3 Implications of Nano-Biosensors in the Early Detection of Neuroparasitic Diseases

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Abstract

Parasitic diseases affecting millions of people globally cause fatalities and incapacitating conditions. It is, therefore, essential to detect parasitic diseases by looking for the parasite/s or their specific proteases that they produce at different phases of their life cycles. Numerous symptoms and indicators can result from a parasitic infection of the neurological system, but it is still challenging to diagnose an infection because the symptoms are frequently vague or minor. It is more likely that a parasite infection of the nervous system will be identified and treated well if one is familiar with fundamental epidemiological traits and distinctive radiography findings. For accurate diagnosis of these neurological disorders, proper identification and adoption of acceptable public health measures for the management of epidemic outbreaks are required. For numerous diseases, conventional in vitro techniques are time-consuming and need centralized facilities. So, the development of biosensor technology could lead to point-of-care diagnostics that are as accurate, fast, and affordable as or better than current standards. Modern biosensors include varied sensing techniques, such as optical, electrical, and mechanical transducers, as well as micro- and nanofabrication technologies. Only a handful of well-known biosensor examples have success-

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fully transitioned from laboratory research to clinical applications despite the need for the medical community. Biosensor-based diagnosis of protozoan diseases like malaria, leishmaniasis, American trypanosomiasis (Chagas disease), and toxoplasmosis has been accomplished but is still in the infancy stage. In addition to the advancements in biosensors for the diagnosis of parasitic infections, we highlight the considerable challenges that must be overcome in order to bring integrated diagnostic biosensors into use in real-world scenarios.

Keywords

Biosensors · Neurological diseases · Parasites · Diagnosis · Applications

3.1 Introduction

Infections of the central nervous system (CNS) are crucial because they compromise central nervous system health (Sundaram et al. 2011). It has been estimated that 25% of people worldwide are parasite-infected, with infections being more common in developing rural areas and agriculture of subtropical and tropical countries (Youssef and Uga 2014).

It's possible for human parasites to live in the CNS or another unusual area of the body. Globally, CNS parasite infections are regarded as major causes of morbidity and mortality. There are several distinct species that can be categorized as parasites, including metazoans, which are multicellular organisms, and protozoa, which are single-celled organisms (Carpio et al. 2016), which can be either free-living or obligatory in nature (Walker and Zunt 2005). The majority of eukaryotic cells on earth are protozoa, which are vital pathogens for humans as well as animals (Zarlenga and Trout 2004), where they can cause extremely minor to serious, life-threatening illnesses Lim et al., 2016).

Helminths wreak physical havoc on the tissues they inhabit, triggering a strong inflammatory reaction (Graeff-Teixeira et al. 2009). Humans are infected by a wide variety of parasites, and occasionally a substantial number of these parasites move to the central nervous system and cause illness (Nash 2014). Diseases caused by soil-transmitted helminths, *Toxoplasma gondii*, *Schistosoma*, *Taenia solium*, and *Plasmodium* can all result in neurological impairments (John et al. 2015; Abdel Razek et al. 2011).

Molecular recognition of a target analyte is converted into a quantifiable signal by a transducer in a biosensor. The glucose sensor, which was first introduced 30 years ago in its current form and is still in use today, is the most well-known example. It has completely changed how diabetes is managed. Assays using lateral flow, such as those used in home pregnancy tests, are other prevalent examples (Luong et al. 2008). Biosensors have the potential to provide a user-friendly, sensitive, and affordable technology platform for infectious disease diagnosis and therapy prediction (Foudeh et al. 2012). Low energy consumption, short test times, multiplexing capability, and high portability are some benefits, including small fluid

volume manipulation (cheaper cost and less reagent) (Whitesides 2006). Biosensors that can carry out the intricate molecular tests necessary for many infectious diseases have recently been developed as a result of recent advancements in micro- and nanotechnology. Parallel to this, important strides have been achieved in our understanding of pathogen genomes, proteomics, and interactions with the host (Mairiang et al. 2013). While biosensor-based immunoassays may boost the sensitivity of pathogen-specific antigen detection, multiplex detection of host immune response antibodies (serology) may increase overall specificity. Additional system integration might make it easier to build assays that incorporate both pathogen-specific targets and indicators of host immune responses at various phases of infection (Mohan et al. 2011).

The first-ever Global Neglected Tropical Disease Day was founded in 2020 (on January 30) to commemorate the recent advancements in the battle against diseases, to inspire businesses and nations to take action in remembrance of the challenges yet ahead, and to celebrate the achievements. Despite joint efforts to develop effective and safe treatments and remove vectors, precise and early identification is the initial action needed to speed up the therapy. Some diseases can be quickly identified through clinical evaluation or pattern recognition of the physical symptoms, while asymptomatic disorders and diseases that are just beginning to manifest are more challenging to identify. The most common course of action, utilizing knowledge of the pathogen genome and the host's immunologic response, is a molecular and serological diagnosis using techniques like enzyme-linked immunosorbent assay (ELISA) and reverse transcription-polymerase chain reaction (RT PCR) (Lammie et al. 2011).

The downsides of these and other tests include the need for high-quality personnel, pricey tools and chemicals, and time-consuming procedures along with inadequate infrastructure and resources. Furthermore, these tests continue to exhibit cross-reactivity, such as with the arboviruses, dengue, and Zika (Zaidi et al. 2020), as well as false-negative and false-positive results, as is seen in the case of SARS-CoV-2 pandemic (Lorentzen et al. 2020). The creation of diagnostic systems that can identify diseases in their earliest stages with high specificity, cheap cost, sensitivity, and robustness while also being simple to use becomes of vital importance. These benefits of biosensors are in addition to the potential for the creation of miniature loco determination systems, which meet the needs of low-income nations and remote areas like conflict zones or native tribes.

With an emphasis on the differences between various signal transducer techniques and their potential for clinical translation, this chapter focuses on developments in biosensor technology for neuro-parasitic disorders. Labelled and label-free assays are the two types of detection techniques, among which label-free assays directly detect the presence of an analyte through biochemical processes on a transducer surface (Rapp et al. 2010).

A biosensor is a sensing device or a measurement system that is specially created for the estimation of a substance using biological interactions and then interprets these interactions into a readable form using transduction and electromechanical methods (Chaudhary et al. 2023). Figure 3.1 gives us information about the three

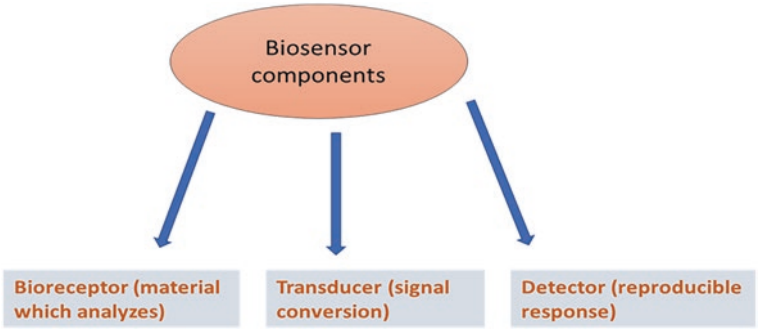

Fig. 3.1 Block diagram of biosensor

main components of a biosensor. These parts are the bioreceptor, the transducer, and the detector in terms of the conceptual and fundamental manner of functioning. A biosensor's primary job or objective is to detect a substance with a biologically specified composition. These substances frequently consist of proteins, immunological compounds, antibodies, enzymes, etc.

It is accomplished by utilizing a different physiologically delicate substance that contributes to the creation of the bioreceptor. In other words, a bioreceptor is the part of a biosensor that acts as a template for the substance to be detected. Bioreceptors can be made from a variety of materials.

For instance, a protein is screened using its equivalent selective substrate, while an antibody is screened using antigen and vice versa. The transducer system is the second element. This device's primary job is to electrically represent the interaction between a bioanalyte and the appropriate bioreceptor. "Trans" signifies change, and "ducer" implies energy, according to the name itself.

Transducers, then, essentially change one kind of energy into another. The first form, which is produced by a particular interaction between the bioanalyte and bioreceptor, is biochemical in nature, whereas the second form is typically electrical in character. Transducers are used to convert the biological response into an electrical signal. The detection system is the third element.

It does this by receiving the electrical signal from the transducer component and amplifying it appropriately so that the related response can be correctly read and analyzed. The availability of immobilization schemes that may be utilized to immobilize the bioreceptor in order to increase the feasibility and efficiency of its reaction with the bioanalyte is a crucial necessity for nano-biosensors in addition to these components. The performance of the systems based on this technique is also impacted by changes in temperature, pH, interference with pollutants, and other physicochemical fluctuations, which makes immobilization the overall process of biological sensing more affordable (Kissinger 2005).

In essence, nano-biosensors are nanomaterial-based sensors that are interestingly not specialized sensors that can detect tiny events and occurring (Gautam 2022). Nanomaterials, or materials with one of their dimensions between 1 and 100 nm, are a special gift that nanotechnology has given to humanity. These materials are

extremely unique due to their size limitations. They differ greatly from the same materials at the bulk scale in all significant physicochemical aspects and have the majority of their constituent atoms localized at or near their surface. They can perform extremely effective functions in the biosensor technology's sensing mechanism. Nanoelectromechanical systems (NEMS), which are highly active in their electrical transduction mechanisms, are created when devices made of nanomaterials are integrated with electrical systems. On the basis of their electrical and mechanical characteristics, a number of nanomaterials have been investigated for use in enhanced biological signaling and transduction pathways.

