

Current Challenges and Developments in Perovskite-Based Electrochemical Biosensors for Effective Theragnostics of Neurological Disorders

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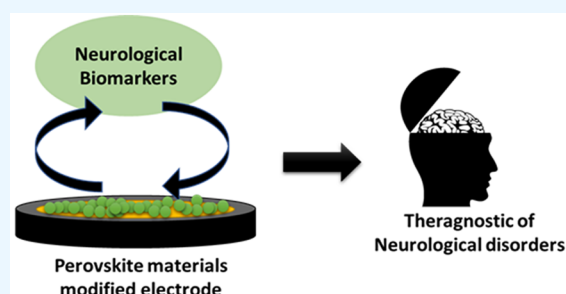
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ABSTRACT: Early-stage diagnosis of neurological disease and effective therapeutics play a significant role in improving the chances of saving lives through suitable and personalized courses of treatment. Biomolecules are potential indicators of any kind of disorder in a biological system, and they are recognized as a critical quantitative parameter in disease diagnosis and therapeutics, collectively known as theragnostics. The effective diagnosis of neurological disorders solely depends on the detection of the imbalance in the concentration of neurological biomarkers such as nucleic acids, proteins, and small metabolites in bodily fluids such as blood serum, plasma, urine, etc. This process of neurological biomarker detection can lead to an effective prognosis with a prediction of the treatment efficiency and recurrence.

While review papers on electrochemical, spectral, and electronic biosensors for the detection of a wide variety of biomarkers related to neurological disorders are available in the literature, the prevailing challenges and developments in perovskite-based biosensors for effective theragnostics of neurological disorders have received scant attention. In this Mini-Review, we discuss the topical advancements in design strategies of perovskite-based electrochemical biosensors with detailed insight into the detection of neurological disease or disorder-specific biomarkers and their trace-level detection in biological fluids with high specificity and sensitivity. The tables in this Review give the performance analysis of recently developed perovskite-based electrochemical biosensors for effective theragnostics of neurological disorders. To conclude, the current challenges in biosensing technology for early diagnosis and therapeutics of neurological disorders are discussed along with a forecast of their anticipated developments.

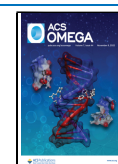


1. INTRODUCTION

Biomarkers or biological markers are the measurable alterations of the biochemical or biomolecule concentrations in any biological medium such as bodily fluids, tissues, or cells.¹ In recent decades, biomarkers have been recognized as potential indicators for various diseases.² The biomarkers can be classified into two types, known as biomarkers of exposure and biomarkers of disease.³ This classification of biomarkers includes the subclasses named susceptibility, diagnostic, prognostic, and predictive biomarkers.⁴ The susceptibility biomarkers are the indicators of objectively measured environmental agents in the biological system. The diagnostic biomarkers are known as indicators for diseases related to disorders in a biological system. The prognostic biomarkers are the indicators of disease recurrence in a biological system irrespective of the treatment provided. Finally, the predictive biomarkers provide information related to the response of a biological system to targeted therapy. This above-mentioned classification of biomarkers was recognized as an order of events by Perera et al. A superlative biomarker should be noninvasive, simple, accurate to measure reproducibly, highly related to a biological process of interest, and predictive in the

progression of the same.⁵ Generally, the anomalous values of the biomarkers in the biological fluids provide basic information on the development of irreversible injury in the biological system and aid the consideration of the pathophysiology of the respective progression. Major examples of the biomarkers range from the pulse and blood pressure of a biological system over elementary chemistries to the highly multifaceted laboratory examination of biological fluids and tissues. The recent development in the field of biomarkers has become more disease-specific, which can be used for the detection of deadly diseases such as cancers, cardiovascular diseases, neurologic disorders, oxidative stress, and metabolic instabilities such as metabolic syndrome, diabetes, chronic gout, cystic fibrosis, etc. The early detection of biomarkers in biological fluids such as blood, urine, and plasma would be

