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REVIEW ARTICLE

Dengue virus: a review on advances in detection and trends – from conventional methods to novel biosensors

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Abstract
Dengue virus is an important arbovirus infection which transmitted by the *Aedes* female mosquitoes. The attempt to control and early detection of this infection is a global public health issue at present. Because of the clinical importance of its detection, the main focus of this review is on all of the methods that can offer the new diagnosis strategies. The advantages and disadvantages of reported methods have been discussed comprehensively from different aspects like biomarkers type, sensitivity, accuracy, rate of detection, possibility of commercialization, availability, limit of detection, linear range, simplicity, mechanism of detection, and ability of usage for clinical applications. The optical, electrochemical, microfluidic, enzyme linked immunosorbent assay (ELISA), and smartphone-based biosensors are the main approaches which developed for detection of different biomarkers and serotypes of Dengue virus. Future efforts in miniaturization of these methods open the horizons for development of commercial biosensors for early-diagnosis of Dengue virus infection.

Keywords Dengue virus · Biosensor · Biomarker · Serotype · Clinical applications · Immunosensor · Limit of detection

Introduction

Dengue is a single positive-stranded RNA virus which belongs to the family of *Flaviviridae*; genus *Flavivirus* with five identified serotypes. It threatens the human life from different aspects since it can lead to severe illness such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) with more than 100 million infections annually. Dengue fever is very common in tropical and sub-tropical regions, especially in Asia and South America. This virus was transmitted through the bites of infected Aedes female mosquitoes [1]. Infection by this virus led to different kinds of pathogenic symptoms such as febrile, fever, and dangerous life-threatening situation [2]. Therefore, it is not only a great menace to society but also a great concern for medical staff. There is less information about pathognomonic features of Dengue infection from other febrile illnesses. So, the diagnosis of this virus in early stages of disease is very crucial [3]. Nowadays, various traditional methods such as virus isolation in cell culture, serological assays, and molecular techniques have been applied for its detection [4]. However, they are unable to detect it in early stages since they require several days for culture and more equipment for isolation. Furthermore, traditional methods need to special or expensive equipment and are time-consuming [5]. In recent years, bio-scientists have focused on the fabrication of efficient biosensors for detection of Dengue virus with high accuracy, sensitivity, specificity, and simplicity [6]. Generally, the developed biosensors in this area can be divided into optical, electrochemical, electronic, microfluidic, and smart phone based biosensors. The optical biosensors and bioassays involve the colorimetric, surface-enhanced Raman scattering, fluorometric, ELISA and PCR

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based methods. The electrochemical biosensors can be also subdivided to voltammetric, amperometric, impedimetric, and conductometric biosensors. From technology view point, the electronic, microfluidic, smart phone-based biosensors have been considered in the recent years as the advanced strategies for Dengue various serotypes detection [7]. By the application of specific bio-receptors, these assays are reliable and sophisticated enough to screen all serotypes of Dengue from other viruses [8]. The advantages of mentioned methods make it possible to design these biosensors for future clinical applications [9]. On the other hand, these methods could eliminate many of the challenges that were unsolved for many decades. For example, obtaining the high accuracy and rate of detection simultaneously is the stunning and spectacular properties of these methods. From structural overview, the basics of these methods open new horizons in designing portable and lab-on-a-chip biosensors. In this principle, the mechanism of detection plays a key role in the large scale productions of biosensors. Meanwhile, development of the portable and rapid detection systems for detection of Dengue biomarkers can make great impression on its early-detection and treatment. In this review, we focused on the detection methods from different aspects like as biomarkers type, sensitivity, accuracy, the rate of detection, possibility of commercialization, availability, limit of detection, concentration range of detection, simplicity of method, mechanism of detection, and ability of usage for clinical applications.

Optical biosensors and bioassays

Among the wide variety of biosensors, optical biosensors are broadly investigated by researchers [10]. Optical biosensors accumulate information by measuring the photons rather than electrons, as in the case of electrochemical biosensors. In the other words, they are based on the evaluation of absorbance, reflectance or fluorescence emissions from the target or bio-recognition events [11]. According to the employed structure, optical biosensors can be divided into two kinds, labeled or label-free biosensors [12, 13]. The implementation of selectively labeled tracers results labeled-based approaches while the unlabeled or unmodified trace molecules provide label-free methods. The former contain colorimetric, SERS, SPR, and flourimetric approaches but the latter mainly contain the photonic crystal biosensors. Both of the described groups allow the detection of affinity and kinetics of a wide variety of molecular interactions in real samples [14]. These biosensors are appealing since they are accurate and precise in comparison to conventional methods. Numerous label free and labeled biosensors are designed to detect Dengue virus which their characteristic features are briefly discussed in the following [15].

Photonic crystal biosensors

Photonic crystal optical biosensors reveal rapid and sensitive way to diagnose viruses in which the mechanism of signal transduction is based on surface bound matter. In the other words, they use refractive index variation as recognizing transduction signal on a photonic crystal [15, 16]. While being at an early stage, numerous optical label-free biosensors have been designed for detection of viral antigens, and single viruses such as Dengue in a high-throughput and quantitative manner. Since these biosensors are highly sensitive to surface contamination, one of the main challenges in this area is to achieve a high degree of surface cleanliness. To this end, in one study, standard parylene lift-off biopatterning method was employed for immobilization of nucleic acid capture probes via silane and dendrimer linkages onto parallel 1D photonic crystal resonator sensors for design of multiplexed label-free platform. Investigation of surface uniformity and remaining residues by atomic force microscopy (AFM) and scanning electron microscopy (SEM) techniques revealed the removal of 98% of the residues. The residue-free nucleic acid immobilization along with microfluidic functionalization enabled it to detect Dengue virus in multiplexed mode [17]. In another study, the parallelization of the structure of an optical photonic crystal biosensor has been reported by the construction of a waveguide with five side resonators each possessing different cavity spacing. In that design, after immobilization of respective capture probes of four serotypes onto four resonators, the resonant wavelength of each cavity was a red-shifted due to changing in refractive index as a result of binding events. Furthermore, the higher refractive index of the $CaCl_2$ solution was utilized to enable the biosensor in detection of small shifts in the resonances. Therefore, this kind of biosensors outweighs others since they can consist of multiple side resonators on a single waveguide and distinguish multiple analytes in a parallel way [18].

For replacing the bulky spectrometer or optical setup in optical biosensors, in other research, a surface photonic crystal sensing surface along with tunable vertical-cavity surface-emitting laser (VCSEL)-based system were utilized to detect human anti-dengue IgG antibodies. Despite its high sensitivity in compared to ELISA, the results showed that it suffered from false-positive errors and need better surface-blocking protocol to enhance the specificity [19]. According to these facts, the label-free biosensors can eliminate or reduce the complexity of biosensors; thus, facilitating the commercialization process of them.

Colorimetric biosensors

In recent years, the utility of sensor technology for fast and simple detection of wide range of analytes has been increased dramatically. Among them, the colorimetric sensors with a

simple platform, fast response, and acceptable sensitivity and selectivity are one of the most efficient and impressive devices which have been applied for the detection of heavy metal ions, toxic gases, and biomolecules such as protein, DNA and pathogens. In colorimetric sensors, the detection process is accompanied by the changing of the color as a result of specific ligand-target interactions [20, 21], in a solution phase or on a solid support.

As an example of solution phase bioassay, a label-free colorimetric detection technique based on PNA/DNA hybridization was reported by utilization of unmodified gold nanoparticles. In this research, neutral peptide nucleic acid (PNA) was applied as hybridization capture probe. In the absence of targeted dengue DNA, PNA caused the aggregation of unmodified gold nanoparticles (Au NPs). Then, the color of solution was changed from red (color of AuNPs) to purple due to the aggregation process. In contrast, in the presence of dengue DNA, a new complex formed by hybridization of PNA probe and targeted DNA. According to the negative charge of PNA/DNA complex, the Au NPs remained dispersed and did not aggregate. Therefore, the color of solution did not change. In comparison to other methods which have utilized DNA as probe, the utility and handling of PNA is easier and its performance and applicability are more efficient and impressive [21]. Besides solution phase colorimetric detection, point-of-care (PoC) platform based on lateral flow immnunosensor (LFIS) has been also reported for visual onsite detection of Dengue virus. This technology is more popular because of its simplicity, ease-of-use, and high sensitivity. It comprises a nitrocellulose membrane in which capturing reagents immobilized on it at test and control zones. By the introduction of liquid sample, it moves along the membrane via capillary forces and in the present of target, Dengue virus, commonly two red color lines were formed. The commercially available LFISs for DENV diagnosis in current market include PanBio Dengue test [22], Bio-Rad NS1 Ag Strip [23], and In-Bios test [24] for qualitative detection of the DENV NS1 biomarker, and Dengue Duo rapid test-SD [25] for detection of NS1 antigen and DENV IgM/IgG antibodies in blood, serum, or plasma samples. In these devices, gold nanoparticles (AuNPs) serve as color detector reagents. The colorimetric biosensors provide the possibility of detection and quantification of this virus in a simple and sensitive way and the LFAs are currently available for PoC applications.

Surface-enhanced Raman scattering (SERS) biosensors

Over the years, a wide range of spectroscopic methods has been applied for immunosensors, and among them, SERS as a multiplexed readout and highly sensitive optical detection technique has been attracted as a great deal of interest in biological sensing [26], cancer theranostic [27], and molecular imaging [28]. Furthermore, the description and characterization of Raman bands are simple and its supporting fingerprint region is considerable; thus, the comprehensive structural information of analytes can be obtained by the analysis of SERS spectra [26, 29]. In addition, unlike many spectroscopic techniques such as fluorescence, the photobleaching process is not a substantial challenge in SERS method [26, 29]. Therefore, according to these specific features and its highly multiplex detection capability, SERS can be a desirable method. In this respect, the detection of specific oligonucleotide sequences of the Dengue virus (serotype 4) was carried out on the surface of SERS active Ag-Au bimetallic nanowave chip which functionalized by DNA probes. According to the homogenous framework of that bioassay, the measurements of SERS signals was accomplished after each incubation step without any further rinsing process in order to eliminate the excessive and unreacted reagents. Unlike many applications, there was no need to label the targeted single-stranded DNA (ssDNA) for detection. Furthermore, the targeted ssDNA could be detected as low as ~6 attomoles. The utility of that biosensor was simple and its susceptibility to false-positive responses was less. Therefore, it can be conclude that the combination of this bioassay with sample preparation techniques can generate novel technologies for PoC diagnostics in the future [30].

In the same way, Zika and Dengue diseases indicate similar, non-particular, and nonspecific symptoms; however, their outcomes are significantly different. Therefore, the fast and early PoC diagnostics and necessary actions from epidemic outbreaks are required to be done. Lateral flow assays (LFAs) as remarkable solutions for PoC diagnostics, which show high potential for extended applications. Nevertheless, their low sensitivity restricts their capability for detection and early diagnostics of low biomarker levels. According to the high sensitivity of SERS spectroscopy, a research group has reported a new SERS based LFA platform in order to distinguish Zika and Dengue nonstructural protein 1 (NS1) as biomarkers from each other. The SERS-encoded gold nanostars were conjugated to specific antibodies to determine and distinguish Zika and Dengue NS1 biomarkers from each other. In this platform, compared to colorimetric LFAs, SERS method can reduce the detection limits of Zika and dengue NS1 to 15-fold and 7.2-fold, respectively with LOD values down to 0.72 $ng.mL^{-1}$ and 7.67 $ng.mL^{-1}$. As a result, apart from multiplexed detection of Zika and Dengue viral biomarkers, the sensitivity of this bioassay is such that the presence of diseases can be detected in early stages where the biomarker levels is very low [31]. Hence, as a versatile method with simultaneous bioimaging and biosensing abilities, the SERS can be considered as a highly potent approach for early detection of Dengue virus, its biomarkers, and serotypes. Furthermore, its combination with LFAs opens new prospects for PoC applications.

