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REVIEW ARTICLE

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Innovations in dengue virus detection: An overview of conventional and electrochemical biosensor approaches

Shadan Raza[1] | **Renu Poria**[1] | **Deepak Kala**[2] | **Nishant Sharma**[1] | **Anil K. Sharma**[3] | **Nkurunziza Florien**[1] | **Hardeep S. Tuli**[1] | **Ankur Kaushal**[1] | **Shagun Gupta**[1]

[1]Department of Bio-Sciences and Technology, Maharishi Markandeshwar (Deemed to Be) University, Mullana, Ambala, India

[2]Centera Laboratories, Institute of High Pressure Physics PAS, Warsaw, Poland

[3]Department of Biotechnology, Amity University of Punjab, Mohali, Punjab, India

Correspondence
Shagun Gupta and Ankur Kaushal, Department of Biotechnology, Maharishi Markandeshwar (Deemed to Be) University, Mullana, Ambala 134003, India. Email: shagun22_88@yahoo.com and ankur.biotech85@gmail.com

Abstract

Globally, people are in great threat due to the highly spreading of viral infectious diseases. Every year like 100–300 million cases of infections are found, and among them, above 80% are not recognized and irrelevant. Dengue virus (DENV) is an arbovirus infection that currently infects people most frequently. DENV encompasses four viral serotypes, and they each express comparable sign. From a mild febrile sickness to a potentially fatal dengue hemorrhagic fever, dengue can induce a variety of symptoms. Presently, the globe is being challenged by the untimely identification of dengue infection. Therefore, this review summarizes advances in the detection of dengue from conventional methods (nucleic acid-based, polymerase chain reaction-based, and serological approaches) to novel biosensors. This work illustrates an extensive study of the current designs and fabrication approaches involved in the formation of electrochemical biosensors for untimely identifications of dengue. Additionally, in electrochemical sensing of DENV, we skimmed through significances of biorecognition molecules like lectins, nucleic acid, and antibodies. The introduction of emerging techniques such as the CRISPR/Cas' system and their integration with biosensing platforms has also been summarized. Furthermore, the review revealed the importance of electrochemical approach compared with traditional diagnostic methods.

KEYWORDS
biosensing platforms, dengue, dengue detection, electrochemical biosensors, nanomaterials, point of care systems

Abbreviations: Con A, concanavalin A; CV, cyclic voltammetry; DENV, dengue virus; DHF, dengue hemorrhagic fever; DPV, differential pulse voltammetry; DW, DNA walker; H1, hairpin 1; HI, hemagglutination inhibition; LOD, low limit of detection; MB, methylene blue; MBA, 4-mercaptobenzoic acid; NASBA, nucleic acid sequence-based amplification; NS1, non-structural 1; OD, optical density; PCR, polymerase chain reaction; PRNT, plaque reduction neutralization test; RT-RPA, recombinase polymerase amplification; TLR3, toll-like receptor 3; UTR, untranslated region.

1 | INTRODUCTION

Dengue is a serious global public health concern affecting around 100 million people each year.[1] This infection arises from a single-stranded positive RNA virus with a genomic size of 10.7 kb and about four antigenically distinct serotypes (DENV-1–4) that are members of the Flaviviridae family.[2] The illness primarily affects tropical and subtropical nations, whereas it is now more common in more and less developed areas. Dengue fever presents with a wide range of symptoms including fever, headache, and myalgia (Figure 1), often overlapping with other febrile illnesses, making it challenging to differentiate without proper diagnostic techniques. However, dengue fever can occasionally manifest more severely, such as in dengue hemorrhagic fever (DHF) or dengue shock syndrome, which exhibit potentially fatal signs like hemorrhage, thrombocytopenia, and vascular leakage.[3,4]

The innate and adaptive immunity are an important component of defense mechanism in dengue virus (DENV) infections. DENV infects the tissue-resident dendritic cells known as Langerhans cells and travel through the lymphatic system to the lymph node regions displaying the viral antigens on their surface, triggering both innate and adaptive immune responses. The cells of innate immunity are first to respond by the use of pattern recognition receptor specific to DENV infections such as cytoplasmic retinoic acid-inducible gene I, endosomal toll-like receptor 3 (TLR3), and TLR7 inducing type 1 interferon responses.[5] The adaptive immune response is triggered when the viral antigens are presented on the surface of T and B cells. The B cells respond by producing antibodies called IgM and IgG that specifically recognize and neutralize the dengue viral particles. The T cells, such as cytotoxic T and killer T cells, recognize and kill the cells that are infected with the DENV.[6]

The early identification of dengue cases is essential to initiate timely treatment, prevent severe complications, and implement effective vector control measures. Focused diagnosis methods aim to improve the accuracy, speed, and cost-effectiveness of dengue diagnosis, aiding healthcare providers in making informed decisions regarding patient care and public health interventions.[7]

DENV infection can be verified using antibodies, viral RNA, antigens, or virion.[8,9] The infection is usually confirmed during the sharp period of diseases (first week after the starting of symptoms) by virus identification in cell culture.[10] As the responsiveness of viral separation and antigen reactivity declines in the latter stages of the illness, serological tests are increasingly used and indicated for identification.[11,12] Techniques for detecting viral antigen (nonstructural 1 [NS1]) are rapid, accurate, and simple to use, but they are unable to distinguish between various viral serotypes.[13] The most reliable diagnostic approach is viral isolation, but it takes a long time and is quite challenging compared to alternative direct viral detection procedures.[14] As opposed to that, the well-liked reverse transcription polymerase chain reaction (RT-PCR) method allows for the quick identification of viral genes with low copy numbers in as little as 48 h.[15] RT-PCR has long been a reliable and swift method for RNA detection, particularly in studying dengue viral presence. Despite its efficacy, false positives can arise from errors in primer design or nonspecific hybridization under varying PCR conditions. Additionally, the amplification process, being time-consuming, costly, and intricate, posed challenges.[16] Consequently, researchers have explored biosensors as a promising alternative technology for detecting DENV and dengue antibodies. This approach boasts numerous benefits, including heightened sensitivity, cost efficiency, uncomplicated construction, potential for miniaturization, swift outcomes with quantitative analysis, and the feasibility of on-site monitoring.[17]

This review summarizes developed identifications of dengue from commonly used techniques (nucleic acid-based, PCR-based, and serological approaches) to novel biosensors. The study provides an extensive inquiry of the current designs and fabrication methodologies involved in developing electrochemical biosensors (nucleic acid-based, immune-based, and lectin-based) for early detection of dengue.

2 | DENGUE STRUCTURE

DENV has a relatively smooth surface, of about 40–60 nm dimensionally, and comprises nucleocapsid protein of 25–30 nm coated by bilayer of lipids (Figure 2).[18] DENV is a virus with a positive (+) sense single-stranded RNA genome which is transcribed into proteins immediately.[19,20] DENV subtypes share roughly 65% of the entire amino acid sequences.[21] The whole genome is 11 kb in length, and they encode seven nonstructural proteins and three structural, respectively. Envelope, capsid, precursor membrane, and membrane are structural proteins, whereas NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 are nonstructural proteins.[22,23] DENV also contains two untranslated 50 and 30 terminal regions in the genome.[24,25] The virus contains three domains that communicate with the host cell most of the time. The envelope/E protein has 4 domains and 495 amino acids, the bulk of which interact with the host cell.[26]

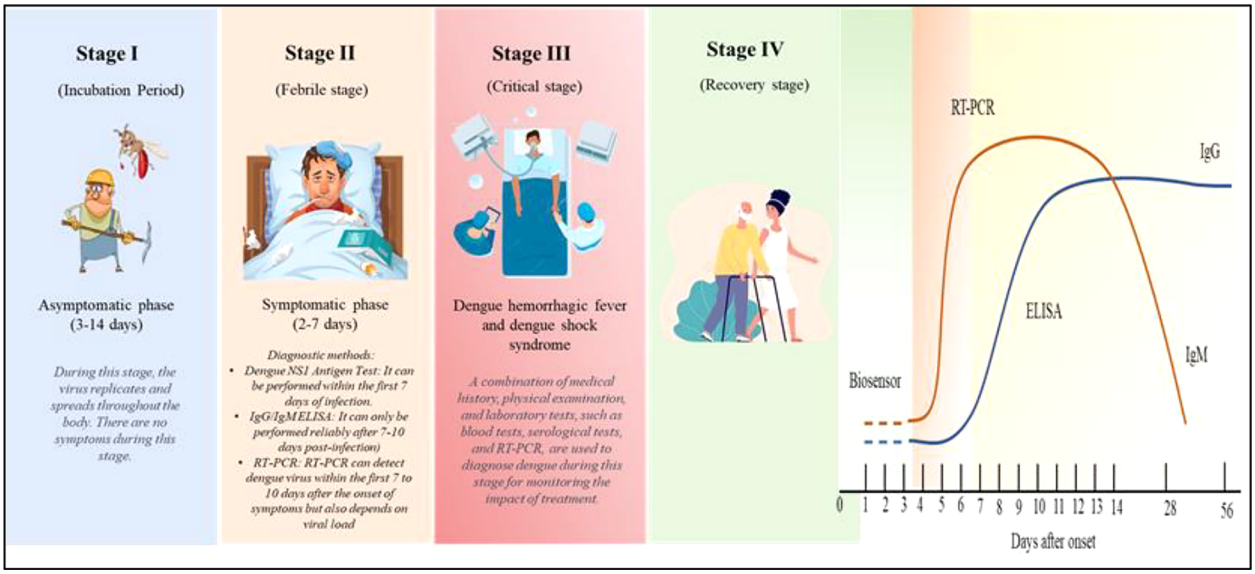

FIGURE 1 Phases of dengue infection and diagnostic approaches for monitoring treatment outcomes.