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highly valued for the early diagnosis and treatment of any specific diseases. Here, the major limitation observed is the selectivity of the biosensor toward the trace-level concentration of biomarkers in the presence of various other biological compounds in the body fluids. The wide variety of biomarkers includes antigens, enzymes, deoxyribonucleic acid (DNA), messenger ribonucleic acid (mRNA), amino acids, proteins, etc. The clinical significance of developing a reliable, rapid, cost-effective, and powerful biomarker detection technique has garnered the substantial attention of research toward biomarker detection which can effectively assist the process of prognosis, diagnosis, and monitoring of the recurrence of diseases.⁶ Various analytical techniques developed over a decade for the detection of biomarkers include enzyme-linked immunosorbent assay (ELISA), mass-sensing biodegradable citrus degreaser (Bio-CD), optical detection techniques (such as fluorescence, chromatography analysis, etc.), electrochemical detection, and gel-electrophoresis analysis.⁷ These conventional techniques with immunoassays facilitate the detection of targeted biomarkers via capture-antibody functionalization on a solid substrate for target capturing and assay readouts. Although some of these techniques provide a stable quantification of targeted biomarkers in biological fluids, they unanimously possess some major drawbacks owing to the nonspecific adsorption of nontargeted proteins onto the surface of a biosensor, which impacts the selectivity, sensitivity, and accuracy of the technique. On the other hand, these techniques necessitate trained manpower, expensive apparatus, and a time-consuming pretreatment process of the sample. To overcome the major drawbacks encountered by the conventional biomarker detection techniques, it is indispensable to achieve a low-cost, simple, rapid, highly sensitive, selective, accurate, and portable sensing technique for point-of-care and clinical diagnostics. These predominant requirements of biomarker detection for clinical and point-of-care diagnostic applications were achieved via wide research and development in the field of biosensors. Generally, an excellent biosensor should possess high specificity, sensitivity, and reusability.⁸ The biosensors can be classified into two types depending on the immobilization process, namely, enzymatic and nonenzymatic biosensors. In an enzymatic biosensor, the transducer has been immobilized with an enzyme to produce a signal proportional to target analyte concentrations.⁹ Nonenzymatic electrochemical biosensors depend on the redox reaction of the targeted analyte on the surface of the transducer. Generally, enzymatic biosensors have been reported with some significant limitations such as instability and low readout signal strength. Depending on the detection techniques employed for the sensing of biomarkers, the biosensors can be broadly classified into electrochemical, spectral, electronic, magnetoresistive, and piezoelectric biosensors, etc.⁸ This article aims to deliver a Review of the current challenges and recent developments in the design strategies using perovskite materials for different types of biosensors and their application in the theragnostics of neurological disorders. It is anticipated that this article will stimulate a broader research interest and insight into perovskite-based biosensors and their efficacy in the successful detection of complex biomarkers in biological fluids. This Review primarily consists of a brief overview of recently reported perovskite-based electrochemical biosensors for the early diagnosis and effective therapeutics of neurological disorders.