Surface Plasmon resonance (SPR) based biosensors

The SPR biosensor is one of the most advanced and novel optical label-free biosensors for detection of Dengue virus. This method is a powerful way to analyze wide variety of analytes in biotechnology, medical, food safety, and security [32, 33]. For early detection of Dengue virus, multiple immunoassays have been fabricated. These immunoassays reveal cheap and convenient option in comparison to virus isolation and RT-PCR methods. However, they suffer from low sensitivity and specificity which influenced by serotype and geographical variability of isolates [34]. Therefore, there is an urgent need to enhance the sensitivity of these assays by providing reliable and more efficient antibody detection methods. In conventional Kretschmann SPR technique, during the bioconjugation event, the change in refractive index of a gold chip was measured as a function of angle. The minimum SPR angle, known as resonance angle, which not only sensitive to the refractive index of the conjugated analytes on sensor surface but also depends on the quantity of the bio-molecular layer [35]. In one study, the resonance waveguide grating (RWG) and SPR biosensor were developed to diagnose a collection of NS1 mAbs. RWG is a powerful method that screens 40,000 molecular interactions within 8 h. In order to rank antibodies, the RWG method was applied as a preliminary affinity screen; as well as, the observation of wide range of affinities from mM to nM. The researchers found that RWG can be used for screening wide variety of analytes; however, kinetic information is lost. They mentioned that although the utilized SPR method has less output than RWG, it gave accurate kinetics parameters such as k_{ass} and k_{diss} for detecting mAbs [36]. Other researchers employed the 16-mercaptohexadecanoic and carbodiimide chemistry to functionalize and activate the biosensor, then, the Dengue IgM and NS1 in patient samples were examined by Long-range surface plasmon polaritons (LRSPP) method. This assay showed high sensitivity in compared to ELISA [37]. Owning to noble-metal plasmonic layer that covers the sensor, the LSPR method exhibits strong electromagnetic wave propagation which could be extended to millimeters in compared to ~90 μm which observed for the conventional SPR [38]. In other investigation, the PBS/Gly buffer solution was used to distinguish purified dengue NS1 antigen. The assay encompassed three different anti-NS1 monoclonal antibodies and lower ratios in comparison to conventional ELISA. However, it was able to detect Dengue NS1 positive patients in real-time and cost-effective way. Utilizing purified anti-NS1 mAb was the turning point of that assay which solved drawbacks of other methods [39]. In the same way, in another work the Dengue Ag–antibody binding interaction on the sensor surface was directly correlated to target concentration. In this assay, antibodies attach to the antigens which immobilized on the surface of biosensor as probes (Fig. 1). Changing the concentration of the binding medium is correlated with the refractive index changes and follows by SPR quantification. This work reveals a promising approach in clinical diagnostics [40].

In brief, although various SPR biosensors have been designed for virus detection but the regulation of temperature, optics, and the size of this biosensor is a big challenge yet. Therefore, efforts to design cost effective, easy to use, and reliable SPR biosensors are still necessary.

Fluorometric biosensors

Fluorescence-based biosensors for detection of Dengue virus are the most popular kind of biosensor among the wide variety of optical biosensors since they are accurate and sensitive for these applications. Most studies in this area have been devoted to the employment of novel fluorescent tags in various formats. In one study, a combination of novel aptamer/nuclease signal transducer, a fluorescent signaling molecule, and an oligonucleotide linker module, which attaches specifically to target nucleic acid, has been reported. After specific binding of capture and target, fluorescent signal was released and subsequently identified over 20 min. The assay employed active EcoRI enzyme in order to cleave multiple signaling molecules and to release detectable signal. According to its simplicity, this bioassay can be applied in developing countries where the disease is most prevalent [41]. In another research, the specific binding of silver ions to the heterocyclic bases of DNA was utilized to generate silver nanocluster strands as fluorescent readout indicators in detection of Dengue serotypes. By extraction of dengue RNA and its conversion to cDNA, the capture probes were designed to hybridize specifically with it to initiate isothermal amplification; thereafter, a nicking enzyme was employed to promote the release of the Ag nanocrystals forming strands. A sensitive and specific bioassay without any cross reactivity for all serotypes was attained with a LOD value down to 100 nM [42]. In another study, an in–vitro method utilizing quantum dots (QDs) and duplex-specific nuclease (DSN) was introduced. Firstly, the QD-capped DNA capture probe (QD–CP) magnetic beads were prepared then RNA-DNA hetero duplexes were made by attaching DNA CPs and Dengue virus RNA strands together. Then, target RNA stands released by DSN and divided the CPs in the hetero duplexes and the free target RNA strands were attached to the QD–CPs. At the end, magnetic beads separated from the mixture, and after incubation, fluorescent signal was measured. Four types of Dengue virus were detected by evaluating characteristic emissions. The biosensor provided fast, simple, and sensitive way to detect Dengue virus and paved the way for other applications [43]. In another investigation, a two-way detection method was

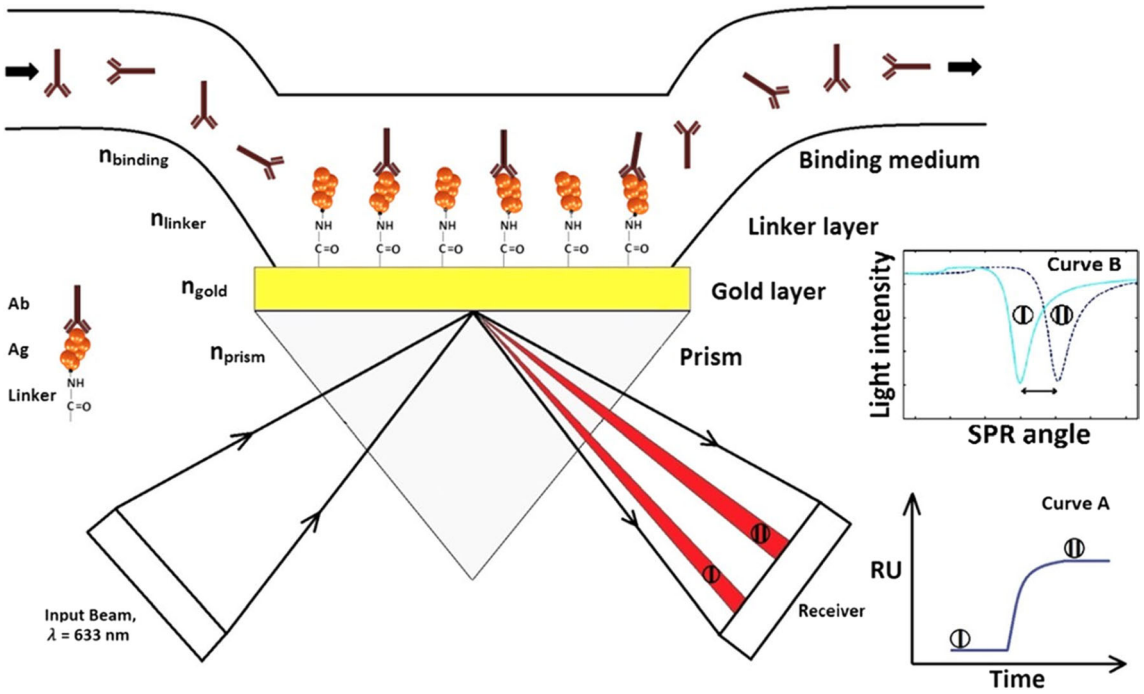

Fig. 1 SPR biosensor for detection of Dengue virus serotype 2 [40]

depicted to identify the four Dengue virus serotypes along with DNA quantification. In that research, a novel nanocomposite based on AuNPs and nitrogen-sulfur co-doped graphene quantum dots (N, S-GQDs) along with four dye-conjugated probe DNAs were employed. The labeling process of targeted DNAs was carried out by the small poly T chain and subsequently its conjugation with N,S-GQDs@AuNP-DNA nanocomposites was performed. According to the obtained results, the nature and essence of each serotype can be characterized and expounded by intended fluorometric signal from the sensor [44]. A new detection system based on protease activity to visualize Dengue virus infection in cells was described elsewhere so that the detection of Dengue viral infections was carried out by fluorescence switch or horseradish peroxidase (HRP) activity in the infected cells. In this study, the measurement of average percentage of EGFP-positive cells against virus titer was accomplished by immunosensor. In addition, the determination of virus titer was indicated by interpolating process. According to the results, without any dilution process, the quantification of viral samples could be carried out between a titer from lower than 10 to upper than 10^6 FFU/well by protease activity detection system (DENPADS). In compared to other titration methods, the DENPADS could be considered as a sensitive, impressive, and precise method with less incubation time, high selectivity, simple performance, and high applicability. Using DENPADS method, four dengue serotypes could be detected in 24 h and the all required and important information could be acquired easily [45].

Besides its sensitivity, the flourimetric approaches suffer from high background signal. To address this issue, the metal-organic frameworks (MOFs) as quenching reagents have been applied for fluorophore-labeled nucleic acid detection. According to the mentioned contents and significance of simultaneous and synchronous detection in clinical pre-diagnosis, a new 3D Cu-based MOF nanostructured fluorescent tag with high solubility and stability in the water has been utilized. In that research, in order to form two probe DNA systems, the synthetic MOF interacted non-covalently with two different fluorophore-labeled DNA probes, resulting fluorescence quenching of them. In the presence of target RNA sequences of Dengue virus (DENV) and Zika virus (ZIKV), the probes were released and the fluorescent signals were recovered. The detection limits of Dengue and Zika viruses were determined as 232 and 192 pM, respectively for single fluorescence analysis. However, by applying synchronous fluorescence analysis the detection limits were reduced down to 184 and 121 pM [46].

On the other hand, some studies in this area have been devoted to development of miniaturized microfluidic systems to reduce the consumption of reagents and to obtain faster and more sensitive assays, which discussed more in section 5. More recently, the application of lateral flow immunoassay platforms are ongoing which described in details in section 6. In summary, the research in this area focused on developing

highly fluorescent tags, easy to use biosensors, and PoC diagnostic systems.

ELISA-based platforms

The enzyme linked immunesorbent assay (ELISA) can be considered as one of the most useful and efficient clinical diagnostic tools in detection of wide range of diseases such as infectious illnesses and cancer biomarkers [13, 47]. In recent years, many of rapid screening test kits have been applied for antigen/antibody detection; however their sensitivity and specificity were not comparable to sandwich ELISA assays. Despite these noteworthy features, conventional ELISA tests are time-consuming and require specific and expensive laboratory equipment and expert technician [48–50]. For these reasons, the researchers were miniaturized the whole procedure of ELISA on Lab-on-a-Chip (LOC) or Lab-on-Compact Disc (LOCD) platforms. The LOCD platform was designed to perform the entire ELISA procedure in a small zone. By employing the absorption spectrophotometry, the optical densities of samples were measured by using monochromatic light emitting diode (LED) and optical sensor, which showed 95.2% of sensitivity and 100% specificity for clinical evaluations. Moreover, its portability, high accuracy and precision, low cost, and easily manufacturability makes it suitable for PoC diagnosis [50]. In another study, methacrylic microspheres (MMS) were used for biomolecular recognition. The MMS consist of triethylene glycol dimethacrylate (TEGDMA) which prepared by free-radical polymerization between methyl methacrylate (MMA) and methacrylic acid (MAA). Then, the fluorescence ELISA was utilized to examine the efficiency of immobilization of antibody on its surface. A sandwich ELISA method was utilized which comprised of 96 well-plates (Fig. 2). In that assay, Dengue antigens were attached to antibodies and recognized them efficiently with the higher fluorescence intensity compared to conventional format [51].

The same group, in another work, introduced paper-based biosensor consisting of polymethacrylate coated electrospun poly(3-hydroxybutyrate) (PHB) fibers. The free-radical polymerization reaction in THF were accumulated to synthesize poly(MMA-co-MAA) and the straightforward method of dip-coating was utilized for fabricating PHB fibers. After preparation of reagents and immobilization of Dengue antibody on polymer coated PHB fibers, sandwich ELISA was utilized for biomolecule detection (Fig. 3). The method was able to detect virus more specifically and more reliably than conventional ELISA. The assay showed a linear range of 3.5×10^{-4} to 3.5×10^{6} pfu.mL^{-1}. In addition, the fiber structure of electro-spun PHB creates large specific surface area for bimolecular interactions [52].

In other investigation, polymer-coated microporous nylon membranes were designed and utilized in ELISA platform (Fig. 4). The special feature of this assay relies on the Dengue antibody attachment on surface –COOH groups via physical attraction or covalent immobilization. The colorimetric sandwich ELISA which conducted in this assay was able to distinguish different concentrations of the Dengue virus but in comparison to ELISA, this assay revealed the higher order of LOD values and low signal intensity for all of the virus concentrations. Despite the utility of of nylon substrates coated with polyacrylate macromolecules in wide variety detection of proteins, producing flexible nylon membranes are in the future prospect of the researchers [53].

