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Journal of Composites and Compounds

Nanobiosensors for early detection of neurodegenerative disease

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ABSTRACT

Early detection of neurodegeneration-related disorders that emerge as people age, is critical for both the disease's treatment and the patient's living conditions. Parkinson's and Alzheimer's illnesses are two well-known instances of neurodegeneration, which are characterized by nerve cell death and dementia. The fact is that some illnesses are only diagnosed clinically after symptoms develop hinders therapy. The biomarkers detection, which are unique chemicals found in bodily fluids and are implicated in neurodegenerative processes, may assist in the early detection of neurodegenerative illnesses. Recent years have seen a surge in interest in biosensor research, with the goal of detecting possible biomarkers of the neurodegenerative process with appropriate precision. Biosensors' main purpose is to identify a specific material with high specificity. This manuscript reviews neuro-biosensors for the prognosis of neurodegenerative illnesses like Parkinson's disease (PD) and Alzheimer's disease (AD), as well as a summary of the field's urgent needs, highlighting the critical importance of early detection along the neurodegeneration pathway in general. This study examines biosensor systems designed to identify biomarkers of neurodegenerative diseases (NDDs), with an emphasis on the last five years.

Peer review under responsibility of JCC Research Group

ARTICLE INFORMATION

Article history:
Received 2 November 2021
Received in revised form 21 December 2021
Accepted 9 February 2022

Keywords:
Early diagnosis
Neurodegenerative disease
Nanobiosensors
Optical biosensors
Electrochemical biosensors

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1. Introduction

Every year, tens of millions of individuals worldwide are affected by neurodegenerative illnesses, which are defined by the inevitable annihilation of non-specific surroundings brain cells and the physical degradation of target neurons associated with the illness [1]. Neurodegeneration, on the other hand, is defined as the functional loss of neurons and gradual structural, resulting in a wide range of pathological and clinical

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https://doi.org/10.52547/jcc.4.1.4

manifestations, as well as worsening of functional architecture [2]. One of humanity's most pressing issues is reducing the harm caused by neurodegenerative illnesses including Huntington's disease (HD), Lou Gehrig's disease/amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD) [1]. Early detection of neurodegeneration-related disorders that emerge as people age is critical for both the disease's management and the patient's living conditions. The treatment procedure is slowed when illnesses like PD and AD are diagnosed until after symptoms arise [3]. As people live longer, it's more important than ever to understand the pathophysiology of neurodegenerative disease (NDD) so that treatment and diagnostic choices can improve and the costs NDD places on the healthcare system can be reduced [4].

Numerous studies on NDD biomarkers (quantifiable signals indicative of injury, contamination, or illness) have been conducted with the goal of identifying disease occurrences before neurological damage becomes too severe to be reversed by therapeutic drugs. Traditional biomarkers have yet to be established, therefore it's unclear if they can be used to diagnose neurodegenerative illnesses early [1]. Moreover, researchers have been forced to collect a sample via peripheral patient-derived biomaterial, that may not accurately reflect the circumstances of neurodegenerative illness due to the difficulties of capturing predominantly disease-associated neurons [5]. Biomarkers, which are unique molecules present in human fluids and are associated with neurodegenerative processes, can improve the early diagnosis of NDDs [3]. Furthermore, micro and nanotechnology advancements have allowed the growth of biosensing devices capable of real-time identification of several biomarkers in therapeutically related samples [6].

Because of the capacity to detect disease-related biomarkers in real-time, cost-effectively, sensitively, quickly, and without using labels, biosensors are one of the most promising technologies [7]. A biosensor is a device with an integrated receptor transducer that may be used to monitor semi-quantitative data or quantifiable [8, 9]. Biosensors are classified as piezoelectric, electrochemical, or optical devices based on the type of signal transducer they use [10]. Recently, NPs have been actively explored because of their prospective uses such as nanosensors [11, 12]. Nanomaterials (NMs) provide intriguing features coming of their high surface area [13-18]. They are prospective candidates for use in biosensor manufacture to decrease detection limits and improve sensitivity [19]. Nanotechnology applied to biosensors (nanobiosensors) is regarded as a quick, low-cost, selective, sensitive, and novel approach that may be miniaturized and automated, and can even replace traditional methods. NPs give nanobiosensors qualities including high conductivity and a large surface-to-volume ratio., which expands their usefulness in the detection of allergenic proteins and improves performance [20].

Quantitative measures of neurotransmitter activity in situ can reveal crucial information on the mechanisms behind NDDs, neural network formation, and stem cell differentiation. Nonspecific detection, low spatial resolution, and no in situ analysis are currently available in neurotransmitter detection systems [21]. To tackle this problem, Choi et al. [21] created a graphene oxide (GO)-hybrid nanosurface-enhanced Raman scattering (SERS) array capable of sensitive and selective dopamine (DA) detection. They were able to correctly and rapidly measure a broad range of DA concentrations (10^{-4} to 10^{-9} M) via the GO-hybrid nano-SERS array. Furthermore, measuring DA from developing neural stem cells is useful for determining neuronal differentiation. In other cases, identification of cytoplasmic DA is still difficult due to the difficulties of keeping cells alive during the operational process and the low amount of cytoplasmic DA [22]. Chang et al. [22] used a solid-phase microextraction (SPME) technology with an integrated nanobiosensor to measure and track DA concentration variations in a single live cell's cytoplasm. They created a bifunctional carbon fiber nanoprobe with a polypyrrole modification that can extract cytoplasmic DA and then conduct electrochemical detection.

Management and detection of mentioned disorders in their early stages are crucial for improving the elderly's quality of life. The ultimate objective of detecting preclinical neurodegenerative illnesses is to be able to apply therapies in their early phases, which may delay, minimize, or even avert the eventual neurological damage that would develop if the problems were left untreated. Current clinic diagnostic procedures for neurodegenerative illnesses, on the other hand, are time-consuming and costly, necessitating the use of expert employees to run certain complex equipment. As a result, it has become increasingly and vitally necessary to create reliable, convenient, low-cost, and simple-to-use diagnostic procedures [23]. The goal of this review is to discuss neuro-biosensors that can identify biomarkers diagnosed in biological for NDDs, as well as to learn about the challenges of this field and an overall view of the critical role of earlier detection, the role of nano-transducers, biomarkers, various biosensors, and the field future direction.