2. PEROVSKITE MATERIALS AND THEIR APPLICATIONS

Perovskite materials are also known as ceramic oxide materials with the general formula of ABX_3 , where A and B are the cations and X is an anion. The X anion can be oxygen or any other element with larger ionic radii such as halides, nitrides, and sulfides. Generally, there are three types of perovskite materials reported depending on the structure of the material: (1) containing localized electrons; (2) containing delocalized energy bands, and (3) the transition state.¹⁰ These ABO_3 perovskite materials form a cubic or nearly cubic crystal structure like any other transition metal oxide materials facilitated with a low-temperature phase transition process. Additionally, these materials are applied for a wide range of applications with respect to their simple crystal structures and extraordinary ferroelectric and dielectric properties. Apart from the ABO_3 perovskite structure, there are several other perovskite structures such as layered (A_2BO_4), double-layered ($A_2BB'O_6$), triple-layered ($A_2A'B_2B'O_9$), etc. Although the oxide perovskite materials possess the basic transition metal oxide structures, their inherent properties highly differ from the basic metal oxides, such as ionic conduction characteristics, insulator–metal transition, dielectric, metallic, and superconducting. Apart from the special structures of perovskites and their tunable electromechanical properties, these materials have gathered a wide spectrum of research interest owing to the large availability of cations and anions across the Periodic Table. Owing to these merits of perovskite materials, they have been widely used in a variety of applications such as random-access memories, actuators, tunable microwave devices display, piezoelectric devices, transducers, wireless communications, sensors, and capacitors. An interesting property of perovskite materials is the phase transition of the material with respect to temperature. Fu and Itoh have reported the phase transition of $BaTiO_3$ (an ABO_3 -type perovskite material) between cubic and rhombohedral with an impact on the dielectric constant of the material.¹¹ This proves that the phase transition mechanism depending on temperature and displacement of the B cation impacts the dielectric property of perovskite materials. Owing to the tunable crystal structure with a wide range of combinational availability and distinguished phase transition mechanisms, perovskite materials have been reported with various physicochemical properties such as electrical conductivity (ReO_3 , $SrFeO_3$, $LaCrO_3$, $LaCoO_3$, and $LaNiO_3$), piezoelectricity property ($Pb(Zr, Ti)O_3$ and $(Bi, Na)TiO_3$), ion conductivity ($La(Ca)AlO_3$, $BaZrO_3$, $CaTiO_3$, and $SrZrO_3$), superconductivity ($La_{0.9}Sr_{0.1}CuO_3$ and $YBa_2Cu_3O_{7-x}$), magnetic property ($LaMnO_3$ and La_2NiMnO_6), ferromagnetic property ($BaTiO_3$ and $PdTiO_3$), and catalytic property ($LaCoO_3$ and $LaMnO_3$), etc.¹²

A variety of synthesis techniques such as solid-state reactions, the Pechini method, the coprecipitation method, hydrothermal synthesis, gas-phase preparations, and wet chemical and sol–gel methods have been evolved in the past few decades to overcome drawbacks such as inhomogeneity, defects in the lattice space, incorporation of chemical impurities, and coarseness of synthesized particles. Perovskite materials are widely used in different kinds of applications as they possess a variety of physicochemical properties via tunable crystal structures depending on the synthesis techniques and the elemental combination. The major applications developed and reported depending on the stability and unique