More recently, paper-based platforms using electrospun fiber mats were designed which is suitable substitution for ELISA in sensitive and accurate detection of Dengue virus. That biosensor was consisted of pillar extensions to incorporate fiber mats into the assay utilizing the well plate. The fiber mats penetrate the assay physically for that reason it was entitled intrant-ELISA (i-ELISA). Both inside of the well and on the fiber mat were used for immobilization of proteins, which increased the surface area and relatively caused specific detection of Dengue virus. The principle and magnified view of the pillar sections of i-ELISA is illustrated in Fig. 5 [54]. The most advanced property of i-ELISA was the utilizing of Poly(3-hydroxybutyrate-co-3-hydroxyvalerate (PHBV) which possess a level of robustness in compared to laborious sandwich ELISA experiments. Moreover, the existence of oxygen atoms in chemical structure of PHBV made it more electronegative than PHB. Additionally, the i-ELISA technology enhanced the detection signal intensity up to 12 times greater than the conventional ELISA [54].

In a similar way, other researchers reported a new paper-liked solid immunoassay platform in order to detect the isotype IgM-Dengue antibodies. In this research, the coating of paper (cellulose sheets, whatsman type-1 and ss903) was carried out by two different ways; in one way, the magnetic nanoparticles were deposited on the surface of paper and then the attachment of human IgM antibodies was accomplished by using polydopamine as a linker. In the second way, the Fe_3O_4@polydopamine (Fe_3O_4@PDA) nanoparticles were coated on the plate surface and then the IgM antibodies were immobilized. Due to homogenous antibody immobilization, the considerable analytical responses with slight fluorescence background were attained by Fe_3O_4@W1-PDA. In compared to traditional ELISA, the Fe_3O_4@W1-PDA platform showed more sensitivity (700 times in PBS and 500 times in serum) and the lower LOD [55]. In another work, the NS1 antigen-specific affibody molecules ($Z_{NS1}12$, $Z_{NS1}16$, and $Z_{NS1}46$) firstly were screened and the highest equilibrium constant was attained for $Z_{NS1}12$ which was significantly stable at high temperatures. Then, the functionalization of $Z_{NS1}12$ on the surface of gold nanoparticles was carried out to acquire the signal amplification agent. In comparison to affibody-based ELISA technique, this sensitive and novel functionalized nanoparticle showed 14.2-fold improvement in detection of Dengue serotype 1 [56]. Since the ELISA approach is considered as a golden method in clinical bioanalysis, its modified

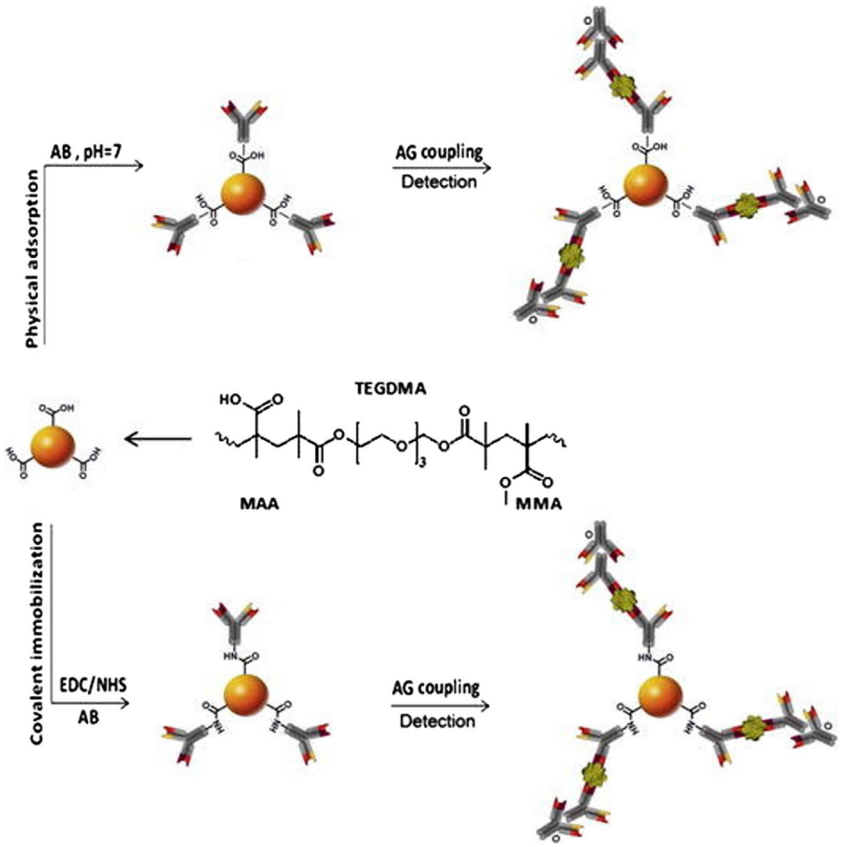

Fig. 2 Illustrating the attachment of Dengue antibody (AB) on MMS with surface -COOH groups and the sandwich ELISA method for its detection [51]

forms hinder some its drawbacks and provide novel signal amplification strategies; hence, it can be described as the most sensitive approach with high commercialization potential.

PCR based assays

The wide range of PCR based assays with different sensitivities and specificities have been developed for detection of Dengue virus genome. One of the recently reported approaches is the simplexa™ Dengue assay which is a RT-PCR method. In compared to conventional RT-PCR and SYBR green RT-PCR, the analysis of patient's sera showed that the detection rate of simplexa™ Dengue assay was higher; also, it was observed that the sensitivities of SYBR Green real-time RT-PCR technique and simplexa™ Dengue assay were higher than conventional RT-PCR [57]. Among the various sensing strategies for low level detection of Dengue virus, the isothermal amplification methods such as reverse transcription loop-mediated isothermal amplification (RT-LAMP) are the most efficient and impressive techniques which do not require expensive equipment and present accurate and reliable results. In recent years, according to the detection significance of Dengue genome sequences, the traditional primer tools cannot support and provide the whole needed information. Therefore, the possibility of detection of four oligonucleotides of DENV1–4 serotypes was evaluated by RT-LAMP method. In that study, the fast-growing databases was achieved by a novel LAMP primer. The related strategy was a combination of phylogenetic analysis, principal component analysis, and LAMP Assay Versatile Analysis (LAVA) algorithm. The proposed assay showed no cross-reactions with other arboviruses and DNA pathogens and its sensitivity was determined in the range of 10^4–10^5 to be 10 molecule/μL [58]. In another research, a fast diagnosis method for early Dengue virus infection was reported based on prototype reverse transcription-recombinase polymerase amplification (RT-RPA) assay. In this study, Dengue RNA can be detected in less than 20 min without any cross-reaction with other arboviruses. At least 12 genotypes of Dengue genome were indicated by RT-RDA primers and exo-probe as well. At the same time, the related sera were evaluated by utilizing RT-LAMP, quantitative RT-polymerase chain reaction (qRT-PCR), and IgM- and IgG-capture ELISA. In detection process of Dengue viremia samples, RT-RPA assay showed a considerable and good concordance ($\kappa \geq 0.723$) with the RT-LAMP and qRT-RPA assays. Furthermore, in combination with ELISA method, the detecting process of acute Dengue infection was improved more than 95.7% by RT-RPA and RT-LAMP assays [59]. A comparison was also made among the recent reported optical biosensors for detection and quantification of Dengue virus in Table 1, considering the detection methods, the employed nanomaterial, the resultant LODs, and linear range for each approach. As a comparison, the ELISA and PCR based platforms have more potential to be used in clinical

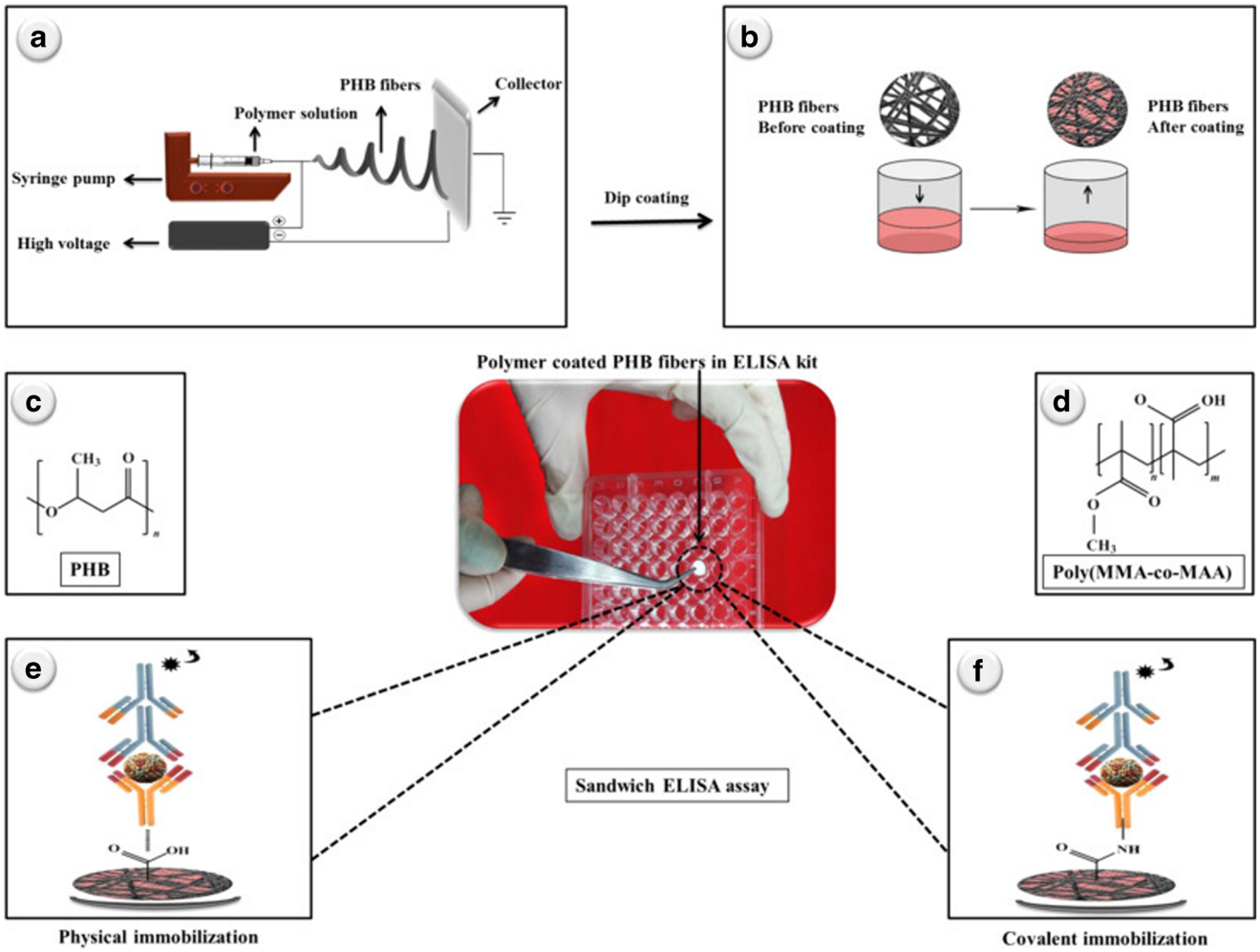

Fig. 3 Illustrating PHB fibers -based ELISA for detection of Dengue virus [52]

laboratories, although the development of portable and easy to use detectors for other approaches provides the facility for on-site applications.