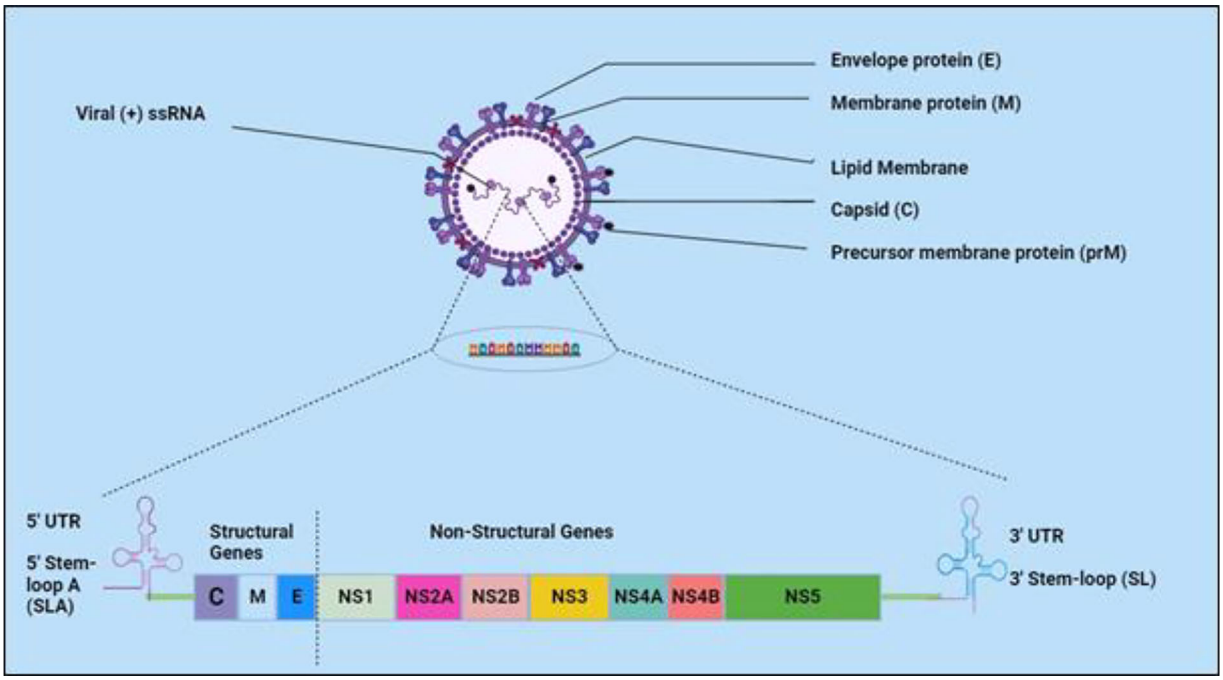

FIGURE 2 Structure of dengue virus.

3 | METHODS FOR DETECTION OF DENGUE VIRUS

For the diagnosis and understanding of the progression of DENV infections, the detections of IgM and IgG antibodies are valuable indicators. IgM antibodies are detectable 4–5 days postinfection and are detectable for approximately 12 weeks. This makes IgM useful in the detection of acute infection as their existence indicates an ongoing infection. In contrast, IgG antibodies are presented as a secondary response to preformed antigens during the primary infection and remain in the body for a longer period of time. IgG indicates an immune specificity to particular DENV serotypes and past infection. In cases, where both IgM and IgG antibodies are present during DENV diagnosis, the distinction between acute condition and past infection is based on the IgM:IgG ratio.[27] The higher the IgM:IgG ratio confirms the primary infections.

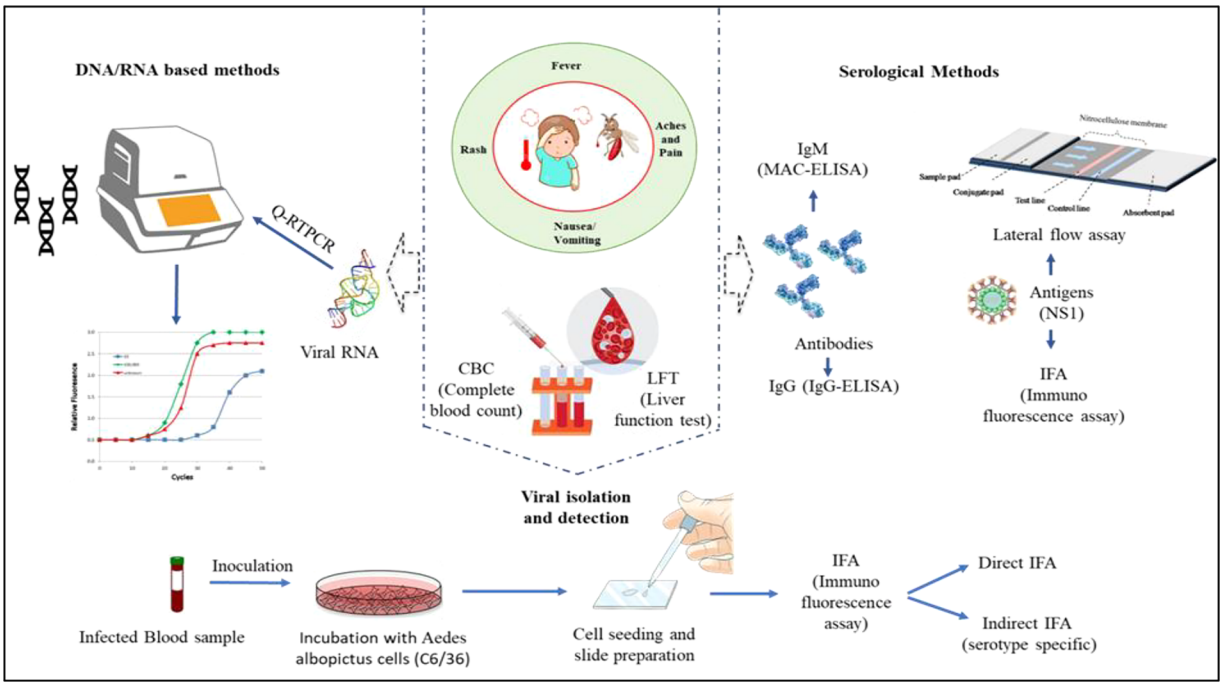

FIGURE 3 Schematic illustration of conventional methods for detecting dengue infection using various approaches.

Other diagnostic methods, such as the NS1 antigen test, can be performed within the first 7 days of infection. The detection of DENV is a critical aspect in the management of dengue infection. More advanced methods of detection, such as RT-PCR, can detect the genetic material of the DENV within the first 7–10 days after the onset of symptoms and are increasingly being utilized for the diagnosis of dengue. The accuracy of RT-PCR is dependent on the viral load. Appropriate detection of DENV is crucial for early identifications and prompts the initiation of treatment, which can help prevent serious complications and reduce the risk of mortality. However, the introduction of emerging techniques such as the CRISPR/Cas system and their integration with biosensing platforms has resulted in advances in diagnosis. The development of new and advanced diagnostic methods continues to be an important area of research in the management of dengue infection (Figure 3).

4 | CONVENTIONAL METHODS

4.1 | Serological tests

In the detection of dengue infections, serological testing assays are more extensively employed because of their affordability and simple handling. These assays enable the identification of IgM and neutralizing antibodies in serum and cerebrospinal fluid specimen. Whole blood and plasma samples, however, are occasionally used as test subjects. The IgG antibody might be used as a dengue detection marker. Different serological-based tests for dengue detection are listed in the following.