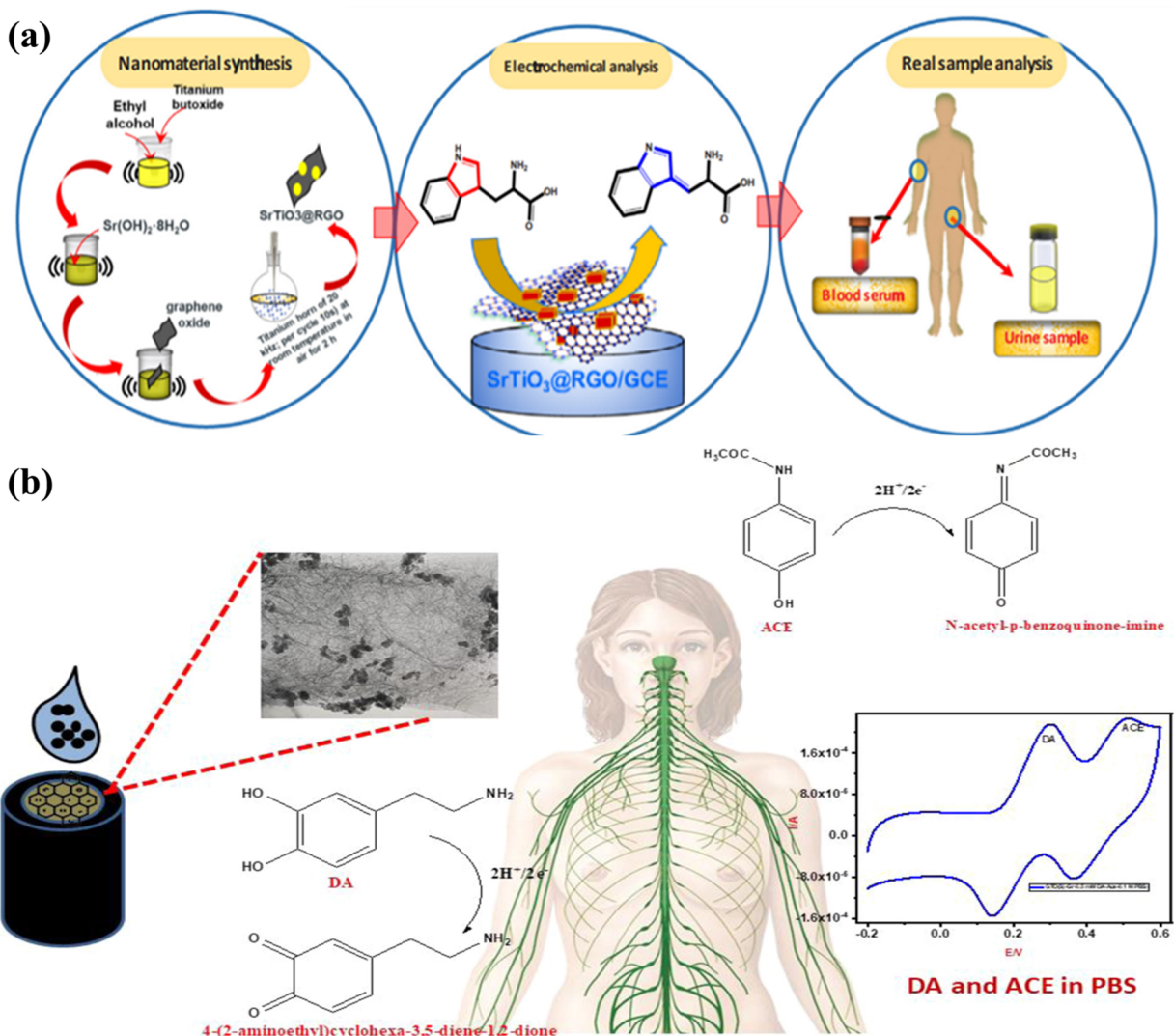


Figure 1. (a) Sonochemical synthesis of SrTiO₃@RGO nanocomposite and its electrochemical sensing of Trp reprinted in part with permission from Govindasamy, M.; Wang, S.-F.; Chih Pan, W.; Subramanian, B.; Jothi Ramalingam, R.; Al-lohedan, H. Facile sonochemical synthesis of perovskite-type SrTiO₃ nanocubes with reduced graphene oxide nanocatalyst for an enhanced electrochemical detection of α -amino acid (tryptophan). *Ultrason. Sonochem.* **2019**, *56*, 193–199. Copyright 2019 Elsevier. (b) Simultaneous trace-level detection of dopamine and acetaminophen in blood serum, tablets, and urine samples using pristine graphene-decorated GdTiO₃ perovskite GCE reprinted in part with permission from Grace, A.A.; Dharuman, V.; Hahn, J. H. GdTiO₃ perovskite modified graphene composite for electrochemical simultaneous sensing of acetaminophen and dopamine. *J. Alloys Compd.* **2021**, *886*, 161256. Copyright 2021 Elsevier.

physiochemical properties of the perovskite materials are as follows; they are used in capacitors, photoelectrochemical cells, drug delivery, catalysts, recording applications, high-temperature heating applications, spintronics devices, thermal barrier coatings, laser applications, frequency filters for wireless communications, sensors, nonvolatile memories, ultrasonic imaging biosensors, actuators, and transducers, etc. Among these mentioned applications of perovskite materials, the electrochemical biosensor has gathered major attention owing to its sensitivity, selectivity, excellent reproducibility, and long-term stability, etc.