Electrochemical biosensors

Voltammetric biosensors

The electrochemical biosensors rely on the measurement of current as a result of oxidation/reduction of an electroactive tag or modulation of electrochemical impedance during bio-conjugate events on a solid surface electrode. The two formers strategies are DC or pseudo-DC approaches but the latter measures the electrical impedance of an interface in AC mode with a constant DC bias. Voltammetric methods could be applied in a broad types of biosensors due to their cost effectiveness, easy availability, and rapid detection systems for a variety of electroactive analytes. Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) are efficient measurement techniques for scientific studies and characterizations [66, 67]. Over the last few years, CV measurements have been applied for supercapacitors [68, 69], electrochemical sensors [70, 71], fuel cells [72], cancer biomarkers and virus detection biosensors [11, 73–76]. Furthermore, the redox reaction pathway and mechanism, microenvironment condition of biosensors, estimation of reaction constant of analyte on electrode, and diffusion restrictions of biological analytes can be evaluated through these methods. In the specific case of virus detection, quantification of low amounts of virus antigens is attractive in biomedical and biological applications. According to recent studies, the application of CV and DPV methods for virus sensing in different formats could detect very low quantities of it in various samples efficiently [77]. As a general overview, in the case of DNA-based biosensors, interaction between immobilized DNA probe and its complementary DNA (as target) leads to change in physical properties of bio-electrode and consequently in CV and DPV diagrams. For example, Rashid et al. introduced the gold nanoparticle/silicon nanowires/Indium tin oxide (AuNPs/SiNWs/ITO)-based electrochemical biosensor

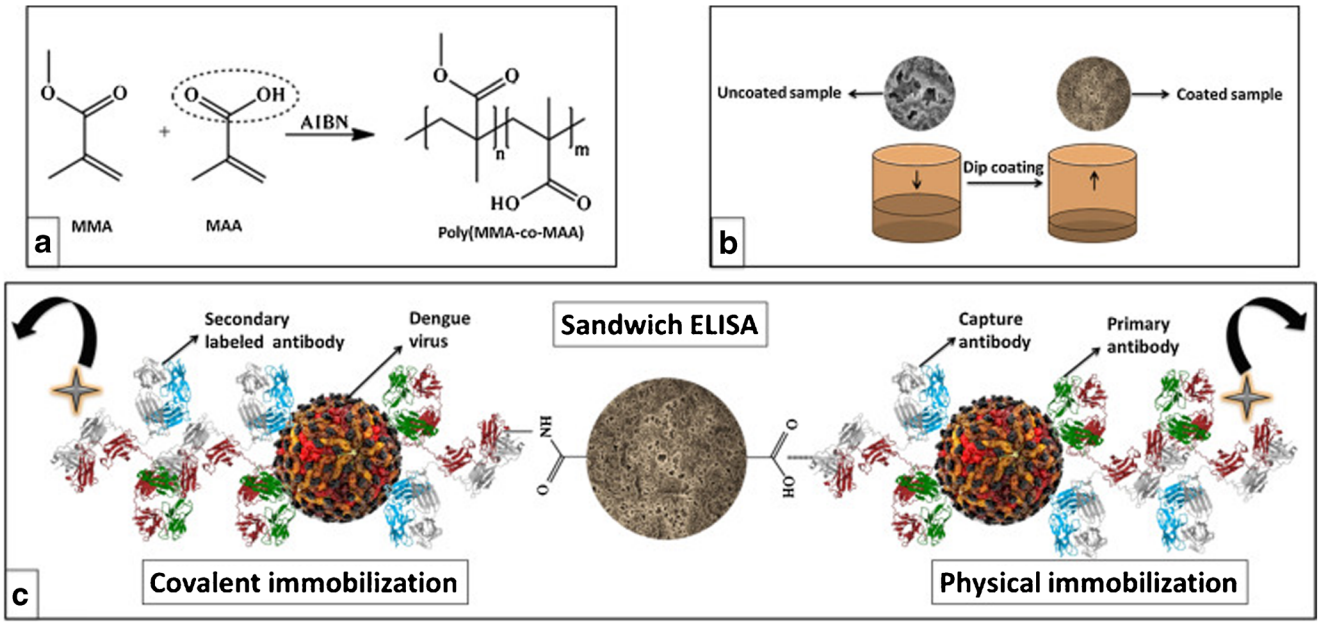

Fig. 4 The use of polymer-coated nylon membranes for Dengue virus detection comprising steps of (**a**) synthesis of polymer, (**b**) dip-coating; and (**c**) attachment of antibody to support and sandwich ELISA assay covalent cross-linking, and physical adsorption of dengue antibodies [53]

with methylene blue as an oxidation/reduction mediator in DPV format for monitoring DNA probe hybridization to respective complementary. A wide range of target DNA from 0.01 nM to 50 Nm with a LOD value under 0.01 nM was attained [78]. The ultra-sensitivity of DNA-biosensors is one of the attractive features of them which makes the possibility of early diagnosis of Dengue virus. In this respect, a DNA nanobiosensor was constructed using GCE/manganese (III) oxide nanofiber that could detect target in zeptomolar ranges. The electrochemical biosensor provided values of 120×10^{-21} M, 360×10^{-21} M and 6.93 kΩ/(mol)/cm^2 for LOD, limit of qualification (LOQ), and sensitivity in blood serum, respectively. Figure 6 illustrates the schematic fabrication steps of electrochemical manganese (III) oxide biosensor [79].

The serotype biosensors are another platform in this area, which makes it possible to detect Dengue virus without any specific analyzes on serotypes. So, a ZnO/Pt-Pd modified fluorine doped tin oxide (FTO) electrochemical biosensor was fabricated that could indicate high potential for consensus DNA sequence. The current reduction in CV and DPV voltammograms implied hybridization process between P-DNA and the target DNA. It provided a broad linear range from 1×10^{-6} M to 100×10^{-6} M with a LOD value of 4.3×10^{-5} M [80].

The immobilization mechanism of capture probe can also influence on biosensor performance. According to this issue, a SiNWs/AuNPs/ITO-based biosensor with a high potential for immobilization of probe DNA and its hybridization mechanism activity was introduced elsewhere. The hybridization process was investigated by DPV resulting the biosensor sensitive to the presence of DNA from 9.0 up to178.0 ng.mL^{-1}. The experimental procedure and schematic fabrication steps of SiNWs/AuNPs/ITO-based biosensor is shown in Fig. 7 [81].

Beside signal generation as a result of probe and target DNA hybridization, the other biological interactions such as antigen and antibody affinity on biosensor surface can be processed in electrochemical methods. The immobilization process of probe DNAs on electrodes surface can be carried out in different ways such as PEGylation and using nanoparticles. In summary, CV and DPV techniques have been implemented for development of simple, highly sensitive, and selective biosensors. In addition, many of researchers agree that these methods are good candidates for commercialization because of low assay time, less sample requirements, rapid preparation procedure, reproducibility of results, and high rate of signal processing. However, the main issue is the development of portable and simple operation electrochemical devices and integrated mini-potentiostat systems needles to an expert user.

Amperometric biosensors

Besides the voltammetry method, the amperometry is one of the remarkable techniques that bio-scientists could utilize it for developing sensitive biosensors. This technique implies the measurement of current as result of reduction/oxidation of an electroactive label or tag which used in bioassay development. Principally, the early detection and diagnosis of Dengue virus in biological systems have been an unsolved challenge, which needs an efficient detection technique. Therefore, a few of methods have ability

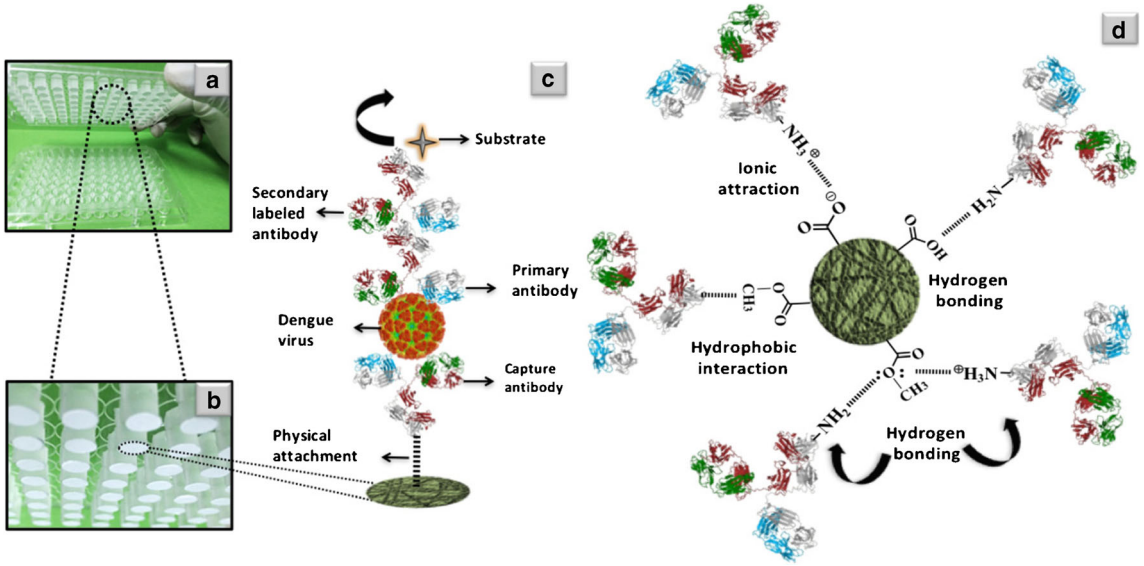

Fig. 5 The schematics of i-ELISA (**a**) and (**b**) its principle and magnified view of the components (**c**) the structure of sandwich ELISA and its physical attachment to the surface; and (**d**) the types of bimolecular interactions [54]

to offer therapeutic and commercial devices for patients. For example, the commercial NS1 immunosensors systems have been restricted by undesirable interactions between NS1 and the various carbohydrates [82]. In recent years, the amperometry has been applied as a versatile technique for biosensors fabrication. This method has broad applications in electrochemical immunosensors. In this respect, Dias et al. designed the NS1 protein based immunosensor using carbon nanotubes as ink-printing. The carboxylic acid functional groups of carbon nanotubes help to homogenize ink and to obtain a unique electrode surface. NS1 antibodies were then immobilized on electrode surface using polyethylene diamine under layer. The electrochemical measurements by amperometry indicated that the electrochemical response of the immunosensor is excellent with LOD and sensitivity values equal to 12 ng.mL^{-1} and 85.59 mA/mM.cm^2, respectively. Moreover, the durability of this immunosensors in real blood samples was acceptable and appropriate [83].

Overall, the amperometry technique is a useful method for studying and characterization of biosensors. The selectivity, considerable sensitivity in ultra-dilute samples, and commercial availability are the main advantages of amperometric methods. Moreover, the exact understanding and knowledge about the mechanism of reactions on biosensors are possible only in amperometric methods. So the amperometric methods have great importance in designing, characterization, and measurements of Dengue virus biosensors.

Impedimetric biosensors

As mentioned before, the impedimetric biosensors operate in AC mode with constant DC bias conditions. This technique conventionally is accomplished by applying a small

Table 1 Optical based biosensors reported for the detection of Dengue virus

Detection Method	Type of Dengue	Nano material	LOD	Linear range	Ref
Optical DNA Biosensor	Dengue virus serotypes 2	Silica nanospheres	0.2 aM	1.0×10^{-16} –1.0×10^{-10} M	[7]
SERS based lateral flow biosensor	Dengue nonstructural protein 1	–	15 ng mL^{-1}	15–500 ng mL^{-1}	[9]
Label-free biosensors	Dengue II E proteins	–	1 pM	–	[15]
Colorimetric biosensor	Different Dengue serotype	Silver nanoparticles	–	–	[60]
SPR biosensor	–	AuNPs	31–260 copies per mL	–	[61]
Optical DNA biosensor	Dengue serotype 2	silica nanoparticles	1 zM	1.0×10^{-15} M –1.0×10^{-11} M	[62]
SRP biosensor	Dengue serotype 2 and 3	–	2×10^4 particles.ml^{-1}	–	[63]
SPW biosensor	NS1 protein of the Dengue virus	–	5.73 pg.mm^{-2}	–	[39]
LRSPP	–	–	~22 pg.mm^{-2}		[64]
LSPR fiber optic sensor	Dengue anti-NS1 anti-body	gold nanoparticles	1.54 nM.	–	[65]

