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Advances in biosensors and optical assays for diagnosis and detection of malaria

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ABSTRACT

Vector-borne diseases are a major concern for human health globally, especially malaria in densely populated, less developed, tropical regions of the world. Malaria causes loss of human life and economic harm, and may spread through travelers to new regions. Though there are sufficient therapeutics available for the effective treatment and cure of malaria, it infects millions of people and claims several thousand lives every year. Early diagnosis of the infection can potentially prevent the spread of disease, save lives, and mitigate the financial impact. Conventional analytical techniques are being widely employed for malaria diagnosis, but with low sensitivity and selectivity. Due to the poor-resource settings where malaria outbreaks often occur, most conventional diagnostic methods are not affordable and hence not effective in detection and controlling the spread of the infection. However, biosensors have improved the scope for affordable malaria diagnosis. Advances in biotechnology and nanotechnology have provided novel recognition materials and transducer elements, discoveries which allow the fabrication of affordable biosensor platforms with improved attributes. The present work covers the advancement in biosensors with an introduction to malaria, followed by conventional methods of malaria diagnosis, malaria markers, novel recognition elements and the biosensor principle. Finally, a proactive role and a perspective on developed biosensor platforms are discussed with potential biomedical applications.

1. Introduction to malaria

Vector-borne diseases are a major concern for human health globally, and malaria is one of the most serious. Malaria is a fatal infectious disease transmitted to humans by mosquitoes in tropical countries. Infected mosquitoes carry single-celled *Plasmodium* parasites that pass into the human bloodstream through saliva during a mosquito bite. Symptoms of malaria include fever, headaches, chills, vomiting, muscle pain and fatigue, which are often neglected or misdiagnosed as other illnesses. Hence, the morbidity and mortality of malaria are high among poor populations with limited health care facilities (Fig. 1). In 2015, malaria resulted in 429,000 deaths globally, out of which 70% were children (World Health Organization, 2016).

Even though malaria infection can be prevented and treated, one in six people lives in a high-risk area. Human mobility and tourism also spread malaria across the world, especially in countries where malaria has been eradicated. Most health agencies, governments and organizations are actively involved in fund-raising, making policies, training personnel and educating global citizens to eradicate malaria. One major hurdle in eradication is that most of the susceptible regions are economically too weak to support the necessary health care infrastructure and practices. For this reason, developed countries and social service foundations contribute generously and support research and development activities.

Though many control and preventive measures are practiced, the high recent mortality of malaria is attributed to the resistance developed by the parasite to the available medicines and insecticides. The approval of a malaria vaccine (Mosquirix) by the European Union in 2015 was a great step toward the elimination of malaria infection. Malaria diagnosis in its early stages is also vital to prevent the disease's spread, to provide medication at the right time to control the disease in suspects and to reduce mortality. Many conventional and established protocols are available for malaria diagnosis, which include microscopic analysis, immunobased rapid diagnostic test (RDT) kits and nucleic acid–based analytical techniques. These methods are widely employed and highly sensitive toward malaria diagnosis. WHO recommends rapid diagnostic tests (RDTs) for malaria screening and diagnosis among febrile patients.

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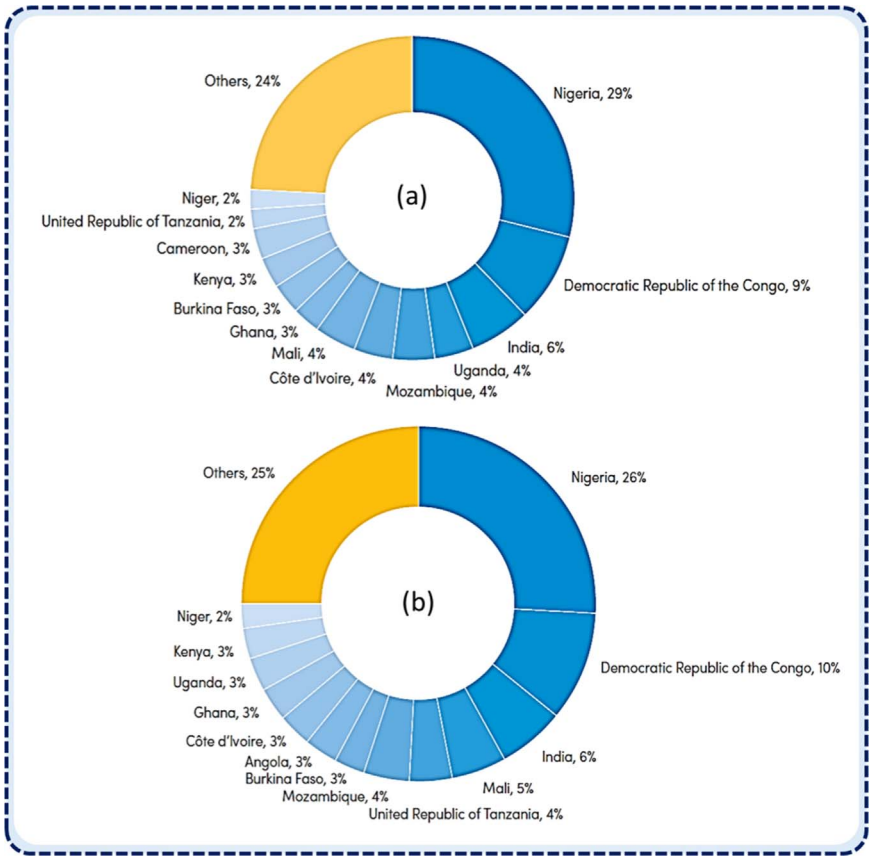

Fig. 1. (A): Estimated country share of total malaria cases in 2015. (B): Estimated country share of total malaria deaths in 2015 (World Health Organization, 2016). Adapted and edited from WHO malaria report 2016 (CC BY-NC-SA 3.0 IGO).

However, most conventional methods carry disadvantages such as requiring multi-step analysis, being time-consuming, requiring costly equipment for analysis and skilled personnel for operation and lacking onsite applicability. Hence, there exists a need for highly sensitive, rapid, simple, low-cost and field-applicable diagnostic methods and sensors for diagnosis and detection of malaria in low-resource settings. Such methods will be highly helpful in eradicating malaria in endemic regions and reducing mortality. Recently developed biosensors have fulfilled some critical requirements and have been successfully demonstrated in laboratory conditions for malaria diagnosis. They offer unexplored potential and are expected to play a major role in eradicating malaria.

In the last decade, the few published reviews have focused mainly on conventional laboratory diagnostic tests for malaria and have not emphasized the novel diagnostic methods (Hawkes and Kain, 2007; Murphy et al., 2013; Murray et al., 2008; Oriero et al., 2015; Roth et al., 2016; Wilson, 2013). In the intervening time, interdisciplinary research work in biotechnology, chemistry, nanotechnology and material science has resulted in major advances in biosensors and bioelectronics for diagnostic application. This review begins by discussing malaria and its transmission, potential biomarkers used as targets for detection and the principle behind conventional methods. Then recent advances such as integration of nanomaterials, electronic devices and novel recognition elements in sensor systems for malaria diagnosis and detection during 2012–2017 are reviewed with respect to their principles, mechanisms and applications. The review aims to provide insight into novel diagnostic methods and concludes with a discussion of the future scope of and trends in malaria diagnosis.

1.1. History

Malaria or a similar disease has infected humans since 1500 BCE, mostly in the tropical regions. More than 100 species of *Plasmodium* are known to cause malaria in humans and animals. Mosquitoes are the only vectors involved in the transmission of malaria from one organism to another. Until the end of the 19th century, the reason for malaria infection was unknown. In 1880, Alphonse Laveran (French army surgeon) camped in Algeria observed *Plasmodium* parasites in the blood of febrile patients and suggested that they were responsible for malaria infection (Mouatcho and Goldring, 2013). In 1897, Ronald Ross, a British officer working in the Indian medical service, demonstrated that mosquitoes act as a vector in transmitting the parasites from infected to healthy people. In 1902, Ross awarded the Nobel Prize for his pioneering work. Due to continuous commitment, research and development activities, malaria was eradicated in the United States by 1950, and tropical countries such as India and Sri Lanka have controlled malaria infection to a great extent. However, in sub-Saharan countries, malaria remains a major contributor to mortality.

1.2. Life cycle of malaria parasites

Malaria in humans is primarily caused by five species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale, Plasmodium knowlesi* and *Plasmodium malariae. Plasmodium falciparum* causes the severe form of malaria that often results in high mortality and morbidity (Snow et al., 2005). Other species cause milder forms of malaria. The *Plasmodium* parasite multiplies by three different routes in the host and the vector. In the first route, an infected female *Anopheles* mosquito bites a person and injects the "sporozoites" from mosquito saliva into the host blood. Sporozoites in the blood vessels travel through the circulation system and enter into liver cells. In the hepatic cells, the sporozoites undergo asexual multiplication, known as schizogony, leading to the production of thousands of infective "merozoites." Eventually, the hepatic cell ruptures and releases the merozoites, which initiates the second route of infection in red blood cells (RBC). In the RBCs, each merozoite divides into numerous merozoites asexually and gets into the

bloodstream by rupturing the cell. At the same time, merozoites in the RBCs will form gametocytes, which further multiply through the union of gametes. In the last route, the gametes unite to form a zygote known as an ookinete, which grows in the mosquito's stomach into an oocyte. Similar to the infected hepatic cell, the oocyte's cell wall is ruptured, releasing sporozoites in the bloodstream, which again divide by one of the routes discussed above (Chenette, 2017; Cowman et al., 2012; Tuteja, 2007).

2. Markers for malaria

Biomarkers indicate the biological state of an organism, often by measuring substances, processes or structures from the sample. The metabolic rate and product formation during a malaria infection are quite different from those of a normal person. Though the function of biomarkers in the host and the parasite may be similar, significant differences in structure are observed and help to diagnose suspected diseased conditions. Enzymes involved in the pathway—such as *Plasmodium falciparum* histidine-rich protein II (*Pf*HRP-II), *Plasmodium falciparum* lactate dehydrogenase (*Pf*LDH), *Plasmodium falciparum* aldolase (*Pf*ALD), *Plasmodium falciparum* hypoxanthine guanine phosphoribosyl transferase (*Pf*HGPRT) and *Plasmodium* glutamate dehydrogenase (*P*GluDH) and products such as hemozoin (Fig. 2)—serve as biomarkers in malaria diagnosis (Jain et al., 2014).

2.1. Histidine rich protein II

Plasmodium falciparum histidine rich protein II (*Pf*HRP-II or HPR-II) is a water-soluble protein, rich in histidine and alanine amino acids confined mostly in the cytoplasm of the parasite. However, substantial amounts of the protein are secreted by the parasite into the host's bloodstream and can be detected in red blood cells, serum, plasma and urine of the infected individuals. Geographical variation in the amino acid sequence of *Pf*HRP-II protein with different structures is reported in the literature. However, due to its presence in various samples of an infected individual, *Pf*HRP-II acts as a biomarker in malaria diagnosis (Mouatcho and Goldring, 2013).

2.2. Lactate dehydrogenase

Plasmodium falciparum lactate dehydrogenase (*Pf*LDH) is one of the most expressed water-soluble enzymes in *Plasmodium falciparum* and is required for anaerobic ATP generation in the parasite. In the last step of glycolysis, the enzyme helps to convert pyruvate to lactate. LDH from other parasite species such as *Plasmodium vivax* Lactate dehydrogenase (*Pv*LDH) has common epitopes and can serve as a biomarker for malaria diagnosis. *Plasmodium* lactose dehydrogenase (*P*LDH) is another common enzyme used as a marker for the parasite irrespective of different species (Barber et al., 2013; Moody, 2002).

2.3. Aldolase

Plasmodium falciparum aldolase (*Pf*ALD) is a homotetrameric protein of size 160 kDa. It plays a major role in energy generation through the parasite's glycolytic pathway by converting fructose-1,6-bisphosphate into glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. The active and soluble form of the enzyme is localized in the cytoplasm of the parasite and also bound to the parasite's membrane. Because aldolase is vital for the survival of parasite, it can be a potential marker or target molecule for the development of sensors for malaria diagnosis (Jain et al., 2014; Manning et al., 2012).

2.4. Glutamate dehydrogenase

Plasmodium glutamate dehydrogenase (*P*GluDH) is an important and ubiquitous enzyme in *Plasmodium* parasites but absent in host red blood cells. It plays an important role in parasite survival and growth by linking the carbon and nitrogen metabolism. Though malaria parasites exhibit various isoforms of *P*GluDH, these enzymes act as a reliable and selective biomarker for malaria diagnosis (Srivastava et al., 2016).