Nanowires, nanotubes, nanoparticles, thin films, and nanorods comprised of nanocrystalline matter are a few examples of these materials that are frequently used (Jianrong et al. 2004). Among these, the usage of nanoparticles has received the most attention and analysis to date. The miracles of nanotechnological implications of the matter have made it feasible for nano-biosensors to play a very important role in the development of biosensor technology (Chaudhary 2022).

Numerous studies throughout the world have looked into a wide range of biosensing tools that use nanoparticles or nanostructures. These can range from employing amperometric tools for the enzyme-based detection of glucose to using quantum dots as fluorescent agents for the binding detection to even using bioconjugated nanomaterials for targeted biomolecular detection. For use in immunosensing and immunolabelling, they include colloidal nanoparticles that can bind to antibodies. These components can also be employed to improve electron microscopy-based detections.

Additionally, metal-based nanoparticles are particularly good materials for electronic and optical applications. By utilizing their optoelectronic capabilities, these nanoparticles can be effectively exploited for the detection of nucleic acid sequences. The primary categories of nanomaterials used to improve upon the sensing mechanisms now in use in biosensor technology are listed in Table 3.1. It emphasizes the potential benefits of a number of nanomaterials used and some proof of their use thus far.

Table 3.1 An overview of nanomaterial used for improving biosensor technology

Nanomaterial used	Benefits	References
Nanoparticles	Aid in immobilization, enable better loading of bioanalyte, and also possess good catalytic properties	Luo et al. (2006)
Nanorods	Good plasmonic materials which can couple sensing phenomenon well and size-tunable energy regulation, can be coupled with MEMS, and induce specific field responses	Kabashin et al. (2009)
Carbon nanotubes	Improved enzyme loading, higher aspect ratios, ability to be functionalized, and better electrical communication	Davis et al. (2003)
Nanowires	Highly versatile, good electrical and sensing properties for bio- and chemical sensing; charge conduction is better	MacKenzie et al. (2009)
Quantum dots	Excellent fluorescence, quantum confinement of charge carriers, and size-tunable band energy	Huang et al. (2005)

In keeping with this theme, carbon nanotubes have also been employed to enhance biosensing processes through their capacity to enable quick detection and much-improved interactions between the analyte and the bioreceptor molecule. For the detection of glucose (Chen et al. 2008) and insulin (Qu et al. 2006), carbon nanotube-based biosensors have been in use. The text that follows discusses the benefits and results of using various nanomaterials, as well as their inherent advantages and the crucial factors that can greatly affect their effectiveness.

3.2 Echinococcosis (Hydatid Disease)

Echinococcus granulosus and *Echinococcus multilocularis* are the two cestode species that infect humans most frequently (Algros et al. 2003). Cystic hydatid disease caused by endemic parasite *E. granulosis* is more frequently occurring in Latin America, the Middle East, and the Mediterranean region (Al zain et al. 2002). Alveolar echinococcosis (also known as alveolar hydatid disease) that is native to China, Turkey, Alaska, and central Europe is caused by *E. multilocularis*. The parasite can infect household dogs and cats, although its primary hosts are red and Arctic foxes. According to epidemiological evidence, rodents and dogs or foxes can transmit the *E. multilocularis* to each other as they come into contact with infected animals. More frequently, females and children suffer disproportionately in endemic nations (Kern et al. 2003).

Canids like dogs and wolves have *E. granulosus* adults in their intestines (Bouree 2001). Following ingestion of egg by ungulates, the oncospheres swiftly move from the small intestine to the liver before moving by lymphatic vessels or blood to the lung, kidney, pericardium, vertebrae, periorbital tissue, and brain, where it develops into hydatid cyst. Hydatid cysts, which are filled with a serous fluid containing scolices, also develop in infected humans (Garret et al. 1977). Solitary hydatid cysts form in the liver as a result of the majority of infections. However, unlike *E. granulosus*, *E. multilocularis* mostly affects the liver. It can also spread by blood or lymphatic channels to other organs. Hydatid cysts are usually taken up by canids along with infected offals, where multiple scolices get released, and they penetrate deeply between villi into the crypts of Liberkuhn and develop to maturity in about 47 days.

Echinococcosis patients frequently have elevated erythrocyte sedimentation rate (ESR) and serum eosinophilia. Eosinophilia in the cerebrospinal fluid (CSF) is normally absent because echinococcal infections are encapsulated. A veterinarian ought to be consulted when echinococcal infection in humans is identified because farm animals or domestic pets, particularly dogs, are frequently the source of the infection. Serum indirect hemagglutination (IHA), indirect fluorescent antibody (IFA), and enzyme-linked immunosorbent assay (ELISA) can all be used to confirm the diagnosis of *E. granulosus* infection, approximately 98% for patients with hepatic cysts, while the test sensitivity values range from 50% to 60% in patients with pulmonary cysts. Serum assays to identify *E. multilocularis* are more accurate and non-cross-reactive than those to identify *E. granulosus* (Jiang et al. 2001). A negative antibody detection test does not rule out the diagnosis of *Echinococcosis*

because some cyst carriers do not produce detectable antibody levels. Serological testing is not advised as a way to gauge treatment effectiveness because it cannot predict CNS involvement (Gottstein 1992).

3.2.1 Biosensor Application for Diagnosis of Echinococcosis

A dreadful parasitic disease that affects millions of people worldwide is echinococcosis and has had disastrous impacts on animal husbandry because it has been neglected. Recent studies have focused on a number of characteristics of *E. granulosus*, including its global distribution, pathology, diagnostic techniques, and innovative therapeutics for both humans and animals (Wen et al. 2019; Eckert and Thompson 2017). Despite the fact that this zoonotic parasite can be diagnosed in a number of ways, many of these tests are expensive, complicated, and call for specialized training. The imaging techniques, like ultrasonography and radiography (X-ray), are among the popular methods used to screen the population at a fair price (Wen et al. 2019). According to McManus et al. (2012) and Gottstein et al. (2014), serology tests are also frequently used to identify indicators from the host (markers of inflammation, cytokines, or chemokines) and parasite (circulating antigens or DNA). For the diagnosis and management of echinococcosis, practitioners can now adhere to precise manuals and algorithms (Wen et al. 2019; Brunetti et al. 2010).

Cystic echinococcosis (CE) is diagnosed in the lab using a variety of substances, including antibodies, antigens, and cytokines. The lack of sensitivity and/or insufficient specificity of these methods, however, make them unsuitable as reliable diagnostic tools (Siles-Lucas et al. 2017). Furthermore, they call for particular infrastructure configurations and qualified employees. Due to the advancement of nanotechnology, the creation of biosensors for the diagnosis of echinococcosis has currently achieved significant advancements. Using the near-infrared transmission angular spectra of porous silicon microcavities, an efficient method for an optical biosensor for the diagnosis of cystic hydatid disease was developed by Li et al. in 2017. A more recent study (Darabi et al. 2019) found that in silico design and evaluation was an effective way to identify the antigens present in hydatid cysts. To swiftly, precisely, and effectively detect parasites, viruses, etc., researchers have been creating portable electroanalytical biosensing equipment or analyzers. More straightforward and quick methods are still desperately needed despite recent significant advancements. Because of their mechanical and chemical characteristics, which are useful in both veterinary and human health, nanoparticle-based biosensors are greatly desired (Cesewski and Johnson 2020; Moulick et al. 2017).

The use of nanometal products has brought attention to the need for efficient parasite management techniques, but the nanoparticles will likely contaminate the environment (Lin et al. 2010), necessitating the establishment of safe use procedures and toxicity thresholds to reduce the impact on helpful bacteria, animals, and the food chain (Kahru and Dubourguier 2010). Gold, silver, chitosan, and oxidized metals have been shown to have antiparasitic and inhibitory effects on protoscolices in a number of studies. Mahmoudvand et al. (2014) employed

different quantities (50–500 mg/mL) of selenium nanoparticles (in the size range of roughly 80–220 nm) for 10–60 min. According to the findings (Mahmoudvand et al. 2014), biogenic Se-NPs at all concentrations have strong scolicidal effects, particularly at concentrations of 500 and 250 mg/mL after 10 and 20 min of application, respectively.

Ag-NPs had the most powerful scolicidal effects, according to the results of Norouzi (2017), and can therefore be employed in CE surgery. Malekifard (2017) looked at the effectiveness of gold nanoparticles on hydatid cyst scolices and found that all concentrations of gold nanoparticles had substantial scolicidal effects. All protoscoleces were killed within 60 min by gold nanoparticles at a concentration of 1 mg/mL (Malekifard 2017). Previous research (Rahimi et al. 2015) looked into the scolicidal effects of green-produced silver NPs at various concentrations (0.025, 0.05, 0.1, and 0.15 mg/mL) and exposure times (10, 30, 60, and 120 min) against protoscolices of CHD. The results demonstrated that Ag NPs had significant scolicidal effects at all doses. After 120 min of exposure, the doses of 0.1 and 0.15 mg/mL indicated mortality rates of 83% and 90%, respectively. Ag-NPs produced by biosynthesis had a 40% scolicidal activity at 0.025 mg/mL for 10 min. According to a report, because they are more affordable, safe, and nontoxic than the commonly utilized chemical materials, biogenic Ag-NPs may be taken into consideration as a viable scolicidal agent for CHD surgery.

The study by Safarpour et al. (2021) suggests an easy, reliable, and useful method for echinococcosis diagnosis. This procedure is based on the development of a sandwich complex between chitosan-gold nanoparticle protein A and an anti-Ag B antibody-bound hydatid cyst antigen (Ag B). By observing a change in color that does not change in the absence of an Ag B biosensor, quick colorimetric results can be obtained. Notably, it also describes a field-applicable method based on blood samples for the prompt detection of infected cases without the need for expert staff or sophisticated equipment. Gold nanoprobes have a long history of usage in biosensing, notably when used to detect DNA, which has been well established.