2. Neurodegenerative disease

Neurodegenerative disorders manifest themselves clinically via a variety of symptoms, including selective loss and neuroinflammation malfunction, aggregates of protein, neurons, and synapses all of which result in severe alterations in cognition and behavior [24, 25]. AD, PD, ALS, frontotemporal dementia, HD, and prion disease are all neurodegenerative disorders that impact a large number of individuals worldwide [26-28]. PD and AD are the most prevalent diseases of the nervous system [29-32]. With increasing age, the chance of developing a neurodegenerative illness grows considerably. According to recent studies, a sizable proportion of people will be affected by neurodegeneration in the next decades, stressing the vital need to understand the reasons and expand innovative ways for management and cure them [33-36]. Recent research estimate that around 30 million individuals globally suffer from AD [7, 37]. As a result, the health, economic, and social consequences of neurodegenerative disorders are enormous [28, 32]. However, the mechanism of neurodegenerative disorders remains a mystery, and clinical medicines for their treatment are still lacking [38, 39]. Numerous possible causes for this failure in managing and treating neurodegeneration conditions involve the blood-brain barrier (BBB) presence, which functions as a defensive mechanism, preventing drugs from entering the brain and thereby treating only the disease's symptoms. Furthermore, the diagnostic markers used are not verified and are still relevant to possible or likely illnesses [40-43]. Worldwide, neurological illnesses are claiming a growing share of disability-adjusted life years, particularly in high-income nations [44].

2.1. Parkinson's disease

PD is characterized by a gradual impairment of motor capabilities as a result of DA-releasing neurons being confiscated [45, 46]. PD affects neurons, resulting in forgetfulness and cognitive impairment, as well as coordination, balance, tremors, trouble walking, and stiffness [7, 30, 47]. PD symptoms begin slowly and increase with time. PD may affect men and women over the age of 50 [48].

PD is mostly associated with death or damage of the neurons or nerve cells in the brain that govern body movement [30, 45, 46]. This leads to decreased DA release, which ultimately results in problems with movement. PD patients also lose nerve endings that generate norepinephrine. There are no particular treatments for PD at the moment, and the therapies, surgeries, and medications provided can only alleviate the illness's symptoms [49-52]. Among the therapy options for PD, the usage of proteins like human glial cell line-derived neurotrophic factor (hGDNF) has shown promise. Ansorena et al. [53] developed a straightforward and rapid approach for producing a large concentration of pure

hGDNF utilizing a mammal cell-derived technology.

In addition, PD has been detected via NP-mediated biomarker detection (Table 1). PD is linked with a specific degeneration of DA substantia nigra and a drop in the striatum's DA level. This deficiency of DA results in motor symptoms (resting tremors, stiffness, and so on) as well as other symptoms such as cognitive impairment [54]. PD, the 2nd most common NDD, is likewise marked by α -synuclein amyloid buildup [55, 56]. Adam et al. [57] developed a biosensor capable of detecting a particular PD biomarker, such as α-synuclein aggregation, which is critical for minimizing the burden of PD and for early detection. Detecting alpha-uneven synuclein aggregation is a potential tool for the early identification of PD. The ZnO nanocomposite affixed to the aluminum microelectrode surface offers an advantageous substrate for effective antibody loading through antigen α-synuclein binding. Aghili et al. [58], on the other hand, created an electrochemical nanobiosensor to detect PD early using the measurement of a circulating biomarker, miR-195. Gold nanowires (GNWs) and exfoliated graphene oxide were used to enhance the surface of a screen-printed carbon electrode (EGO). A single-strand thiolated reagent was designed to precisely hybridize with the target miRNA (miR-195), and doxorubicin was used as an electrochemical indicator for differential pulse voltammetry studies. Based on the findings, physicians may consider using the miR-195 electrochemical nanobiosensor for the medical diagnosis of PD.

2.2. Alzheimer's disease

AD is strongly related to significant cognitive impairments [64, 65]. It's among the primary causes of dementia mostly in older. AD patients first exhibit difficulties with memory imprinting and limited forgetfulness. This develops into impaired short-term memory and eventually to impaired long-term memory [41, 42, 66, 67]. These symptoms manifest as difficulties with reasoning, remembering, and thinking as well as behavioral impairments that impair the individual's activities and everyday life [28, 32, 68]. Thus, AD progresses to the syndrome of dementia, which first impairs the individual's functioning and finally results in full reliance on others to do even the most fundamental tasks [25, 69, 70].

AD has a scientific history dating back to 1906 when Dr. Alois Alzheimer examined the brain of a lady who died prematurely due to a mental disorder. In the brain tissues, he discovered several twisted bundles of fibers and aberrant clusters [71]. These tangles and plaques are thought to be the disease's primary hallmark [29, 36, 70]. AD is most often associated with memory difficulties, although additional symptoms include vision impairments, judgment or poor thinking, trouble locating words, and others [35, 64, 65]. As the condition continues, behavioral and personality changes, difficulty doing everyday duties, being lost and wandering, and difficulty paying and managing cash occur and memory loss becomes more severe. Further phases result in the patient's inability, increased bewilderment, and loss of linguistic control to recognize friends and family [31, 72, 73]. Eventually, the plaques and tangles expand throughout the brain, leaving the sufferer utterly reliant on others. AD therapy is very difficult since no one medicine can adequately cure the illness [24, 74, 75].

At the moment, the definitive diagnosis of AD is achievable only upon postmortem neuropathological investigation. Available diagnostics for suspected patients are prohibitively expensive, limited in availability, or invasive. There is still a need for early detection technologies to improve existing therapy, even before mild cognitive impairment occurs (MCI). The deposition of Aβ in extracellular amyloid plaques is one of the hallmarks of AD, resulting in severe neurodegeneration on a local level. Visualization of these amyloid plaques in living tissues is crucial for determining therapy success, monitoring disease development, and diagnosing AD. Another AD-specific lesion occurs as a consequence of hyperphosphorylation of Tau protein, which causes the protein to dissociate from microtubules and aggregate form neurofibrillary tangles in the intracellular environment. [76, 77]. As a consequence, substantial interest has been shown in creating a molecular imaging agent capable of detecting AD lesions based on these clinical characteristics (Table 2). These agents must be nontoxic and, preferably, capable of crossing the BBB without the need for facilitation.