2.5. Hypoxanthine-guanine phosphoribosyl transferase (PfHGPRT)

Plasmodium falciparum hypoxanthine-guanine phosphoribosyltransferase (*Pf*HGPRT) is an important enzyme involved in the purine metabolism of the parasite. Even though a similar protein is found in bacteria and humans, it can serve as a reliable target for malaria diagnosis and therapeutics development (Raman et al., 2005).

2.6. Hemozoin

During a malaria infection, *Plasmodium* parasites consume RBCs as a

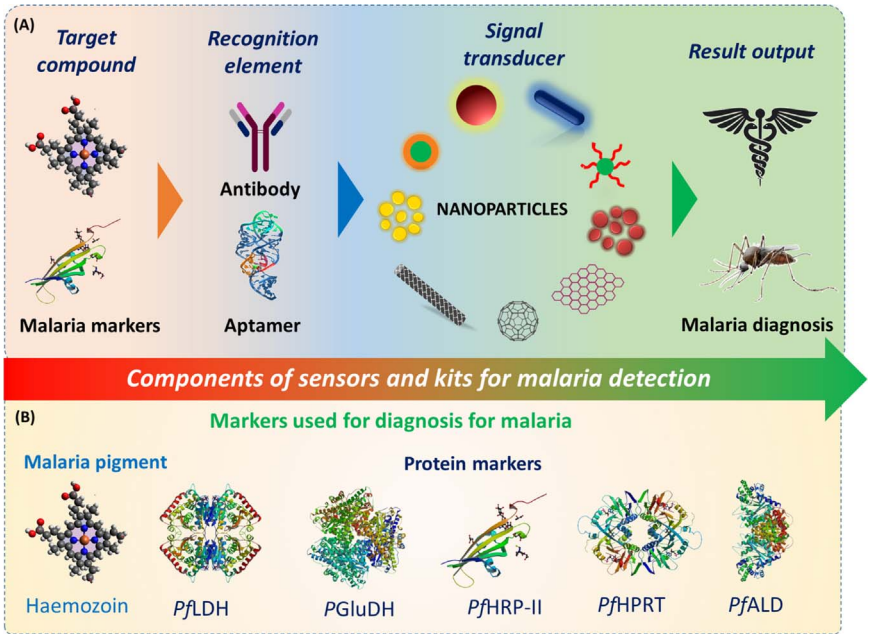

Fig. 2. (A): Components of reported sensors for malaria diagnosis. (B): Commonly used markers in malaria diagnosis.

source of amino acids, leading to the formation of heme, which is quite toxic to the cells. To evade the toxicity of heme and survive, the parasites convert heme into an inert, insoluble, crystalline brownish-red pigment known as hemozoin. In a healthier individual, hemozoin is absent; hence, it acts as a biomarker for diagnosis (Coronado et al., 2014).

Beyond the discussed biomarkers, certain physical and chemical parameters in the parasite and RBCs are used as novel targets for malaria diagnosis in febrile patients. The principles behind the conventional and developed methods are discussed in the following sections.

3. Conventional malaria diagnosis

Diagnosis of malaria at early stages is vital to prevent the spread of malaria and reduce patient mortality through prompt treatment. Conventionally, malaria diagnosis is carried out by empiric/syndromic diagnosis, microscopic analysis, antibody-based rapid diagnostic tests, nucleic acid–based molecular analysis and serological analysis. The most important of these tests are discussed below.

3.1. Microscopic analysis

Microscopic analysis is the “gold standard” for malaria diagnosis. It consists of the microscopic observation of a blood sample as thick or thin smears on a microscopic glass slide aided with staining (Giemsa, Leishman, Romanowsky and Wright stains) using 100× oil immersion objective. The blood sample is mixed with anti-coagulants such as EDTA to avoid coagulation during analysis and is processed immediately to avoid changes in the morphology of the parasite. The advantages of microscopic analysis include quick turnaround time, an ability to determine species (by thin smear), the calculation of the percentage of infected red blood cells in the sample, low expense, the option to store the sample and simple laboratory infrastructure. Diagnostic results from the analysis have an accuracy greater than 75% and can detect as low as 20 parasites per μL of blood sample (Guerin et al., 2002). However, this off-site lab based method requires personnel who are proficient in blood smear analysis and training of those personnel, and gives relatively slower results (Sathpathi et al., 2014; Wilson, 2013). Advanced modes of microscopy such as secondary speckle sensing microscopy and fluorescence in situ hybridization techniques have been reported for improved malaria diagnosis with a higher probability of detection (Cojoc et al., 2012; Shah et al., 2015).

3.2. Antibody-based rapid diagnostic tests

Rapid diagnostic test (RDT) kits are highly recommended for malaria diagnosis in low-resource environments, in the absence of good microscopic facilities and in remote areas. RDTs are basically antibody-based immuno-chromatographic kits that detect either malaria species or malaria antigens. Blood from the patient or suspect is obtained by finger pricking and placed in the RDT strip, which generally provides results within 30 min. Advantages of RDT include onsite analysis, the ability to function without electricity, the ability to detect multiple species, fast results, low cost, the option of using unskilled or less-skilled personnel, and ease of operation and interpretation. Hundreds of varieties of RDT kits are on the market, and this approach is increasingly used for malaria diagnosis in Africa. WHO recommends that suspects undergo either microscopic analysis or RDT to diagnose malaria. It also recommends that the diagnostic kits should fulfill the ASSURED (accurate, sensitive, specific, user-friendly, rapid and robust, equipment-free and deliverable to end users) criteria (Gillet et al., 2011; Mouatcho and Goldring, 2013; Murray et al., 2008; Wilson, 2013; World Health Organization, 2016).

3.3. Nucleic acid amplification tests

Nucleic acid amplification tests (NAATs) rely on detecting the nucleic acid of the malaria parasite. They include loop-mediated isothermal amplification (LAMP), nested, quantitative and real-time quantitative polymerase chain reaction (PCR) and quantitative nucleic acid sequence-based amplification (QT-NASBA) methods. These methods generally include extraction of nucleic acid from a blood sample, followed by amplification of the nucleic acid at a single temperature or range of temperatures. The results are determined by fluorescence in the sample, turbidity or observing bands in agarose gels under UV illumination. Though microscopic analysis and RDT are commonly practiced for malaria diagnosis, they are not sensitive to low parasite density. Therefore, NAATs are preferred for epidemiological and research studies. The advantages of NAATs include high sensitivity, the ability to detect one parasite per μL of blood sample, a qualitative and quantitative test, the detection of multi-parasite infection, the ability to process many samples at a time (high throughput processing) and the ability to detect drug-resistant strains. The disadvantages of NAATs are that they are time consuming and expensive, have poor reproducibility at low concentrations and require good laboratory facilities and skilled personnel (Johnston et al., 2006; Oriero et al., 2015; Roth et al., 2016; Wilson, 2013; World Health Organization, 2016). Some of the improved methods, such as nucleic acid–based lateral flow immunoassay, have better performance (Mens et al., 2012).

Even though the above discussed diagnostic methods involve multiple steps, they are reliable and widely followed in malaria diagnosis (Fig. 3). However, with the advances in bio-technology, material science, nanotechnology and sensor systems in past two decades, many novel diagnostic methods and detection systems have been demonstrated to overcome the drawbacks of conventional diagnostic methods. Developed sensors or diagnostic systems have better sensitivity; are inexpensive, reliable and easy to operate; and allow for multi-species analysis and better record-keeping (Tay et al., 2016; Turner, 2013; Vashist and Luong, 2016; Zhang and Liu, 2016). In the following sections, important sensor and diagnostic systems are grouped and discussed.

4. Sensors for malaria and their classification

4.1. Aptamer-based sensors

Aptamers are novel bio-recognition elements composed of either single-stranded nucleic acid (DNA or RNA) or peptide with a molecular weight below 25 kDa. These unique molecules have defined three-dimensional structural conformation along with the specific property of “induced fit binding,” which gives them high sensitivity and selectivity toward the target molecule. Aptamers are capable of differentiating chiral molecules and can bind from metal ions to bacterial cells. Aptamers specific to any target molecule can be selected from an in-vitro technique known as “systematic evolution of ligands by exponential enrichment” (SELEX). Compared to their counterparts, such as antibodies and enzymes, aptamers are highly specific toward their target molecule with dissociation constants comparable to monoclonal antibodies in the pM range. Furthermore, they are stable over wide range of temperatures, are easy to functionalize and can be produced in a lab without animal cruelty. These properties make them a potential bio-recognition element for onsite-diagnosis biosensors (Bazin et al., 2017; Gopinath et al., 2016; Jo and Ban, 2016; Radom et al., 2013; Ragavan et al., 2013; Seok Kim et al., 2016). Aptamers that are integrated into colorimetric, electrochemical and fluorescence-based biosensors for malaria diagnosis are discussed below.

Lee at al. identified versatile single-strand DNA aptamers for *Pf*LDH, a biomarker for malaria, via the Systematic Evolution of Ligands by Exponential Enrichment (SELEX). The *P*LDH aptamers selectively bind to the target proteins with high sensitivity (Kd = 16.8–49.6 nM) (Lee

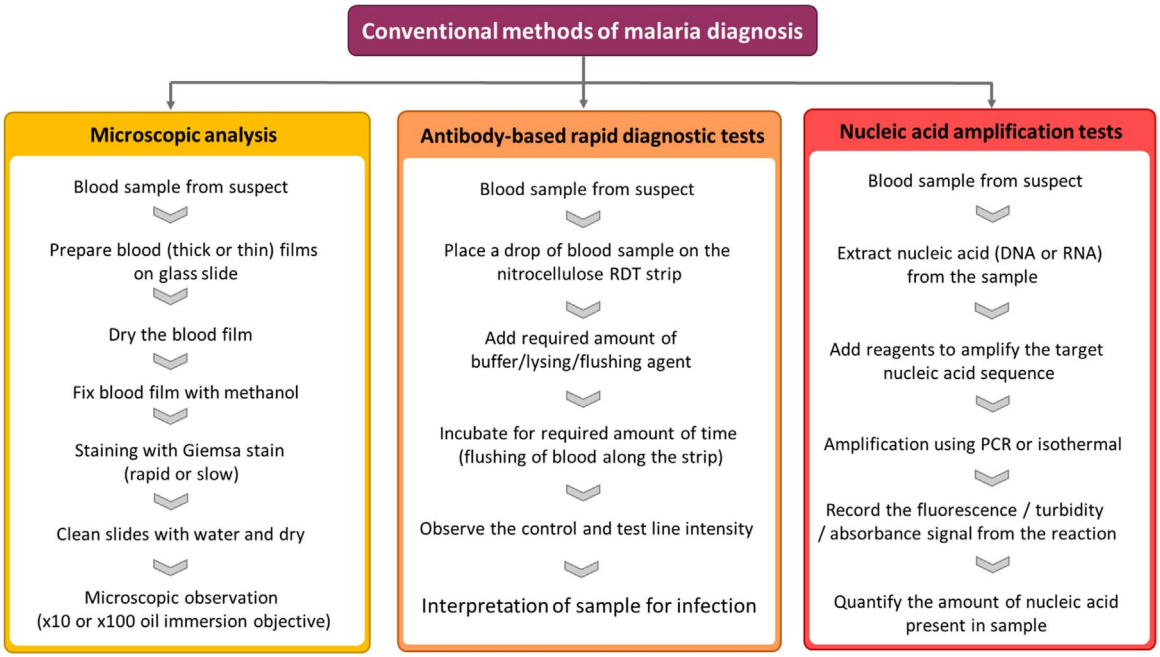

Fig. 3. Classification and steps involved in conventional methods of malaria diagnosis.

et al., 2012). Jeon et al. proposed an aptamer and gold nanoparticle–-based colorimetric sensor for visual malaria diagnosis. They used aptamer (pL1), which is highly specific toward *P*LDH, along with cationic polymers such as poly(diallyldimethylammonium chloride) (PDDA) and poly(allylamine hydrochloride) (PAH) to control the distant dependent color properties of GNPs in the assay. In the absence of the target molecule, the cationic polymers form a duplex with the aptamer through electrostatic interaction between the negatively charged nitrogen bases of the aptamer and the positively charged groups of the cationic polymer, thereby retaining the red color of gold sol. In the presence of the target (*P*LDH), the aptamer will bind more strongly to the enzyme through the "induced fit binding" mechanism. The free cationic polymers in solution will adsorb non-specifically on the GNPs' surface by electrostatic interaction, known as the crosslinked aggregation mechanism. As a result, GNPs come closer and turn blue in color due to a shift in the surface plasmon resonance (SPR) peak toward the longer wavelength. In real samples, this method can detect *P*LDH at pM concentrations and less than 100 parasites per μL in 40 min (Table 1). Moreover, the specificity test proved that the Aptasenor is very specific in targeting proteins over other interfering proteins (Jeon et al., 2013).