3. ELECTROCHEMICAL BIOSENSORS FOR THERAGNOSTICS OF NEUROLOGICAL DISORDERS

In the past few decades, a significant number of electrochemical biosensors were reported for various biomarker/biomolecule sensing uses for clinical diagnosis and other applications.¹³ The vital component in any electrochemical

sensor is the working electrode; this determines the efficacy of the sensor. To improve the performance of these sensors toward the targeted analytes, conventional electrodes such as glassy carbon electrode (GCE), screen-printed carbon electrode (SPE), etc. were reported with different surface chemical modification processes and materials.¹⁴ Apart from these electrode modification processes via different functional materials, the surface of the electrodes was additionally immobilized with different chemical groups such as amine and carboxyl (1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide: EDC), aldehyde (hydrazide), thiol (maleimide), etc. to ensure the solid support for the labeling biomarkers such as enzyme, antibody, and nucleic acid. Although these kinds of immobilization processes improve the selectivity, sensitivity, and chemical and electrochemical stability in larger usable potential windows with resistance to fouling, the unsuitable immobilization may cause loss of activity, less specificity, and low biocompatibility of the sensor. Recently,

Table 1. List of Perovskite-Based Chemically Modified Label-free Electrochemical Biosensors and Their Performance Towards Various Biomolecules^a

perovskite material	synthesis technique and crystallographic phase	targeted biomolecule	modified electrode and technique	disease identified	sensitivity	limit of detection	dynamic range of detection	real sample analysis	ref
NaNbO ₃	solid-state reaction—orthorhombic	dopamine	GCE DPV	neurological diseases	99 nA/nM·cm ²	6.8 nM	0.010–1000 μM	simulated blood serum	15
SrPdO ₃	sol–gel—orthorhombic	dopamine	CpE DPV	neurological disorders	0.88 μA/μM·cm ²	9.3 nM	7–160 μM	urine sample	16
β-NaFeO ₂	solid-state reaction—orthorhombic	dopamine	GCE DPV	neurological disorders	27.16 μA/μM·cm ²	2.12 nM	0.010–40 μM	simulated blood serum	17
SrTiO ₃	sonochemical synthesis—cubic	amino acid (tryptophan)	GCE amperometry	brain disorders	9.11 μA/μM·cm ²	7.15 nM	0.030–917.3 μM	urine and blood serum	18
CuFe ₂ O ₄	wet chemical synthesis—cubic spinel	3-nitrotyrosine	MSPE amperometry	oxidative stress	8.515 μA/μM·cm ²	25.14 pM	0.004–1347.5 μM	urine and blood serum	21
LaFeO ₃	solid-state reaction—orthorhombic	dopamine	GCE DPV	neurological disorders	0.81 μA/μM·cm ²	10 nM	10–180 μM	human blood sample	22
LaCoO ₃	hydrothermal—rhombohedral	dopamine	GCE DPV	neurological disorders		3.53 μM	5–50 μM		23
LaFeO ₃	wet chemical synthesis—orthorhombic	dopamine	GCE amperometry	neurological disorders		59 nM	0.02–1.6 μM		24

^aGCE, glassy carbon electrode; CPE, carbon paste electrode; GPE, graphite paste electrode; MSPE, multipurpose screen-printed electrode; DPV, differential pulse voltammetry.

various electrochemical biosensors were developed and reported with high sensitivity and selectivity using carbonaceous functional materials for electrode modifications. Similarly, a variety of 2D materials with different morphologies were also studied as potential functional materials for chemically modified electrochemical biosensors. The major drawbacks encountered by both the carbonaceous and 2D materials were the surface fouling effect known as adlayer formation along with the chemical and electrochemical instability of the materials after the process.¹⁴ Along with various developments in electrochemical biosensors, the induction of label-free biosensors garnered significant research interest because of its simple analysis without involving any complex labeling procedures. The label-free electrochemical biosensors have been widely reported for biomarker detection, DNA and protein sensing, etc. Here in this Review, we focus on the development of a label-free electrochemical biosensor using a perovskite material which was employed in the detection of a range of biomolecules in biological fluids amid various clinical diagnoses.