Due to reproducibility and stability issues in biological samples, there are many substantial hurdles associated with the scalable and regular manufacture of biosensing devices. Additionally, relatively few studies employed genuine samples of AD patients, and the majority of biosensors were evaluated in the buffer, manufactured samples, or real specimens spiked with the desired analytes [78]. Because AD illness is caused by several pathogenic pathways, detecting multipathing is a critical step that is currently sadly lacking. As a result, the panel detection of biomarkers is crucial for enabling reliable and sensitive detection if one is required. Additionally, there are the following difficulties [79]:

1. Amass new knowledge about the pathogenesis of AD and identify better and novel biomarkers.
2. Advances in the development of a repeatable biomarker approach.
3. To minimize matrix interferences, pre-treatment samples, such as extraction and purification, are necessary.
4. Biosensor miniaturization and integration into a single application platform.
5. Cost savings associated with developing and implementing methods

NMs are critical in resolving some of the aforementioned difficulties. Numerous NMs of varying sizes display unique properties that manifest themselves in a variety of optical and electrochemical activities. When biological recognition components and NMs are coupled, an improved diagnostic method emerges [79]. Kang et al. [80] describe the development of a new poly-L-lysine (PLL)-mediated nanobiosensor for the in vitro detection of Amyloid. The PLL molecules were used as an Aβ detection signal amplifier. Amyloid has been detected using both the indirect enzyme-linked immunosorbent test (ELISA) and the sandwich ELISA methods. PLL was used to modify a commercially available ELISA plate, and the amplified amino groups were triggered using a functional

Table 1.
PD: a selection of NP-based assays for the identification of particular indicators

Marker of disorder	NP	Diagnosis modality	Experiment type	BBB crossing	Ref.
α-Synclein	Immuno/magnetic particle	Immunoassay	In vitro	Not applicable	[59]
	Gold nanorod	Surface plasmon	In vitro	Not applicable	[60]
DA receptor	Immuno-targeted far-red QDs	Fluorescence	In vivo (acute rat brain slide)	Intraventricular injection	[61]
DA	PEGylated PFPBA NPs (100 nm)	Near-infrared fluorescence	In vivo (mouse)	Yes	[62]
	PEGylated PFPBA NPs (120 nm)	Fluorescence quenching	In vivo (zebrafish)	Yes	[63]

group specific for Amyloid binding. As a consequence, the PLL-mediated indirect ELISA nanobiosensor demonstrated the highest sensitivity for Amyloid detection. Alternatively, Amini et al. [81] suggested an improved nanobiosensor for AD detection in their study. They improved the metal layer thickness for copper, aluminum, silver, and gold metals using a modified approach to enhance the quality and sensitivity factor. An optimal result is achieved by using gold as the active layer and incoming light with a wavelength and angle of 632 nm and 46, respectively. Finally, AD detection is computed utilizing the improved surface plasmon resonance (SPR) structure. The researchers can measure even minute amounts of molecular structure present in blood samples and cerebrospinal fluid (CSF) using this approach.

2.3. Multiple sclerosis

Multiple sclerosis (MS) is defined by the development of inflammatory lesions mostly in the white matter of the spinal cord and brain. Axon and neuronal loss, as well as axon demyelination, are the hallmarks of these lesions. MS is also defined by peripheral macrophage migration across a weakened BBB and microglial activation, resulting in axonal injury and demyelination [91]. Leukocyte infiltration is conceivable as a result of endothelial cell activation, which increases the synthesis of adhesion molecules including intercellular cell adhesion molecule-1 (ICAM-1) and vacuolar cell adhesion molecule-1 (VCAM-1) [92].

Recent breakthroughs in the area of nanoscience provide a novel approach to overcoming these obstacles and establishing a more fertile ground for monitoring neurological illnesses and innovation in medication development. Numerous neuroimaging methods are available to assist in diagnosing the neurological complications associated with neurodegenerative illnesses. Single photon emission CT, positron emission tomography, and nuclear medicine research are all examples of these approaches. Magnetic resonance spectroscopic imaging, ^{1}H, and ^{31}P magnetic resonance spectroscopy, and CT and MRI are all morphological investigations [93-96]. Nanotechnology's recent advancements are critical in the biomedical industry because they provide enhanced electrophysiological and neuroimaging techniques for fundamental clinical research. Nanotechnology aids in the progression and discovery of central nervous system (CNS) illnesses, providing the creation of innovative diagnostic methods and fresh insight into CNS physiology. Nanotechnology-based systems are utilized to increase the power of neuroimaging by using more precisely targeted probes of molecular imaging and contrast. In addition, it may be integrated into a sophisticated biosensor system inside the brain for testing circuit physiological principles. Using the unique and improved biological, chemical, and physical features of NMs, may be considerably improved present approaches for detecting severe CNS illnesses and used new insights into brain physiology to generate innovative treatment options [97-99]. These strategies may be used to deduce the underlying neurological mechanisms that contribute to illness development. Thus, diffusion tensor imaging (DTI), CT, and MRI are often utilized in conjunction with neurological and clinical evaluations to aid in the identification of many degenerative CNS illnesses [100-104].

Due to the heterogeneity of MS, which is characterized by diverse demyelination patterns, it is exceedingly implausible that a single diagnostic marker would cover the whole range of MS subtypes [105]. Lolli et al. [106] created CSF114(Glc), a synthetic glycoprotein antigen probe, for the detection of autoantibodies seen in the blood of MS patients. The authors demonstrated that CSF114(Glc) antibodies identified oligodendrocyte and myelin autoantigens in human brain tissue. This understanding enables the creation of a unique approach for identifying MS patients who had demyelination caused by antibodies, a subgroup of MS patients. Later that year, the same group published a paper describing the creation of a gold SPR biosensor with covalently bonded CSF114(Glc) for real-time detection of multiple sclerosis (MS) in blood [107]. When utilized to differentiate MS patients from healthy blood donors, this SPR biosensor demonstrated a poor sensitivity (36%), but a high specificity (95%). Apart from MS detection, further clinical correlation and multiple autoantibody identification may be utilized to guide treatment and track its response. MS also has been detected via NP-mediated biomarker diagnosis (Table 3).