The detection of the microorganisms that cause tuberculosis and malaria was accomplished in a beautiful work by multiplex non-cross-linking colorimetric technology (Veigas et al. 2015). Chitosan has reportedly been used in the past to improve the production of gold nanoparticles and cause observable color changes, according to Mohan et al. (2019). It has been suggested that chitosan-capped gold nanoparticles or gold nanoparticles functionalized or stabilized with organic polymers, such as chitosan nanocomposites, are the best delivery systems since they do not have the toxicity like that of other chemical reagents (Abrica-Gonzalez et al. 2019; Saeed et al. 2020).

As a matter of fact, chitosan-based biosensors have shown good sensitivity, stability, and selectivity for the detection of a variety of targets, proteins, DNAs, bacteria, glucose, and a number of tiny biomolecules (Jiang and Wu 2019; Shrestha et al. 2016). Unexpectedly, colorimetric biosensors and gold nanoparticles have demonstrated considerable uses in diagnostics (Chang et al. 2019; Aldewachi et al. 2017).

3.3 Schistosomiasis (Bilharzia)

The five species of blood flukes (digenetic trematodes), *Schistosoma mekongi*, *Schistosoma japonicum*, *Schistosoma haematobium*, *Schistosoma intercalatum*, and *Schistosoma mansoni* are responsible for schistosomiasis, which affects up to 300 million people annually globally (El-Garem 1998). Three of the five species *S. japonicum*, *S. haematobium*, and *S. mansoni* have been implicated for their role in the pathology of the central nervous system (CNS) (Pittella 1997). At least 30 other mammals are similarly susceptible to infection, but humans are the only known hosts.

Schistosomiasis is considered a "man-made disease" by some specialists since it gets transmitted when one comes in contact with water as endemicity necessitates the presence of an intermediate mollusk host (aquatic or amphibious snails) (Zheng et al. 2002).

In general, endemicity rates are greater in nations with inadequate sanitary infrastructure and access to clean water. Unfortunately, by damming up or irrigating with contaminated diseased water in impoverished nations in an effort to enhance inadequate sanitary conditions and water supplies, endemicity is frequently increased (Babiker et al. 1985). Moreover, travelers who are cautioned to avoid drinking tap water in countries where the schistosome is prevalent frequently ignore less obvious ways to contract it, such as washing clothes, going barefoot, and bathing.

The furcocercous cercariae pierce human skin and cause the first infection. The larva migrates into the venous system, preferring venules and venous plexi, after shedding its tail. Schistosomiasis's clinical signs can appear at various phases of the parasite's life cycle and vary depending on the species that is infected.

The preferred locations in the human body for each of their distinct species are peribladder veins (*S. haematobium*), superior mesenteric veins (*S. japonicum*), or mesenteric veins (*S. mansoni*), (Pollner et al. 1994). Sixty percent of all schistosomal brain infections are caused by *S. japonicum* eggs, which are smaller than eggs from other schistosomal species. In contrast, *S. mansoni* eggs, which are larger, typically only cause spinal cord infections (Pittella 1994). According to Scrimgeour and Gajdusek (1985), *S. haematobium* can infect either the spinal cord or brain.

The CNS is not believed to be a place where adult worms travel, nor is it believed that worm eggs develop into worms there. It is hypothesized that Batson's plexus serves as a route for entry into the central nervous system. Once within, eggs cause a granulomatous reaction as tissues work to enclose the invading parasite. Granulomas have exudative and necrotic characteristics after persistent infection. Vascular walls and nearby tissue can both have severe necrosis (File 1995).

3.3.1 Biosensor-Based Diagnosis of Schistosomiasis

The *Schistosoma* genus of trematodes worms causes the neglected tropical disease known as schistosomiasis. It is the second-most common parasitic disease globally. *S. mansoni*, *S. japonicum*, and *S. haematobium* are the principal disease-causing species. In Mediterranean Europe, Southeast Asia, sub-Saharan Africa, South America, and the Middle East, 779 million people are at risk of catching HIV, and it has the potential to affect up to 300 million people annually. Non-endemic areas are also susceptible to it. Schistosomiasis in humans is one of the most common parasite illnesses. Particular freshwater snails act as intermediary hosts in the transmission cycle, which involves the contamination of surface water with excrement (de Albuquerque et al. 2020; Gryseels et al. 2006; McManus et al. 2020). Schistosomiasis can be managed by both prevention and treatment. The two most important ways to avoid schistosomiasis are to improve cleanliness and get rid of snail hosts. To assess the success or failure of schistosomiasis control programs and to ascertain whether control efforts have led to elimination, precise and sensitive diagnostic tests are needed.

Diagnoses for schistosomiasis are crucial for identifying and treating infections in both prevalent and non-prevalent locations because they inform case detection, morbidity estimations, and control strategies (Ajibola et al. 2018; Odundo et al. 2018).

Schistosomiasis can currently be diagnosed by molecular, immunological, and conventional parasitological techniques (Katz et al. 1972). Utilizing a microscope to identify parasitic eggs in the urine and feces or using an immunological method (antibody or antigen detection) are two common classical parasitological techniques (van Etten et al. 1994; Odundo et al. 2018). According to Caldeira et al. (2012), the Kato-Katz approach is affordable and practical and gives a high level of specificity. The sensitivity of the test depends on the severity of the sickness, the method, and the post-infection host's perception.

According to Odundo et al. (2018), only 65–86% of existing antibody analyses are fully understood. Recently, clinical sciences and food and drug analysis process control have given screen printing electrode biosensors a lot of attention. These sensors are capable of measuring extremely small concentrations of analytes by identifying changes in potential, current, and conductance brought on by an immunological response (Taleat et al. 2014). According to Lin et al. (2008) and Yang et al. (2009), nanotechnology has been utilized to improve and increase the correctness of existing procedures as well as unexpectedly produce new ones. The creation of extremely sensitive, adaptable diagnostic care devices has shown significant promise when using NPs in immunosensing (Dequaire et al. 2000; Baptista et al. 2008; Wan et al. 2013). Table 3.2 lists a variety of nanosensors that have been utilized to improve the detection of schistosomal infections.

In order to identify the *S. mansoni* genome, Santos et al. (2019) created an impedimetric biosensor. Using cyclic voltammetry and electrochemical impedance spectroscopy, the biosensor was identified. With a limit of detection of 0.6 pg/L, the created genosensor could identify minute amounts of *S. mansoni* DNA.

Table 3.2 List of nanosensor/nano-material used in improving the diagnostic ability against schistosomal infections

Nanosensor nano-materials used	Efficacy	*Schistosomes* spp.	References
GICA	GICA identification strips of *S. japonicum* in mice, rabbits, buffaloes, and goats show high sensitivity (100% in each spp.) and specificity (100%, 100%, 94.23%, and 88.64%, respectively). When compared with ELISA, the GICA strips exhibited similar sensitivity and specificity in the diagnosis of schistosomiasis in mice, rabbits, buffaloes, and goats. Besides, only 5 μL of serum is required for the test, and the detection can be completed within 5 min	*S. japonicum*	Xu et al. (2017)
AuNPs-Mab/ELISA	ELISA's sensitivity and specificity for detecting circulating schistosomal antigen (CSA) using AuNPs-Mab was 100% and 97.8%. A more significant positive correlation was detected on the use of AuNPs-Mab/ELISA ($r = 0.882$). Loading AuNPs with Mab (6D/6F) improved the precision of sandwich ELISA for the determination of CSA, allowing active and mild infections to be identified easily	*S. mansoni*	Kame et al. (2016)
MPTS-AuNPs-DNA probe system	The proposed biosystem detected the *S. mansoni* genome sequence in urine samples, cerebrospinal fluid system, and serum in varying amounts. It measured concentrations in urine (27–50 pg/L), cerebral fluid (25–60 pg/L), and serum (27–42 pg/L). The limit detection (LOD) of the biosensor was 0.6 pg/μL. The developed labeled free genosensor was able to detect small concentrations of *S. mansoni* DNA in complex biological fluids	*S. mansoni*	Santos et al. (2019)
AuNP-IgG nanosensor	Immobilized AuNPs combined with bilharzia antibodies proved their diagnostic potential. The detection range of bilharzia antigen in stool samples was 1.13×10^{-1} ng/mL to 2.3×10^{3} ng/mL, with a detection limit of 8.3887×10^{-2} ng/mL, showing the ability of the nano biosensor for detection of bilharzia antigen in stool samples	*S. mansoni*	Odundo et al. (2018)

(continued)

Table 3.2 (continued)

Nanosensor nano-materials used	Efficacy	*Schistosomes* spp.	References
MBA-Fe_3O_4-NPsAuNPs-DNA probe system	On the changed surface of the electrode, the probe system exhibits an efficient electrochemical response. At varied DNA quantities in the genome, the proposed biosystem was capable of identifying *S. mansoni* unique nucleotide sequences in cerebrospinal fluid (CFS) and blood samples. At higher DNA concentrations, bio-recognition caused an increase in electron transfer resistance and a decrease in current peaks during electrochemical testing. The established platform had detection limits of 0.781 and 0.685 pg/L DNA for serum and CFS, respectively	*S. mansoni*	Santos et al. (2017)
AuNP-IgG conjugate	Conjugate was tested as the analyte with a differing concentration of conjugate soluble egg antigen (SEA). The single response was directly proportional to the SEA concentration. A SEA concentration plot against the current change was obtained. The detection limit of 3.31×10^{-5} ng/mL was obtained with formula 3σ/slope, where σ is the standard deviation of three blank solutions	*S. mansoni*	Naumih et al. (2016)
NCE-AGs	The proposed NCE electrode's quantitative response and great sensitivity to Abs of *S. mansoni* are as low as 38 pg, indicating that it may be developed as a site-user, low-cost, and rapid electrochemical immuno-sensor	*S. mansoni*	Shohayeb et al. (2016)

Table 3.3 provides an overview of a number of biosensors developed for the detection of schistosomiasis. Schistosomiasis is the second most common parasite disease in the world, yet little is being done to create biosensors for early detection of the condition. There aren't many articles on this topic that have been published, and the ones that have are often lacking in figures of worth and terms of optimization. The only study that described a genosensor for *S. haematobium* detection using RNA isolated from adult worms as the analyte was by Mach et al. (2015). However, various study teams have sought to demonstrate the viability of such a development because the systems testing shows no differences from those seen for other disorders that are obviously present. When contrasted, the detection systems were even more adaptable, allowing for the development of novel and improved devices. These techniques included AP, DPV, ASV, QCM, and EIS, as well as specialized electrochemical markers like silver, tetramethylbenzidine, ferrocene, and ferro/ferricyanide.