Neurotransmitters are well-known potential biomarkers for various neurological diseases like Parkinson's disease, Alzheimer's disease, and depression.¹⁵ The low concentration of dopamine in biological fluids (10⁻⁸–10⁻⁶ M) demands an ultrasensitive and highly selective electrochemical biosensor for real-time clinical diagnosis. In recent years, perovskite materials such as NaNbO₃, SrPdO₃, LaFeO₃, LaCoO₃, LaFeO₃, and β-NaFeO₂ have been reported as the functional material for the chemically modified based electrochemical biosensors targeting dopamine in biological fluids. Unlike 2D materials and other carbonaceous materials, perovskite materials are not known for their electrocatalytic activity, but they too have intense electrocatalytic active sites which favor the electro-oxidation of dopamine into dopamine-*o*-quinone.¹⁵

3.1. Perovskite Based-Electrochemical Biosensors.

The electrochemical sensing mechanism using perovskite-based chemically modified electrodes reported depends on the electrocatalytic active sites. These are the octahedral sites of

the perovskite structure with Nb⁵⁺ cations which favors the delocalization of charge carriers during the redox reaction at the electrode–electrolyte interface.¹⁵ Similarly, Atta et al. reported SrPdO₃-modified CPE as an electrochemical biosensor for dopamine sensing in which the homogeneously distributed Pd⁴⁺ cations at the octahedral sites of the perovskite enhanced the rate of electron transfer during the redox reaction of the dopamine molecule in the medium.¹⁶ The β-NaFeO₂ material was examined for dopamine sensing, and it was observed that the Fe³⁺/Fe⁴⁺ oxidation states of Fe in the respective octahedral and tetrahedral sites of the perovskite structure favored the delocalization of the charge in the electrocatalytic reaction.¹⁷ These concluding statements prove the structure-oriented electrocatalytic activity of the perovskite materials and their high chemical stability.^{16,17}

On the other hand, the major imbalance between the free radicals and the antioxidants in a biological system indicates neurological disorders (such as Alzheimer's, Parkinson's, etc.). L-Tryptophan (Trp) is the major therapeutic biomarker in the treatment of various inflammatory diseases including schizophrenia, hallucinations, delusions, nausea, headache, Alzheimer's, hepatic diseases, and Parkinson's. Owing to improper metabolization, the high concentration of Trp can be very harmful to the brain. Govindasamy et al. reported a label-free electrochemical biosensor for the detection of Trp in biological fluids such as urine and blood serum samples using SrTiO₃@RGO/GCE via amperometry analysis. The enhanced sensitivity and selectivity of the sensor were attributed to the large active surface area of RGO and π-to-π interaction between RGO and SrTiO₃.¹⁸ The basic sensing mechanism via electrochemical oxidation of Trp is shown in Figure 1a. Wang et al. reported a LaNi_{0.5}Ti_{0.5}O₃ (LNT) nanoparticle-modified carbon paste electrode for the nanomolar detection of L-cystine. The enhanced sensitivity and selectivity of the LNT/CPE toward L-cystine were attributed to the Ni centers in the perovskite structure facilitated by a Ni³⁺/Ni²⁺ electro-oxidation mechanism.¹⁹ The current–time responses of CPE and LNT/CPE upon the successive addition of different

concentrations of L-cystine were given. Grace et al. reported the pristine graphene-decorated GdTiO₃ perovskite, a binary composite-modified GCE for simultaneous trace-level detection of dopamine and acetaminophen in blood serum, tablets, and urine samples as shown in Figure 1b. The outstanding sensitivity, selectivity, and stability of the electrode have been ascribed to the π interactions between the graphene and the perovskite.²⁰ The sensing performance of reported perovskite-based electrochemical biosensors for the theragnostics of neurological disorders is given in Table 1.

4. CURRENT CHALLENGES

The major challenge of the electrochemical biosensor for the theragnostics of neurological disorders is the trace-level concentrations of the targeted biomarker in the presence of other interfering analytes.¹⁷ The secondary challenge that has attracted research interest toward the perovskite-based electrochemical sensor is the selection and synthesis of a suitable perovskite material as the sensing platform for different neurological biomarkers. Generally, perovskite materials are reported with a large number of electrocatalytic active sites which provides high sensitivity and stability.^{15–18} However, the selectivity of the sensor toward the targeted biomolecules would be compromised because of interfering biomolecules present in the biofluids. Generally, this drawback is addressed via the immobilization of antibodies through the enzymatic process. The enzymatic sensing of the biomarkers was reported with its drawbacks such as instability and operational constraints like pH, temperature, and humidity.¹⁷ On the other hand, the nonenzymatic detection of biomarkers based on nanomaterials was reported with high stability owing to the unique morphology and high surface area. Also, the sensors exhibited high selectivity and sensitivity owing to the presence of electrocatalytic active sites and variable oxidation states. However, the pH and operational temperatures are the two major factors that impact the efficacy of any perovskite-based chemically modified biosensors.