Table 2.
AD: a selection of NP-based assays for the identification of particular indicators

Marker of disorder	NP	Diagnosis modality	Experiment type	BBB crossing	Ref.
Tau tangles	Gold NP-anti-tau	Two-photon Rayleigh scattering	In-vitro	No need of BBB Crossing (CSF)	[82]
Cerebrovascular amyloid deposit	Cross-linked chitosan	single-photon emission computed tomography (CT)/ Magnetic resonance imaging (MRI)	In-vivo	Antibody targeted to the vessel wall	[83]
	Monocrystalline iron oxide NPs	MRI	Ex-vivo	No need of BBB crossing (vessel's wall)	[84]
Amyloid plaques	NPs- Bovine Serum Albumin-Sialic Acid	MRI Fluorescence	In-vivo In-vitro	Without any facilitation	[85]
	Curcumin-magnetic NP	Immunohistochemistry	In-vitro	Without any facilitation	[86]
	Liposomes-ET6-21	MRI Immunohistochemistry Near-infrared	In-vivo Near-infrared	Without any facilitation	[87]
	Ultrasmall particles of iron oxide-PEG-Aβ (1-42)	μMRI	Ex-vivo In-vivo	Without any facilitation	[88]
	Ultrasmall particles of iron oxide-PHO	MRI	In-vivo	Without any facilitation	[89]
	Magnetic iron oxide NPs-antiferritin	MRI Immunofluorescence	Ex-vivo In-vitro	Facilitated (mannitol)	[90]

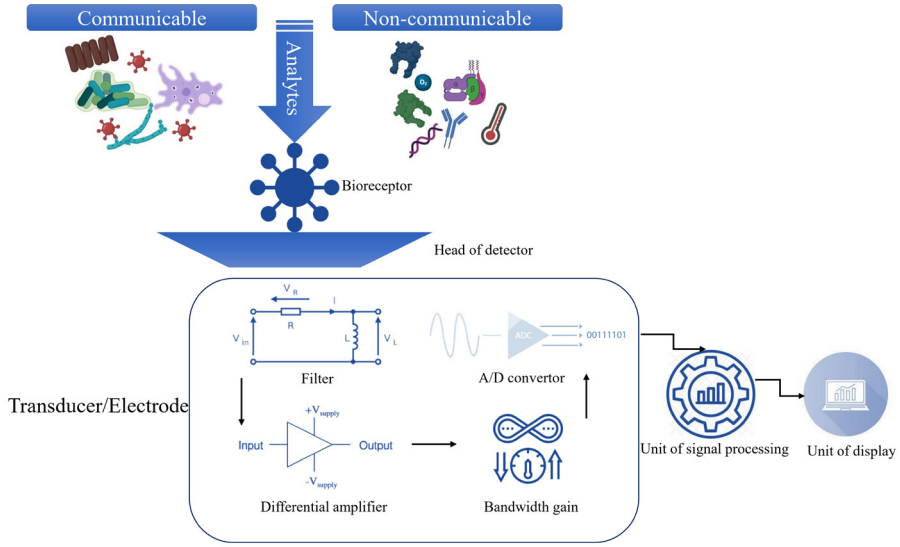

Fig. 1. A working biosensor's block prototype.

2.4. Amyotrophic lateral sclerosis

ALS, also referred to as Lou Gehrig's disease or motor neuron disease (MND), is a rapidly progressive NDD that damages the neurons that control muscular movement. Worldwide, ALS has a morbidity rate of around one to three individuals per 100,000. At the moment, there is no significant therapy for ALS, and the typical life expectancy of ALS patients is stated to be between 24 and 48 months following diagnosis. ALS predominantly affects motor neurons in the spinal cord, brain, and brainstem (Fig. 1A), causing progressive muscle atrophy and motor neuron degeneration that eventually results in paralysis and death due to respiratory failure [112]. There's been advancement in identifying potential biomarkers for sporadic and familial ALS identification. As previously noted, the Bcl-2-SODox complex subtype observed in individuals with sALS and fALS may be used as a biomarker because of the identical mutant SOD1 protein structure that binds to mitochondrial Bcl-2 [113]. The predictive capacity of cytostatin c from patient CSF was determined using a quantitative ELISA technique. While cystatin c levels are lower in ALS patients than in healthy controls and the ELISA test correlates with individual ALS disease progression and patient survival, it was shown that it is not predictive of ALS. [114]. However, a three-protein CSF biomarker panel discovered by Pasinetti et al. [115], which includes the peptic fragment of the neurosecretory protein VGF and cystatin c, provided the best prediction of ALS with 91 percent sensitivity and 97 percent specificity when compared to using individual protein species alone. In individuals with ALS, there was a decrease in ALS-specific proteins compared to healthy controls. Another panel of 14 biomarkers was identified, consisting of analytes reflecting iron homeostasis, growth factors, and pro- and anti-inflammatory cytokines, with 5 proteins correctly distinguishing ALS patients from healthy controls with an accuracy of 89.2 percent, a sensitivity of 87.5 percent, and a specificity of 91.2 percent [116].

Table 3.
AD: a selection of NP-based assays for the identification of particular indicators

Marker of disorder	NP	Diagnosis modality	Experiment type	BBB cross-ing	Ref.
Peripheral immune cell infiltration	Iron oxide NPs in T cells	MRI	In vivo (mouse)	Yes	[108]
	Iron oxide NPs in T cells	MRI	In vivo (mouse)	Yes	[109]
Immune cells activation	Iron oxide NPs	MRI	In vivo (mouse model of MS)	Yes	[110]
Vascular inflammation	An-ti-VCAM-1 magnetic particle iron oxide	MRI	In vivo (mouse model of MS)	Yes	[111]
	Anti-ICAM-1 magnetic particle iron oxide	MRI	In vivo (mouse model of MS)	Yes	[92]

3. Importance of early diagnosis

Neurodegenerative illnesses are detected years after they begin, when the majority of particular neurons die and the brain's neuroplasticity is depleted, by the manifestation of specific symptoms [117-119]. This explains why conventional symptomatic treatment is ineffective [120-125]. It is considered that the development of preventative treatment and early (preclinical) diagnosis may extend a patient's pleasant life during the preclinical period [126]. Despite significant attempts, no early diagnosis for neurodegenerative disorders has been created. This calls into question the process utilized to produce it [127]. The term "neurological disorder" refers to any conditions produced by nervous system or brain malfunction that manifest as psychological and/or physical symptoms. Neurological illnesses are the second cause of disability worldwide, accounting for 276 million disability-adjusted life years (DALYs) annually, with 80 percent occurring in middle- and low-income countries. No one examination can provide a conclusive diagnosis for the majority of neurological diseases. Numerous neurological tests are performed in conjunction with EEG (electroencephalography), EMG (electromyography), and MRI. Enzymatic evaluations (for example, hexosaminidase A Tay–Sachs assay) and immunosorbent tests (for example, ELISA for Alzheimer's amyloid-peptides) are both used in conventional biochemical research. Standard genetic testing is used to decide whether to utilize polymerase chain reaction (PCR); for instance, allele-specific Tay–Sachs PCR or RT-PCR (for example, retroviral detection). Traditional immunoassays have limitations in terms of scientific automation, time, and accuracy [128]. Recovery from any illness and treatment is essentially determined by the efficacy of the diagnostic procedures and their early-phase detention. Even though immunofluorescence (FRS), immunosorbent approaches, and microscopic methods have been proved to be therapeutically essential in a variety of disorders treatment. They do, however, have several drawbacks, including their bulky nature, cost, inaccuracy, stumpy specificity, and reduced sensitiv-