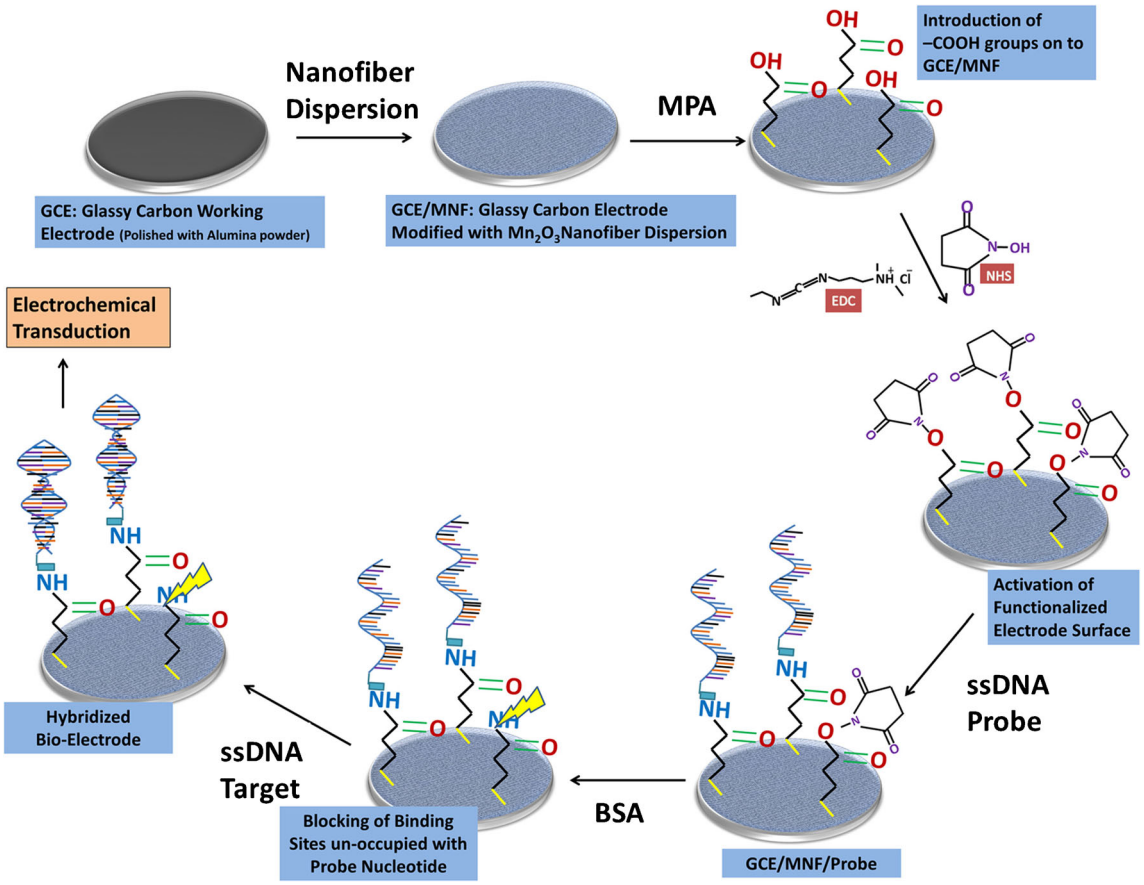

Fig. 6 Fabrication process of manganese (III) oxide biosensor and the used material in each step (MPA: Mercaptopropionic acid; EDC: 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide; NHS: N-hydroxysuccinimide; MNF: Mn_2O_3 nanofiber; BSA: Bovine Serum Albumin) [79]

sinusoidal voltage at a particular frequency followed by measuring the resulting current; then, the current-voltage ratio gives the impedance [84]. The electrochemical impedance spectroscopy, with high capability in detection of resistance between junctions, has attracted a lot of attention in plenty of biomedical and biological fields [85]. Because of weak interactions between different biological species, the sensitive techniques to reveal their interactions are attractive. For example, the weak interaction between Dengue virus and C-type lectins domain family 5 (CLEC5A) can be measured by EIS. According to this fact, Tung et al. reported that these weak interactions could be detected by EIS. They used uniform deposited AuNPs as substrate on electrode in the fabrication of biosensor. Moreover, the interaction of receptor and virus has been modeled for cancer therapy and interaction of receptor and cancer surface glycoproteins. The changes in the charge transfer resistance of this biosensor implied to good sensitivity and measurement ability of biosensor [86].

The use of antigens and their related antibodies as an efficient strategy opens new horizons for the design of improved assays for Dengue virus diagnosis. According to this fact, the NS1 as an antigen and IgG and IgM as antibodies have been utilized [87] and a label free antigen/antibody biosensor was developed to sense the presence of virus in contaminated samples. A self-assembly method in functionalization and immobilization of poly ethylene glycol (PEG)-thiol moieties during biosensor fabrication was used. Detection of antigen/antibody interactions was made by electrochemical impedance spectroscopy and their results provided LOD, linear range, and sensitivity of 340 $pg.mL^{-1}$, 1–5000 $ng.mL^{-1}$ and 4.5% per decade, respectively. Similarly, these results for IgG antibody were 231 $pg.mL^{-1}$, 1–1000 $ng.mL^{-1}$, 6.3% per decade [16]. The obtained LOD was much better than that obtained by using a carbon nanotube biosensor, which was 12 $ng.mL^{-1}$ [83]. Recently, Cecchetto et al. studied the NS1 biomarker-based biosensor using gold as substrate with high potential for detection of Dengue virus in neat serum. They used mercaptoundecanoic acid for anti-NS1 immobilization and 6-mercaptohexanol as spacer in self-assembly fabrication method. The $Fe(CN)6^{3-/4-}$ was used as a redox couple. According to their results, NS1 biomarker-based biosensor has linear range, sensitivity, and LOD equal to 0.01–2.00 $\mu g.mL^{-1}$, 14.1% per decade and 3.0 $ng.mL^{-1}$, respectively in PBS solution. Moreover, these parameters were 0.01–1.00 $\mu g.mL^{-1}$, 10.4 percentage/decade and 30 $ng.mL^{-1}$, for neat serum sample, respectively. So, this biosensor has

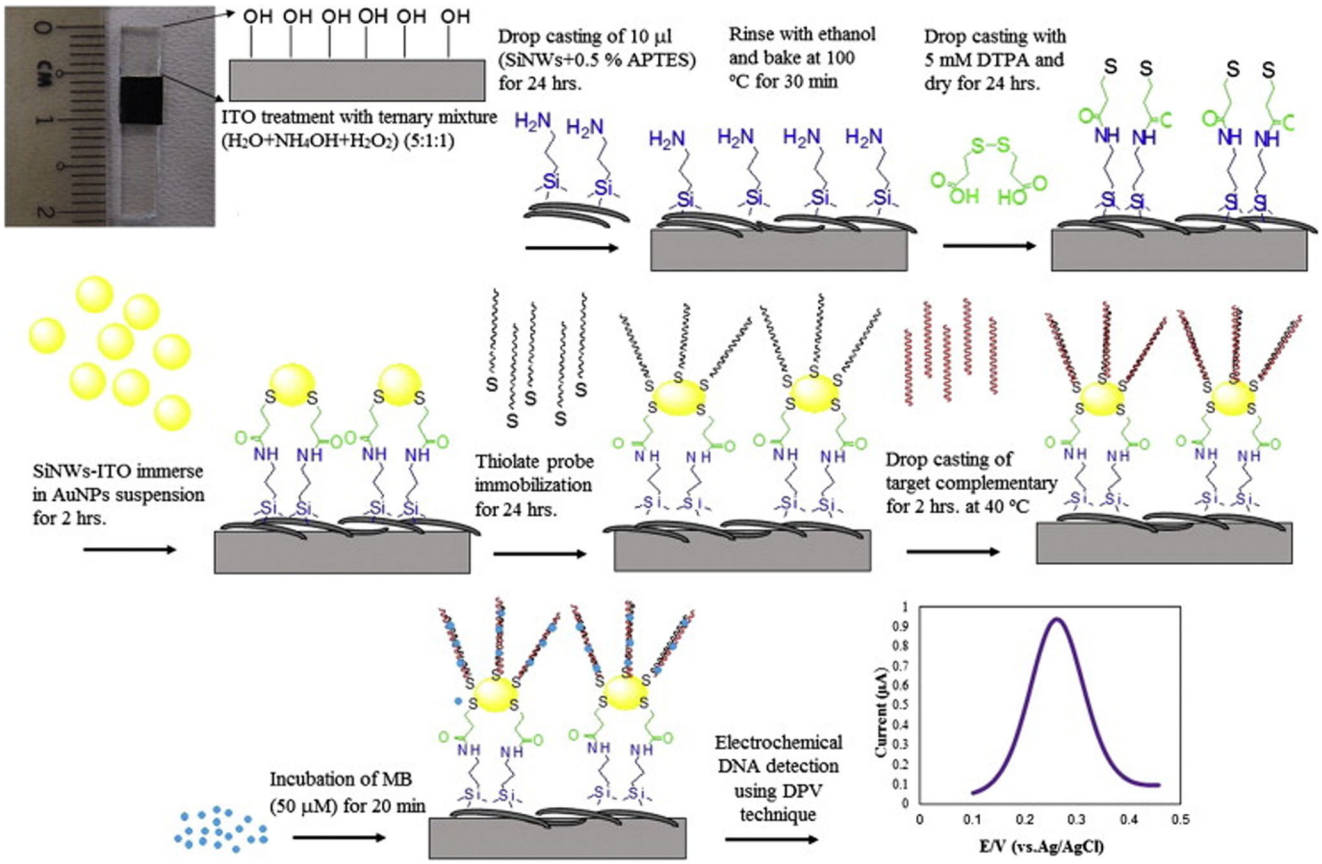

Fig. 7 The steps of SiNWs/AuNPs/ITO-based biosensor fabrication procedure from treatment of ITO substrate to receive an electrochemical signal [81]

excellent capabilities for real sample analysis. The details of procedures for modification of gold substrate surface in the fabrication of biosensor are given in Fig. 8 [88].

One of the main and crucial advantages of impedimetric methods is the ability to report the charge transfer resistance during hybridization process between probe DNA and target DNAs and between antigen and antibodies. The charge transfer resistance has been known an electrochemical parameter that could help researchers to detect hybridization event. Not only the charge transfer resistance helps us to consider the interactions between probes and target DNAs, but also opens a new way to study the configuration of species in the process of interactions. On the other hand, the sulfur-contained materials for modification of gold electrode surface are one of the important steps in biosensors fabrication which the coverage amount of these materials can be remarkable impact on biosensor performance. Luna et al. reported the immunosensors with capability of Dengue target DNA sensing. They used cysteine and 4-mercaptobenzoic acid (MBA) for self-assembly immobilization of probe DNA on AuNPs, followed by covalent attachment of Dengue virus antibody. The charge transfer resistance as hybridization reaction criteria (R_{CT}) between probe and target DNA has been reported for different antibodies of Dengue viruses. The ΔR_{CT} from type 1 to type 4 were 66%, 63%, 58% and 87%, respectively. The fabrication of immunosensor by using cysteine and MBA have been depicted in Fig. 9 [89].

Detection of Dengue virus serotypes in ultra-dilute solutions has been investigated in the last decades. Currently, Nascimento and co-workers investigated the polyaniline (PANI) and AuNPs composites and they reported that these new nanomaterials have high ability for using in Dengue detection-based biosensors. They indicated that in composition of AuNPs-PANI, the SH-groups play the immobilizer role and it has good capability in picomolar level quantification of samples. The electrochemical methods helped to consideration of diffusion process of redox process in bare AuNPs-PANI and AuNPs-PANI-serotypes biosensors. For detection of target DNA, they introduced R_{CT} as AuNPs-PANI-modified charge transfer resistance that the increasing of this parameter showed the meaningful increasing in hybridization process efficiency. Therefore, they reported the ΔR_{CT} for different AuNPs-PANI-modified biosensors. The ΔR_{CT} for serotype 1, serotype 2, and serotype 3 in 7 picomolar of target DNA were 87.5%, 71.03% and 64%, respectively [90].

