE: copper nanotubes (NCNTs); polydopamine complex/multiwalled carbon nanotubes modified glassy carbon electrode.

# **Statements and Declarations**

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### Declarations

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