4.1.1 | IgM-based tests

In response to antigen exposure, B-lymphocytes cells and T-lymphocyte cells produce Ig proteins such as Ig (IgG, IgM, IgA, IgE, and IgD).[28] Five days following the early start of an infection, IgM antibodies are created and can last up to 3 months. Taking patient samples prior 5 days negative window period is the major problem with dengue antibody detection technology. According to Armed Forces Research Institute of Medical Sciences, the IgM antibody response is greater in first-time dengue infections, but the IgG antibody response is higher to identify IgM of dengue.[29] Normally, antihuman IgM antibodies on solid surface are used to catch the dengue IgM from patient serum. Recombinant dengue-derived antigen and DENV are used to form the sandwich type immunoassay.[27] FDA (the US Food and Drug Administration)[30] is the one which confirmed initial test named DENV detects IgM Capture ELISA by InBios International, Inc. It uses a 96-well plate to capture human IgM antibodies on to DENV recombinant antigens, allowing for qualitative detection.[14] To confirm the +ve result, a plaque reduction neutralization test (PRNT) result is used.[31] Five clinical investigations in distinct locations have been carried out by FDA to verify the usefulness of the InBios test. The initial

polyclinic survey indicated that for 2–3 days are of start fever, whereas 4–5 days are of onset fever, a favorable outcome was only 28.7% and 40.3%.[18] However, after 6–7 days, the proportion of positive results grew to 75.9%, and after 8–10 days, it increased to 88.7%. The cross-reactivity of the tests was investigated in another investigation. Cross-reactivity was only seen in West Nile virus.[32] This test had a 96% sensitivity and 40% specificity.[33]

4.1.2 | IgG-based tests

Past and present infections can be determined using IgG-based tests. IgG antibodies are formed after IgM antibodies and can stay significantly longer, possibly for the rest of one's life.[34] After a recent infection, IgG antibodies may increase up to fourfold.[35] Common identifications (Seoul, South Korea) and PanBiotic (now Alere Inc.) have both marketed IgG-based ELISA assays.[18] Conventional IgG antibody-based ELISA diagnostics has 81.2% and 39.8% of sensitivity and specificity respectively. Contrarily, PanBío demonstrated a sensitivity of 63.5% and a specificity of 95.3%. Companies like Neuroimmune, Abcam, and InBios provide IgG ELISA assays.[36] Although IgG testing is important to some examples, IgM and NS1 ELISA are superior for severe infections. IgG-based tests are challenging to use to detect early infection because of cross-reactivity with other flavivirus IgG antibodies.[37]

4.1.3 | IgM/IgG ratio tests

To distinguish between first-time and recurring infections, IgM/IgG ratio tests are widely used.[38] In both IgM and IgG ELISA testing, the optical density (OD) is assessed. Primary infection is indicated by a ratio of more than 1.32, whereas secondary infection is indicated by a ratio of less than 1.32.[39] In order to assess the infection's fate, the OD ratio threshold value is frequently regulated in specific laboratories. The optimal cut-off ratio of 1.1 is determined by a laboratory in north India.[18] The infection type may be determined using both IgM and IgG. Threshold ratio will differ according to IgM and IgG tests conducted.

4.1.4 | Hemagglutination inhibition (HI) tests

In order to identify both early and late DENV infections, doctors frequently use the hemagglutination inhibition (HI) test,[40] despite its inability to detect early infection. In the presence of viral antigen, RBCs or an emaciated human O RBCs agglutinate. This test measures the level of inhibition and agglutination.[41] Although first-level infections produce a low number of antibodies, subsequent infections produce high antibody titers, frequently surpassing 1:1280. When the result is less than 1:1280, a primary infection is usually assumed.[42] A study employed IgG ELISA and HI to investigate whether it could discriminate among acute and secondary infections.[43] The sample OD was divided by the use of the calibrator OD in the IgG ELISA. Primary infection was defined as any value below 1, whereas secondary infection was defined as any value over 1.[44] A study shows hem agglutination inhibition and IgG identify primary infection in 16/16 samples. In the event of secondary infections, however, HI was found to be inferior to the test based on IgG, 23 of 73 secondary infections were recognized by the hem agglutination inhibition test, but 72 of 73 samples were identified by the IgG ELISA test.[45] IgG ELISA testing is less time-consuming and more accurate than HI testing. HI also has failed in distinguishing different flaviviruses.[18,46] However, HI tests are less time-consuming than PRNT as they do not require viral culture.[47]

4.1.5 | Plaque reduction neutralization test (PRNT)

By identifying precise neutralizing antibodies, this test enables one to identify the precise point of infection in those who have elevated levels of the immune globulin M. In 1967, Russell and Nisalak[47] created the PRNT test for the first time. The World Health Organization considers PRNT to be the gold standard method for assessing vaccine immunogenicity.[48] When serological information or case confirmation is necessary, the PRNT test is commonly used. Typically, it is performed either in microtiter plate or in petri plate.[46] The virus can be neutralized by a specific antibody. Plaques cannot develop in neutralized viruses.[42] To start, cells are coated in semisolid medium and put in a test tube to prevent the progeny of virus from spreading. After being serially diluted, the serum sample is combined with a set quantity of viruses.[49] Plaques will form in the coming days and can be counted as they die, allowing plaques to be monitored. After then, the plaques are compared to see how much overall viral infectivity decreases as a function of virus concentration.[18] At Centers for Disease Control and Prevention either (CDC) or a CDC-approved facility, they can perform PRNT. However, there is not even a single globally accepted PRNT test standard.[50] Comparing findings against PRNT without a specified standard can be time-consuming and can affect how results are interpreted.[31] Despite its cross-reactivity with other DENV serotypes, PRNT is still employed to diagnose asymptomatic DENV infections.[51]

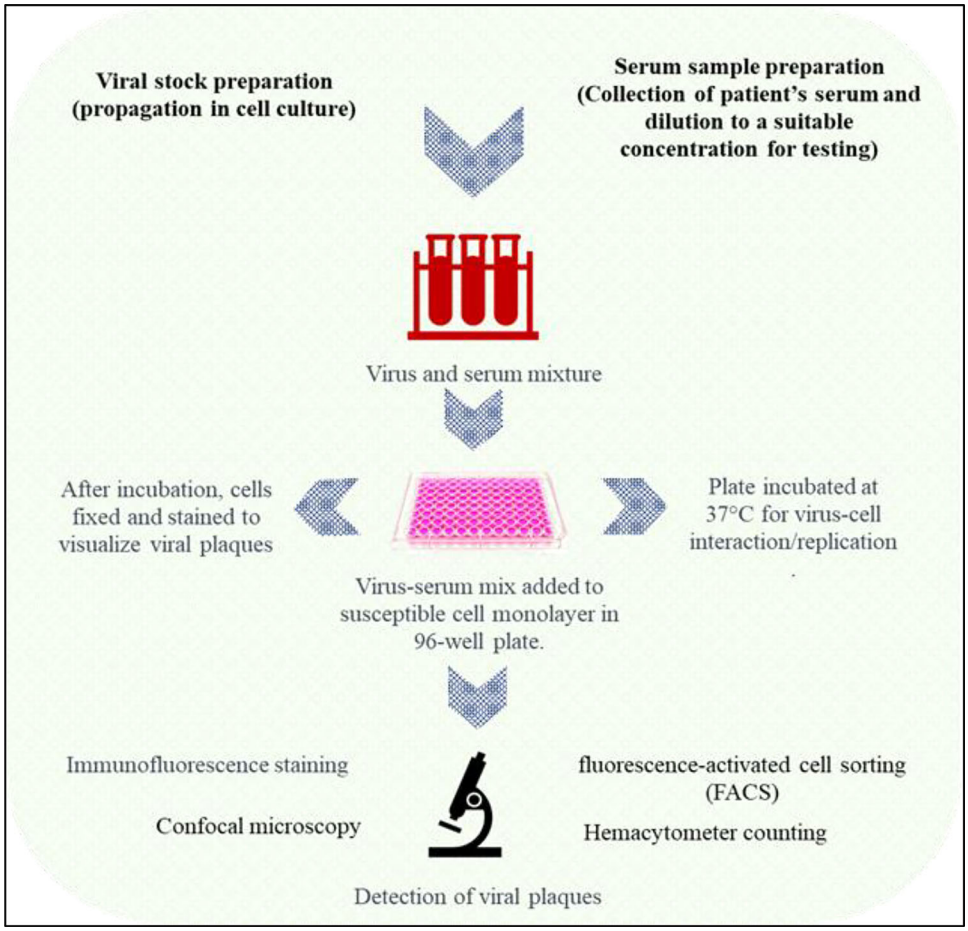

FIGURE 4 Graphic illustration of steps involved in plaque reduction neutralization test (PRNT).