Table 3.3 Electrochemical biosensors for Schistosomiasis disease diagnosis

Sensor	Electrode	Analyte	Technique	Modification	Sample	Reference
Immunosensor	GQC	Rabbit anti- *S. japonicum* SEA	QCM	MPA/ME/SjAg	Rabbit serum	Wang et al. (2012)
Immunosensor	MPPCPE	Rabbit anti-*Schistosome* labelled with colloidal gold	ASV	Fe_3O_4/Au/MCH/EDC/NHS/SEA	Rabbit antibodies	Xu et al. (2010)
Immunosensor	NCE	Anti-*S. mansoni*	DPV	GA/CS/schistosomiasis antigen	Synthetic antibodies	Shohayeb et al. (2016)
Immunosensor	GQC	SjCAg	QCM	ImRS/NRS or SPA/InRS	Rabbit and human serum	Wen et al. (2011)
Immunosensor	SPCE-16	Anti- *S. japonicum* SEA	CV	EDC/NHS/SEA/SjE16	Human serum	Deng et al. (2013)
Immunosensor	SPCE	Inhibitor of *S. japonicum*	DPV	GA/SEA	Human serum	Zeng et al. (2012)
Immunosensor	NCE	Anti *S. mansoni*	DPV	GA/CS/schistosomiasis antigen	Synthetic antibodies	Shohayeb et al. (2016)
Genosensor	Au	*Schistosoma* DNA and genomic material	EIS	MBA/EDC/NHS/Fe_3O_4NPs/AuNPs/ thiolated oligonucleotide probe	Human specimens	Santos et al. (2017)
Genosensor	Au	RNA extracted from *S. haematobium* eggs	AP	Thiol/capture probe	Human urine	Mach et al. (2015)
Genosensor	Au	*S. mansoni* DNA	EIS CV	AuNPs/MPTS/oligonucleotide probe	Human specimens	Santos et al. (2019)
Immunosensor	SPGE	Mouse *Schistosome* SEA	DPV CV	AuNP-rabbit anti-schistosome	Stool sample	Odundo et al. (2018)

MPA mercaptopropionic acid, *MCH* 6-mercapto-1-hexanol, *ME* mercaptoethanol, *SjAg Schistosoma japonicum* antigen, *NHS N*-hydroxysuccinimide, *EDC* 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide, *SPA Staphylococcal* protein A, *SEA* native soluble egg antigen, *ImRS* immunized rabbit's sera, *InRS* infected rabbit's sera, *GA* glutaraldehyde, *MBA* mercaptobenzoic acid, *SjE16 Schistosoma japonicum* calcium-binding protein, *Fe_3O_4 AuNP-IgG* gold nanoparticle-anti-bilharzia conjugate, *NP* magnetite nanoparticles, *SjCAg Schistosoma japonicum* circulating antigens, *MPTS* mercaptopropyltrimethoxysilane, *AuNPs* gold nanoparticles, *MPPCPE* magnetic porous pseudo-carbon paste electrode, *GQC* gold quartz crystal, *SPCE-16* 16-channel screen-printed carbon electrode array, *NCE* nanocarbon-screen-printed electrode, *SPCE* screen-printed carbon electrode, *Au* gold, *SPGE* screen-printed gold electrode, *QCM* quartz crystal microbalance, *ASV* anodic stripping voltammetry, *EIS* electrochemical impedance spectroscopy, *DPV* differential pulse voltammetric, *CV* cyclic voltammetry, *AP* amperometry

3.4 The Role of Biosensors in the Early Detection of Cerebral Malaria

Malaria, spread by the female *Anopheles* mosquitoes, is still a significant parasite disease that affects humans globally. The disease is mostly prevalent in tropical and subtropical regions around the world (Jain et al. 2014; WHO 2018). The endemic countries, which are primarily malaria, spread by the female *Anopheles* mosquitoes, is still a significant parasite disease that affects humans globally. The disease is mostly prevalent in tropical and subtropical regions around the world (Jain et al. 2012; WHO 2018). The endemic countries, which are primarily developing nations, bear a heavy economic cost from the disease. A parasitic alveolate protozoan belonging to the genus *Plasmodium* is the causative agent of malaria. There are six species in this genus, which are known to infect humans: *Plasmodium vivax*, *Plasmodium cynomolgi*, *Plasmodium malariae*, *Plasmodium falciparum*, *Plasmodium ovale* (*Plasmodium ovale* curtisi and *Plasmodium ovale* wallikeri), and *Plasmodium knowlesi*. Considering the World Health Organization's (WHO) target of eradicating malaria by 2030, the goal can only be reached if every case is correctly diagnosed and handled (Feachem et al. 2019). Routine testing in suspected cases is still unavailable to some of the endemic communities. For instance, in public health institutions in 2018, only 74% of individuals who had malaria suspicions had access to testing procedures (WHO 2018). During this time, there were 228 million cases worldwide, with 405,000 fatalities (WHO 2018).

Various control measures have been successful, but they have been constrained by inadequate early diagnostic techniques for identification, particularly in low parasitemia conditions. The identification of asymptomatic people has a significant impact on the malarial dynamics including its spread, control, and perhaps treatment. Diagnostic procedures may aid medical professionals in pursuing additional research into other febrile illness etiologies, preventing severe illness and likely death, and minimizing the presumed usage of antimalarial medications and their related side effects (White 1991).

Numerous technologies have up to now tried to get around the difficulties in diagnosing malaria by focusing on rapid diagnostic requirements and early-stage detection of cerebral malaria. Therefore, the chapter thoroughly reviews the most current developments in biosensor technology in this area, with an emphasis on analytical performances, development, and applicability for rapid diagnosis of the most targeted biomarkers of malaria.

3.4.1 Role of Cerebral Malaria-Related Complications in Neurodegenerative Diseases

Cerebral malaria is a severe and potentially life-threatening complication of malaria caused by the parasite *Plasmodium falciparum* (Fig. 3.2). It occurs when infected red blood cells adhere to the blood vessel walls in the brain, leading to inflammation, impaired blood flow, and the accumulation of infected cells, causing cerebral

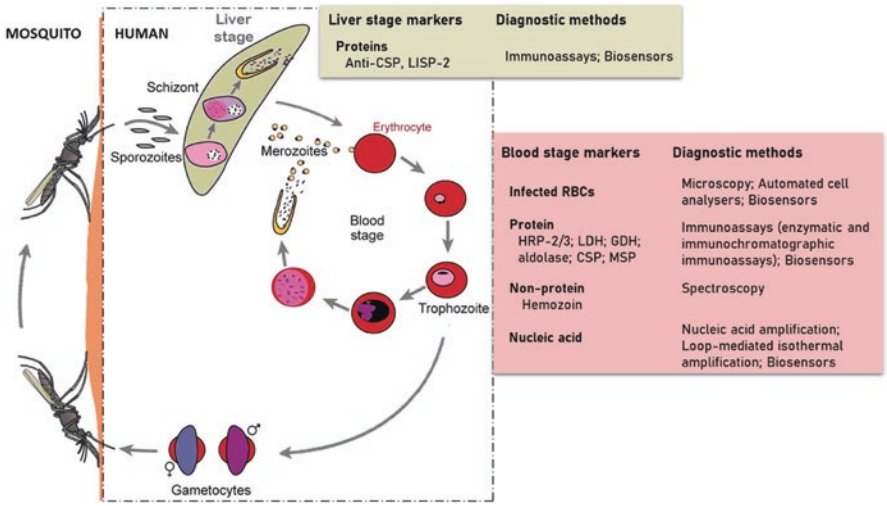

Fig. 3.2 Life cycle of *Plasmodium* spp. (Adapted from Krampa et al. 2020)

edema and increased intracranial pressure. In some cases, this can result in seizures, coma, and death if not promptly treated. While the immediate consequences of cerebral malaria are primarily related to acute brain injury, there may be long-term neurological consequences, potentially linking it to neurodegenerative diseases. Persistent immune responses triggered by the parasite or residual parasites in the brain could create a pro-inflammatory environment that leads to neuronal dysfunction and degeneration, similar to what is observed in certain neurodegenerative disorders. Chronic inflammation and neuronal damage associated with cerebral malaria may contribute to the development or exacerbation of neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). However, further investigation is needed to establish a direct causative relationship between cerebral malaria and these neurodegenerative diseases, as various factors can influence their development and progression. Understanding the potential long-term neurological implications of cerebral malaria could aid in developing targeted therapies to mitigate its impact on brain health.