In the GNPs and aptamer-based colorimetric assay, a single-stranded aptamer specific to *Pf*LDH (Kd = μM) adsorbs on the GNPs' surface through the electrostatic interaction of positively charged nitrogenous bases and negatively charged citrate ions. In the absence of *Pf*LDH, the aptamer remains adsorbed on the GNPs' surface and protects the GNPs from NaCl-induced aggregation, thereby keeping them dispersed with a red-colored sol. However, if the sample contains *Pf*LDH, aptamers—-being more specific to the target—desorb from the GNPs' surface and bind more specifically with *Pf*LDH, leaving the GNPs aggregated. This results in a purple/blue colored sol. The change in the color of the gold sol is proportional to the concentration of *Pf*LDH in the sample and can be qualitatively correlated for infection with the naked eye, overcoming the requirement of instruments (Jain et al., 2016a). Similar to NaCl-induced aggregation of GNPs, cationic surfactants such as benzalkonium chloride (BCK), cetyltrimethylammonium bromide (CTAB) and didodecyl dimethyl ammonium bromide (DDAB) were used to design a non-crosslinking aggregation-based colorimetric aptasensor for the detection of *Pf*LDH (Jain et al., 2016a; Lee et al., 2014). In the first step of the assay, the aptamer is added to a blood sample from an infected person, and the aptamer, being specific to *Pf*LDH, binds with it. In the following steps, the cationic surfactant and GNPs are added successively, and due to the negligible interaction between the cationic surfactant and the aptamer–*Pf*LDH complex, the former remains free in solution. However, if GNPs are added, the free cationic surfactants aggregate them due to the interaction between positively charged nitrogen atoms of surfactant and the negatively charged citrate ions of GNPs, leading to a color change from red to blue. In blood from a healthy person (a negative sample), due to the absence of *Pf*LDH in the solution, the aptamers and cationic surfactant interact to form a complex through π–π interaction and other weak forces of interaction. With the addition of GNPs to the solution, there is no interaction between the aptamer–surfactant complex (supramolecular structure) and GNPs. As a result, the red color of the dispersed GNPs is retained (Fig. 4). BCK was observed to have improved sensitivity compared with other surfactants with a LOD in pM, which is marginally better than NaCl-induced aggregation (Table 1) (Jain et al., 2016a). In a similar design for a GNP and aptamer-based colorimetric sensor, CTAB was used for the detection of LDH from *P. falciparum* and *P. vivax* with detection limits of 2.94 and 1.25 pM respectively in human serum (Lee et al., 2014).

In one interesting attempt, *Pf*LDH-specific aptamers were used to develop point-of-care device prototypes such as a paper-based syringe test and a solution-based well test for onsite malaria diagnosis. Both prototypes were developed upon an "aptamer-tethered enzyme capture (APTEC) assay" in which a biotin-functionalized, *Pf*LDH-specific aptamer was conjugated with streptavidin-coated microbeads. The microbeads were used to capture the *Pf*LDH in samples. Collected blood samples were lysed and then incubated with the aptamer-functionalized microbeads, and the aptamers present on the surface of the microbeads captured *Pf*LDH and formed a supramolecular complex. In the next step, a development reagent comprising L-lactate, nitrotetrazolium blue chloride (NTB) and 3-acetylpyridine adenine dinucleotide (APAD) dehydrogenase was added. *Pf*LDH converted the L-lactate to pyruvate, and the reaction was coupled with APAD dehydrogenase for the conversion of NTB to diformazan (a blue-colored complex) in positive malaria samples (Fig. 5). The developed color was proportional to the amount of *Pf*LDH present in the sample with a detection limit around 5 ng/mL in both methods. Another important advantage of the proposed method is the low cost, much less than conventional antibody-based RDT (refer to the table in the cited article). Being similar to RDTs, but with better attributes, APTEC is a possible alternative to the

Table 1
Features and performance of the developed sensors, kits and devices for malaria diagnosis.

Principle	Marker/target	Components			Response/detection time	Linearity and limit of detection	Ref.
		Recognition element	Transducer	Output			
Aptamer based sensors							
GNPs based aptasensor	*Pv*LDH and *Pf*LDH	DNA aptamer (pL1)	GNPs with PDDA polymers	Colorimetric assay	40 min	*Pv*LDH: 8.7 pM, 80 parasites per μL *Pf*LDH: 10.3 pM, 92 parasites per μL	(Jeon et al., 2013)
	*Pv*LDH and *Pf*LDH		GNPs with PAH polymers			*Pv*LDH: 8.3 pM 74, parasites per μL *Pf*LDH: 12.5 pM, 97 parasites per μL	
GNPs based aptasensor	*Pv*LDH *Pf*LDH	DNA aptamer (pL1)	GNPs with CTAB	Colorimetric assay	40 min	*Pv*LDH: 1.25 pM *Pf*LDH: 2.94 pM	(Lee et al., 2014)
GNPs based aptasensor	*Pf*LDH	DNA aptamer (p38)	GNPs with NaCl GNPs with BCK	Colorimetric assay	45 min	55 pg per μL 38 pg per μL	(Jain et al., 2016a)
Aptamer-tethered enzyme capture (APTEC) assay	*Pf*LDH	*Pf*LDH specific DNA aptamer	Aptamer decorated microbeads	Syringe based colorimetric assay Well based colorimetric assay	Less than 1 h	5 ng per mL 4.9 ng per mL	(Dirkzwager et al., 2016)
Electrochemical sensors							
Aptamer based EIS sensor	*Pf*LDH *Pv*LDH	5' thiol modified DNA aptamer (pL1)	EIS with gold electrode	Impedance (Nyquist plots)	1 h	*Pf*LDH: 120.1 fM *Pv*LDH: 108.5 fM	(Lee et al., 2012)
Electrochemical immunosensor	*Pf*HRP-II	Monoclonal antibodies specific to *Pf*HRP-II	Copper doped ZnO nanofiber	Impedance response	–	LOD: 6.8 ag per mL Sensitivity: 28.5 kΩ/(g/mL)/cm^2	(Brince Paul et al., 2016)
Aptamer based electrochemical sensor	*Pf*LDH	*Pf*LDH specific aptamer P38(SSDNA)	GO functionalized GCE	Impedance and voltammetry response	10 min	0.5 fM	(Jain et al., 2016b)
Aptamer based impedance sensor	*Pf*LDH	5'-Thiol modified DNA aptamer (2008s)	Gold electrode	Cyclic voltammogram and EIS readings	–	0.84 pM	(Figueroa-Miranda et al., 2018)
Label free electrochemical detection	Infected RBC	Antibody specific to infected RBCs (mAbD2)	AuNPs electrodeposited on SPE	EIS	10 min	10^2–10^8 cells per mL	(Kumar et al., 2016)
Nanofiber based flexible chemiresistive biosensor	HRP-II	HRP-II specific antibodies	Disposable PET based electrode	Change in resistance	30 min	LOD: 0.97 fg per mL Sensitivity: 8.29 kΩ g^{-1} mL	(Paul K et al., 2017)
CNT based electrochemical biosensor	CSP protein 210-247	Antibodies specific to CSP	CNTs coated SPE	Cyclic Voltammetry, EIS and square wave voltammetry	30–60 min	6 pg per L to 70 μg per L	(Cardoso et al., 2017)
Immunosensors							
GNPs based Immunosensor	*Pf*HRP-II	Monoclonal antibody specific to *Pf*HRP-II	Screen printed gold electrodes functionalized with GNPs	Cyclic Voltammetry measurement	–	2.95 ng per mL	(Hemben et al., 2017)
		Monoclonal antibody specific to *Pf*HRP-II with horse radish peroxide tagged probe antibodies		Cyclic Voltammetry based on oxidized TMB signals	–	40 pg per mL	
Electrochemical magneto Immunoassays	*Pf*HRP-II	Monoclonal IgG and IgM antibodies specific to *Pf*HRP-II	Magnetic nanoparticle with graphite-epoxy composite	Optical measurement and electrochemical signal	–	0.36 ng per mL	(de Souza Castilho et al., 2011)
LAMP based detection							
RealAMP method	Genus specific DNA	Genus specific primers	SYBR green dye bound to amplified ds DNA	Fluorescence intensity	Around 40 min	*Plasmodium falciparum:* 1–100 parasites per mL *Plasmodium vivax* and *Plasmodium ovale:* 10 parasites per mL	(Lucchi et al., 2010)
Isothermal recombinase polymerase amplification	18S rRNA gene	Oligonucleotide Primers	GNPs tagged with antibodies	Colorimetric	Less than 20 min	100 fg	(Kersting et al., 2014)

(*continued on next page*)

Table 1 (*continued*)

Principle	Marker/target	Components			Response/detection time	Linearity and limit of detection	Ref.
		Recognition element	Transducer	Output			
AnyMDx: LAMP based microfluidic device	Genomic DNA of *Plasmodium falciparum*	Parasite specific primers	Calcein bound to amplified ds DNA	Fluorescence	40 min	0.6 parasites per μL	(Choi et al., 2016)
Colorimetric sensors							
μPad based on Indicator displacement method	*Pf*HRP-II	Murexide dye and Ni^{2+}	Competitive displacement of Murexide dye from its complex with Ni^{2+} by *Pf*HRP-II	Microfluidic paper based colorimetric assay	5 min	LOD: 30 ± 9.6 nM Linear range: 10–100 nM	(Chakma et al., 2016)
Fluorescence sensors							
FRET based MoS_2 aptasensor	*P*LDH	FAM labelled *P*LDH aptamer	Single layer MoS_2 nanosheets	Fluorescence emission at 527 nm	10 min	LOD: 3.9 nM	(Kenry et al., 2016)
FRET based MoS_2 aptasensor using surface blocking strategy	*P*LDH	FAM labelled *P*LDH aptamer	MoS_2 nanosheets with BSA	Fluorescence signals at 527 nm	Less than 30 min	LOD: 19.2 ng per mL (550 pM)	(Geldert et al., 2017)
Surface plasmon resonance sensors							
Apo-hemoglobin based SPR sensor	Heme	PAA conjugated with Apo-hemoglobin	Self-assembled amine monolayer on Au chip	SPR response	Less than 10 min	LOD: 2 μM (1.3 μg per mL)	(Briand et al., 2012)
Surface enhanced Raman spectroscopy							
Butterfly wing based SERS sensor	Hemozoin crystals in blood lysate	Gold coated *Graphium weiskei* butterfly wings as SERS substrate		Raman signals	Less than 10 min	0.005–0.0005% of infected RBCs	(Garrett et al., 2015)
Silver nanorods based SERS sensor	*Plasmodium falciparum* infected RBCs	Silver nanorods based SERS substrate		Raman spectra	Less than 10 min	1.5×10^7 per mL	(Chen et al., 2016)
Quartz crystal microbalance sensors							
Piezoelectric immunosensor	*Pf*HRP-II	*Pf*HRP-II specific IgG antibodies from rabbit	Thioctic acid & 1-dodecanethiol SAM on gold surface of quartz crystal	Frequency change proportional to concentration	–	12 ng per mL	(Sharma et al., 2011)
QCM based DNA Biosensor	Amplified specific DNA	Biotinylated DNA probe specific to *Plasmodium*	Hybridization between amplified & immobilized probe	Shift in frequency	–	Sensitivity: 10 μg per mL	(Ittarat et al., 2013)
Silver fabricated QCM	DNA fragment of 18S rRNA gene	Biotinylated DNA probe specific to *Plasmodium*	Biotinylated Probe on silver surface	Shift in frequency	30 min	100 μg per mL	(Wangmaung et al., 2014)
Real time measurement cytoadhesion using QCM	*P. falciparum* infected erythrocytes	CD36 & CSA receptors	CD-36 & CSA functionalized gold coated quartz surface	Shift in frequency	2.5 h	1.5×10^5 infected RBCs per mL	(Kömpf et al., 2016)
Lab on a chip and microfluidic devices							
Rolling circle amplification based Microfluidics platform	*Plasmodium* topoisomerase I (*P*TopI)	Specific DNA sequence of *Plasmodium*	Binding of fluorescein and rhodamine dye with rolling circle products	Fluorescent dots	2.5 h	Less than 1 parasite per mL in unprocessed blood 60 parasites per mL in saliva samples	(Juul et al., 2012)
Paper based sensors							
2-D Paper network based immunoassay	*Pf*HRP-II	Murine *Pf*HRP-II antibody	Gold enhancement reagent	Colorimetric	20–40 min	2.9 ng per mL	(Fu et al., 2012)
Microfluidic blood-plasma separation device integrated with paper based sensor	*Pf*HRP-II	*Pf*HRP-II specific antibody conjugated to eosin	Polymerization based signal amplification	Colorimetric	–	7.5 nM to naked eye in whole blood sample	(Shatova et al., 2016)
Multiplexed Patterned- Paper Immunoassay	Malaria: HRP-II and *P*LDH Dengue: NS1- type 2	Monoclonal antibodies specific to each target molecule	Colloidal GNPs conjugated with anti-bodies	Colorimetric	–	10–50 parasites mL	(Deraney et al., 2016)
Paper based device based on Lateral Flow Immunoassay (LFA) with micellar two phase system	*P*LDH	Monoclonal antibodies specific to *P*LDH	GNPs conjugated with anti-bodies	Colorimetric	20 min	1.0 ng per μL	(Pereira et al., 2015)
Cellphone based sensors							