In continue, Navakul et al. introduced the graphene oxide/polymer composite-based biosensor for detection

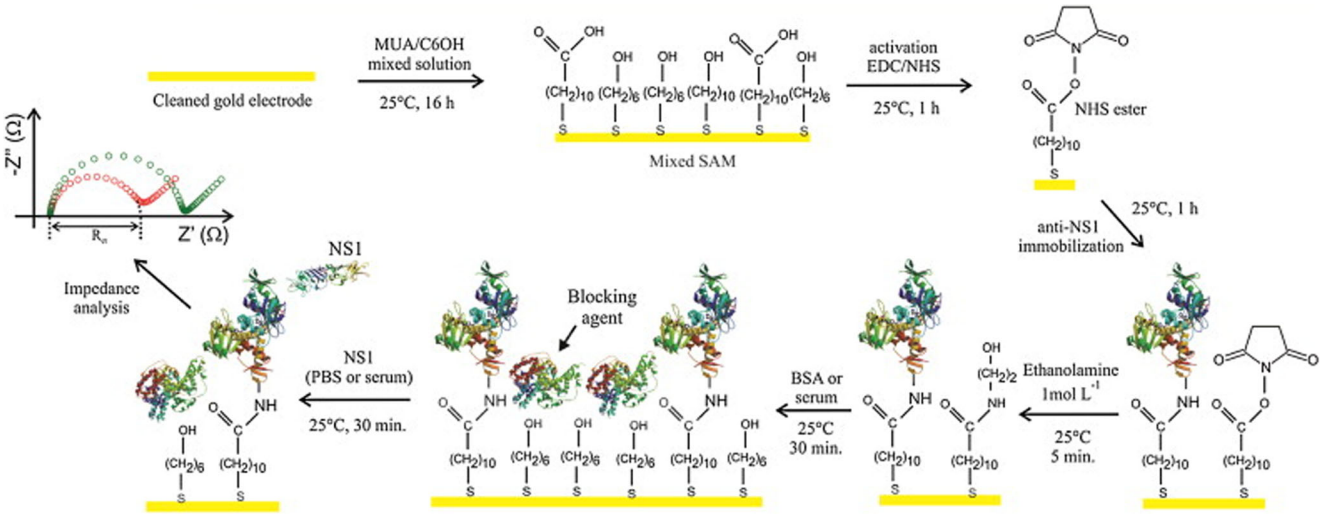

Fig. 8 Gold surface modification and different steps of NS1 biomarker-based biosensor fabrication [88]

and classification of Dengue target DNA by using EIS method. According to their results, a linear range of 1 to 2×10^3 pfu.mL^{-1} with LOD value of 0.12 pfu.mL^{-1} was attained. The linear dependence between virus concentration and deviation of charge transfer resistance was formulated as ΔR_{CT} (kΩ) =0.2872log C (Dengue virus) +0.1556. The polymer and graphene oxide composite have been deposited using self-assembly method on gold substrate electrode, as shown in Fig. 10 [91].

Another strategy for detection of Dengue viruses that has good potential of usage in real samples analysis is Cratylia mollis (CramoLL) lectin modified hybrid nanostructure of AuNPs/PANI/ CramoLL/serotypes (AuNPs-PANI-CramoLL-serotype). By employing three serotypes of Dengue virus in detection process, the charge transfer resistances of serotype contained biosensors showed the higher values than the bare one with the highest value for serotype 3 modified biosensor. As more explanation, the increasing in charge transfers on electrode surface were related to distinguish and attachment of abnormal glycoproteins of patients sera. So, AuNPs-PANI-CramoLL-serotype-based biosensors are a tremendous candidate for glycoprotein diagnosis. Figure 11 shows the AuNPs-PANI-CramoLL-serotype electrode fabrication process [92].

Darwish et al. reported the biomarker-based electrochemical biosensor by deposition a hybrid of anti-bodies and AuNPs on ITO for fabrication of biosensor substrate. They applied 1,4-phenylenediamine, 4-trimethylammoniophenyl, and 4-sulfophenyl molecules as ITO surface modifiers, the AuNPs as charge transfer reducer and the monoclonal NS1 antibodies as intermediate between NS1 antigens and functionalized AuNPs on ITO substrate. The electrochemical impedance spectroscopy measurements indicated the linear range of 5–4000 ng.mL^{-1} and good durability and stability for 21 days. The R_{CT} and virus concentration dependence was formulated as ΔR_{CT} (kΩ) =1.611ln C (NS1) -2.7682. Although, the detection of biomarkers in real human sera samples remained as a main challenge, NS1 antigen detection immunosensor has high capability for solving that issue. Therefore, the label-free, stable and selective NS1 nano-biosensors are capable for medical and clinical therapeutic actions on patients with Dengue virus infections [93].

Recently, Solanki et al. reported the deposition of MoS_2 and AuNPs composition on ITO for the development of an EIS biosensor. According to their results, not only the MoS_2-AuNPs composite has the synergetic influence on the conductivity of biosensor, but also the high loading capacity for antibodies immobilization can make the biosensor more sensitive and precise in electrochemical detection process. The clinically applicable LOD values of1.67 ng.mL^{-1} and 1.19 ng.mL^{-1} for standard and spiked samples, respectively and broad linear range of 10^2 to 10^8 ng.mL^{-1} were obtained [94]. In addition, the portability of immunosensors is one of the critical points that make it possible for on-site applications. In this communication, the lateral flow immunosensors are one of the best options. For this, Sinawang and co-workers designed an immunosensor in lateral class and they used the combination of gold nanoelectrode and glassy fiber plate of cellulous in a sandwich-like mini kit. The glassy fiber plate of cellulose had the immunosensing ability of Dengue virus antigens. Their small and efficient biosensors had suitable features like the broad linear rang and low LOD (1–25 ng.mL^{-1} and 0.5 ng.mL^{-1}) [95]. The rapid assay of Dengue virus NS1 proteins is the most promising ability and advantage of this mini-kit bioassays [96]. Moreover, the small kits were appropriate candidates for

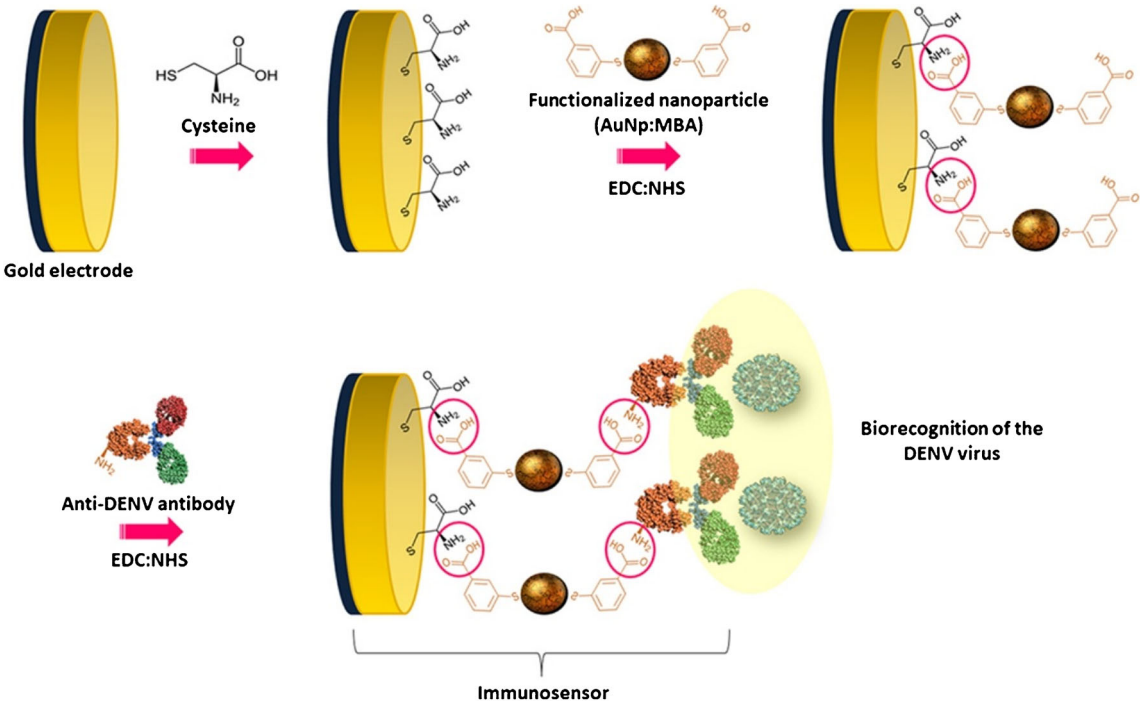

Fig. 9 AuNPs-based immunosensor fabrication process using MBA and cysteine modifier on gold surface [89]

elimination of sample preparation step. In the recent years, a few reports mentioned the utilization of non-blood samples for detection of Dengue virus. For this, as a simple, fast, and economical strategy for quantification of saliva, as a sign of early detection, was reported by Wasik and coworkers. They developed the functionalized single walled carbon nanotubes (SWCNTs) with Dengue virus antibodies and used it for detection of NS1 antigens with a linear range from 1 ng.mL^{-1} to 1000 ng.mL^{-1} [97].

Finally, the EIS is the only method which helps us to study and understand the models of interactions between biolayers. The resistance of biosensor interface layers has deep effects on charge transfer resistance and subsequently description of interactions between probe and target DNAs or antigens and antibodies open new horizon for bio-scientists to understand about biomolecules arrangement on bio-electrode for designing efficient nanobiosensors specially for Dengue virus detection.

Conductometric biosensors

Principally, physical methods of Dengue virus diagnosis are faster and easier than chemical methods and among them, the conductometric methods as efficient physical methods have shown the good performance in different DNAs diagnosis processes. Unlike the other electrochemical reaction driven approaches of electrochemical detection, the non-reactional conductometry method detects the interactions between capture and target by the calculation of conductance in different ionic spices. The conductance and ion transfer are the important parameters that have crucial effects in this approach. Furthermore, conductometry methods are one of the cheap and highly sensitive techniques for detection of many different viruses. Recently, the applications of conductometric methods as efficient, sensitive, and non-reactional techniques are expanding. According to recent scientific reports, the conductometric methods have been applied in many of different biological and electrochemical measurements such as DNA detection and cancer biomarkers. Moreover, the conductometric method could be applied in analyzing of nucleic acids from different viruses. Senapati et al. developed a biosensor with nano-membrane structure that works by ion exchange in surface and charge inversion. According to their report, the cheap, highly selective, and sensitive detection of Dengue virus nucleic acids are possible by using nonporous membrane-based biosensor with proper selection of cationic layer. They reported a value of 1 pM for LOD of nanomembrane-based biosensor and 15 min assay time in analysis of nucleic acid in real samples. Their results indicated that the similar results could be obtained from short DNA analyzing. So, the biosensor showed high ability in detection of DNA from *Escherichia coli* and *Brucella* in different samples. The fabrication process of nanomembrane-based biosensor, it's mechanism and actions of different parts of it are presented in Fig. 12 [98].

A summary of electrochemical nanobiosenors are given in Table 2, which included the critical factors in each case. Considering simplicity and sensitivity, the amperometric and EIS biosensors are superior to the others.

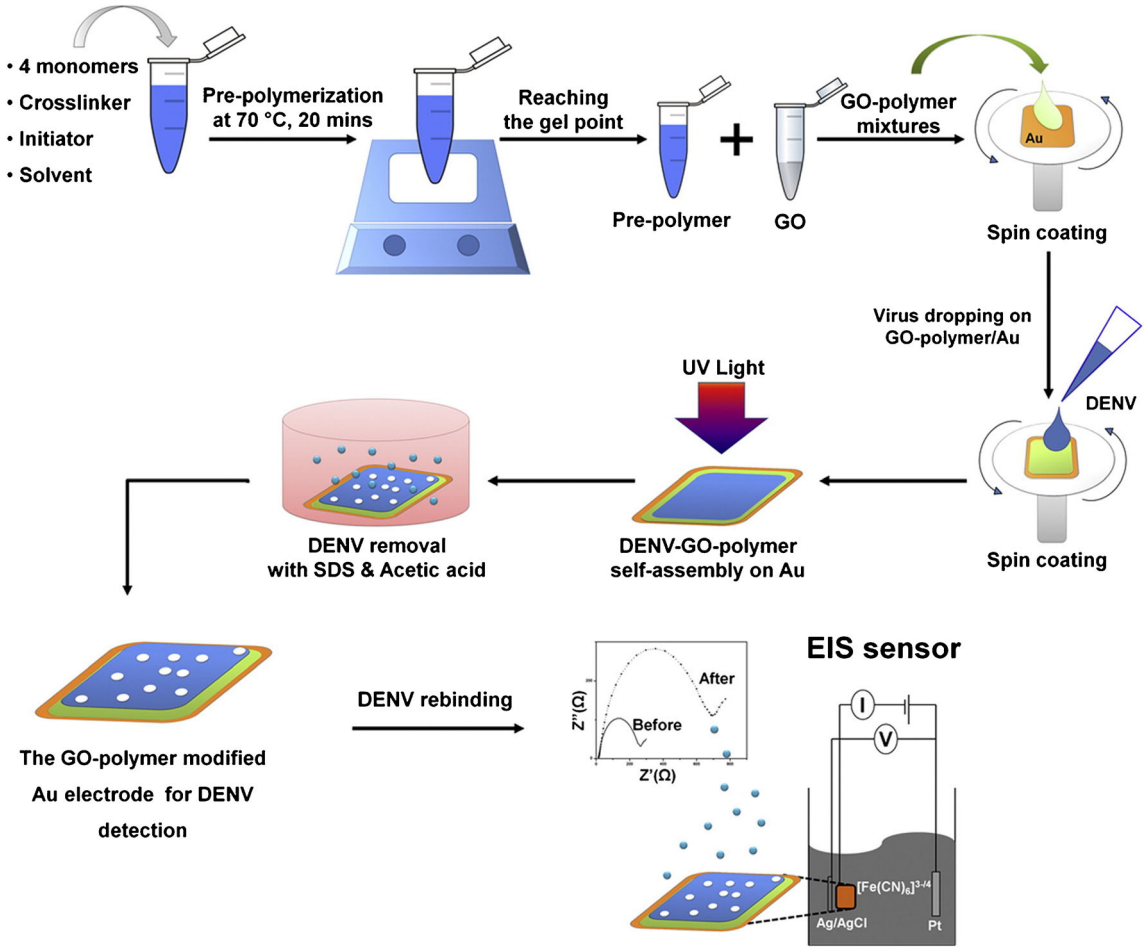

Fig. 10 Fabrication process of polymer matrix/graphene oxide composite-based biosensor for detection and anti-body screening of Dengue virus. The experimental procedures of biosensor have been illustrated schematically. The construction process of biosensor involved the pre-polymerization and mixing of graphene oxide and deposition of composite on gold substrate electrode [91]