This test has the disadvantage of being labor-intensive and time-consuming. Figure 4 gives a full illustration of PRNT method.

4.1.6 | NS1-based tests

DENV replication in the host cell requires the antigen NS1. Infected individuals produce and release the antigen into the bloodstream that makes it a promising biomarker for early detection of flavivirus infection.[31,52] Because NS1 lasts longer in the blood than viremia, NS1 assays are particularly effective in clinical settings for detecting the viruses' acute phase.[53] In laboratory-based testing, antigen-capture ELISAs are used. However, rapid detection is performed using quick tests based on the lateral flow of assays.[54] In the first week of infection, NS1-based assays produce similar results to molecular tests, according to the CDC.[42] In the United States, DENV detect NS1 ELISA is the only FDA-approved NS1 test that delivers qualitative findings.[55,56] There are now seven commercially accessible tests, four of which are rapid tests.[57] Rapid testing can be done in resource-strapped situations where adequate healthcare facilities are lacking (usually within 30 min). Correct NS1 certifies a DENV infection; at the same time, incorrect outcomes do not get rid of infection possibility. IgM-based test is then performed if incorrect outcome occurs.[58] After 7 days, SN1 is not recommended, which is its major limitations.

4.2 | Molecular detection test

Molecular tests like nucleic acid tests (NATs) are carried out in streamline laboratory requiring high-tech equipment and highly trained personnel. NATs are more accurate and sensitive at identifying and quantifying viral RNA/DNA in the severe stage. Five days after the first symptoms appear, the viral genome can be found. A number of assays enlisted in the following allow quantitative, semiquantitative, or qualitative detection of viral nucleic acids.

4.2.1 | Polymerase chain reaction (PCR)

PCR is the most often used DENV NAT, and it is also regarded as the gold standard for identifying DENVs in

the early stage of illness because of its higher sensitivity.[11] RT-PCR is performed, in the isolation of viral RNA from a number of sources, like plasma, blood, urine, and serum. After that, complementary DNA is formed from viral RNA and then is amplified, and the fluorescence of those PCR products after amplification is analyzed to reveal +ve with −ve outcomes.[59] Almost all RT-PCR-based technologies point and determine each and every serotype. Currently, a multiplexed RT-PCR test, for identifying serotypes in blood samples, was developed.[60] The assay was found to be effective against all DENV serotypes and could detect 100 viral copies per milliliter. On the other hand, a single-step RT-PCR test was devised using primers to differentiate DENV from Zika virus, yellow fever virus, and chikungunya virus.[61] The test was found to be exceptionally sensitive, without cross-reactivity. Amplification procedure was therefore automated using an insulated isothermal PCR assay for traditional PCR that requires trained personnel and lab resources.[40] The FDA has approved two NAT assays as CDC DENV-1–4 real-time RT-PCR multiplex test, and the other one is triplex real-time RT-PCR assay.[62] The former assay is used whenever the DENV is the main source of illness. This test distinguishes between dengue serotypes. The triplex rRT-PCR reaction methods are used if DENV, chikungunya, and Zika are present.[63] This permits simultaneous testing of all three viruses. FDA-conducted research to show the effectiveness of CDC DENV RT-PCR multiplex assay having a limit of detection of 1×10^3 pfu mL^{-1} was observed in serum and plasma.[33] A prospective and retrospective investigation was done by the FDA. In perspective trial, there was 97.2% positive occurrence and 100% negative occurrence. In retrospective investigation, FDA identified RNA in 98.04% of samples. Research also compared the complement-dependent cytotoxicity test (CD) to a lab-built assay. Comparatively, the laboratory assay's sensitivity was 97.4%, whereas the complement-dependent cytotoxicity assays were 87.1%. The DENV, ZIKV, and chikungunya viruses can all be distinguished by the triplex.[7] On the other hand, it cannot differentiate between serotypes. Blood donors are not permitted to use the trioplex; only symptomatic patients are permitted. The test indicates that urine is not a source of dengue, but serum, cerebrospinal fluid, and blood are. In this complex, the limit of detection of DENV varies between 6 and 15 copies/reaction.[64] There was no cross-reactivity with other flaviviruses, according to the test.[65]

4.2.2 | Isothermal amplification-based assays

Isothermal multiplication of genomic dengue viral RNA is another sort of molecular diagnostics, in which the multiplication procedures only need single temperature. Access to lab-based PCR testing, for example, may be difficult in distant places. Isothermal amplification-based tests do not need a thermocycler, so the price and the complication in comparison to PCR can be mitigated. So far, US Centers for Disease Control and Prevention has not authorized any isothermal DENV detection products. However, approaches like RT-recombinase polymerase amplification (RT-RPA), nucleic acid sequence-based amplification (NASBA), and RT loop-mediated isothermal application (RT-LAMP) use the isothermal amplification strategy. The RT-LAMP test was invented by Notomi and consists of six primers, including two loop primers, two inner primers, and two outer primers, that reorganize eight different target areas.[66,67] This technique was created as a potential pathogen detection strategy, amplifying the viral target at a constant temperature of 60–65°C using simply a water bath or a basic heating block.[68] RT-LAMP typically starts by transcribing the target to DNA, prior to creating a loop structure that copies the target, Both UV light and the human eye can perceive the enlarged target.[69] A study was conducted a study to show the value of RT-LAMP.[70] They created the RT-LAMP test, which had success rates of 100% and 98.9% for detecting clinical DENV strains and infected individuals, respectively. The RT-PCR in their investigation exhibited 93% and 84.2% sensitivity for clinical strains and individuals who were infected, respectively. The RT-LAMP did not produce any false positives. A single-tube reaction approach using RT-LAMP primers that targets the *CprM* gene of all DENV serotypes in 30 min[71] was developed. DENV LAMP was used to amplify RNA sequenced using a portable MinION sequencer in a recent work.[72] The advantages of RT-LAMP are its speed, low cost, isothermal nature, sensitivity, and specificity. In multiplexing and viral quantification applications, however, PCR outperforms loop-mediated isothermal amplification-based techniques.[73]

A LAMP-based test often yields qualitative (Yes/No) answers with no quantitative data. Another extensively used isothermal amplification technique is NASBA. The fact that this test targets the RNA in DENV samples in a single isothermal step gives it an advantage.[74,75] Clinical blood or plasma samples are processed via silica to extract RNA, which is then amplified at 41°C without the need of a thermocycler.[76] The amplification can be finished in 30 min, and the results can be diagnosed by electrochemiluminescence.[76] Recently, a number of NASBA-based DENV detection assays were created.[53] Yrad et al. revealed the DENV-1 RNA detection platform using gold nanoparticles (AuNps).[77] NASBA amplifies DENV-1 RNA. The development of a sandwich combination between the DENV capture probe and the AuNps probe came next. This compound was visually recognized in

pooled human sera with a low limit of detection (LOD) of 1.2×10^4 pfu mL^{-1} using a lateral flow biosensor. NASBA increases the sensitivity of the biosensor while being easy to use and inexpensive. However, careful treatments of viral targets and sample preprocessing are needed.[53,78]

The RPA test[79] is another cutting-edge isothermal amplification method for detecting infections. At a constant temperature of 37–42°C, RPA can identify 1–10 DNA copies of target per reaction in 20 min.[80,81] Teoh et al. introduced an RPA-based DENV diagnostic method that targets highly conserved 30-untranslated region (UTR regions).[70] This assay yielded data in less than 20 min and had a limit of detection of each reaction produces 10 copies of DENV RNA. In order to enable sensitive DENV detection, a point-of-need mobile RPA device was designed and put into use in Thailand and Senegal.[82] By concentrating on DENV-1–3 and DENV-4's 30-UTR regions, the team was able to capture all serotypes. RT-RPA-based assay[83] was created, using lateral flow dipsticks to detect DENV-1 at concentrations ranging from 1 to 106 copies L^{-1}. Taking into account all of the prior, it is obvious that this platform needs economic infrastructure given the RPA-based tests and may be used to detect DENV with excellent accuracy in resource-constrained settings.[84]

4.3 | Electrochemical-based biosensor for detection of dengue

Biosensors are very precise and conscious platform that can detect even a very little quantity of analytes, making it possible to make an early diagnosis that is crucial to limiting the spread of disease outbreaks. It is made up of a transducer with a biological recognition component and an electrical component that amplifies signals. The response is evaluated in terms of current, impedance, and potential changes in electrochemical biosensors. For the detection of the DENV, many electrochemical biosensors have been developed recently and are detailed in the following.