(*continued on next page*)

Table 1 (*continued*)

Principle	Marker/target	Components			Response/detection time	Linearity and limit of detection	Ref.
		Recognition element	Transducer	Output			
Cellphone based RDT reader for lateral flow immunochromatographic assay	*Pf*LDH	Monoclonal antibodies specific to *Pf*LDH	RDT kit and CMOS sensor	Quantification of test line color intensity	Image processing in less than 0.2 s	–	(Mudanyali et al., 2012)
Universal mobile based electrochemical immunosensor detector	*Pf*HRP-II	*Pf*HRP-II specific antibodies	Horse radish peroxidase tagged antibodies and oxidation of TMB on a SPE	Chronoamperometric responses	Electrochemical response: 20 s Overall immunoassay: 3–4 h	20 ng per mL	(Nemiroski et al., 2014)
Mobile based electrochemical immunosensor	*Pf*HRP-II	*Pf*HRP-II specific antibodies	Horse radish peroxidase tagged antibodies and oxidation of TMB	Electrochemical response	30 min	16 ng per mL	(Lillehoj et al., 2013)
Optical imaging							
Hemozoin- generated vapor nanobubbles for detection of malaria	Hemozoin in infected RBC	Formation of vapor nanobubble	Near infrared picosecond laser pulse	Pressure (acoustic) pulse of H-VNB	Few seconds	0.00034% of infection	(Lukianova-Hleb et al., 2014)
Miscellaneous sensors							
Nucleic acid based amplification	*P. falciparum* DNA	Three specific probes of target DNA	Mach-Zehnder Interferometer	Based on phase change	Less than 60 min	Less than 1 parasite per μL	(P.Y. Liu et al., 2016; Q. Liu et al., 2016)
Coffee ring like colorimetric sensor	*Pf*HRP-II	Ni(II)nitrilotriacetic acid (NTA)	Gold coated polystyrene particles	Visual detection, intensity of ring proportional to concentration of *Pf*HRP-II	75 min	10 pM	(Gulka et al., 2014)

conventional RDT kit for malaria diagnosis in low-resource settings (Dirkzwager et al., 2016).

4.2. Electrochemical sensors

Electrochemical sensors consist of electrodes and an electrochemical unit for measuring the changes in current, impedance, conductance, voltage or potential difference in the system. Electrodes act as transducers and are often improved with various nanomaterials and by conjugating a layer of a bio-recognition element on their surface for better selectivity (Wan et al., 2013). In most sensor systems, the larger surface area and the electrical and catalytic properties of the nanomaterials are used to improve the signals of redox reactions. Electrochemical systems carry the advantages of sensitivity, reproducibility of results, simplicity of operation, low cost and possibility of real-time application (Bollella et al., 2017; Chen and Chatterjee, 2013; Du et al., 2011; Zhu et al., 2015). Electrochemical-based diagnostic systems for malaria diagnosis are discussed below.

A copper-doped ZnO nanofiber-based electrochemical immunosensor has been demonstrated for sensitive detection of *Pf*HRP-II. In the developed sensor, nanofibers were synthesized using an electrospinning technique, coated on a glassy carbon electrode and further functionalized with mercaptopropylphosphonic acid (MPA). Monoclonal antibodies specific to *Pf*HRP-II were adsorbed on the electrode surface through MPA (Fig. 6). A hybrid nanostructure improved the impedance response of the electrode with a sensitivity of 28.5 kΩ/(g/mL)/cm^2. As a result, the charge transfer resistance of the electrode was observed from μg to ag levels of *Pf*HRP-II, with a detection limit of 6.8 ag/mL (Brince Paul et al., 2016). To improve the specificity of the electrochemical sensor, an ssDNA specific to *Pf*LDH was used to immobilize the electrode surface using graphene oxide (GO) as an immobilization matrix (Jain et al., 2016b). Aptamer–GO-coated electrodes have a better charge transfer resistance, which improved the sensitivity of the impedance-based detection of *Pf*LDH. To ascertain the activity of LDH, it was coupled with NAD/NADH, which resulted in lactate formation. The current response from the electrode was proportional to the amount of LDH in the blood sample, correlated with the lactate concentration with a detection limit of 0.5 fM (Table 1).

Recently, a highly sensitive and selective aptamer-based electrochemical impedance spectroscopy (EIS) sensor was reported. In the electrochemical sensor, a thiol-capped, *Pf*LDH-specific DNA aptamer was functionalized on a gold electrode surface through Au-S bonds, and the blank regions were functionalized with 6-mercaptohexanol. The binding of aptamer with *Pf*LDH at different pH resulted in varied responses with potassium ferricyanide as a redox probe. If the pH was less than the pI of *Pf*LDH (pH 8), it resulted in the attraction of ferricyanide ions toward the electrode surface with low impedance. If the reaction pH was above the pI of *Pf*LDH, the ferricyanide ions were repelled from the electrode surface, leading to enhanced impedance, which resulted in better sensitivity of the electrochemical sensor. The reported method has a detection limit of 0.84 pM in tenfold-diluted serum samples with a good reusability of the electrode for multiple analysis (Figueroa-Miranda et al., 2018).

Evolving amino acid sequences and the dynamic structure of the malarial markers are a part of an evasion mechanism followed by the parasites, which makes them less reliable than whole RBCs for malaria diagnosis. An antibody-based EIS sensor was demonstrated for label-free, whole-cell detection of malaria-infected RBCs. An SPE surface was electrodeposited with GNPs, a process that facilitates the binding of antibodies and improves the electrochemical performance of the sensor. Monoclonal antibodies specific to the parasite-infected RBCs were immobilized on the electrode surface. These antibodies specifically recognized the infected RBCs in the sample, leading to enhanced impedance signals compared to healthier RBCs in the sample. An infected cell concentration in the range of 10^2–10^7 cells/mL induced a change in charge transfer and impedance in the sensor (Kumar et al., 2016).

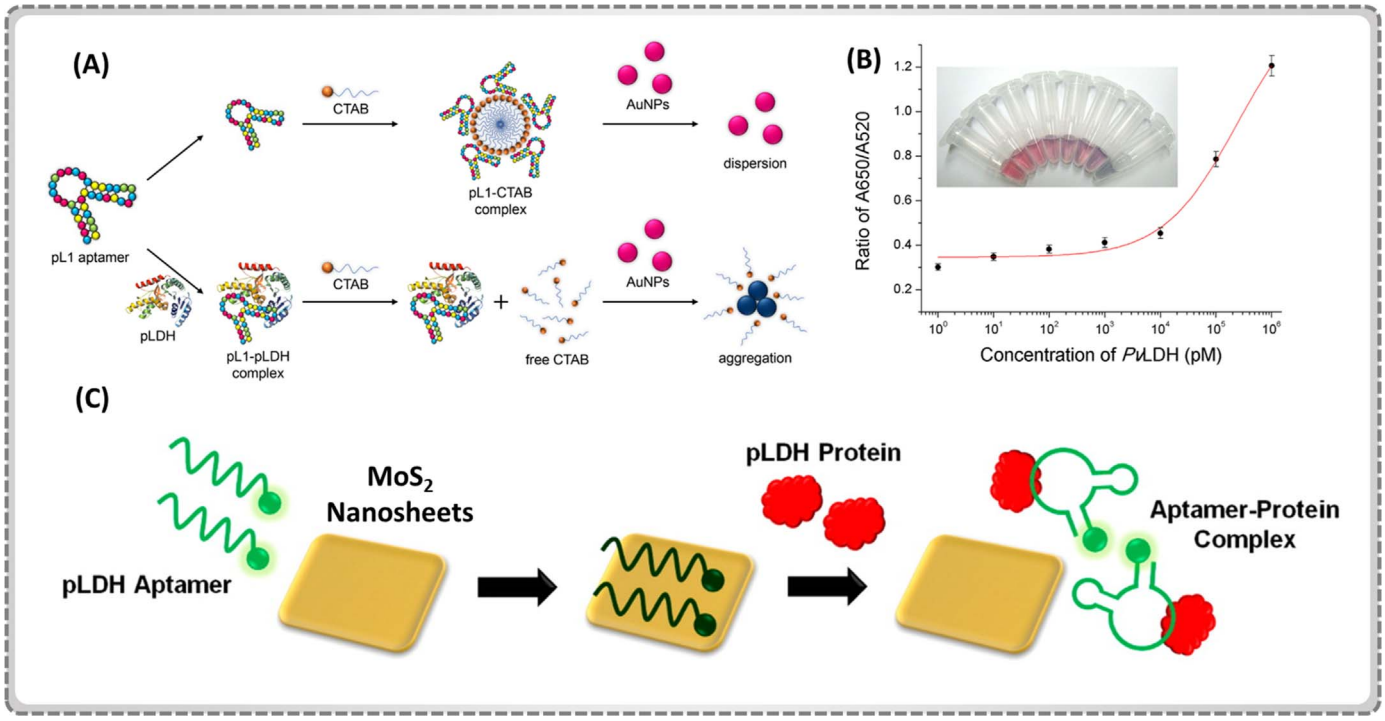

Fig. 4. (A): Working principle of cationic detergent (CTAB) and gold nanoparticle based colorimetric aptasensor for the detection of *P*LDH. (B): Visual and colorimetric response of the aptasensor for different concentrations of *P*LDH (Lee et al., 2014) (CC BY 4.0). (C): MoS_2 nanosheets and FAM labelled aptamer based FRET sensor for the detection of *P*LDH. "Reprinted with permission from Kenry et al. (2016). Copyright {2016} American Chemical Society".

A multi-walled carbon nanotube (MWCNT) and zinc oxide (ZnO) nanofiber composite-based chemiresistive biosensor for the detection of HRP-II has been demonstrated. Instead of conventional electrodes, they used a thin, flexible film of polyethylene terephthalate (PET), which is inexpensive and suited for onsite diagnosis in low-resource settings. A PET surface is spattered with gold to form source and drain electrodes on its surface by photolithography. The gap between the source and drain electrodes was then coated with MWCNT–ZnO nanofibers through an electrospinning technique. Antibodies specific to HRP-II were covalently conjugated to the carboxyl terminal of the ZnO nanofibers through amide bond formation. If HRP-II was present in the sample, it bound to the antibody on the electrode surface and led to a change in the resistance of the electrodes. The developed biosensor had a detection limit of 0.97 fg/mL with a sensitivity of 8.29 kΩ/g/mL and a linear response in the range of 10 ng/mL to 10 fg/mL (Paul K et al., 2017).

In a recent work, a new mechanism involving recognition between antigenic molecules such as circumsporozoite protein (CSP) and thrombospondin-related anonymous protein (TRAP) with circulating antibodies is reported. The SPE surface was functionalized with an amino group for the binding of CSP and TRAP, which selectively recognizes circulating antibodies and elicits an electrochemical signal at a low concentration of 6 pg/L up to 70 µg/L in serum samples (Cardoso et al., 2017). In the future, screen-printed and paper electrode–based electrochemical sensors are poised to play a major role in developing compact sensors for onsite diagnosis.