Metal oxide based electronic biosensors

The electronic biomedical devices with small size and low cost are the important types of detection systems for many of diseases. These devices work based on the contact between a biomolecule and metal oxide under layer, which the charge transfer from biomolecule to under layer makes the electrical signal. The sensitivity of these types of biosensors extremely depends on the under layer specific area. Recently, electronic sensors have been developed for measurements of different biological and non-biological analytes such as alkali metal ions [114], nucleic acids, and proteins [115, 116]. Many of reports focused on detection of viruses by electronic biosensors. The ultra- low detection capabilities, low assay time, and availability have made them as a good candidate for clinical and therapeutic application. However, one of the main challenges in this area is the Debye length, which restricts the detection of large biomolecules such as DNAs and RNAs. Hence, some of the researches have reported the SiNW-based electronic biosensors with high ability for detection of Dengue virus. In addition, the carbon nanotubes are the important materials with high surface area that have good potential for binding between biomolecules for using in electronic nanobiosensores [117]. The flexibility of carbon nanotubes is the other issue that can influence on detection of large size biomolecules such as DNAs from different viruses [118]. However, the electronic biosensors that work based on anti-body system able to detect Dengue virus more effectively. In this respect, Zhang et al. developed the nucleic acid-hybrid DNA-based electronic biosensor that could to overcome to Debye restriction due to the large size of analyte molecules. According to high risk of infections in secondary type of Dengue virus serotype in comparison to other ones, the small part of peptide nucleic acid sequence of secondary serotype has been selected and applied as capture probe. The hybridization process between probe DNA and target one was led to induction of negative charge on SiNW surface. According to their results, the nucleic acids-hybrid DNA-based electronic biosensors have good selectivity and sensitivity for Dengue virus. They report the 1 fg per mL for LOD of biosensor. The assay time was reduced from one hour to ten minutes that is a good advantage for electronic biosensor. The different parts of

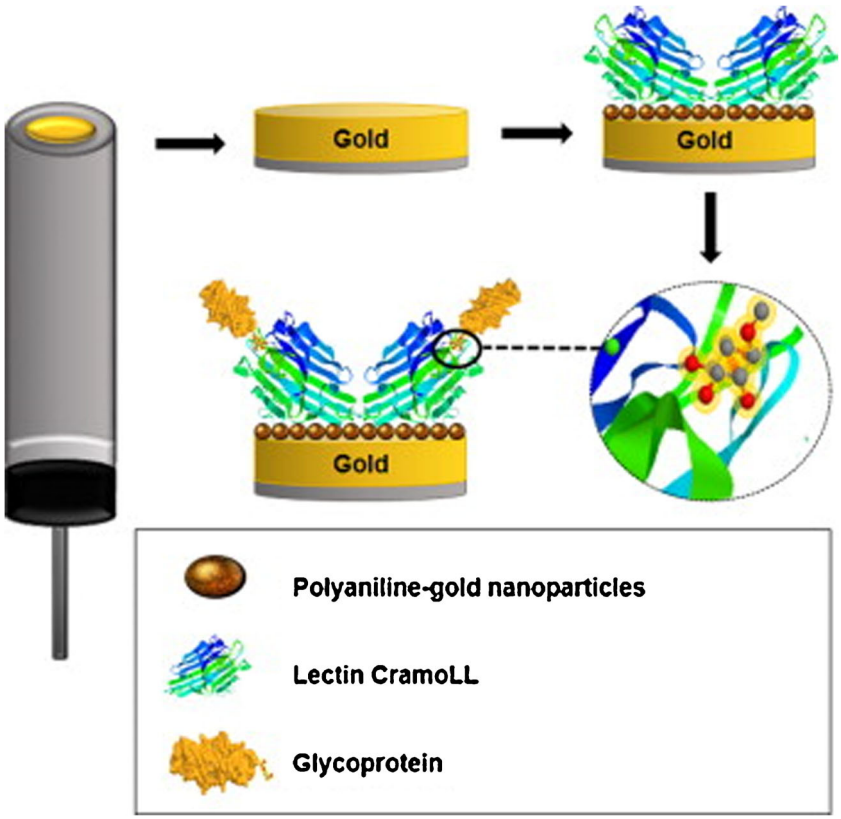

Fig. 11 Schematic illustration of fabrication process of AuNPs-PANI-CramoLL-serotype-based biosensor. The fabrication process involves gold electrode treatment, thin layer deposition of AuNPs-PANI, Lectin CramoLL immobilization, and interaction between Lectin CramoLL and glycoprotein [92]

biosensor including surface topography, functionalized area and schematic illustration of nucleic acids-hybrid DNA-based electronic biosensor are described in Fig. 13 [119].

Currently, the SWCNTs-based electronic biosensors have shown great progress in biomedical and biological science. For example, Wasik et al. demonstrated the electronic biosensors by functionalization of SWCNTs by heparin in order to detect dengue virus. Their results indicated that the heparin has an adapting role on the charge amount of CNTs surface. Therefore, the changing in surface charge results change in the resistance of biosensor surface. The biosensor showed linear action from 8.4×10^2 $TCID_{50}.mL^{-1}$ to 8.4×10^5 $TCID_{50}.mL^{-1}$. The deviation of charge transfer resistance has been formulated by ΔR_{CT} (%) = 0.1log C [Dengue virus ($TCID_{50}.mL^{-1}$)] -0.25 and sensitivity of this biosensor was 10% with LOD of 8.4×10^2 TCID50/mL (~8 DENV/chip) [118]. In other report, Wasik et al. used the NS1 antibody as recognition element and fabricated the network of CNTs by lithography technique on gold patterned substrate for immobilization of NS1 antibodies. According to results, the biosensor has linear functional range from 0.03 $ng.mL^{-1}$ to 1.39×10^2 $ng.mL^{-1}$ by ΔR_{CT} (%) = −7.47log C [Dengue virus ($mg.mL^{-1}$)] -59.19. The sensitivity and LOD of biosensor were − 7.47 per logarithm $ng.mL^{-1}$ and 0.09 $ng.mL^{-1}$ [120].

Using mechanical induced change, the piezoelectric biosensors that are sensitive to the mass difference can provide the detectable electrical signals. There are limited materials with piezoelectric properties like as quartz that can resonate in the external potential. The application of piezoelectric materials in Dengue virus biosensing has been proposed in recent years. The acceptable LOD values and wide linear ranges are the most benefits of them which result the same popularity of electrochemical and optical sensing approaches [121–123].

As a summary, the main advantages of electronic biosensors are the resolving the Debye limitation for detection of large biological molecules and ultra-sensitivity which studies focused in this area.

Microfluidics systems and diagnostic kits

Microfluidics is a multidisciplinary technology that links several different sciences and represent several advantages including low consumption of reagents, minimal handling of materials, short assay time, fast response, multiplex analysis, portability, and versatility in design [124]. In early detection of Dengue virus, microfluidic based detection systems provide more efficient and precise results than electrochemical methods. In this regard, Hosseini et al. developed a combination of polymethacrylate microspheres and a microfluidic system that was sensitive to the Dengue virus antibodies, which

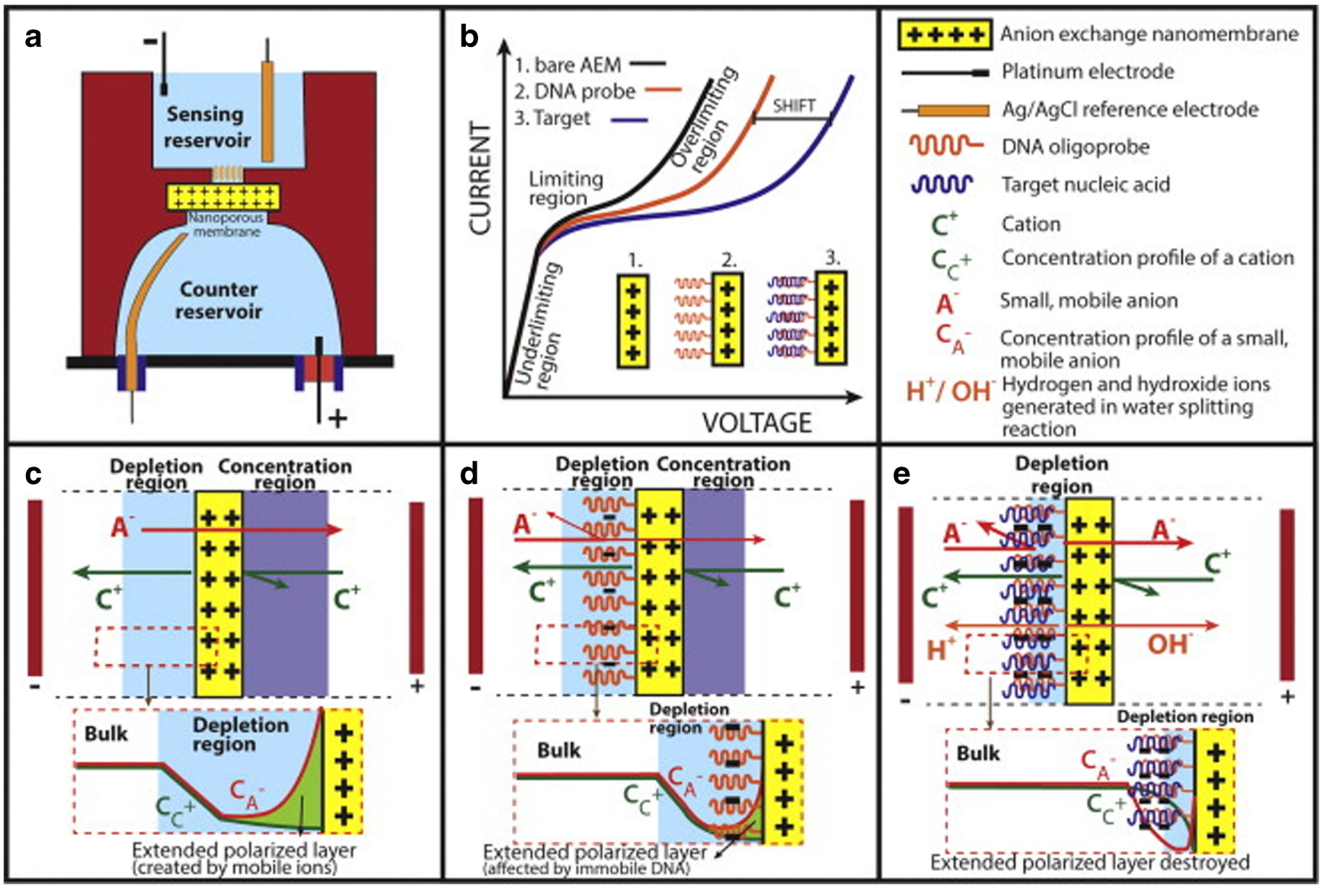

Fig. 12 Fabrication process and mechanistic description and illustration of nanomembrane-based electrochemical biosensor. **a** nano-membrane electrochemical setup for construction of DNA probe electrode, **b** current versus voltage diagrams for biological spices, **c** mechanistic description of under limiting region, **d** adsorption of DNA on membrane because of changing the limiting region and (**e**) mechanistic description of over limiting region during water splitting process in the high concentrations of DNA [98]