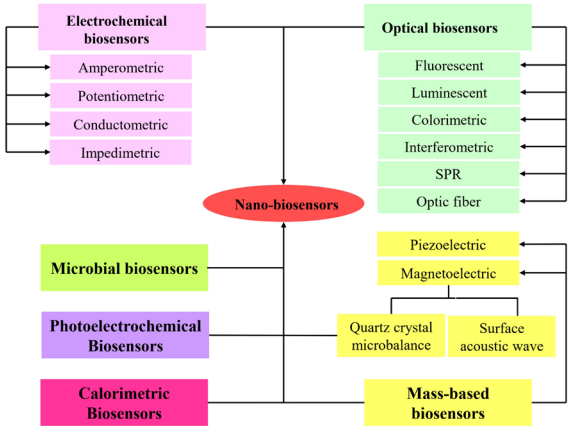

Fig. 2. Several of the most prevalent biosensor types and subtypes.

ity. To address these problems, high-throughput, effective, biocompatible, and quick analytical techniques are becoming more necessary in healthcare/clinical/biomedical. Even with advances in scientific understanding, mankind continues to face several issues related to non-communicable and communicable illnesses. As indicated in the Introduction, the most effective strategies for detaining and preventing such illnesses, as well as the efficacy of treatment and diagnostic processes, are early detection and prevention, as well as the effectiveness of treatment and diagnosis procedures. As a result, various novel techniques, such as the use of biosensors/nanobiosensors for illness detection and therapy, have continued to be beneficial in this area [129, 130].

4. Importance of nano-transducers

Whether the condition is contagious or not, recovery and treatment are dependent on a timely and accurate diagnosis. While immunofluorescence, immunosorbent assays (ELISA), and microscopic techniques are clinically significant, they all have certain disadvantages, including high cost, inaccurate findings, low specificity, inconvenient nature, and limited sensitivity [131]. To overcome the aforementioned disadvantages, clinical needs for high-throughput, biocompatible, effective, and rapid diagnostic procedures remain unfulfilled. Various sensing approaches have been used in recent decades to detect and identify biological markers linked with NCD and communicable diseases [132]. These technologies use high-conductivity electrodes capable of tracking or detecting electroactive proteins present in the body that are specific to an illness condition and provide a strong signal [133]. All of the above-mentioned features are present in a sensing device referred to as a biosensor. Thus, using biosensors to detect biological markers may be a viable strategy. Additionally, recent breakthroughs in biosensor technology have ushered in evolutionary changes in a variety of sectors, including food processing, agriculture, healthcare, and biological research [134].

At the moment, biosensors are generally classified according to their biological element, which may be a nucleic acid or enzyme, antibody, or their transducing element, which may be calorimetric, optical, acoustic, or electrochemical [135, 136]. The enormous surface area of NPs acts as a powerful transducer, and so combining the NMs with electrical systems might result in proactive electrical transduction processes in smart nanoelectromechanical devices (NEMS) [137].

Without a doubt, contemporary biosensor mechanisms have several advantages, including observable, quick, and increased sensitivity and accuracy, and multiplicative results when compared to previous glucose/chemical-based biosensors [138]. Biosensors use tissue-specific macromolecules, organic organelles, microorganisms, enzymes, and immunosensors (antibodies) as detecting/sensing mechanisms. The methods of transduction are based on the physiochemical distinction generated by detecting/sensing processes. As a result, several biosensor transducer mechanisms include calorimetric, optical, piezoelectric, and electrochemical [139]. Acoustic and ultrasonic are two of the most significant biosensor methods based on piezoelectric transducers; electrochemical, amperometric, and conductometric are three of the most important electrochemical transducer biosensor mechanisms; and optical transducer biosensor mechanisms include fluorescence, absorbance, and chemiluminescence (CL) [128, 140-142].

Biosensors work on the concept of cell signaling, and as previously said, the primary components of a functioning biosensor are electronic parameters, a biotransducer, and a biorecognition element that may include a monitor/display, amplifier, and a microprocessor [143]. The sensing or biorecognition component is a bioreceptor that is specifically intended to act or detect on a certain analyte (the target substance) whose related qualities are to be assessed or recognized [144]. The transducer gets input from the bioreceptor and transmits a signal to the signal processor, depending on the transducer used. The amplitude of the output signal is proportional to the concentration of the analyte. Following that, electrical equipment amplifies and processes the signal [145].

In the case of an amperometric sensor, the bioreceptor consists of a specialized bio-material that is kept in close proximity to the transducer or deactivated enzyme. The analyte has a chemical reaction with the biomaterial. This results in the formation of a new analyte that provides the calculable electrical response. Occasionally, an analyte is transported to the system which is discharged, cooled, or heated with hydrogen ions or electrons. The transducer could then control the associated mechanism and convert it to electrical signals that could be calculated and adjusted [140, 145, 146].

A biosensor's components are critical to its functioning. To begin, each biosensor is designed to accomplish a certain purpose. The mode of operation of a biosensor is determined by the bioreceptor (antibody, phage, DNA, enzyme, etc.) and the sensing technique (the functions of the transducer). The electrical signal from the transducer is usually tiny and is superimposed over a pretty high baseline. Typically, signal processing begins with the derivation of a signal indicating the baseline position from a comparable transducer that is not coated with any biocatalyst. The relatively sluggish response rate of the biosensor considerably alleviates the problem of electrical noise filtering. At this phase, the direct output is an analog signal. On the other hand, the signal may be digitized and sent to a microprocessor unit, which analyses the data, routes it via selected units, and exports it to a data storage. A biosensor may operate within or outside of a live creature; nonetheless, the characteristic parameter being measured/detected by the instrument is often derived from the environment or organism. Fig. 1 illustrates the primary components of a working biosensor with display and processing capabilities [128].