4.3. Immunosensors

Immunosensors are one of the most successful sensor platforms, with applications ranging from disease diagnosis to food safety (Abhijith et al., 2013; Sagaya Selvakumar et al., 2013). An immunosensor uses antibodies as a recognition element, which have high affinity toward the target molecule (antibody–antigen complex) with a low dissociation constant in the nanomolar range. They are protein molecules composed of four polypeptides linked by disulphide bonds with two antigen binding sites (regions for binding target molecules). Different classes of antibodies—such as polyclonal (affinity toward different parts of the molecule), monoclonal (affinity toward a single, specific part of a molecule) and recombinant antibodies—are used to develop enzyme-linked immune sorbent assays (ELISA), lateral flow assays, dipsticks, RDTs and various biosensor platforms (Fig. 7). Antibodies are widely used because of their high sensitivity, ease of functionalization with nanoparticles and molecules, reproducibility, reliable results and low cost. Monoclonal and recombinant antibody-based diagnostic kits and assays have great market potential, play a major role in malaria diagnosis in low-resource settings and provide point-of-care testing (Holford et al., 2012; Wan et al., 2013; Wilson, 2013).

The role of nanomaterials in improving the sensitivity of an ELISA-based immunosensor for the detection of *Pf*HRP-II has been demonstrated. In the assay, monoclonal antibodies specific to *Pf*HRP-II were adsorbed on the screen-printed gold electrode surface, which binds with the *Pf*HRP-II in the sample. In the simple immunoassay, the detection limit was found to be 2.95 ng/mL in serum samples. To improve the sensitivity, they conjugated GNPs with horseradish peroxidase–tagged anti-*Pf*HRP-II antibodies, which acted as a detection probe by oxidizing TMB to generate electrochemical signals. Based on the cyclic voltammetry readings, the sensitivity of the immunosensor improved to 40 pg/mL in serum samples (Hemben et al., 2017).

Similar to the work described above, magnetic nanoparticles have been used to improve the sensitivity of the electrochemical immunosensor for the detection of *Pf*HRP-II. In the fabrication of the sensor, *Pf*HRP-II-specific monoclonal IgM antibodies were functionalized on a magnetic nanoparticle surface, which captures the target from the sample. Another monoclonal IgG antibody specific to *Pf*HRP-II conjugated with horseradish peroxide was used as a probe for colorimetric detection and electrochemical signal generation (Fig. 8). With the developed strategy, a detection limit of 0.36 ng/mL of *Pf*HRP-II in spiked serum samples was reported, which is better than conventional immunoassays (Table 1) (de Souza Castilho et al., 2011). Most recent detection platforms for immunosensors are electrochemical systems (discussed in an earlier section) compared to colorimetry.

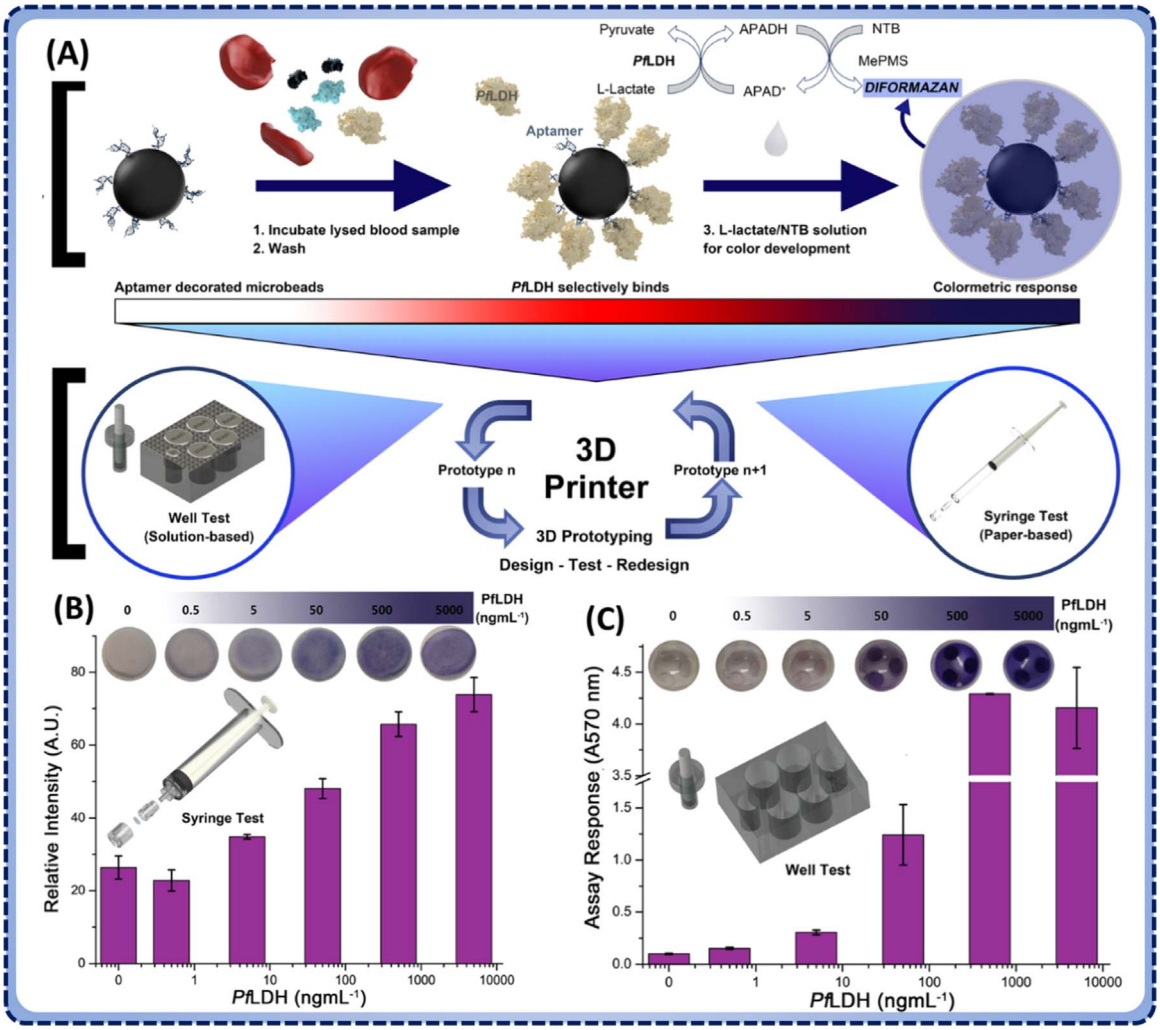

Fig. 5. Working principle and construction of 3D printed well and syringe based APTEC prototype device with gold coated polystyrene beads. (B): Response of well based APTEC for various concentrations of *Pf*LDH. (C): Response of syringe based APTEC for for various concentrations of *Pf*LDH. "Reprinted with permission from Dirkzwager et al. (2016). Copyright {2016} American Chemical Society".

4.4. Loop-mediated isothermal amplification

Loop-mediated isothermal amplification (LAMP) is a novel molecular technique increasingly employed for malaria diagnosis. In this method, target DNA is amplified using specific primers along with *Bst* polymerase at isothermal conditions (60–65 °C). The whole reaction takes around 1 h, and the DNA amplification process produces magnesium pyrophosphate as a by-product, which causes turbidity in the solution. Turbidity in the solution is directly correlated with target DNA in the sample. For the visual detection of target DNA, manganese ions and calcein (green fluorescent dye emits light due to the formation of a metal complex with divalent ions) are added along with the reagents in the reaction. LAMP includes isothermal operation, unlike polymerase chain reaction (PCR), a difference which circumvents the need for expensive equipment like a thermal cycler, overcomes the use of EtBr (carcinogen, used as an intercalating and fluorescent tag in PCR). LAMP is also faster than PCR (PCR takes around 3 h), reliable and relatively inexpensive. A final advantage of LAMP is that, unlike in PCR, the reaction is not inhibited by components present in the blood sample, such as antibodies and hemoglobin. Overall, LAMP is the simplest and yet sensitive method available for molecular diagnosis of various diseases including malaria (Abdul-Ghani et al., 2012; Han, 2013; Tomita et al., 2008).

In an interesting study, a fluorescence-based LAMP method was demonstrated for real-time malaria diagnosis (RealAmp method). Initially, DNA from the parasite was extracted using a hot water method, which is simple and efficient compared to conventional DNA extraction protocols. DNA coding for 18s RNA was amplified with the help of primers at 63 °C using Bst polymerase in 90 min. SYBR green dye binds specifically to the double-stranded DNA (amplification product) and emits green light, which can be quantified using an ESEQuant tube scanner. Even though the developed method uses equipment, it is field applicable, sensitive (40 parasites per μL) and reliable (Lucchi et al., 2010). A new process similar to LAMP known as “isothermal recombinant polymerase amplification” was demonstrated for malaria diagnosis in suspects’ blood samples (Fig. 9). In this method, a specific sequence in the 18s RNA of *P. falciparum* was amplified at 38 °C for 10 min. The amplified product (amplicon) was visualized through a gold nanoparticle–based lateral flow assay. The amplified target sequence is tagged with digoxigenin at the 5’ end, whereas the complementary sequence used to hybridize with the target is tagged with carboxyfluorescein at the 5’ end. The lateral flow strip was developed by conjugating digoxigenin-specific antibody at the test line and anti-rabbit antibodies at the control line. Gold nanoparticles are conjugated with the polyclonal antibody from rabbits against carboxyfluorescein and serve as optical tags. If the sample contains the target sequence, it is amplified and binds at the test line through immune-complex formation between the digoxigenin of amplicon and antibodies at the test line. In

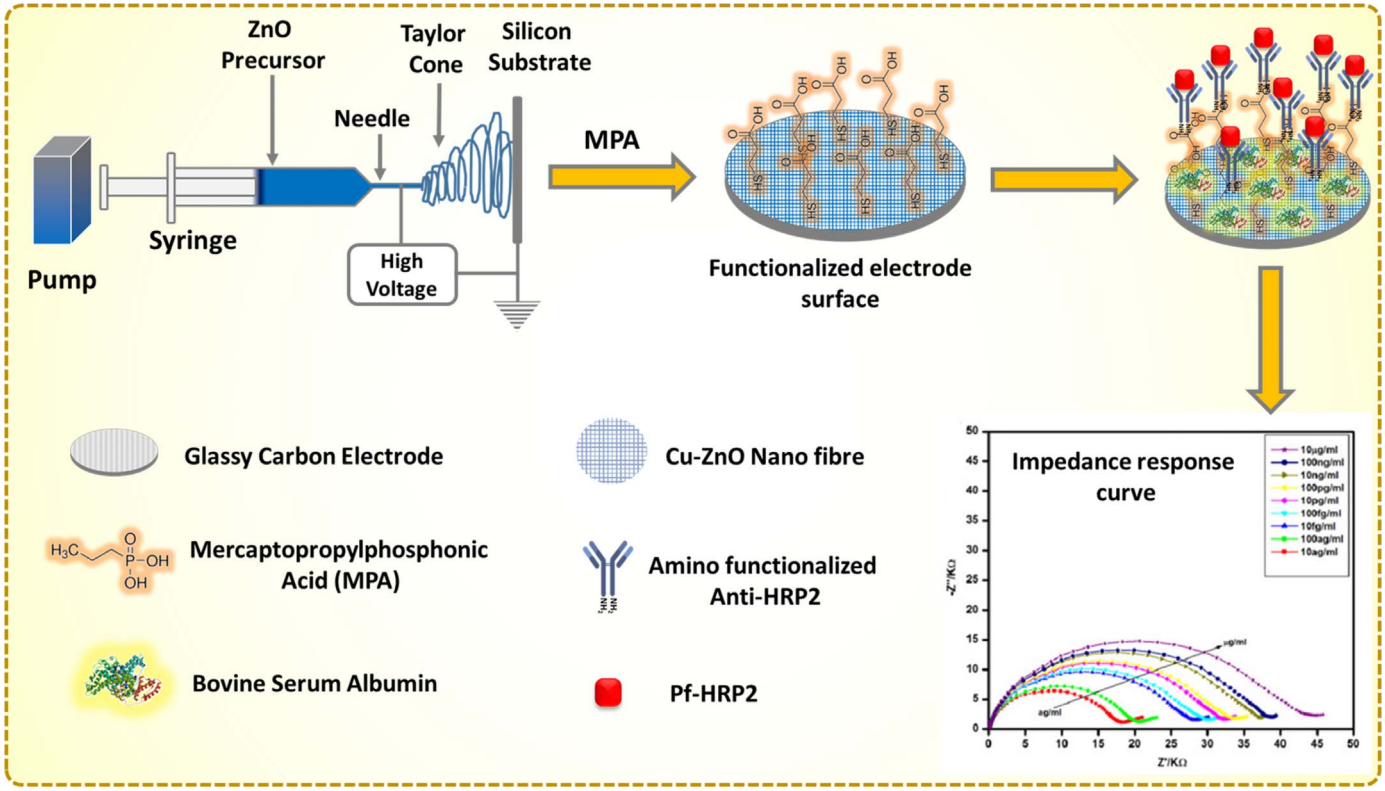

Fig. 6. (A): Working principle of ZnO nanofiber based impedance sensor for the detection of *Pf*HRP-II (Brince Paul et al., 2016).

the next step, antibody-tagged gold nanoparticles will bind to the other end of the amplicon and produce a colored line on the test strip. The method is highly selective for *P. falciparum* and can detect 100 fg of target DNA in less than 20 min, with the advantage of onsite application (Table 1) (Kersting et al., 2014).