reduced the assay time from two hours to two minutes [125]. A semi-disposable microfluidic biosensor was reported for detection of Dengue serotype 3 sequences. Thanks to signal enhancement by liposomal encapsulated fluorescent reagent, the sensor was able to detect 20 and 25 long capture oligonucleotides with LOD value of 10 pmol L^{-1} [126]. More recently, a fluorescence immunosensor utilizing microfluidic dielectrophoresis (DEP) chip for in–vitro detection of Dengue virus has been reported. The assay was able to detect small amounts of samples (~15 μL) in 5 min. In that assay, the DEP force mechanism was utilized to capture the modified beads, and the Dengue virus was modified with fluorescence label, as the detection target. In comparison to previous methods, it required less time, low cost, and small amount of sample [127]. Kwakye et al. designed the electrochemical microfluidic biosensor so that the reporter probe was connected to liposomes containing a redox reagent. On the other hand, the capture probe was connected to supermagnetic particles so that after hybridization and magnetic separation, the lysis of liposomes led to release of $Fe(CN)6^{3-/4-}$, which then quantified by amperometry. The LOD for this microfluidic biosensor has been reported equal to 0.01 μM. The microfluidic methods not only have good capability in detection of Dengue virus, but also is one of the commercial and cheap methods that require small amounts of samples i.e. 3–10 μL of blood sample for analyzing [128].

The other strategy for rapid diagnosis of Dengue virus can be the kit-type of detection systems that have been used in recent years [129] which benefit from rapid assays based on microfluidic dielectrophoresis chips. This new type of biosensor can detect the Dengue virus under 5 min [127]. The simultaneous visual detection of Dengue, Zika and Chikungunya viruses under thirty minutes can be possible using the multiplex kits [130]. The paper-based microfluidic kits are the other interesting bio-devices for rapid assay that make it possible the commercialization of these portable biosensors for Dengue virus diagnosis. But their moderate sensitivity and weakness in control of fluid flow restricted their applications. For this means, the agarose-based papers can be an appropriate material [131]. For broad clinical applications with high rate of assay and accuracy, some commercialized kits are available for early diagnosis of Dengue virus [132, 133]. As a summary of this part, the high rate of assay, acceptable accuracy, portability, easy to use set up, and ability of usage for detection of

Table 2 The reported electrochemical nanobiosensors in detection of Dengue virus

Detection Method	Biomarker	Nanomaterial	Sample	Virus	LOD	Linear range	ΔR_{CT} (%)	Ref
DPV	Clone 3H5, isotype IgG	Nanoporous alumina-modified platinum	–	Dengue type 3	1 pfu. mL^{-1}	1–10^3 pfu. mL^{-1}	–	[99]
CV, EIS	BSA	NanoAu-Concanavalin A-polyvinyl butyral	Blood serum, sera		–	–	162.2, 136.3	[100]
CV, EI	Bauhinia monandra lectin (BmoLL)	AuNP-PANI	Serum, sera	Dengue serotypes 1, 2, 3 and 4	–	–	57.10, 145.60, 35.91, 5.11	[101]
CV, EIS	CramoLL lectin and fetuin	PVB–Fe_3O_4NPs	Serum	Dengue serotypes 1, 2 and 3	–	–	92.61, 4.84	[82]
CV, DPV	DNA oligomer	SiNWs/AuNPs	–	Dengue serotype 1, 2, 3 and 4	1.63×10^{-12} M	1.0×10^{-11}-1.0×10^{-7} M	–	[102]
DPV	5′-aminated DNA	Nanoporous alumina membrane	–	Dengue	9.55×10^{-12} M	10^{-12}–10^{-6} M	–	[103]
CV	Double-stranded DNA (dsDNA)	Chitosan	–	Dengue	–	–	–	[104]
DPV	TS-1P nucleic acid	Graphite	–	Dengue serotype 1	0.92 nM	1–40 nM	–	[105]
DPV	22-m DNA sequence	Graphite	Serum		3.09 nM	10–100 nM	–	[106]
Alpha-A analyzer	Aptamer	Cu_2CdSnS_4	–	Dengue	17 nM	–	–	[107]
EIS	Aptamer	APTES-SiO_2, SiO_2@APTES-GO	–	Dengue	1fM	–	120.4, 223.4	[108]
Multiplex detection method	Peptide nucleic acids (PNAs)	SiNW	RT-PCR amplicon	Dengue serotype 1, 2, 3 and 4	1 pM	–	22.9, 19.88, 28.01, 18.89	[109]
DPV, EIS	DNA oligonucleotides	Aluminum oxide membrane	–	Dengue	2.7×10^{-12} M	1×10^{-12} -1×10^{-6} M	–	[110]
EIS	IgG antibody	Nanoporous alumina	–	Dengue	–	1–900 plaque forming unit per mL	–	[111]
CV, EIS	1,2-dipalmitoyl-sn-glycero -3-phosphocholine (DPPC)	Concanavalin A (ConA) and lipid membranes	Serum glycoproteins	Dengue serotype 1, 2, 3	–	–	5.73, 5.43, 4.89	[112]
EIS	BSA	AuNPs-PVB	Serum glycoproteins		80 dilution fold	10–80 folds	256.0	[113]

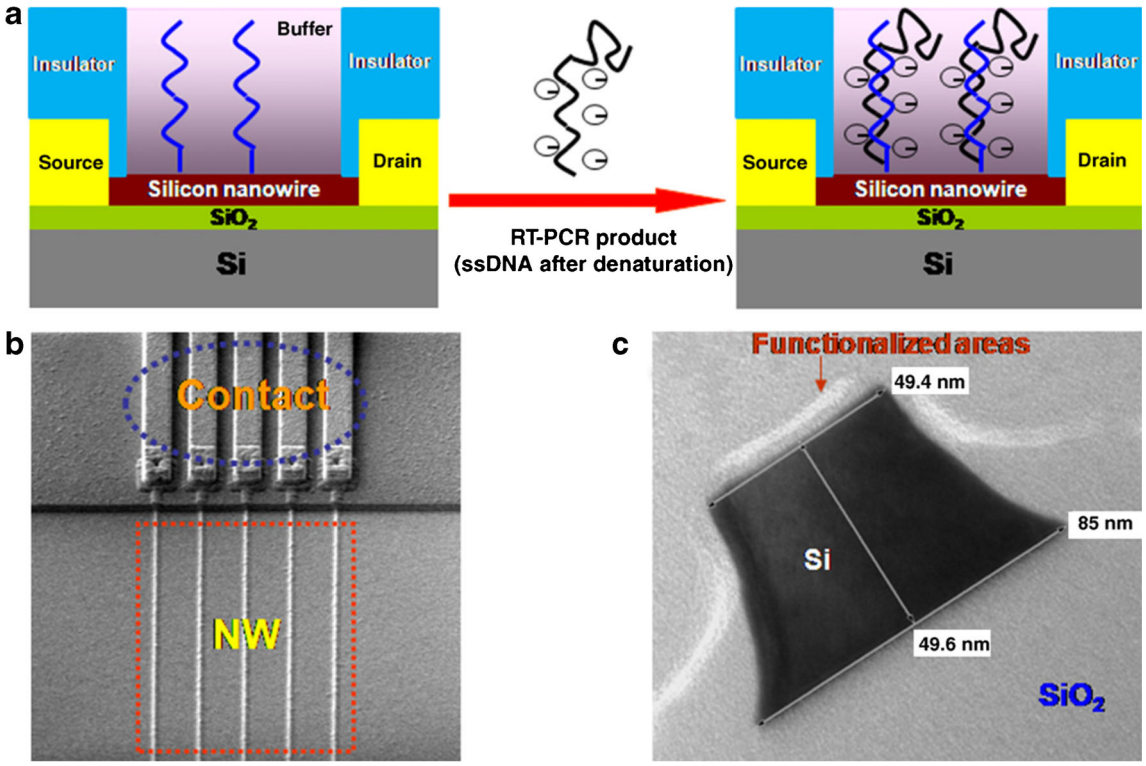

Fig. 13 Nucleic acid-hybrid DNA-based electronic biosensor illustration. **a** immobilized DNA on SiNW and mechanism of their interactions with complementary target DNA of Dengue virus (negative charge induction on Si nanowire), **b** topographical top-view image of nucleic acids-hybrid DNA-based biosensor and (**c**) TEM image of Si nanowire surface that functionalization and hybridization process were both carried out on biosensor surface [119]

Dengue virus in non-blood samples are the main advantages of microfluidics and kits. So, the microfluidic and diagnostic kits are the most capable candidates for clinical applications because of their potentials in small LOC biosensors.

Smart phone-based methods

Thanks to popularity, portability, miniature components, data acquisition and transferring abilities, high-quality camera lenses and cost-effectiveness, the smart-phones are regarded as novel POC devices in nanobiosensing [134]. On the other hand, the easy to use characteristic of biosensors is one of the most vital requirements of them in commercialization process. According to the reports, many of the methods discussed in previous sections do not have this feature. In recent years, using smart phones for this aim attracted many of attentions because of the facilitation of the detection process needless to complex instruments. For this, the smart phone-based point-of-care set up has been fabricated by Ganguli and co-workers which is a microfluidic platform based on real-time RT-LAMP. Basically, this set up is a LOC plat from that can detect the Dengue, Zika and Chikungunya viruses simultaneously. The blood sample date processing was done using smart phone rapidly under 35 min [135]. The coupling of RT-LAMP approach and quenching of unincorporated amplification signal reporters (QUASR) technique is other strategy that can assist to reach the high affordability, acceptable performance, and accuracy. The linear range for this case was from 10^2 pfu to 10^3 pfu and the LOD was 22 pfu.mL^{-1} [136]. Therefore, the smart phone-based biosensors are highly-potent options for affordable, point-of-care approaches. The easy to use, low assay time and high performance are the most important advantages of this method.

Other techniques

As other techniques for the detection of the Dengue virus we can mention the RT-PCR method that enables the simultaneous detection of three pathogens (e.g. Dengue, Zika and Chikungunya viruses) [137–139]. The optomagnetic method coupled with Loop-mediated isothermal amplification (LAMP), with a high rate of assay in ultra-dilute solution of Dengue virus DNA, can be as other method with 100 fM LOD and twenty minutes of detection time [140]; So, as a result, because of the importance of the Dengue virus epidemic the improvement in the novel prospective methods with broad linear range, low LOD, rapid assay and affordability still required.

Conclusion and future perspectives

There is an urgent need for proper and precise detection of Dengue virus. An initial warning system is required for on–time and early diagnosis of virus presence. Abundant types of traditional and novel methods have been conducted for this purpose over decades. For instant, isolation in cell culture, serological testing and PCR are the dominant conventional methods. In recent years, biosensors, such as electrochemical and optical have been revealed for early detection of these pathogens. Both conventional and novel techniques encompass some advantages and disadvantages. For example, isolating as the most direct and conclusive approach for detection is unable to detect virus in early stages since it requires several days and more equipment to be isolate. Moreover, the traditional methods are rigid and time–consuming, which leads to misleading results. Among the mentioned methods, PCR-based techniques such as RT-PCR are able to detect various serotypes of virus more sensitively. However, it is vulnerable to contamination and needs advanced technologies. Overall, the traditional methods are expensive, time consuming and need for expert operators.

In contrast, novel approaches such as electrochemical techniques are cheap, available, and highly sensitive for measurement and characterization of Dengue. Furthermore, one of the main advantages of impedimetric methods is its ability to report charge transfer resistance during hybridization process between probe DNA and target DNAs or between antigen and antibodies affinity interactions. The literature survey show that the development of microfluidic biosensing systems, lateral flow assays, and smart-phone based biosensing strategies will be dominant in the future studies in development of biosensors for Dengue virus detection and diagnosis.

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