4.3.1 | Nucleic acid-based biosensor

In dengue biosensors, nucleic acid fragments are typically used as biorecognition elements. It works by looking for complimentary bases that match to the analyte of interest with immobilized nucleic acid sequence.[85] A recent achievement in genosensor creation using nanotechnology provided a new channel for monitoring the analyte. A substance that can be measured is called an analyte. Genosensor is a gene or DNA-based biosensor that recognizes molecules using DNA probes on the sensor surface and specifies the precise attachment affinity between them. The most prevalent interactions are among protein–ligand molecules, DNA–RNA, or DNA–DNA. Singhal et al. demonstrated a genosensor based on a ZnO/platinum–palladium modified ITO glass substrate with probing DNA common to all four dengue serotypes immobilized on the electrode surface for the detection of the DENV consensus DNA sequence with methylene blue (MB) as redox indicator.[86] The electrochemical response was examined by using cyclic voltammetry (CV) and differential pulse voltammetry (DPV). The platform revealed an LOD of 4.3 μM. Similarly, a molecular gate control-based biosensor was developed for dengue identification.[87] Here, nanolithography was used to design silicon nanowire, and the surface was stimulated by three-phase procedures; like hybridization, DNA immobilization, and surface modification. All those steps behave like a molecular channel to create the electric identification for 27-mers base targets of dengue DNA oligomer. This oligomer-based DNA sensor illustrated an LOD of 2 fM with the responsiveness of 45 μAM^1. Graphene is being employed to raise responsiveness, low LOD, and persistent steadiness in a DNA sensing platform during the last two decades, and it has become a prominent material in electrochemical biosensors. A graphite-based DNA biosensor was developed to identify DENV-3 serotype.[88] The probe DNA with a 22-mer conserved sequence was chosen due to its recognition of the envelope (E gene, which is in charge of attaching and fusing with the host cell membrane). A pencil-graphite electrode was used to immobilize the probe. DPV was used to analyze the electrochemical response between DENV-3 DNA probe and the DENV-3 complementary sequence. The LOD was observed to be 3.09 nM.

Because of their features like easy synthesis, chemical steadiness, high surface area, and detection of biomolecules via interactivity to aggressive molecules, nanoporous anodized alumina was widely used in biosensor, for example, alumina and platinum wire electrodes nanoporous whose 5′ tagged DNA probes are used in electrochemical identification of DENV. A single-stranded 31-mer complementary sequence of DENV-1 and DENV-3 was selected as the target analyte. The suggested biosensor has an ultrasensitive LOD of 9.55×10^{12} M.[89] A desegregated layer sensing policy built on an anodic aluminum oxide layer, and the sequence of DNA probe also was used in the identification of DENV DNA. Detection of changes inside the nanopores on DNA binding was performed by the help of electrochemical impedance spectroscopy; in which RP (pore resistance) directly raises in varying concentration of the DNA in the range 1×10^{12}–1×10^{-6} M with LOD of 2.7×10^{-12} M of 31-mer complementary analyte. The complementary sequences from target sequences with 21 base mismatch and single base mismatch were

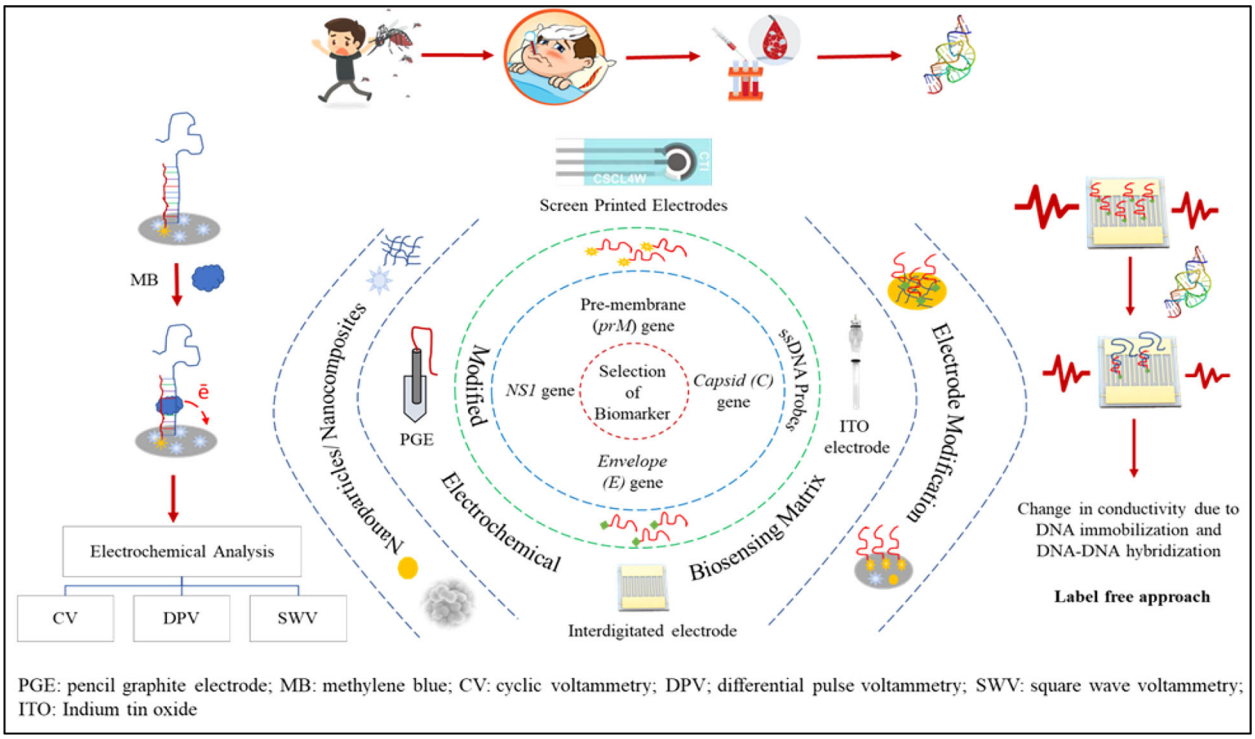

FIGURE 5 Schematic representation of advanced DNA sensing techniques for comprehensive detection of dengue virus.

chosen separately by this biosensor.[90] Interdigitated electrodes have lately gained popularity as a capacitive structure for sensing as they are more effective in achieving dielectric properties. Photolithography is used to fabricate electrode surfaces.

The interdigitated electrodes detect the electric impulses produced by sensing materials. A desegregated biosensor for DENV-2 DNA identification was constructed.[91] Cu_2CdSnS_4 quaternary alloy nanoparticles were synthesized and placed on an oxygen-etched silicon substrate (O_2/Si).[91] Here, the quaternary alloy works as a platform for the immobilization of DENV-specific DNA probes. The developed biosensor identified ssDNA concentration ranging from 100 fM to 10 nM using amperometric analysis, having LOD of 17 nM and sensitivity of 24.2 μA nM^{-1} cm^{-2}. Nanomaterial-assisted electrochemical identification of DNA hybridization has an unusual effect in medical areas.[92] For instance, a very LOD 120 × 10^{-21} M with linear identification varies between 1 nM and 1 μM was revealed by the zetamolar identification of dengue consensus primer by the electrochemical platform using electrospun semiconducting manganese(III) oxide nanofibers for DNA hybridization identification.[92] Figure 5 shows that the advanced DNA sensing techniques for the comprehensive detection of DENV include sample collection, extraction of virus RNA, fabrication of biosensing platform, and detection through techniques like amperometry, followed by the analysis of results.

4.3.2 | Immuno-based dengue sensor

B-lymphocytes and plasma cells, two different subtypes of blood cells, produce serum proteins known as antibodies. It is created in contrast to immunogen, which is an antigen that causes an immunological reaction. In electrochemical immunosensors, antigen or antibody serves as biorecognition element in conjugation with electrochemical transducers. To date, various immunoassay-based electrochemical methods have been devised because of their excellent specificity, affinity, and sensitivity.[93] In most of the immunosensors, biotin–streptavidin linkages[94] or conductive polymers by means of covalent bonding[95] are the most common immobilization methods. Recently, a DENV biosensor using Ig of dengue, DENV-2 (NS1) glycoprotein, was reported.[16] CNT was used to create the biosensor electrode, whereas polypyrrole and *N*-hydroxysuccinimide 11-(pyrrol-1-yl) film were used to immobilize the antibodies (Figure 6).