A highly sophisticated LAMP-based microfluidic prototype device named "AnyMDx" was designed and built for portable onsite malaria diagnosis. The device contains a microfluidic compact disc that purifies DNA from the blood lysate sample using magnetic beads and amplifies the biological target using 6 different parasite-specific DNA primers. The overall time required for the assay is 40 min, and the amplified product is monitored in real time using fluorescence analysis. The developed method has a detection limit of 0.6 parasite per μL and costs 176 USD for the prototype device and 1.14 USD per sample (Choi et al., 2016).

4.5. Optical sensors

4.5.1. Colorimetric biosensors

Colorimetric sensors use the strong light absorption properties of metal nanoparticles to serve as optical tags in various sensor platforms such as aptasensors, immunosensors, lateral flow assays, dipsticks and others (Fig. 4). Gold and silver sol have high molar extinction coefficients in the visible region of electromagnetic radiation, which leads to brightly colored sol at nanomolar concentrations. Another reason for the bright color of gold and silver sols is the localized surface plasmon resonance (LSPR) phenomenon. Incident light resonates with the surface plasmons of noble metals' nanostructures if the particle size is smaller than the wavelength of the incident light and the color can be tuned over the visible region by size, composition and surface capping. The intense color of these sols are 3–4 orders higher than dyes and also offer advantages such as surface functionalization and catalytic and electrical properties (Ragavan et al., 2013; Sharma et al., 2015).

Label-free colorimetric sensor for the detection of *Pf*HRP-II in serum samples based on indicator displacement assay was proposed by Goswami and his coworkers (Chakma et al., 2016). In the work, murexide complexed with nickel ions is used as a colorimetric indicator which forms an orange complex with absorption at 482 nm. In the presence of *Pf*HRP-II, the complex is broken, and the murexide turns pink with adsorption at 515 nm, proportional to the concentration of *Pf*HRP-II in the serum sample with a detection limit of 1 pM. For real-time application, the proposed method was fabricated in the form of a microfluidic paper-based analytical device (μPAD) using chromatographic paper. μPAD requires a much smaller sample (20 μL) and has been found to be linear between 10 and 100 nM with a detection limit of 30 nM for *Pf*HRP-II within 5 min. The developed method costs 0.07 USD per analysis and is reported to have a detection time of 5 min, which enables it as a promising prospect for novel paper-based sensors for malaria diagnosis in low-resource settings (Table 1). Some GNP-based colorimetric sensors are discussed in the earlier aptamer-based sensor section.

4.5.2. Fluorescence sensors

Fluorescence is the emission of light during the transition of a molecule from an excited state to the ground state. The emitted light usually has a lower energy and a longer wavelength than the excitation source (Stokes shift), as observed in fluorescence dyes, proteins, nanoclusters and quantum dots (QDs). On the contrary, emitted light has higher energy and shorter wavelength compared to its excitation source (anti-Stokes shift), a peculiar phenomenon observed in up-conversion nanoparticles. QDs are semiconductor nanoparticles with a size less than 10 nm. They have distinct size-dependent emission properties, a better quantum yield than dyes and photo stability (Kairdolf et al., 2013). Nanoclusters are smaller nanostructures than QDs, composed of a few atoms of a metal or a combination of metals, and exhibit interesting fluorescent properties (Tao et al., 2015). Up-conversion nanoparticles are novel nanostructures composed of lanthanide series elements that can emit light in the visible region by absorbing light in the infrared region. They have better properties than QDs in terms of chemical and physical stability, ease of functionalization, non-toxicity

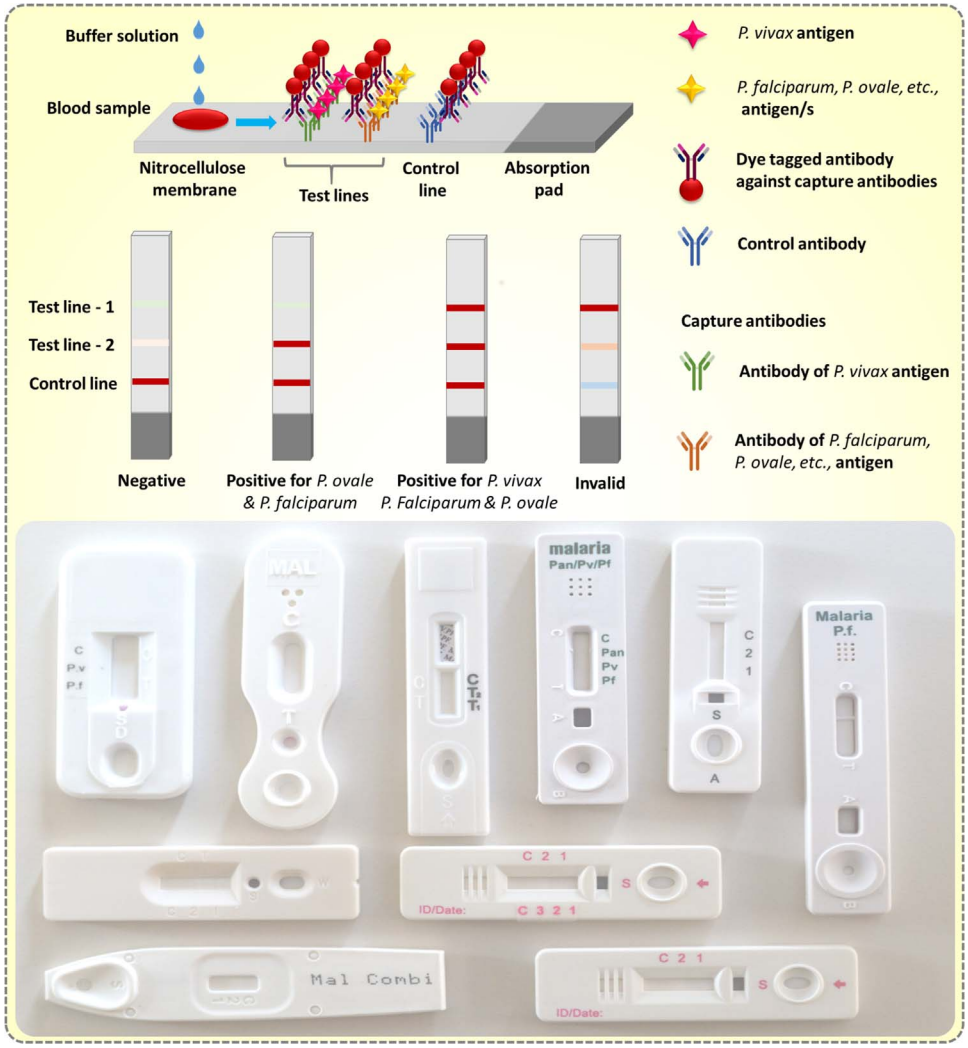

Fig. 7. (A): Principle behind lateral flow immunoassay for the diagnosis of different *Plasmodium* species. (B): Commercially available immuno based RDT kits (Gillet et al., 2011) (CC BY 2.0).

and low background noise (Wang et al., 2011; Weng and Neethirajan, 2016). These nanomaterials are used as fluorescent tags in the development of fluorescence sensors for malaria detection and diagnosis.

Apart from the above-discussed property, 2D nanomaterials with large surface areas such as graphene and transition metal dichalcogenide (TMD) nanosheets are good fluorescence energy quenchers (Lee et al., 2016; Tian et al., 2017). A recent study demonstrated an aptamer specific to *P*LDH functionalized with 6-carboxyfluorescein (FAM) and a single-layer MoS_2 nanosheet-based "capture release" fluorescent sensor for the detection of *P*LDH. In the assay, if the sample was negative without *P*LDH, the FAM-labelled aptamer was adsorbed on the surface of MoS_2 nanosheets through weak forces of interaction, without fluorescence emission at 527 nm. The aptamer and MoS_2 nanosheets were close enough within the Forster radius, so fluorescence energy from the FAM was transferred to the MoS_2 nanosheets through the fluorescence resonance energy transfer (FRET) process (Fig. 4). In the case of positive samples, the aptamer, being specific to *P*LDH, desorbed from the MoS_2 nanosheet surface and bound with it. As a result, the FAM-labelled aptamer and MoS_2 nanosheets were beyond Forster radius and FRET did not occur, leading to an emission peak proportional to the concentration of *P*LDH in the sample (Table 1). The target molecule at a concentration of 3.9 nM induced a change in the intensity of fluorescence emission within 10 min (Kenry et al., 2016). Non-target proteins in the blood/serum sample adsorbed non-specifically on the MoS_2 surface and increased the fluorescence signals, resulting in higher values than actually present in the sample. To overcome the nonspecific adsorption of non-target molecules, BSA was used as a surface blocking agent, a step which significantly improved the specificity and sensitivity of the assay (Geldert et al., 2017). The developed sensor design has improved attributes, but it requires a fluorimeter to quantify the signals from the assay.

The cloning and expression of fluorescent protein probes in malaria parasites have been demonstrated for designing fluorescent biosensors for measuring the amount of heme in cells (Wißbrock and Imhof, 2017). In the sensor, two fluorescent proteins—enhanced cyan and yellow fluorescent proteins (ECFP and EYFP)—were linked by *Pf*HRP-II for a FRET-based fluorescent sensor. *Pf*HRP-II has the capacity to bind 15–18 heme molecules non-specifically with a low affinity of 0.3 μM. The binding of heme with *Pf*HRP-II should have led to fluorescence energy transfer from ECFP to EYFP; however, the fluorescence intensity was totally quenched in the "turn-off" sensor. It was found that binding of heme to *Pf*HRP-II led to a conformational change of protein structure, but heme quenches the fluorescence statically and dynamically proportional to the heme concentration (Abshire et al., 2017). In the future, a similar mechanism can be used for malaria diagnosis based on the concentration of heme in healthy and infected cells.

4.5.3. Surface Plasmon Resonance sensors

Surface Plasmon Resonance (SPR) is a novel biosensor technique used for the detection of analytes by measuring the changes on the chip surface and refractive index due to ligand–target interaction. It is one of the most preferred biosensor platforms due to its high sensitivity, label-

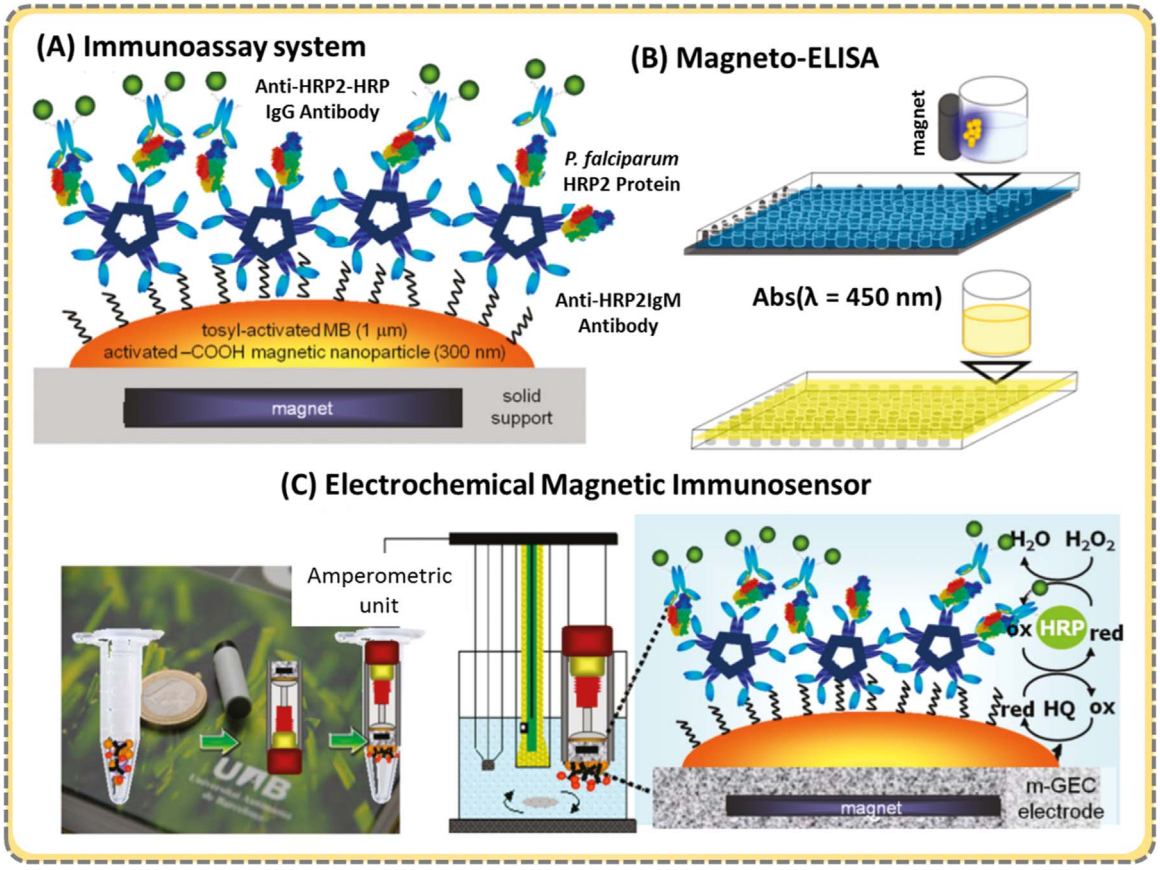

Fig. 8. (A): Magnetic immunoassay format involving IgM and IgG antibodies specific to *Pf*HRP-II. (B): Magnetic nanoparticle based ELISA assay. (C): Magnetic nanoparticle based electrochemical sensor with HRP based catalytic reaction for generation of electrochemical signals. "Reprinted with permission from de Souza Castilho et al. (2011). Copyright {2011} American Chemical Society.".