3.4.2 Biosensors-Based Detection of Malarial Biomarkers

With numerous analytical advantages and cost-effectiveness, biosensors and immunosensors have emerged as promising sensing instruments in recent years (Perkins and Bell 2008; Turner 2013). This development has been influenced by the rising demand for point-of-care diagnostic devices. Electrochemical biosensors are one of the sensor types that have drawn a lot of attention in diagnostics due to pivotal design benefits, ease of handling and better performance over traditional laboratory methods (Belluzo et al. 2008; Wang 2008). As attempts are made to improve and

miniaturize sensor systems to make them easily operable, these properties make them suitable for point-of-care use. Table 3.4 summarizes different biosensor-based detection methods for malarial parasites.

Table 3.4 Biosensor detection of various malaria biomarkers

Analytes	Sensing technique	Transducer	Biomarker	Receptor molecule	Reference
Antigens	Colorimetric	–	pLDH (PvLDH, PfLDH)	pL1 aptamer	Jeon et al. (2013)
	EIS	Gold electrode	pLDH	pL1 aptamer	Lee et al. (2014)
	EIS	GCE	pLDH	P38 aptamer (90 mer ssDNA)	Jain et al. (2016)
	EIS	GCE	HRP-2	Anti-HRP-2 antibody	Brince et al. (2016)
	Chemiresistive (electrical conductance)	–	PfHRP-2	Anti-HRP-2 antibody	Paul et al. (2017)
	–	–	PfHRP-2	Anti-PfHRP-2	Gikunoo et al. (2014)
	EIS	Gold disc electrodes	*Pf*GDH	ssDNA aptamer (NG3)	Singh et al. (2018)
	Potentiometric (FET)	Gold micro-electrodes	*Pf* GDH	ssDNA aptamer (NG3)	Singh et al. (2019)
	Amperometric	Gold-SPE	PfHRP-2	Anti-PfHRP 2 mAb	Hemben et al. (2017)
	Amperometric	Gold-SPE	pLDH	pLDH capture antibody	Hemben et al. (2017)
	Spectrophotometric indicator displacement medium	–	PfHRP-2	NA	Chakma et al. (2016)
	Colorimetric	–	PfLDH	2008s-biotin DNA aptamer	Dirkzwager et al. (2016)
	Colorimetric	–	PfLDH	2008s aptamer	Fraser et al. (2018)
	Amperometric	SPE	PfHRP-2	Mouse anti-PfHRP-2 antibody	Sharma et al. (2008)
	FRET	–	pLDH	Fluorescently-labeled aptamer (36 mer ssDNA)	Kenry et al. (2016)
	Amperometric magneto Immunosensor	–	PfHRP2	Anti-HRP2 IgM antibody	De Souza Castilho et al. (2011)

(continued)

Table 3.4 (continued)

Analytes	Sensing technique	Transducer	Biomarker	Receptor molecule	Reference
Antibodies	SPR	Gold disc	Antibodies of *Pf*	PfHRP2	Sikarwar et al. (2014)
Nucleic acids	Quartz crystal microbalance	–	*Pf* msp2 gene	Biotinylated probe	Potipitak et al. (2011)
	Droplet microfluidic platform	–	*Pf* topoisomerase I	ds DNA substrate	Hede et al. (2015)
	SERS Nanoplatform	–	Pf DNA sequences	Magnetic bead and nanorattle	Ngo et al. (2016)
	Quartz crystal microbalance	Silver electrode	18s rRNA gene (Pf and Pv)	Immobilized probe	Wangmaung et al. (2014)
Infected red blood cells	EIS	SPE	*Pf* infected RBCs	Monoclonal antibody	Kumar et al. (2016)
	Microfluidic separation and MRR	–	Infected RBCs	–	Kong et al. (2015)

EIS electrochemical impedance spectroscopy, *FRET* fluorescence resonance energy transfer, *GCE* glassy carbon electrode, *SPE* screen-printed electrode, *SERS* surface-enhanced Raman spectroscopy, *SPR* surface plasmon resonance

3.4.2.1 Detection of *Plasmodium falciparum* Histidine-Rich Protein 2 (PfHRP-2)

Plasmodium falciparum-specific histidine-rich protein 2 (PfHRP-2) is secreted during parasite growth and development and is involved in the detoxification of heme. The antigen's high levels of expression throughout the parasite life cycle can be credited for its widespread use in electrochemical and optical immunosensors. Although largely present in the blood, trace levels can also be detected in the patient's saliva, urine, and cerebrospinal fluid, providing a chance for noninvasive testing (Rodriguez-del Valle et al. 1991; Parra et al. 1991). In the case of the detection techniques, electrochemical techniques have been found to perform better than optical methods. Amperometric immunosensors have utilized nanoparticles, particularly gold (AuNP), for signal amplification (Cao et al. 2011; Liu et al. 2013; Ju et al. 2011). Because of their small size and simplicity in immobilizing bioconjugate probes, there is a larger surface concentration of detecting antibodies that are enzyme-tagged, leading to stronger indicators from the reaction between substrate and enzyme.

Magnetic nanoparticles (MNPs) have been used to create a malaria immunosensor that is incredibly sensitive. A monoclonal antibody that binds a specific epitope of the target antigen was tagged with horse radish peroxidase in order to provide an electrochemical signal, while anti-HRP-2 was coupled to magnetic nanoparticles as catch components (De Souza Castilho et al. 2011). The anti-HRP-2 magnetic nanoparticles were trapped on a magnetic graphite-epoxy composite electrode in a sandwich assay configuration and treated with anti-HRP-2-HRP and

HRP-2-stimulated serum. According to amplitude measurements, the limit of detection was significantly more than what has been reported in earlier studies (Sharma et al. 2008). However, this technique would need magnetic electrode supports to be applied in the field (De Souza Castilho et al. 2011).

Even though antibodies are typically used as capture molecules in biosensing platforms for disease indicators, antibody stability is a challenge for immunoassays. Genetic modifications that increase the permanency of antibodies, as well as the usage of artificial substitutes like aptamers, have been some attempts to get around these disadvantages (Ravaoarisoa et al. 2010). The parental monoclonal antibodies (mAb) and the recombinant Fab fragments had similar binding properties. This technology suggests a financially advantageous substitute to large-scale antibody manufacture for diagnostic purposes by offering the choice of individual antibody fragments with better stability, resistance to denaturation even with prolonged exposure, and affinities.

Further, some diagnostic procedures examine the close receptor and target recognition by themselves in addition to adding molecular labels and nanoparticles for enhanced diagnosis (Thukral et al. 2023). Since there are no potentially confusing chemical labels, utilizing such label-free formats reduces the complexity of the assay, the amount of time needed for preparation, and the cost of the analysis. Various other techniques have been designed and utilized to detect PfHRP-2 in patients' blood, such as indicator displacement assay (IDA) and electrochemical impedance spectroscopy (EIS)-based methods, which have various advantages for the use a detection models in point-of-care testing.

3.4.2.2 Detection of *Plasmodium* Lactate Dehydrogenase (pLDH)

Lactate dehydrogenase is produced by *Plasmodium* during its intraerythrocytic stages. The glycolytic pathway benefits greatly from the catalytic activity of the enzyme. It is generated by parasites within infected red blood cells that are metabolically active. It serves as a telltale sign of a recent infection. As a result, it is more accurate in locating recent and untreated infections.

Aptamer-based sensors that target pLDH appear to be on the rise (Jeon et al. 2013; Lee et al. 2012; Figueroa-Miranda et al. 2018). Aptamers have several advantages over antibodies, including reduced size, thermostability, a longer shelf life without functional degradation, affordability, simplicity of synthesis, and adaptability.

Single-stranded DNA aptamers (pL1 aptamers) have been utilized to target recombinant *Plasmodium falciparum* LDH (PfLDH) and *Plasmodium vivax* LDH (PvLDH) in buffer and real samples as a potential method for asymptomatic and early diagnosis of malaria. Impedance measurements are used to identify the interaction between pL1 and the target proteins with great sensitivity and specificity. A colorimetric test was used to measure the intrinsic enzymatic activity of LDH utilizing microbeads that were functionalized with aptamers. Due to the beads' large surface area for analyte binding, the aptamer-tethered enzyme capture (APTEC) assay produced a LoD for recombinant PfLDH of 4.9 ng/mL (Dirkzwager et al. 2016; Fraser et al. 2018).

The aptamer-tethered enzyme capture assay was then integrated into a transportable microfluidic biosensor. The platform addressed some of the assay's original issues with large sample and reagent volumes while identifying *P. falciparum* in clinical samples and culture samples with excellent specificity and sensitivity (Dirkzwager et al. 2016; Fraser et al. 2018).

3.4.2.3 Detection of Glutamate Dehydrogenase (GDH)

In *Plasmodium* parasites, glutamate dehydrogenases (GDH) are involved in ammonium assimilation and catabolism of glutamate. Significantly soluble amounts of the enzyme are present during parasite's development, thus a potent target to detect the presence of the parasite in a patient's body (Li et al. 2005). By grafting a gold electrode with a thiolated ssDNA aptamer (NG3) particular to *P. falciparum* (PfGDH), a label-free capacitive aptasensor was created. The sensor has a range of 100 fM–100 nM and produced a limit of detection in serum of 0.77 pM. To create a sensitive and trustworthy miniaturized aptaFET biosensor, the NG3 aptamers were immobilized on interdigitated gold microelectrodes (IDE) and coupled to the field effect transistor (FET). FET-type devices offer the benefit of permitting straightforward and sensitive electrochemical measurements without the requirement of a traditional redox marker. In the presence of similar plasmodial and human proteins, the FET-based potentiometric sensor was highly selective, making it suitable for real-world sample analysis for the detection of malaria (Park et al. 2012; Singh et al. 2018, 2019).