A good fullness in a huge concentration vary (10^{-13}–10^{-5} g mL^{-1}) was revealed by both and EIS analysis. As a various method, 4-mercaptobenzoic acid (MBA)-modified nanoparticles were used on self-assembled cysteine monolayers with DENV Ig as a sensing platform.[96] Anti-DENV antibodies were immobilized by forming covalent bond on amino group from amino acids residue and carboxylic group of the MBA. The CV study certified a potential to identify four dengue serotypes DENV-1–4,

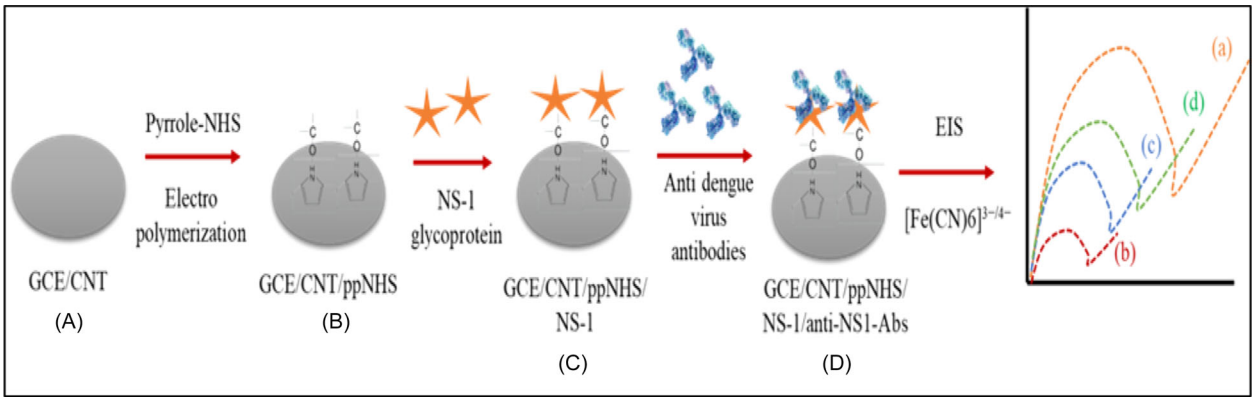

FIGURE 6 An impedimetric biosensor for the detection of anti-dengue virus antibodies in patient serum samples using a label-free approach.

respectively. Meanwhile, the performance of the biosensor was monitored via the exchange in charge transfer resistance (ΔRCT). The outcomes showed a better connection degree and gave good interactivity between antigen and antibody for all DENV immunosensors. Correspondingly, the linear dependence of randomized controlled trial (RCT) versus virus concentrations varied between 1 and 2×10^3 pfu mL^{-1} DENV with LOD of 0.12 pfu mL^{-1} was reported from the polymer matrix composites/graphene oxide immunosensor for all DENV serotypes.[97] In other work, anti-NS1 was immobilized in a mixed self-assembled monolayer consisting of 11-mercaptoundecanoic acid for anti-NS1 attachment and 6-mercaptohexanol as a spacer from which an impedimetric label-free immunosensor based on anti-NS1 modified gold electrode was designed for the identification of viremia in dengue diagnosis. A label-free electrochemical dengue sensor with the dual maker for rapid sensitive quantification of NS1 and IgG was developed. They used a self-assembled single layer including PEG moieties and a tethered redox thiol, and both markers are identifiable around polyclinical relevant stages in seconds without any damage of systemic standard like linearity, sensitivity, and variance.

4.3.3 | Lectin-based dengue biosensor

Viruses, bacteria, fungi, animals, and plants all include lectins, which are glycan-recognizing proteins.[98] Because lectins are natural glycan interaction partners, it is crucial to separate glycoproteins from non-glycoproteins in glycan assays.[99] It belongs to a vast family of proteins with complex specificities that allow them to recognize different monosaccharides within a glycan chain, and distinct glycan branching or saccharide monomer bonds.[100] Lectins have been employed to analyze and detect glycoproteins, P-glycoprotein, carcinoembryonic antigen, α-fetoprotein, malignant cells, and viruses due to their properties.[101] Lectins have been employed in several biosensors in recent years, including glucose sensors,[102] bacterial sensors,[103] viral sensors,[104] and cytosensors.[105] Concanavalin A (Con A) is the most studied lectins (*Canavalia ensiformis*) among various lection types that are usually isolated from seeds of jack bean. Polyvinyl butyral was used to immobilize Con A lectin on the gold electrode of a DENV biosensor, and CV and EIS were used to analyze the sensing response using 10 mM$[Fe(CN)_6]^{3-/4-}$ as a redox probe. The sensor response for various sera from dengue fever patients who had contracted DHF was distinguished using RCT variation. Additionally, all different sera samples responded well to the examination of 3D impedance spectra.[106] A biosystem based on Con A lectin and lipid membranes, on the other hand, was created to identify glycoproteins in the serum of DENV-1, DENV-2, and DENV-3 patients (Figure 7). This biosystem revealed the redox probe reactions with a huge straight result to various concentration sera of DENV-1, DENV-2, and DENV-3, respectively. In all these three serotypes, glycoproteins present in the DENV-3 serotype showed a higher impedimetric response was observed.[107]

Another kind of lectin identified from cratyliamollis seeds (family: Leguminosae) is known as Cramoll. By evaluating the interactivity among fetuin and Cramoll lectin, a biosensor device was designed for detecting glycoprotein[108] in the serum of people infected with dengue serotypes DENV-1, DENV-2, and DENV-3. A polyvinyl butyral occlusive layer, Cramoll lectin was immobilized on a gold electrode coated with Fe_3O_4 nanoparticles and a huge straight result to various concentration sera of dengue serotypes with a great outcome to glycoproteins present in DENV-2 serotype was revealed from Fe_3O_4-Cramoll-PVB biosystem. Avelino et al.[109] suggested a biosensor that immobilized Cramoll on gold nanoparticles/polyaniline (AuNps–PANI) electrode for the

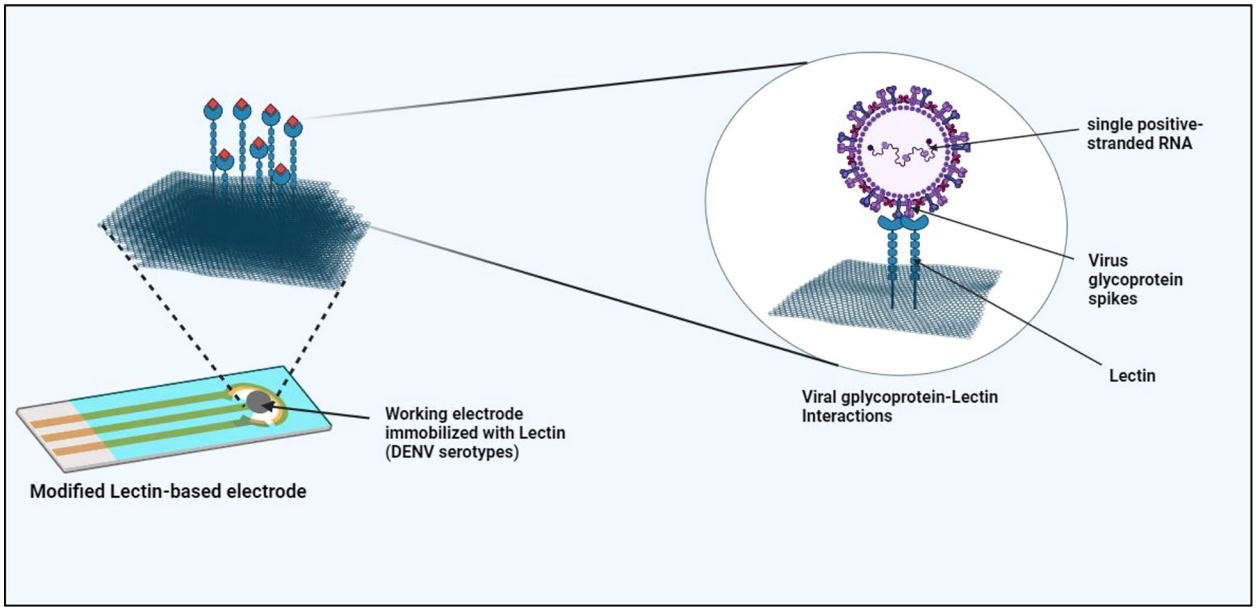

FIGURE 7 Biosensor based on lectin and lipid membranes for detection of serum glycoproteins.

detection of dengue serotypes DENV-1, DENV-2, and DENV-3.[109] The systemic production of the interconnection among AuNps–PANI hybrid composites and Cramoll was evaluated using the impedimetric sensor. Similar research was conducted by Andrad[110] using BmoLL, a different kind of lectin extracted from Bauhinia monandra. BmoLL was immobilized on a hybrid composite of AuNps and polyaniline. The negatively charged BmoLL was electrostatically adsorbed to the positively charged nanocomposite-modified surface after that the hybrid composite was chemically coated on the gold electrode surface. Three DENV serotypes mainly DENV-2 with a high degree of specificity, reproducibility, and selectivity were able to be identified by the AuNPs–PANI–BmoLL. Thus, the survey about naturally occurring lectins as biorecognition element in DENV biosensors is important to assign several figures of glycoproteins in the sera infected by DENV.