As a consequence, Fig. 2 depicts many different kinds of biosensors, including mass-based biosensors, calorimetric biosensors, photoelectrochemical biosensors, microbiological biosensors, and optical biosensors, and electrochemical biosensors, as well as their subtypes. Electrochemical biosensors are a subclass of biosensors that incorporate an electrochemical transducer and are classified as impedimetric, conductometric, potentiometric, and amperometric sensors, whereas optical biosensors incorporate an optical transducer system and a biorecognition sensing constituent. Optical biosensors are classified into the following categories: optic fiber, SPR, interferometric, colorimetric, luminescent, and fluorescent. A microbial biosensor, on the other hand, is a device that uses a biomolecule (a component of a microbe) as a transducer to provide a measurable signal indicative of the analyte concentration. Photoelectrochemical biosensors make advantage of the photon to elec-

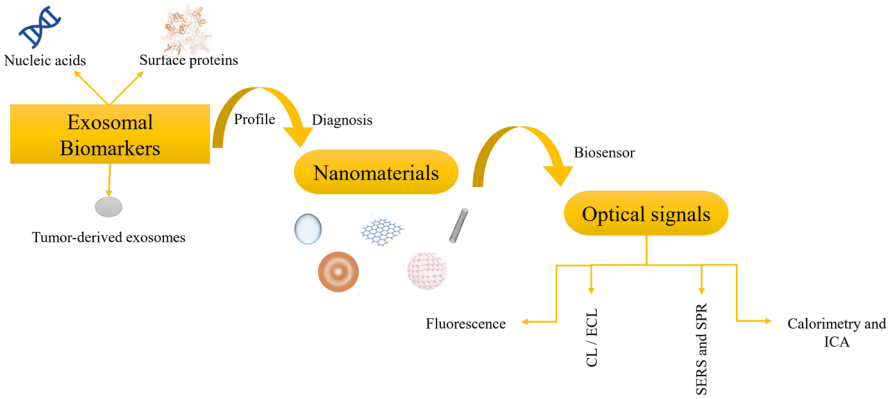

Fig. 3. A summary of the method and concept behind the development of optical biosensors based on NMs for the detection of exosomal biomarkers. Abbreviations: SERS abbreviation for surface-enhanced Raman scattering; SPR abbreviation for SPR; ICA abbreviation for immunochromatographic assay; CL abbreviation for chemiluminescence; ECL abbreviation for electrochemiluminescence.

tric exchange process that occurs concurrently with photon absorption and charge separation. Calorimetric biosensors are used to determine the amount of heat received or emitted by a chemical reaction. In general, mass-based biosensors work by detecting binding events and the corresponding mass increase at the sensor surface through a change in the oscillation of the surface acoustic wave [128].

5. Biomarkers

The last ten years have witnessed a surge in the number of research aimed at eventually validating and identifying biomarkers for NDDs in human patients. Biomarkers are objective laboratory measurements that represent changes in numerous biological processes associated with disease progression [3], and they are useful in a variety of settings, including clinical trials and the pharmaceutical development process. Biomarkers will presumably help in more precise and quick illness diagnosis, stratify the patient population in order to select individuals who will respond to medication therapies and establish that medicine is "hitting its target" in the CNS or peripheral nervous system (PNS), provide prognostic information about disease progression, and respond best to a particular drug. Biomarkers will help in the preclinical drug development from a drug development standpoint and research and identification of novel therapeutic targets. Additionally, biomarkers may serve as a vital link between the human patient population and preclinical disease models, with biomarkers shared between the patient population establishing critical mechanistic connections and revealing possible treatment targets and the model system. Due to the inherent heterogeneity of a patient population with NDDs, which includes both numerous and sporadic genetic variants, patient stratification via biomarkers will result in a considerable decrease in the number of patients necessary to conduct clinical studies and will benefit clinical trial design significantly. [147].

Biomarkers are quantified in a variety of ways and come in a variety of forms, including imaging-based, biochemical, and genetic biomarkers. At the moment, genetic mutations associated with a specific NDD are the most clinically useful type of biomarker, with newer technologies identifying additional candidate biomarkers for epigenetic alterations associated with specific NDDs, miRNAs, and messenger RNA. Recently, it was shown that long noncoding RNAs serve as biomarkers for some neurologic diseases and contribute to neurodegenerative processes. Numerous research is underway to assess the use of extracellular RNAs as biomarkers for a number of human conditions, like brain injury and NDDs. Thus, genetic indicators for neurodegenerative illnesses span the whole spectrum of noncoding RNA, RNA, and DNA. Numerous RNA-based biomarkers are conserved across neurodegenerative illnesses, showing not just shared molecular pathways but also the overlapping activities of many of these RNAs and genes within the CNS cell types [147].

Recent failures of AD disease-modifying drugs may reflect the fact that the patients included in these clinical studies are already clinically unwell. Thus, it is crucial for treatment advancement that well-validated biomarkers are available for the correct diagnosis and early detection of AD's preclinical stages. Combining biomarkers derived from biological fluids, such as CSF, with advanced neuropsychological testing and molecular imaging may eventually achieve the diagnostic specificity and sensitivity required to identify patients in the earliest stages of the disease, when drug modification is most likely possible, and stratify them according to their likelihood of responding to particular drug treatment. Brain hypoperfusion or hypometabolism as measured by 18F-fluorodeoxyglucose (FDG)-PET, brain atrophy as measured by MRI, elevated CSF tau and/or phosphotau levels, low CSF amyloid-1–42 peptide (A42) levels, and positive amyloid or tau PET imaging have all emerged as biomarkers for the progression to AD with potential clinical utility [147].

While biochemical biomarkers are still under development, they may serve as pharmacodynamic biomarkers in clinical trials, aid in medication development, and be used as diagnostic tools. As a consequence, there is an urgent need to supplement presently existing biomarkers for PD and to expedite the identification and validation of biomarkers at crucial clinical junctions in the illness, such as biomarkers to detect individuals shifting from pre-motor to motor symptoms. Numerous non-motor symptoms that might arise years before motor symptoms manifest, such as mood problems, olfactory impairments, bowel dysfunction, and sleep disruption are not unique to PD and so are not accurate predictors of individuals who will convert to motor symptoms. Biomarkers that can be used to predict illness progression to the state of motor symptoms would be very beneficial in studies evaluating drugs that prevent disease progression to the state of motor symptoms [148]. Additional biomarkers are required to help in medication evaluation in illness progression monitoring and clinical trials, which may potentially comprise a mix of biochemical, imaging, and genetic indicators [149].