3.4.2.4 Detection of Hemozoin

The malaria parasites consume between 60% and 80% of erythrocytic hemoglobin at this stage of their life cycles, resulting in the production of heme and polymerization into insoluble hemozoin crystals (Chugh et al. 2013). Since hemozoin is only found in the digestive vacuoles of parasites, its presence in the blood is a reliable indicator of *Plasmodium* parasites that are actively engaged in metabolism. It has been demonstrated that surface-enhanced Raman spectroscopy (SERS) has the ability to multiply the hemozoin's Raman signal by several orders of magnitude (Pagola et al. 2000). Uninfected lysates do not exhibit a Raman shift when exposed to a gold-coated butterfly wing as a SERS substrate, but parasitized RBCs do.

When parasitemia levels were between 0.0005% and 0.005% in the early ring stage, the spectrum markers of hemozoin from infected RBC could be detected. A different SERS method that used synthesized silver nanoparticles inside parasites to achieve close contact with hemozoin demonstrated an ultrasensitive hemozoin detection at 0.00005% parasitemia level in the ring stage (2.5 parasites/L), whereas enhancements of Raman signals occur when hemozoin crystals are in direct contact with metal surfaces (Chen et al. 2016). Although Raman spectrometers are expensive, especially those with high spectral resolutions, several SERS techniques have demonstrated promising results. Magnetic resonance relaxometry (MRR) has been utilized to achieve label-free detection using the paramagnetic characteristics of hemozoin crystals. The MRR technology has achieved early parasitemia detection at a level of 0.0005% when used in conjunction with a microfluidic setup (Krampa et al. 2020).

There aren't many known malaria biomarkers; hence, the collection of parasitized RBCs has been suggested as a workaround. In order to find a diverse range of aptamers that specifically bind various epitopes found on parasitized RBC surfaces, a unique microfluidic SELEX (I-SELEX) was used. Monoclonal antibodies were used as capture elements for cells infected with malaria after being immobilized on an AuNP-modified screen-printed electrode. The interaction of monoclonal antibodies with parasitized RBCs resulted in impedimetric changes that allowed infected RBCs to be distinguished from healthy, uninfected RBCs (Garcia 2007; Birch et al. 2015). In addition to the protein and antibody-dependent detection methods in malaria, various nucleic acid markers have also been explored as an alternative.

Additionally, parallel testing may be the best method for delivering healthcare because of its higher throughput, decreased reagent/assay setup, and reduced labor requirements. A multitargeted diagnostic approach between different parasitic species is the main goal of multiplexed malaria testing. To differentiate between passive/resolved or active infections and to discriminate between *falciparum* and non-*falciparum* malaria, the most widely used techniques combine PfHRP-2/LDH or PfHRP-2/aldolase (Jepsen et al. 2012; Iqbal et al. 2004; Lafleur et al. 2012; Deraney et al. 2016).

3.5 Applications of Biosensors in the Early Detection of Human African Trypanosomiasis (HAT)

Human African trypanosomiasis (HAT), also referred to as sleeping sickness, is a disease that only affects sub-Saharan Africa. The parasite was discovered for the first time in humans in 1902. A trypanosome parasite-group protozoan is responsible for HAT. *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* are the two distinct subspecies. Around 90% of cases are caused by the *Trypanosoma brucei gambiense*, which causes a persistent infection in patients asymptomatically and increases the likelihood that the disease will progress to an advanced state. When a person is sick, their central nervous system is impacted, which makes it more difficult to treat or control the illness (Büscher et al. 2017; Bottieau and Clerinx 2019).

On the other hand, *Trypanosoma brucei rhodesiense* infections manifest symptoms weeks or months after first coming into touch with the parasite. This species quickly damages the neurological system by causing an acute infection. The patient's medical history and course of treatment influence the symptoms in both species (Bottieau and Clerinx 2019). Intermittent fever, pruritus, headaches, lymphadenopathy, anemia, and hepatosplenomegaly are a few typical traces. The meningoencephalitis stage, which manifests as neuropsychiatric and sleep disorders, aberrant movement, limb paralysis, hemiparesis, violent behavior, or psychotic behaviors, is said to start when the parasite penetrates the blood-brain barrier (BBB) (Bonnet et al. 2015; Masocha and Kristensson 2019; Radwanska 2010).

One of the neglected tropical illnesses is human African trypanosomiasis (HAT), and early detection is just as crucial to therapy as it is to prevention. The biosensor-based detection assays have also been attempted for its point-of-care diagnosis. The development of the HAT identification system from human blood samples was reported by Tweed-kent et al. in 2012 (Tweed-kent et al. 2012). The assay's methodology was based on a glassy carbon cylindrical rod electrode (GCCRE) that has been enhanced with carboxylated single-walled carbon nanotubes (CSWCNT), and the assay's approach was based on an immobilized aptamer created by a *Trypanosoma brucei* RNA. It is crucial to emphasize the 4.0 fmol/L limit of detection that was attained in actual samples. The hybrid aptasensor that the authors describe is a quicker and more affordable alternative to current commercial tests for diagnosing HAT. It represents a development in the usage of modified ion-selective electrodes (Cordeiro et al. 2021). The diagnosis of HAT is quite challenging due to differences in reactivity toward different parasite species, the symptoms, and affordability of the conventional tests. The current tests include the following:

1. Antibody detection using Card-Agglutination Trypanosomiasis Test (CATT) (Penchenier et al. 2003).
2. Parasite Detection by Lymph Node Examination (WHO 2013), Mini Anion Exchange Centrifugation Technique (mAECT) (Lutumba et al. 2006; Buscher et al. 2009), and Capillary Tube Centrifugation (CTC) (WHO 2013).
3. Stage diagnosis, which involves the use of microscopic techniques to detect trypanosomes in cerebrospinal fluid (Brun et al. 2010; Sekhar et al. 2014).

Existing diagnostic techniques require specialized mobile teams that are skilled in doing quick testing utilizing invasive methods, making them difficult and time-consuming to apply. The goal is to provide straightforward tests that make it possible to incorporate HAT diagnosis-related activities into the public health infrastructure. Some of the novel HAT staging biomarkers are under investigation and are discussed as follows:

Antibody levels such as that of intrathecal IgM, particularly in *Trypanosoma brucei gambiense* patients, are preferable over WBC counting as a measure for HAT staging (Courtioux et al. 2006).

Another area of research being looked into is the modification of immune effectors, such as cytokines and chemokines, for the development of new diagnostic techniques for HAT staging. Early macrophage and astrocyte activation, a rise in inflammatory cytokines, and the appearance of Mott cells (plasma cells expressing IgM) are some characteristics of late-stage HAT neuroinflammation. Two significant sources of inflammatory cytokines and chemokines in the brain are activated astrocytes and macrophages. Both *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* levels of these cytokines and chemokines have been tested to investigate their diagnostic potential (Cordeiro et al. 2021).

The measurement of the differences in protein expression between infected and noninfected settings is a different strategy that is currently being researched. Only a few studies have defined the CSF protein patterns for the first and second stages of

HAT illness. For stage 2 patients, there is a significant increase in immunoglobulin levels (Courtioux et al. 2006; Tiberti et al. 2013), but there are also 73 proteins that differ in expression between the two stages. Osteopontin and beta-2-microglobulin have both been shown to be reliable indicators of patients in the first and second stages (Tiberti et al. 2010). It is now possible to study new protein biomarkers, particularly for differentiating between stages 2 and 1 of the disease, thanks to the development of new tools for protein and peptide analysis (Geiger et al. 2011).

Recent research has focused on the alteration of the typical sleep-wake cycle, the most common clinical sign of HAT (Brun et al. 2010). For these studies, polysomnography has been employed.

A polysomnography can be used to investigate sleep disorders and includes tests such as an electroencephalogram, electromyogram, and electrooculogram. Other physiological measurements like heart rate and respiratory rate are also recorded. According to studies, stage 2 patients have a high number of SOREMPs during the course of their sleep, not just at night but also during the day (Buguet et al. 2012).

For illness staging, it has been suggested to use PCR to amplify particular parasite DNA sequences found in blood, CSF, urine, or saliva samples. For staging HAT illness, the loop-mediated isothermal amplification (LAMP) technique exhibits great specificity and sensitivity. Additionally, this technique amplifies the target DNA at a constant temperature, allowing for the use of the test in low-tech laboratories or in the field in HAT-endemic areas with little equipment (Cordeiro et al. 2021).

3.5.1 American Trypanosomiasis (Chagas Disease)

The majority of the nations in South and Central America are endemic to *Trypanosoma cruzi* (Moncayo 2003). Reduviid bug bites are the most common way to contract the infection, although they can also spread transplacentally, through eating infected guinea pigs, through blood transfusions, or through organ transplants (Busch et al. 2003). Infection has migrated from rural Latin America to the United States and other countries due to rising urbanization and emigration (Dias et al. 2002). Endemicity is at its highest level wherever *Triatoma* spp. is present. The reduviid bug usually lives in damp environments; however, it has evolved to live in cities (Leiby et al. 2002).

When migrants from rural areas with high endemicity donate infected blood to blood banks, transmission via transfusion happens more frequently in urban settings (Sanchez-Guillen et al. 2002). However, trypanosome-infected transfusions continue to be widespread in many South American nations (Busch 2003). The prevalence of contaminated blood products has decreased in some locations due to increased blood product screening. Immune-suppressed patients have replaced tourists and immigrants as the group in the United States with the highest risk of contracting an infection (Leiguarda et al. 1990).