free detection and the minimal sample preparation required during analysis. In a typical setup, near-infrared or infrared radiation of known intensity is passed through a prism of high refractive index coated with a thin layer (< 100 nm) of noble metal on the prism surface. Due to the change in the refractive index at the junction of the aqueous sample and prism surface, the total internal reflection of the incident radiation occurs at an angle. Part of the incident light intensity is lost at the metal junction, is converted into plasmons and travels on the thin metal surface. Any biological, physical or chemical event on the chip surface leads to a change in the refractive index, which changes the angle and intensity of the reflected light. The change in the reflected wave properties is measured and correlated for quantification of the analyte (Homola, 2008).

An SPR sensor was demonstrated to characterize and screen

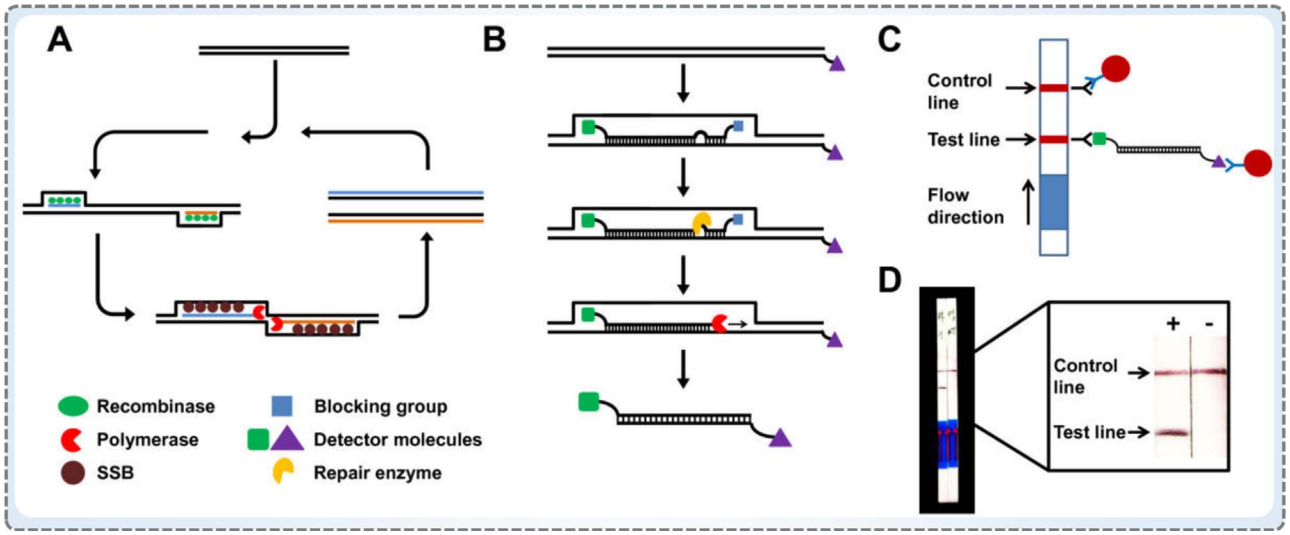

Fig. 9. Reaction principle and strategy in the recombinase polymerase amplification based later flow assay for malaria diagnosis. (A): Amplification strategy in the assay. (B): Labelling and hybridization of target sequence. (C): Working principle of the gold nanoparticle based lateral flow assay based on sandwich immunoassay format. (D): Image showing the lateral flow strip for the diagnosis of malaria in a sample (Kersting et al., 2014) (CC BY 2.0).

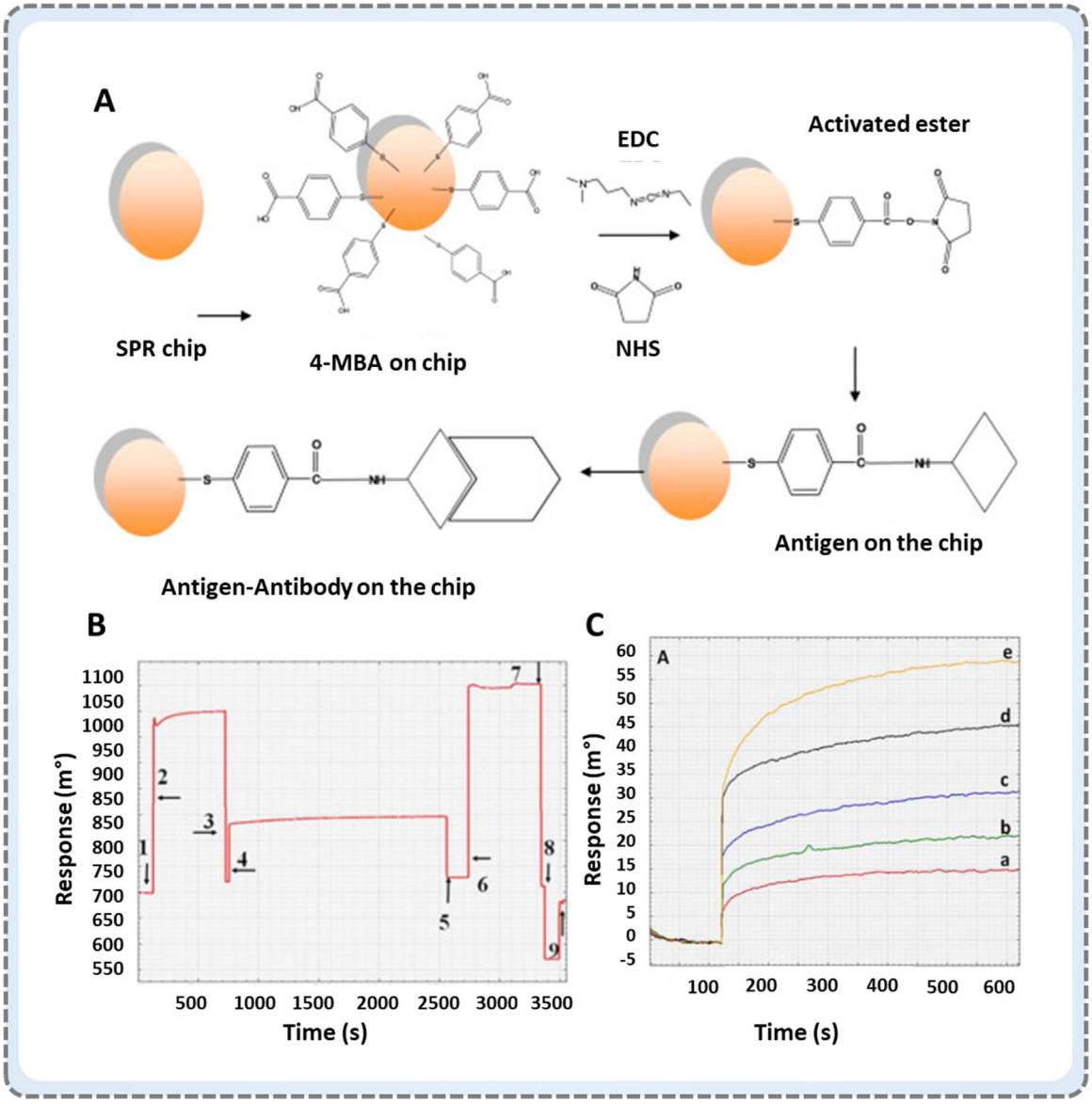

Fig. 10. (A): Various immobilization steps involved in the preparation of the SPR chip. (B): Response from the SPR sensor chip during various steps of the assay. (C): Response of SPR sensor to dilution of antibody and antigen (Sikarwar et al., 2014).

appropriate bio-recognition elements (monoclonal and polyclonal *Pf*HRP-II) for the fabrication of a malaria sensor (Fig. 10). To create this sensor, a gold-coated SPR chip was coated with recombinant HRP-II through 4-mercaptobenzoic acid conjugation. The binding of the antibody to the HRP-II on the chip induced a shift in the reflected angle with respect to the antibody's sensitivity. It was found that monoclonal antibodies had better sensitivity than polyclonal antibodies with a detection limit in picograms (Sikarwar et al., 2014).

In another work, an SPR chip was functionalized with monoclonal antibodies specific to *Pf*LDH through DSP and protein A. The presence of *Pf*LDH in the sample led to a change in the refractive index which was proportional to the concentration of the biomarker in the sample (Cho et al., 2014). In a further interesting work, a novel bio-recognition was used for the fabrication of an SPR-based heme sensor. A gold-coated SPR chip surface was covalently functioned with polyacrylic acid and hemoglobin forming a protein–polymer complex. Heme from the complex was selectively removed, leading to the formation of an apoprotein polymer complex, which acts as a highly sensitive and selective bio-recognition element for heme. The sensor has a detection limit of 2 μM of heme in serum, and the SPR chip can be reused 12 times without compromising its performance (Table 1) (Briand et al., 2012). An SPR-based sensor can be a potential candidate for fabrication of highly selective and sensitive label-free point-of-care devices. However, miniaturization of the overall equipment is desired for onsite and real-time monitoring.

4.5.4. Surface-enhanced Raman spectroscopy

Surface-enhanced Raman spectroscopy (SERS) is a highly sensitive optical technique that is drawing interest for the development of sensors and analysis. The enhancement is mainly due to long-range amplification of the electromagnetic field and short-range amplification of chemicals by novel plasmonic materials (Guven et al., 2011; Yang et al., 2016). Ag and Au are preferred for their enhancement factor and stability compared to Cu, metallic alloys and novel nanomaterials such as graphene, quantum dots and TiO_2 (Sharma et al., 2012; Wang et al., 2013).