5. FUTURE PERSPECTIVES

Despite the availability of a wide spectrum of biomarkers, the identification of suitable biomarkers for the relevant application of diagnosis is of the highest priority. First, the low physiological concentration of various neurotransmitters must be addressed, as the biomarkers demand an ultrasensitive detection technique. Second, the presence of these biomarkers in the biological fluids discloses the presence of other biomolecules and cell tissues in the complex. This demands a selective biosensing platform that is active toward the targeted analyte and inactive to other biomolecules. Thereby, a highly selective biosensor is required for clinical sample analysis. Third, stability and reusability are two vital parameters for any biosensor defining the efficacy of the sensor. These parameters should be improved when compared to the current progress status of the reported biosensor. This can be achieved through the application of various highly stable perovskite-based nanomaterials with unique structures and properties. The cost-effective development of biosensing technology is highly crucial for the commercialization of biosensors and related early point-of-care diagnosis applications. Finally, the miniaturization of the biosensors for the evolution of handy and wearable point-of-care diagnostic devices remains a vital

challenge for early diagnosis and therapeutics of neurological disorders.

The future scope in the field of biosensors is anticipated to rely on the development of highly stable, sensitive, and selective detection of complex biomarkers for early diagnosis of rare and deadly diseases. As mentioned above, the evolution of a low-cost, facile, highly selective, and sensitive biosensing platform has gathered a wide scope of research interest toward the point-of-care and wearable diagnostic applications. In this aspect, the perovskite-based nanostructured material is a promising special structured material with high stability, selectivity, and unique electronic and piezoelectric properties. Despite the advantages of the perovskite materials, only a few reports are presented for biosensor applications (discussed in this Review). The overall advancement expected in the field of biomarkers in the near future would be directed toward the following: (1) A user-friendly biosensing platform integrated into smartphone applications for the detection of complex biomarkers in various biological fluids. (2) Development in various active functional materials for microfluidic devices for in vivo and in vitro diagnosis and therapeutics. (3) Depending on the versatile properties of specially structured nanomaterials, an exponential development in the efficiency of biomarker detection is expected using new electrochemical sensing techniques such as photoelectrochemical analysis, sonoelectrochemical analysis, microwave-activated electrochemical analysis, etc. (4) The development of wearable biosensing devices for early disease diagnosis and therapeutics of neurological disorders. (5) Provided with the miniaturization of these biosensing platforms, they could be integrated with a microelectromechanical system (MEMS) for a novel drug delivery application.

6. SUMMARY

In summary, this Review provides insights into the current challenges and development in perovskite-based biosensors for effective theragnostics of neurological disorders in human beings. Biomarkers are the biological constituents of the bodily fluids which can indicate the normal and abnormal processes of a biological system. The detection of an abnormal concentration of targeted biomolecules in bodily fluids is associated with various diseases and disorders. In this regard, the most recent pertinent articles on different electrochemical biosensors using different perovskite-based chemically modified electrode-based biosensors and their analytical performance toward an early clinical diagnosis of neurological disorders were assessed. In short, every biosensing technique has its advantages and disadvantages in the detection of targeted biomolecules. However, recent research has progressed through simultaneous biomarker detection techniques for effective and low-cost clinical diagnosis of different diseases. On the other hand, the miniaturization process of the biosensors provided with the application of novel perovskite-based nanostructured materials has paved a new avenue of research for wearable and user-friendly point-of-care diagnosis. Also, the authors believe that this broad insight into different perovskite-based electrochemical biosensors and their applications would encourage more research in the field of biosensing based on stable, low-cost perovskite materials.

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Notes

The authors declare no competing financial interest.

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