The vector excretes feces containing *T. cruzi* stages while consuming a blood meal from a potential host, and these stages are then left behind on mucous

membranes or skin (Kirk and Schofield 1987). During scratching at the site of an insect bite, skin breaches occur that allow stages to enter the human host. These then reproduce by binary fission. These cells shed into the bloodstream, where they travel to distant regions and grow into adult intracellular organisms. Unlike African trypanosomes, *T. cruzi* only divides after infecting a new cell or after unintentionally ingesting a host. Infected cells burst, releasing infectious parasites as well as potent inflammatory parasitic chemicals that strongly induce a host response (Hall and Joiner 1993).

A *trypanosome* can be seen in serum or CSF, which is required for a conclusive diagnosis (CDC 2003). Blood can reveal intracellular motile creatures when examined under a microscope. Direct visualization of the parasite is unusual during persistent infection. Both chronic and acute forms of infection can be detected by serum antibody detection tests, which are specific and sensitive (Matsumoto et al. 1993). When deciding on a course of treatment, clinical history plays a more significant role than diagnostic tests in identifying how chronic the illness is. Leishmaniasis-related cross-reactivity can happen (Umezawa et al. 2001).

3.5.2 Advances in Biosensors for the Detection of Chagas Disease

The two types of biosensors that have been studied for Chagas disease diagnosis are electrochemical and optical. Amperometric and impedimetric sensors are involved in electrochemical sensors (Erdmann et al. 2013), but only surface plasmon resonance (SPR) transducers are documented for optical sensors (Luz et al. 2015).

Pumpin-Ferreira et al. released a study in 2005 about a biosensor for the detection of Chagas disease. The amperometric immunosensor requires an electrochemical contact; hence, the measurements were performed with a potentiostat-galvanostat. Potentiostats are strong pieces of machinery, but they are too huge and heavy to be used as a portable biosensing system. Because these biosensors offer greater miniaturization and integration possibilities for portable systems, further electronics for readout systems need to be created for them. Salinas et al. also published a study on an amperometric immunosensor in the same year (Salinas et al. 2005) with an analysis time of no more than 23 min. In comparison to the ELISA approach, this group achieved a higher level of sensitivity.

For the diagnosis of Chagas disease, Luz et al. (2015) created the first biosensor based on SPR transducers. They collected the parameter relating to the presence of antibodies against *T. cruzi* shown in human serum in around 20 min. In 2016, the same group of researchers found that their immunoassay distinguished Chagas disease from other infectious diseases with a higher percentage of accuracy compared to ELISA and also displayed a higher sensitivity of 100% compared to other diagnostic methods, such as PCR, which has a sensitivity of 90% and an acceptable specificity of 97.2% (Luz et al. 2016). However, because the integration of a light source is necessary for the laser generation and light detectors, the SPR transducing principle now results in high volume and hefty commercial apparatus. The only

applications for this technology at the moment are lab tests. Additionally, SPR equipment costs more than $50,000 USD, even though optical biosensors can be quite sensitive. This makes it difficult for many researchers to afford such systems (Coltro et al. 2014). In order to diagnose viral diseases using magnetic microbeads, Corina et al. created a portable electrochemical biosensor platform. A mini-portable potentiostat with eight channels that the group created and produced was used to make this platform portable. With assay reading durations of 20 s, they were able to successfully show the platform's application for the diagnosis of Chagas disease, and the findings they got in terms of sensitivity and selectivity were comparable to those of ELISA. But the system isn't currently offered in stores. In order to conduct the tests, the technique also necessitates the detection of electrochemical processes, which results in indirect steps. These procedures might be avoided in the future by using different detecting methods, including sound sensors.

Additionally, Regiart et al. (2016) reported the development of an electrochemical immunosensor detecting anti-IgM *Trypanosoma cruzi* antibodies. By boosting the sensor's active surface area, they used gold nanoparticles to raise its limit of detection. In this study, a detection limit of 3.03 ng/mL was attained. In the same year, Janissen et al. used a nanowire biosensor based on field-effect transistor (FET) technology for the CD protein marker IBMP8-1, achieving a limit of detection of about 6 fM (Janissen et al. 2017). This study illustrates the potential of this highly sensitive biosensor for the management of this condition.

Table 3.5 summarizes various nanomaterials that have been used for drug delivery in preclinical studies of Chagas disease.

Table 3.5 List of different nanomaterials with varying composition that have been used for drug delivery in preclinical studies of Chagas disease

Nanomaterial	Preparation method	Active agent	Composition	Size (nm)	References
Polymeric nanoparticles	Simple emulsification	Bis-triazole D0870	PLA-PEG	100–200	Molina et al. (2001)
	Nanoprecipitation	Ursolic acid	Poly-εcaprolactone	172.2	Abriata et al. (2017)
	Nanoprecipitation	LYC	NC-PCL-PLAPEG	105.3	Branquinho et al. (2014)
		Nifurtimox	PACA	≤200	Gonzalez-Martin et al. (1998)
	Nanoprecipitation	LYC	PCL-PLA-PEG	100–250	Branquinho et al. (2017)
	Self-emulsifying	RAV	SEDDSs	100–250	Sposito et al. (2017)
	Ionotropic gelation	Nitric oxide	RSNO	270–500	Contreras Lancheros et al. (2018)
	Nanoprecipitation and freeze-drying	BNZ	Multiparticulate benzonidazole polymers	233	Seremeta et al. (2019)
Quantum dots	Colloidal chemistry	CdTe	–	NI	Vieira et al. (2011)
Liposomes	Extrusion	ETZ	pH-sensitive liposomes	379	Morilla et al. (2005)
Mesoporous–silica nanoparticles	Hydration	BNZ	Mesoporous silica nanoparticle and chitosan coating	3.3	Hu et al. (2014)
Nanoemulsions	Emulsification	Clove oil	Sulfonamides	35–100	Vermelho et al. (2018)
		Ursolic acid		57.3	Vargas De Oliveira et al. (2017)
Solid lipid nanoparticles	High-pressure homogenization and microemulsion	*S*-Benzyldithiocarbazate	H2bdtc-SLNs	127.4	Carneiro et al. (2014)

mv millivolt, *SEDDSs* self-emulsifying drug delivery systems, *BNZ* benznidazole, *RAV* ravuconazole, *PACA* poly(alkyl cyanoacrylate) nanoparticles, *nm* nanometer, *PN* nanoparticles with poly-ε-caprolactone, *ZP* zeta potential, *NC* nanocapsules, *PEG* polyethylene glycol-polylactide, *PCL* poly-ε-caprolactone

3.6 Advances in Biosensors for the Detection of Toxoplasmosis

Toxoplasmosis are caused by the protozoan parasite *Toxoplasma gondii* (Berger-Schoch et al. 2011). Even though many infections only cause minor symptoms like weariness, fever, and enlarged lymph nodes, they can cause serious disease and even death in people with compromised immune systems or when the parasite is passed on genetically (Xiao and Yolken 2015). The identification of certain antibodies against the *Toxoplasma* parasite is frequently required for the diagnosis of toxoplasmosis. To get around the shortcomings of traditional methods, poor sensitivity, low specificity, and device complexity, a number of tools have been developed, including electrochemical, optical, and piezoelectric devices. According to Nambiar and Yeow (2011), biosensors have a number of benefits over traditional analytical techniques, including excellent selectivity and sensitivity, the potential for miniaturization and portability, quick response, small sample quantities, real-time detection, and low cost.

Electrochemical sensors have been utilized to detect specific IgG anti-*T. gondii* antibodies, which serve as important markers for the determination and confirmation of toxoplasmosis infection (Li et al. 2017). Another detection method involves the use of an electrochemical immunosensor based on *T. gondii* IgM antibodies (Tg-IgM) to verify the presence of toxoplasma infection (Jiang et al. 2013). The majority of biosensors described in the literature for toxoplasmosis rely on immunoassays to detect anti-*T. gondii* antibodies.

In one approach, an agglutination-based piezoelectric immunoassay was developed to directly detect anti-*T. gondii* immunoglobulins in infected rabbit serum and blood. This method utilizes antigen-coated gold nanoparticles that undergo specific agglutination in the presence of the corresponding antibody, leading to a frequency change detected by a piezoelectric device. The system demonstrated sensitivity to anti-*T. gondii* antibody dilution ratios as low as 1:5500 (Wang et al. 2004; Ding et al. 2005) developed an electrochemical biosensor employing enzyme-catalyzed amplification. The surface of a gold electrode was immobilized with *T. gondii* antigen to capture anti-*Toxoplasma* IgG, followed by the addition of anti-*Toxoplasma* IgG horseradish peroxidase conjugate. Transduction methods such as quartz crystal microbalance, electrochemical impedance spectroscopy, and cyclic voltammetry were employed, achieving a detection limit of 1:9600 in dilution ratio.

Luo et al. (2013) utilized two aptamers with high affinities to antitoxoplasma IgG in the development of a quantum dots-labeled dual aptasensor. The presence of anti-toxoplasma IgG leads to the formation of an aptamer-protein-aptamer sandwich complex, which is captured on a multi-well microplate. The fluorescence emitted by quantum dots is then measured, allowing for quantitative analysis. The aptasensor demonstrated linearity within the range of 0.5–500 IU, with the lowest detection limit of 0.1 IU. Another detection method, described by He et al. (2015), utilized magnetic fluorescent nanoparticles in the development of a genosensor for the detection of *T. gondii* DNA oligonucleotides. This fluorimetric method achieved a limit of detection of 8.339 nM.