4.3.4 | State-of-the-art CRISPR/Cas biosensor

CRISPR-based detection of dengue is a powerful and sensitive method for detecting DENV in a sample. This approach uses the specificity of the CRISPR-Cas' system to target and detect the presence of DENV genetic material in a sample. This method has been shown to have high accuracy and sensitivity and can detect DENV in both blood and saliva samples. In addition, the CRISPR-based approach is relatively simple and cost-effective, making it a valuable tool for the rapid detection of dengue in resource-limited settings.

To use the CRISPR/Cas' system for diagnostics, it must be combined with other measurement techniques such as DNA sequencing, fluorescence, immunochromatography, and electrochemistry. Most CRISPR/Cas-based assays require a pre-amplification step for picomolar sensitivity,[111] but this increases the length and turn-around time of the assay. Electrochemical CRISPR sensors do not require pre-amplification and have high sensitivity and LODs in the femtomolar range. These electrochemical platforms are fast, sensitive, and have a low LOD.[112]

In the development of electrochemical biosensors for detecting dengue, various CRISPR systems, including Cas13 and Cpf1, have been used (Figure 8). Cpf1 offers an advantage over Cas13 as it does not need PAM sequences for target DNA recognition and cleavage, yet it retains the capability of performing trans-cleavage activity.[113] In a recent study, researchers have designed an electrochemical biosensor based on the CRISPR reaction that can multiply the signal by fusing MB and AuNPs without the need for a target nucleotide amplification step.[114] The target nucleic acid activates the CRISPR/Cpf1 complex, which leads to a degradation of the immobilized MB-AuNPs on the working electrode via SH-ssDNA-biotin. This results in a decrease in the electrochemical signal from the MB-AuNPs. The square wave voltammetry was used to confirm the highly sensitive target detection, which is more delicate and dependable approach. The MB-AuNPs serve as role in that the signal can easily be favorite due to the large amount of MB on the AuNPs and the connection to the SH-ssDNA-biotin. The AuNP-assisted sensing system demonstrated its potential as a highly sensitive and rapid detection strategy by generating an enhanced electrochem-

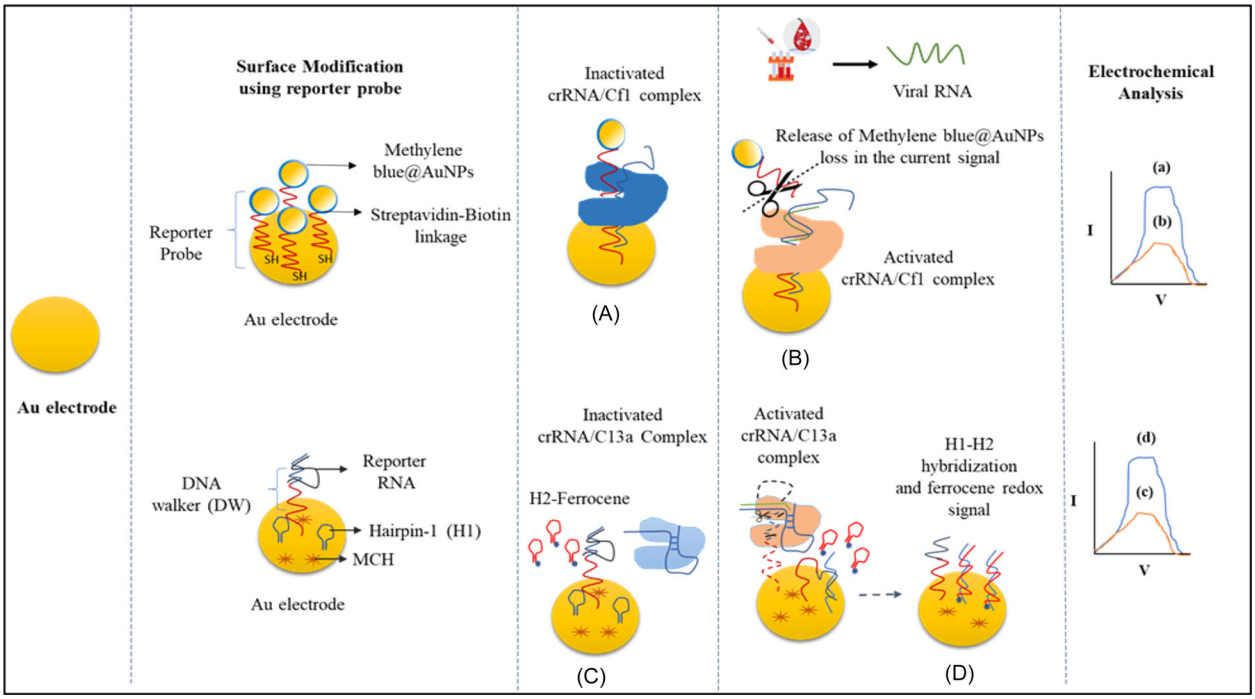

FIGURE 8 Schematic illustration of CRISPR/Cas-based DNA sensor-based approaches developed for early-stage detection of dengue virus (DENV) RNA.

ical signal compared to a single MB molecular probe and measuring low concentrations of DENV-4 RNA as low as 100 fM within 30 min.

In a recent study, the sensitivity of electrochemical sensing was enhanced with the development of an electrochemical biosensor for the identification of the DENV using the CRISPR/Cas13a system.[115] The Cas13a protein, a Class-II, Type VI effector, targets specific RNA sequences and cleaves both the target sequence and nearby nontarget sequences, such as labeled DNA or RNA with a fluorophore or redox dye.[116] This process significantly amplifies the signals in the biosensor, resulting in increased sensitivity and accuracy in the detection of DENV. The application of CRISPR/Cas13a in biosensing technology has the potential to revolutionize the field of diagnostics.

A novel electrochemical biosensing method was designed for the identification of DENV[117]. The approach leverages the specificity and cleavage ability of the CRISPR/Cas13a system and the processivity of a swing arm DNA walker (DW). The method begins with the hybridization of a reporter RNA molecule to the DW, which is then co-immobilized with a large number of hairpin 1 (H1) molecules on a gold electrode surface. In the presence of target DENV-1, the CRISPR/Cas13a system is activated and cleaves the reporter RNA, releasing the DW. This released DW acts as an initiator for a catalytic hairpin assembly process on the electrode surface, involving the opening of immobilized H1 molecules and the hybridization of ferrocene-labeled hairpin 2 (H2-Fc) molecules. This leads to the capture of a large number of H2-Fc on the electrode, resulting in an amplified electrochemical signal that is proportional to the amount of target DENV-1 present in the sample. This CRISPR/DW-based electrochemical biosensing method offers high accuracy, sensitivity, and cost-effectiveness, making it a perfect device for the quick identification of DENV in resource-limited settings. The sensitivity of the CRISPR/DW-based electrochemical biosensing[114,115] method for the detection of DENV was determined to be in the range of 5 fM to 50 nM, with LOD of 0.78 fM. This sensitivity is among the greatest reported in the literature, demonstrating the method's effective role in clinical diagnostic importance. The reported sensitivity and LOD indicate that the method is capable of detecting extremely low levels of the target virus, making it a valuable tool for early and accurate diagnosis of DENV infections. Various electrochemical biosensors employed for dengue detection are enlisted in Table 1.

4.4 | Advantages of electrochemical dengue biosensor

Treatment of the DENV strains is most important to be aware about the developmental conduct of virus as well as infections. Economically available diagnostics include specific soluble DENV antigen, detection of viral RNA,

TABLE 1 Electrochemical biosensors employed for dengue detection.