The bulk of research on NPs as diagnostic agents for PD has been on DA nanobiosensors [150]. Shin et al. [151] produced novel silver-molybdenum disulfide (Ag/MoS2) NPs for DA detection and revealed an enhanced electrochemical signal of the synthesized Ag/MoS2 electrochemical biosensor, suggesting potential uses in PD. . Vazquez-Guardado et al. [152] created an enzyme-free DA biosensor system by combining an active nanostructured plasmonic substrate (NPS) with a passive plasma separator microfluidic chip and oxygen-deficient cerium oxide (CeO2) NPs. Their results indicated the feasibility of developing complicated label-free tests for the detection of antigens and biomarkers in raw biological fluid in the future.

6. Optical biosensors

Specificity and sensitivity are two critical parameters to consider when evaluating a biosensor. A basic biosensor consists of a biologi-

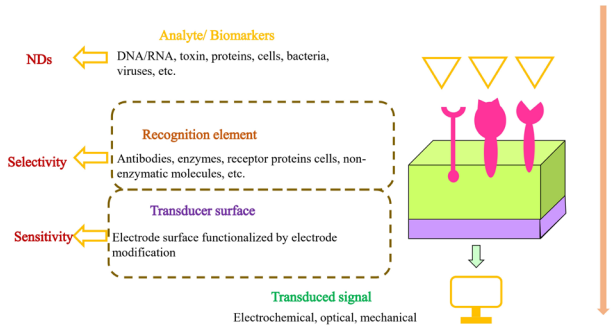

Fig. 4. The basic concept of a biosensor system and the major components used to detect NDs.

cal recognition section capable of capturing the desired analyte and the sensing section capable of converting the biological variation to chemical or physical signals. Specificity is characterized by the available combination of biological sensing sections and recognition, whereas sensitivity is determined primarily by the receptor, which may be a microbe, enzyme, nucleic acid (e.g. aptamer), or antibody, as well as the immobilization sensing, substrate, and process approach. In recent years, optical substrates constructed from NMs with unique optical characteristics such as quantum dots, carbon nanotubes, graphene, and Ag and Au NPs have been extensively exploited to boost the sensitivity of target detection. For example, quantum dots are regarded as a fluorophore for fluorescence detection due to their broad absorption band and photobleaching resistance. Metallic NPs are utilized to improve the signal in SERS-based detection. In general, several kinds of NMs perform a variety of functions in a biosensor-based system. The development of optical biosensors for target detection based on NMs is a novel and current trend in the area of analytical diagnostics. Due to its rapid detection time, simplicity of use, and high sensitivity, optical biosensors based on NMs have emerged as a potentially useful analytical tool for cancer diagnostics. The optical techniques for exosomal cancer biomarkers are classified according to the optical detection methods used, which include fluorescence, electrochemiluminescence (ECL), CL, immunochromatographic assay (ICA), colorimetric, SPR, and SERS (Fig. 3) [153].

The work by Shawky et al. [154] set out to develop a simple apparatus for the absolute measurement and detection of nucleic acid transcripts by using an optical biosensor based on gold NPs. The nucleic acid transcripts tyrosyl DNA phosphodiesterase 2 (TDP2) and topoisomerase 1 (TOP1) were selected as markers of genomic instability due to their association with a number of neurologic and malignant disorders. The obtained mRNA was promptly measured and identified using the gold aggregating gold (GAG) test, which eliminates the need for amplification, which is presently necessary for transcript quantification. Instead of difficult, expensive, and time-consuming real-time PCR, the GAG test may be used to determine the absolute amount of RNA in many applications. Haes et al. [155] developed a nanoscale optical biosensor based on localized SPR spectroscopy to monitor anti-ADDL specific antibodies, amyloid-derived diffusible ligands (ADDLs), and antigen contact. The study of human brain extracts and cerebrospinal fluid samples from healthy controls and AD patients indicates that the LSPR nanosensor gives fresh information useful for the understanding and potential diagnosis of AD.

7. Electrochemical biosensors

The electrochemical sensor's essential principle, represented in Fig. 4, is the process by which a variable or constant voltage is supplied to the electrode, and the detection material changes on the electrode surface, resulting in the formation of an electrical signal [156]. Electrochemical sensors are primarily used to determine the electrochemical and electrical characteristics of target substances or molecules in order to perform quantitative or qualitative detection and analysis. Chemically modified electrodes are a popular topic of study in the electrochemical area at the moment. At the moment, the majority of research is concentrated on electrochemical biosensors, which may be roughly classed as affinity or catalytic biosensors. The former makes use of enzymes' transferability and catalysis. However, the necessity for enzyme activity to be maintained in a neutral environment has resulted in increasingly severe criteria for operating conditions and material selection; also, enzymes are rather expensive [157]. Thus, creating more effective ways for designing electrochemical enzyme-free sensors, stabilizing immobilized media, and using and discovering efficient electron transfer media are only a few of the issues that need development in this sector. Electrochemical sensors, in comparison to other sensing systems like calorimetric, magnetic, weight, piezoelectric, optical, and acoustic approaches, have a high sensitivity, are compatible with microfabrication technology, and are portable, economical, and simple to use. As a result, they are often employed in therapeutic settings. Neurobiological indicators are present at very low concentrations in biological fluids, necessitating the use of extremely sensitive detection technologies [158].

Numerous ways have been used to change the electrode surface of (bio)sensors in order to increase their accuracy, sensitivity, and selectivity [158]. Lyons and Clark introduced the notion of the glucose enzyme electrode for the first time in 1962; the field of biosensors has advanced significantly since then [159]. Biosensors may be traced back to the enzyme electrodes that sparked their development. Due to the specificity of enzymes, electrochemical sensors based on enzymes demonstrate a high degree of selectivity and may therefore be used to measure individual enzymes in complex mixtures. directly [160]. However, changes in environmental parameters such as pH and temperature have a significant effect on the activity of enzymes and other physiologically active chemicals, severely restricting the application range of enzyme biosensors. Additionally, the manufacturing procedure for the enzyme sensor is complex, and an uneven thickness might result in low repeatability and interference from oxygen [161]. Furthermore, enzyme-based biosensors may be prohibitively expensive owing to the high cost of enzymes. [162]. As a result, the use and development of non-enzyme biosensors have become a new area of study. There are various enzyme-free methods for detecting biomarkers of neurodegenerative illnesses, including colorimetric sensors, surface-enhanced Raman scattering biosensors, fluorescence imaging sensors, and electrochemistry [163].