Alves et al. (2019), developed an immunosensor for detecting anti-*Toxoplasma* antibodies, which can distinguish various stages of infection. Although IgM is commonly used as a marker for toxoplasmosis, it is not detectable in some patients, making the measurement of IgG a more reliable diagnostic tool (Medawar-Aguilar et al. 2019). Glyco-sylphosphatidylinositol glycolipid-anchored proteins (GPI-Aps) are important for cell signaling and communication during infectious diseases and are present on the surface of *T. gondii*, *T. brucei*, and *P. falciparum* (Tsai et al. 2012). GPI-Aps can be used for detecting anti-GPI IgG and IgM antibodies in seropositive patients (Echeverri et al. 2020). A simple colorimetric method based on gold nanoparticles has been developed using synthetic polymorphic peptides derived from the GRA6 antigen, specific for type II *T. gondii*, which can efficiently detect anti-GRA6II antibodies in serum samples. This biosensor-based immunoassay using AuNPs conjugated with polymorphic synthetic peptides can be used as a serotyping device (Sousa et al. 2021).

3.7 Application of Biosensor in Early Detection of Neurocysticercosis

Taenia solium, commonly known as the pork tapeworm, is a helminth parasite that is responsible for causing a condition called cysticercosis (Fig. 3.3). Cysticercosis occurs when animals and humans become infected with the eggs of *T. solium*, often through the consumption of contaminated pork. Neurocysticercosis is a parasitic infection of the central nervous system caused by the metacestode of the tapeworm *T. solium* (Garcia et al. 2003). It is a leading cause of acquired epilepsy worldwide, especially in developing countries. Early detection of neurocysticercosis is critical for effective treatment and prevention of seizures and other neurological complications. The eggs of *T. solium* hatch and release oncospheres that have the ability to invade the nervous system of humans. This invasion can lead to the development of adult-acquired epilepsy and other neurological complications. Ingesting raw or undercooked meat from pigs infected with cysticercosis can result in the development of a tapeworm infection known as taeniasis in humans.

Patients with taeniasis may experience various symptoms including epigastric discomfort, nausea, insomnia, anorexia, irritability, diarrhea, and weight loss. Detecting *T. solium* infection is crucial for early diagnosis and effective management of the disease. Different immunoassays have been developed to detect *T. solium* infection in both infected humans and livestock animals. However, these methods often require centralized laboratory facilities and are time-consuming, labor-intensive, and have longer turnaround times. This can delay the diagnosis and treatment of infected individuals.

To overcome these limitations, there is a need for innovative diagnostic approaches that are rapid and sensitive and can be performed at the point of care. Biosensors offer a promising solution in the early detection of *T. solium* infection. These analytical devices utilize bioreceptors to recognize and interact with specific molecular targets, producing a detectable signal that indicates the presence of the

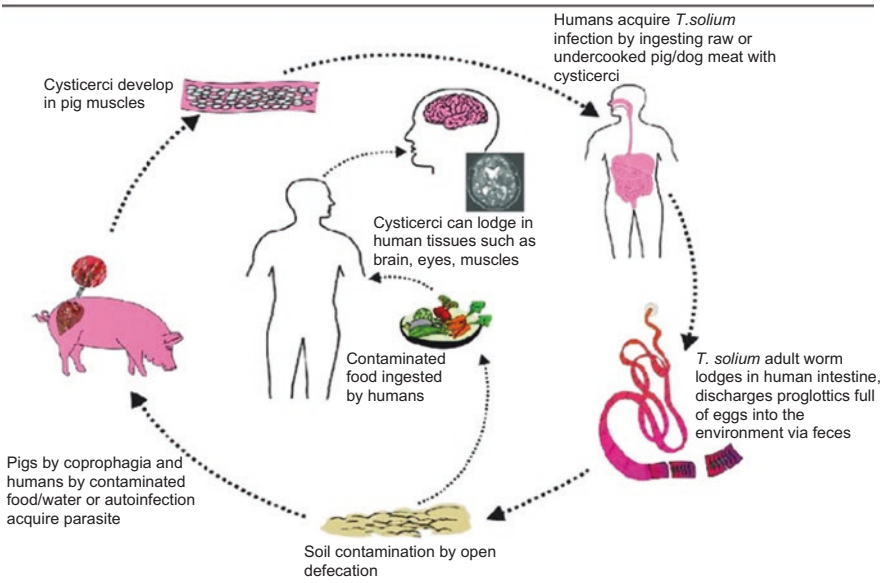

Fig. 3.3 Lifecycle of *Taenia solium*. (Adapted from Siddiqua and Habeeb 2020)

infection. Biosensors can provide several advantages in the diagnosis of these infections, including rapid results, minimal sample requirements, portability, and potential for on-site testing. By utilizing biosensors, healthcare providers can obtain real-time information about the infection status, enabling timely intervention and appropriate treatment (Zhao et al. 2019; Kulkarni and Goel 2020).

Biosensors have emerged as a promising tool for the early detection of this disease. Biosensors are analytical devices that combine a biological recognition element (such as an enzyme or antibody) with a transducer to convert a biological signal into a measurable signal. Biosensors offer several advantages for the early detection of neurocysticercosis, including their high sensitivity, specificity, and selectivity. They can detect the presence of the parasite's antigens or antibodies in various biological samples, such as serum, cerebrospinal fluid, and saliva. One type of biosensor that has been developed for the early detection of neurocysticercosis is the electrochemical biosensor. This biosensor consists of a working electrode, a reference electrode, and a counter electrode. The biological recognition element is immobilized on the working electrode, and the transducer measures the electrochemical signal generated by the interaction between the recognition element and the target antigen or antibody. The electrochemical biosensor can detect the presence of the parasite's antigens or antibodies in biological samples with high sensitivity and specificity.

Another type of biosensor that has been developed for the early detection of neurocysticercosis is the optical biosensor. This biosensor utilizes light to measure the interaction between the biological recognition element and the target antigen or antibody. The optical biosensor can detect the presence of the parasite's antigens or antibodies in biological samples with high sensitivity and selectivity.

Biosensors offer several advantages for the early detection of neurocysticercosis over conventional diagnostic methods, such as ELISA and PCR. Biosensors are portable, simple, and rapid, and they can provide real-time results. They can also detect low levels of the parasite's antigens or antibodies in biological samples, which may not be detectable by conventional methods.

The detection of neurocysticercosis, caused by the infection of *T. solium* (pork tapeworm) can be facilitated by various biosensor-based approaches. One such method involves the use of a lateral flow test utilizing nano-sized up-converting phosphor (UCP) reporter particles and a portable analyzer. This test detects antibodies in serum samples that react with bacterial-expressed recombinant T24H, a specific marker for neurocysticercosis cases (Corstjens et al. 2014). The UCP-LF assay incorporates TSOL18 and GP50 antigens, which are known to be highly protective, immunogenic, and specific for the early diagnosis of cysticercosis (Gomez-Puerta et al. 2019). Compared to ELISA, the UCP-LF assay demonstrates higher sensitivity (93.59% for TSOL18 and 97.44% for GP50) and specificity (100% for both antigens), providing a rapid, small-volume and reliable method for cysticercosis diagnosis (Zhang et al. 2021).

Another approach involves the use of a localized surface plasmon resonance (LSPR) biosensor utilizing colloidal gold nanoparticles (AuNPs). This biosensor detects *T. solium* antigens and demonstrates the ability to differentiate between positive and negative human serum samples, representing diseased and non-diseased individuals with neurocysticercosis (Arcas et al. 2021). The LSPR biosensor, employing AuNPs synthesized through a specific protocol, exhibits improved stability during biofunctionalization and offers potential for the diagnosis of neurocysticercosis (Soares et al. 2018).

In addition, a biosensor based on quantum dot aptasensor (Q-DAS) technology has been developed for the detection of antitoxoplasma IgG, which is relevant in *Toxoplasma* screening. This biosensor employs specific aptamers as coating and detection probes, enhancing sensitivity compared to conventional antibody-based assays (Luo et al. 2014).

Peptides have also gained interest in biosensing for their unique characteristics, such as biocompatibility, stability, ease of synthesis, and sequence versatility. Peptide-based biosensors have been explored for the enhanced detection of pathogens, including *T. solium*. These biosensors offer advantages over antibody-based assays in terms of resistance to harsh conditions and suitability for on-field applications (Karimzadeh et al. 2018).

Among various transduction systems used in biosensors, electrochemical and optical platforms are the most prevalent, followed by mass-based systems. Bioreceptors such as antibodies, nucleic acids, aptamers, peptides, and bacteriophages have been employed to construct these biosensors, with the choice of bioreceptor being crucial for achieving reliable detection with high sensitivity and specificity (Bhardwaj et al. 2017; Wu et al. 2014, 2015; Vidic et al. 2019; Vizzini et al. 2021; Bruno 2014; Islam et al. 2022; Karimzadeh et al. 2018; Qiao et al. 2020; Tertis et al. 2021; Karoonuthaisiri et al. 2014; Anany et al. 2018).

3.8 Conclusion

Despite numerous efforts from committed individuals, the number of new cases and fatalities from neuro-parasitic diseases continue to be frightening. Neuroparasitic diseases have a severe influence on the entire world. The challenges are enormous, ranging from accessing isolated and unsafe regions to having treatments available to help entire communities. To expedite the right diagnosis and, consequently, the treatment, low-cost and miniature equipment like biosensors can be used in these conditions.

In order to diagnose neuroparasitic disease early on, biosensors have become a viable tool. In comparison to traditional diagnostic techniques, they have a number of advantages and have excellent levels of specificity, selectivity, and sensitivity for detecting the presence of the parasite's antibodies or antigens in a variety of biological samples. Biosensors have the potential to improve the diagnosis and treatment of neuro-parasitic disease and reduce the burden of this disease worldwide.

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