Biosensing matrix	Detection method	Target analyte	LOD	References
Carbon nanotube-screen printed electrode	Chronoamperometry	Nonstructural-1	12 ng mL^{-1}	118
ssChitosan–carbon fiber electrode	Amperometry	DENV envelope	0.94 ng mL^{-1}	119
Polycyclic aromatic hydrocarbons/multiwalled carbon nanotubes	Amperometry	Nonstructural-1	0.035 μg mL^{-1}	30
Copper cadmium tin sulfate/oxygen etched silicon substrate	Amperometry	Deoxyribose nucleic acid-DENV-2	17 nM	91
Gold/compact disk-trode	Differential pulse voltammetry	Nonstructural-1	0.33 ng mL^{-1}	120
Platinum/nanoporous alumina	Differential pulse voltammetry	DENV-2	1 pfu mL^{-1}	121
Pencil GE	Differential pulse voltammetry	DENV-1-specific-complementary oligonucleotides	0.92 nM	122
Nanoporous alumina/Pt wire	Differential pulse voltammetry	DENV-1-specific-complementary oligonucleotides	9.55×10^{-12} M	123
Zinc oxide/platinum–palladium	Cyclic voltammetry/differential pulse voltammetry	DENV target single-stranded DNA	4.3×10^{-6} M	124
Mn_2O_3	Cyclic voltammetry/differential pulse voltammetry/IMPM	Stranded DNA	120×10^{-21} M	125
Thiophene-screen printed electrode/gold nanoparticles protein A	Cyclic voltammetry	Nonstructural-1	0.015 μg mL^{-1}	118
Pencil graphite electrode	Differential pulse voltammetry	DENV-3 complementary DNA	3.09 nM	126
Glutaraldehyde/cysteine/gold	Potentiometry	Nonstructural-1	0.09 μg mL^{-1}	127
Gold	Impedimetric	Nonstructural-1	30 ng mL^{-1}	128
ITO	Impedimetric	Nonstructural-1	0.035 μg mL^{-1}	129
Nanoporous alumina/platinum	Impedimetric	DENV-2 and 3	0.230 pfu mL^{-1} (DENV-2), 0.710 pfu mL^{-1} (DENV-3)	130
Gold/liposome	Impedimetric/cyclic voltammetry	DENV-1–3	–	131
Gold nanoparticles/polyvinyl butyral	Impedimetric/cyclic voltammetry	Dengue fever and dengue hemorrhagic fever	–	132
Ferric oxide/polyvinyl butyral	Impedimetric/cyclic voltammetry	DENV-1–3	–	133
Gold nanoparticles	Impedimetric	DENV-1,2	–	77
Polyaniline/Cramoll	Cyclic voltammetry	DENV-3	–	109
Gold nanoparticles/polyaniline/BmoLL	Impedimetric/cyclic voltammetry CV	DENV-1–3	–	134
Carbon nanotube/polypyrrole-*N*-hydroxysuccinimide	Impedimetric/cyclic voltammetry	DENV-2	–	135

(Continues)

TABLE 1 (Continued)

Biosensing matrix	Detection method	Target analyte	LOD	References
Cysteine_Mercaptobenzoic acid-gold nanoparticles	Impedimetric/cyclic voltammetry	DENV-1–4	–	136
Graphene oxide	Impedimetric/cyclic voltammetry	DENV-1–4	0.12 pfu mL^{-1}	137
Anodic aluminum oxide	Impedimetric/cyclic voltammetry	DENV complementary single-stranded DNA	2.7×10^{-1} M	138
Silicon dioxide/aminopropyl triethoxy silane-graphene oxide	Impedimetric	DENV DNA and RNA	DENV DNA and RNA	77

Abbreviations: LOD, low limit of detection.

TABLE 2 Merits and demerits of both conventional and biosensor methods for dengue detection.

Method	Merits	Demerits
Viral isolation	• Highly specific • Reliable result • Identifies serotypes	• Expertise, equipment for cell culture, and fluorescence microscopy are required • Incapable of distinguishing between primary and secondary infections • Detectable within the viremia phase only as well as it takes a long time to detect (6–10 days) • Lower sensitivity, expensive, and laborious steps
Genomic detection	• Highly specific and extremely sensitive • Possible to determine the serotype • Results in within 24 h • Reliable outcomes	• Expensive laboratory equipment and expertise are required • Difficult to distinguish between a primary and secondary infection • Potential false result due to cross-contamination • Involves the use of costly and potentially hazardous chemicals • Require acute sample
Antigen detection	• Easy sample preparation and execution • Rapid results (within a few hours) • Confirmed infection • Less expensive than virus isolation or RNA detection	• Lower sensitivity • High cross-reactivity with another antigen/antibody • False-positive/negative results • The antigen is difficult to immobilize on the electrode surface
Antibody detection electrochemical biosensors	• Easy to operate • Confirmed infection • Inexpensive • Rapid results (in a few hours) • Can detect primary and secondary infection	• High cross-reactivity with other flaviviruses and antigen/antibody • IgM levels may be low or undetectable in some secondary infections • Lower sensitivity • A febrile sample is required • Confirmation requires two or more serum samples
Electrochemical biosensors	• Highly sensitive and rapid • Easy to operate • Cost effective • Label-free • Small volumes samples	• Low coping ability for complex clinical samples • Less sensitive in nonspecific binding

and specific dengue Ig. In the early stages of dengue fever (within 5 days of illness), RT-PCR is used to assess DENV viral RNA and serotyping by type-specific multiplex PCR, whereas the presence of DENV infection in blood samples is assessed by anti-dengue IgM. In many cases, the diagnosis for dengue infection is initiated by PCR, serological tests, or culture of the virus. Effective isolation and growth of virus requires serum from a severe patient in which

a sufficient amount of virus has been collected within a few hours before the onset of fever. In addition, these approaches require a biosafety level 3 laboratories with expensive laboratory instruments, chemicals, and specialists, so they are time and labor-intensive. Evaluation by RT-PCR methods causes problems and false positives due to differences in DENV strains. In any instance, the PCR inhibitors such as antibiotics and hemoglobin will provide reduction in responsiveness because of fusion between DNA polymerase and DNA. PCR may only be used to identify DENV in untimely stage of their infections, and it is inadequate after 5–7 days. In antibody detection tests (serological approaches), the antibodies such as IgM, IgG, and NS1 are diagnosed from body fluids or serum. Incorrect response in antibody detection tests; using IgG and IgM showed strong cross-reactivity with antibodies against other flaviviruses co-transmitted as a result of previous infection or vaccination. In contrast, the ELISA test is rapid and inexpensive, although it requires evaluation of paired acute and convalescent phase sera to confirm a positive DENV infection. All the conventional techniques are either expensive, labor-intensive, involve time-consuming sample preparation protocol, and require a sophisticated infrastructure facility. Table 2 summarizes the merits and demerits of both conventional and biosensor methods for dengue detection. To date, electrochemical biosensors are inexpensive, easy to use, require little sample preparation time, and use fully computerized and portable devices.

5 | CONCLUSION AND FUTURE OUTLOOKS

Twenty years ago, biosensing techniques have made significant advancements in the identification of infectious microorganisms, opening up positive implications for future illness diagnosis. This article gives an extensive outline of the electrochemical identification of DENV. In this review, various comprehensive points of view on electrochemical biosensing technology, synthesis, design, and the fundamental assumptions on transduction were demonstrated. Additionally, an attempt has been made to illustrate with examples the various electrochemical biosensing techniques used for DENV diagnosis. Correspondingly, the significance of biorecognition elements in DENV biosensor and various kinds of biologically based matters used in the sensor have been discussed. Even though DENV electrochemical biosensing has made considerable progress, more advancements are still required that could improve the efficacy of the biosensors. Right now, the barrier to biosensing is the lack of elemental understanding of the biorecognition molecule, which is crucial for high-throughput biosensing applications. Simultaneous detection of dengue strains requires little or no cross-reactivity between the ligand and acute biomaterials. Therefore, it takes a lot of work to understand it; how an atomic-sized biosensing agent attaches, how it oscillates when attached to electrodes, how it can be oriented to provide the correct direction for biosensing, how it remains viable and stable under existing conditions, and how it achieves good biosensing interaction between biorecognition particle and point analyte bio particle. Again, important and innovative selection schemes are needed to explain the procedure in electrochemical detections. In addition, the integration of atomic-sized materials into DENV sensors shows an important evaluation of atomic-sized structures in terms of environment-friendliness and naturalness. To date, nano-sized particles with modified proteins, signal aptamers, low-molecular-weight polymers, and so forth are crucial for the development of a coherent biosensor. Finally, innovation in the field of highly selective, lifetime stable, environment-friendly, and valuable DENV detection will be extraordinary important for other commercial usages.

AUTHOR CONTRIBUTIONS

Conceptualize and written the whole manuscript: Shadan Raza and Renu Poria. *Participated in the design of study and improves grammar*: Nkurunziza Florien, Nishant Sharma, and Deepak Kala. *Helped in review and editing*: Anil K. Sharma and Hardeep S. Tuli. *Designed; validated; supervised the whole manuscript*: Shagun Gupta and Ankur Kaushal.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Anil K. Sharma https://orcid.org/0000-0002-9768-1644
Shagun Gupta https://orcid.org/0000-0002-1981-8801

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