Khalilzadeh et al. [164] devised an electrochemical approach based on microRNA (miR) to detect miR-146a, a well-characterized biomarker for neurological illness. The capture microRNA (C-miR) was self-assembled on the gold surface and utilized to quantify the target microRNA (T-miR) of miR-146a in this bioassay. To do this, they immobilized an optimum concentration of C-miR on the surface of a gold electrode and utilized it to collect the target analyte (T-miR). The results obtained using an unprocessed human blood sample demonstrate unequivocally that the designed microRNA-based biosensor is capable of detecting miR-146a as a biomarker for NDDs. Using Exo III-assisted recycling amplification and a graphene-modified electrode, Liu et al. created a ratiometric electrochemical biosensor for quantitative detection of the trinucleotide repeat sequence d(CAG)n. The double-signals are hairpin DNAs tagged with ferrocene and methylene blue, which may hybridize to target DNA. This innovative ratiometric electrochemical biosensor offers an effective and reliable approach for analyzing d(CAG)n trinucleotide repeats and may be used as a simplified clinical tool for neurodegenerative illnesses.

8. Challenges and future perspective

The main trends over the recent years have been the identification of novel types of NMs with improved detection and optical capabilities; a move toward more biomimetic NMs that mimic the properties of naturally circulating NPs; and finally, the combination of multiple functions on a single particle, referred to as NPs with multiple detection modalities or as theranostic NPs [165].

Biosensor-based accessories are often innovative and promising in modern biomedical applications, and will be the future of next-generation detection. . Advances in the capabilities of biosensors for in vivo and in vitro detection of histone acetyltransferase [166] and DNA methylation [167] may be a significant step toward a thorough knowledge of molecular genetics. In the creation of DNA sensors, engineering bioreceptors with modified molecular manipulators such as DNA polymerases and Cas9 as members of the DNA-modifying enzyme family may greatly improve specificity [168]. Attempting to manipulate host cells, such as red blood cells, to deliver nanobiosensors in vivo for biomedical applications such as bio-imaging may provide a novel technique for disease diagnosis [169]. In the future, wearable, flexible, transportable conductive hydrogel-based, multifunctional, and miniature sensors for real-time individualized health monitoring and control of cybernetic prosthesis may be regarded as a rising branch of commercialized nanobiosensor applications [170-172]. Exploiting innovative nanostructured materials such as borophene [170], photonic crystals [173], and quantum dots [174], as well as biological markers such as transcription factors [175], is only the tip of the iceberg in terms of potential. Additionally, nanotechnology advancements in biosensor development are revolutionary and could be accelerated further through strategic investments in smart technologies such as big data analytics, artificial intelligence (AI) with deep learning accessibility, and the Internet of things (IoT), which is built on advanced telecommunication networks [176-178]. Emerging debates over nanobiosensors and smart technologies such as the Internet of Things (IoT) have spawned unique ideas such as the Internet of BioNanoThings (IoBNT) and the Internet of NanoThings (IoNT) [179]. In basic words, the Internet of Things refers to any physical items, such as smartphones, that are linked to the internet and capable of exchanging data instantly through a unique identifier, allowing safe data transmission without the need for human-to-computer or human-to-human contact [180]. Hybridizing this technology with the use of nanotechnology to detect biological macromolecules with the accuracy and precision enabled by IoBNT is currently being viewed as the future major intervention that warrants more investigation. These massive heterogeneous big data sets or data sets created may be rapidly turned into information with a high throughput value using AI with deep learning accessible, which would be prohibitively expensive and time-consuming otherwise. Combining AI, which is the emulation of human intelligence in robots meant to behave and think like humans, might be automated and upgraded [181]. Combining AI-based biosensors for point-of-care detection with biological monitoring is the other developing area of modern hybridization. This combination could shed light on the critical role of algorithms of machine-learning in the development of futuristic nano-based biosensors, as well as microchip-based essential disease biomarkers, computational techniques, and the Internet of Things for patient compliance and real-time health monitoring [182, 183].

As the need and necessity for employing biosensors for quick analysis with cost-effectiveness increases, bio-fabrication is required to create a path for identifying cellular to entire animal behavior with a detection limit of high precision for single molecules [184]. Biomolecules have unique activities and structures, and figuring out how to properly use the function and structure of biomolecules and nanomaterials to produce single molecule multifunctional nanoelectrodes, nanofilms, and nanocomposites remains a significant issue. Nanomaterial tailoring, the availability of high quality nanomaterials, interface issues, characterization, processing, and the principles dictating the behavior of these nanoscale composites on the surface of electrodes are all significant obstacles for currently available approaches. Ways to improve the signal-to-noise ratio, as well as signal amplification and transduction, are important hurdles. Nonetheless, nanomaterial-based biosensors have a lot of potential and will be widely used in environmental monitoring, process control, food analysis, and clinical diagnosis in the near future [185].

9. Conclusions

Biosensors provide a potentially transformative strategy for the precise and effective diagnosis of biological protein markers linked with a variety of communicable and non-communicable illnesses. The accuracy and precision may be enhanced by using nanotechnology, paving the way for nanobiosensors. The study provides a comprehensive overview of the use of nano-based biosensors in neurodegenerative illnesses, emphasizing many potential indicators. Because these intermediary molecules are regarded to be unique to the route in which they are engaged, designing a tailored biosensor for their detection may be advantageous. Additionally, as nanotechnology advances, innovative nanostructured materials such as borophene, photonic crystals, and quantum dots are emerging that may improve the persistence and accuracy of nanobiosensors. The economic potential of nano-based biosensors is highlighted since it is one of the critical components necessary for enough personnel and financing. Future implementations or applications and conceptualizations of revolutionary computing methods, AI with access to deep learning, big data analytics, IoT, and microchip-based approaches coupled with nano biosensors might be a fantastic method for illness identification. As a result, research into these intelligent systems coupled with nanobiosensors must be promoted in order to advance the development of next-generation diagnostics . In our opinion, nanotechnology approaches are potent candidates for early detection of neurodegenerative disorders, since the smaller the trancducer, the higher sensibility and selectivity and smaller amount of biomarkers are detectable.

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