A novel SERS substrate was designed using the sharp conical structure of butterfly (*Graphium weiskei*) wings for the development of a highly sensitive SERS sensor for malaria diagnosis. The conical structures of the wing were coated with a thin gold film that acts as a

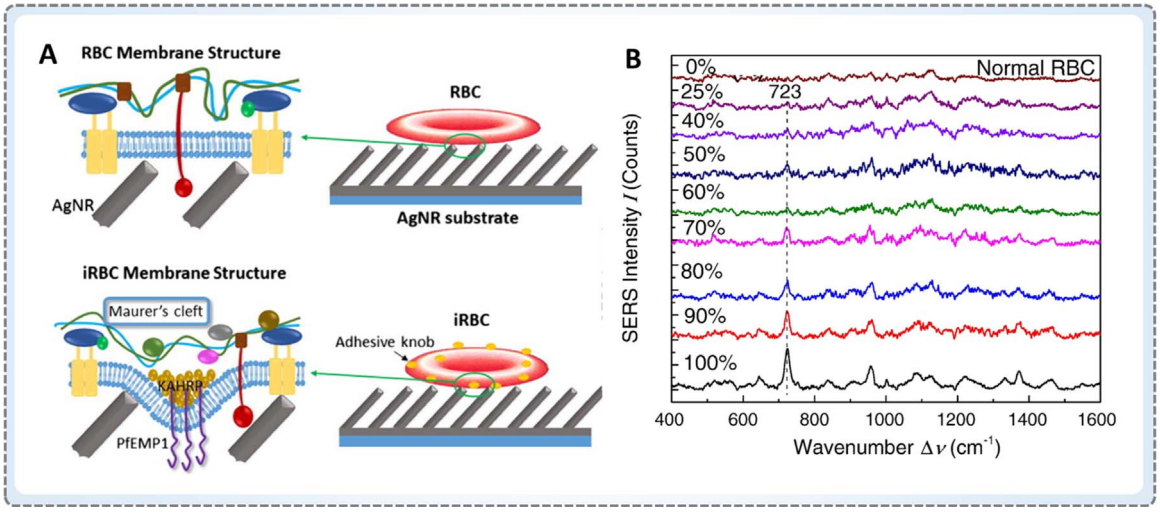

Fig. 11. (A): Interaction of the cellular components with the AgNRs of the SERS sensor for malaria diagnosis. (B): Change in the intensity of Raman signals at 723 cm^{-1} from the samples containing various proportion of normal RBCs and schizont stage infected RBCs (Chen et al., 2016).

plasmonic material for enhancement of Raman signals. Based on the interaction of hemozoin crystals with the SERS substrate, malarial infection in the early-stage levels of 0.0005–0.005% can be detected through the change in Raman signals from the blood lysate (Table 1). This work offers the scope of naturally available, inexpensive materials such as SERS substrate for the large-scale fabrication of biosensors (Garrett et al., 2015).

An attempt has been made to differentiate infected and healthy RBCs based on Raman signal enhancement using silver nanorods (AgNRs) (Fig. 11). Infected RBCs have distinct Raman spectra due to the expression of *Plasmodium* specific proteins. As discussed earlier, silver-based nanostructures enhance the weak Raman signals, a process which improves the sensitivity of the assay by 10^8 times. With the enhanced signals, infected RBCs in different stages can be differentiated, and malaria infection can be detected (Chen et al., 2016). However, for onsite application, a miniaturized portable device is preferred.

4.6. Quartz crystal microbalance sensors

Quartz crystal microbalance (QCM) sensors work on the principle of the piezoelectric effect, i.e., a change in mass on the crystal surface leads to a shift in the frequency of the electric current. A QCM sensor fundamentally contains a thin slice of circular quartz crystal positioned between two circular metallic electrodes on its opposite faces. In biosensor fabrication, gold electrodes are commonly employed, and the area covered by the electrodes constitutes the active surface from which the frequency is picked up. In a typical biosensor platform consisting of a liquid sample, the signal measurement does not follow the classical mass-frequency relationship described by Sauerbrey. The viscoelastic properties of the fluid also influence the frequency on the crystal surface; however, the variations in the calculations are insignificant with the working concentrations of target compounds in biosensors (Mecea, 2006; O'Sullivan and Guilbault, 1999; Skládal, 2016). To improve the sensitivity of QCM sensors, recognition elements such as antibodies, aptamers, ribozymes and receptors are often included in the design. The advantages of QCM biosensors include precise measurements, real-time measurement in flow-based models, selectivity and sensitivity to nanogram concentrations.

In a typical QCM setup, a gold-coated quartz crystal surface was coated with rabbit IgG antibody for selective detection of *Pf*HRP-II through EDS-NHS conjugation. For better adsorption and proper orientation of the antibodies, a self-assembled monolayer of thioctic acid and 1-dodecanethiol was formed on the gold film. The presence of the antigen in the samples causes an immunoreaction with the IgG antibodies, which elicits a frequency change in the circuit proportional to the antigen's concentration. The sensor had good sensitivity in the nanogram range (Table 1) and retained more than 50% of its activity after 2 weeks of storage. The sensor's advantages compared to electrochemical sensors are that the former avoids multiple steps and is label-free, simple, and reusable (Sharma et al., 2011).

In another study, oligonucleotide-based silver-coated quartz crystal was used as a resonator for the detection of *P. falciparum* and *P. vivax*. To improve the specificity toward the pathogenic DNA, specific oligonucleotide sequence was used as a probe by conjugating it on the silver film through avidin–biotin linkage. Three different primers were selected to amplify the target DNA from the parasite through PCR amplification. In the presence of the target DNA, in the PCR conditions, DNA is amplified and leads to hybridization with the target oligonucleotide on the crystal surface. A change in mass on crystal surface because of hybridization leads to a frequency shift, which is proportional to the number of parasites in the blood sample. This method is highly sensitive, reliable and selective for malaria diagnosis (Ittarat et al., 2013).

The same research group has improved the performance of the QCM sensor with additional features such as the detection of mixed infections (Fig. 12). Avidin was conjugated on a silver-coated crystal surface through mercaptopropionic acid and EDC-NHS based covalent conjugation, which improves the conjugation stability. In a similar fashion, the probe oligonucleotide was conjugated by avidin–biotin mediated conjugation. The genomic DNA was initially extracted and amplified in PCR conditions with the help of two reverse primers specific to the parasites, which enabled the sensor to detect the infection with different ratios of parasites. The sensor was found to be highly stable (after 180 days), field applicable, low cost, highly sensitive and selective (Wangmaung et al., 2014).

In an interesting study, researchers have used unique recognition elements for malaria diagnosis. Cyto-adhesion is one of the important virulence properties of the parasites displayed in the later stages of infection to overcome the host's immune system. Cyto-adhesion occurs between the infected cell and the receptors of endothelial cells (CD36 and Chondroitin sulfate A), leading to the coagulation of blood and blockage of blood vessels in important organs. A gold-coated quartz crystal surface was conjugated with CD36 and Chondroitin sulfate-A through poly-lysine linkage. Interaction of infected cells with the above receptors on the QCM surface leads to an increase in mass, triggering a shift in frequency relative to the amount of infected cells in the sample. This sensor opens a new avenue for the selection of highly specific recognition elements and malaria diagnosis (Kömpf et al., 2016). Overall,

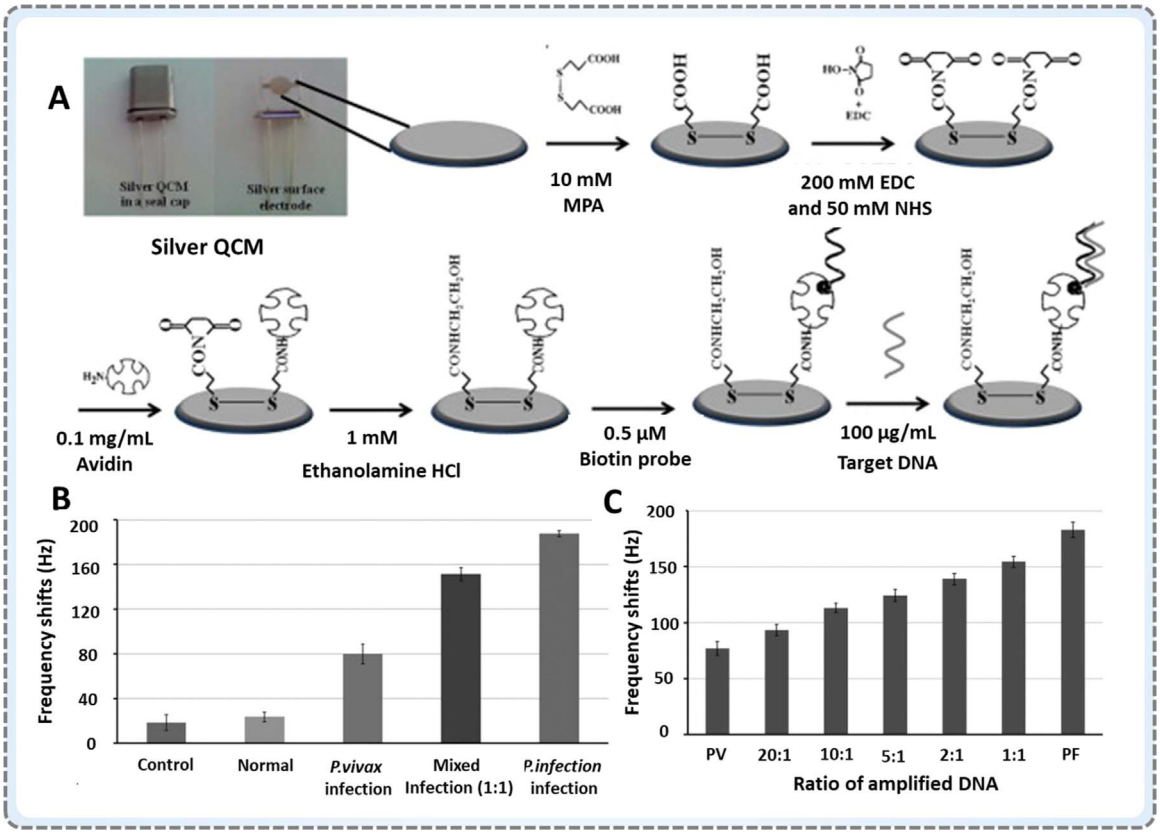

Fig. 12. (A): Immobilization steps involved in the fabrication of QCM sensor for malaria diagnosis. (B): Shift in the frequency with different isolated and mixed infection. (C): Frequency shifts from different ratio of amplified DNA in the sample (Wangmaung et al., 2014).

QCM-based sensors are highly sensitive, and their features are improved with novel recognition elements.

4.7. Lab-on-a-chip and microfluidic devices

Microfluidic lab-on-a-chip sensors are miniature devices that integrate multiple functions of various sensing platforms to be performed together using low-volume samples. This process therefore requires less sample, reagents and energy for efficient operation along with the interesting effects on fluid properties (reduced viscosity, flow kinetics and surface tension) at the micro scale (Lafleur et al., 2016). Microfluidic lab-on-a-chip devices are being widely researched for potential application in the fabrication of point-of-care devices for diagnosis.

In one interesting study, a rolling-circle enhanced enzyme activity detection (REEAD) system consisting of *Plasmodium* topoisomerase I (*P*TopI) was combined with a droplet microfluidics– based lab-on-a-chip platform for the sensitive diagnosis of malaria (Fig. 13). *P*TopI is a highly specific endogenous enzyme that catalyzes the cleavage and ligation of single-stranded DNA into numerous micrometer-sized rolling circle products (RCP). The formation of RCPs can be visualized by conjugating the products with fluorescein and rhodamine dye. Due to the enhanced enzymatic activity of the *P*TopI, the reported method can detect *Plasmodium* parasites with a sensitivity of 0.06 parasites per µL in unprocessed blood and saliva samples of suspects (Table 1) (Juul et al., 2012). Even though the price of microfluidic chip-based sensors is higher than that of paper-based sensor platforms, the former has the potential to detect a very low number of parasites in unprocessed blood samples, which helps in malaria diagnosis in the initial stages of infection.

4.8. Paper-based sensors

Paper-based sensors are one of the most preferred detection platforms for malaria diagnosis. In this category, a novel gold nanoparticle amplified immunoassay in the form of a 2D paper network-based lateral flow test was recently demonstrated. In the fabricated kit, different wells containing buffer, gold enhancement reagent and sample pads were placed adjacent in the design to facilitate the lateral flow of reagents for color development. On the test line, a murine antibody specific to *Pf*HRP-II was coated as a capture reagent for the antigens in the sample. To visualize the binding reaction, a secondary antibody specific to *Pf*HRP-II tagged with GNPs was used as an optical tag. To improve the signal intensity, a gold enhancement reagent was used, which bound with the GNPs; the size of GNPs increased, leading to a high-intensity blue color. Even though the amplification of signals took 20 min longer than an unamplified immunoassay, the amplified assay had an improved detection limit of 2.9 ng/mL. The method fulfills the ASSURED requirements for diagnostic kits recommended by WHO (Fu et al., 2012).

To overcome the complex sample matrix in malaria diagnosis, a novel microfluidic device capable of efficient separation of blood plasma and RBCs has been designed and reported. The portable device is hand driven and reduces clogging and fouling in the device through appropriate design. From the separated plasma, the concentration of *Pf*HRP-II was detected through a paper-based colorimetric sensor (Shatova et al., 2016).

Generally, fever is a common symptom for many of the parasite-based infections. To ascertain the nature of the infection, a patterned paper-based immunosensor for the detection of malaria and dengue has been reported. In the sensor, HRP-II, LDH and dengue non-structural protein (NS1) type 2 are used as target molecules in the blood lysate, using respective monoclonal antibodies as capture antibodies.

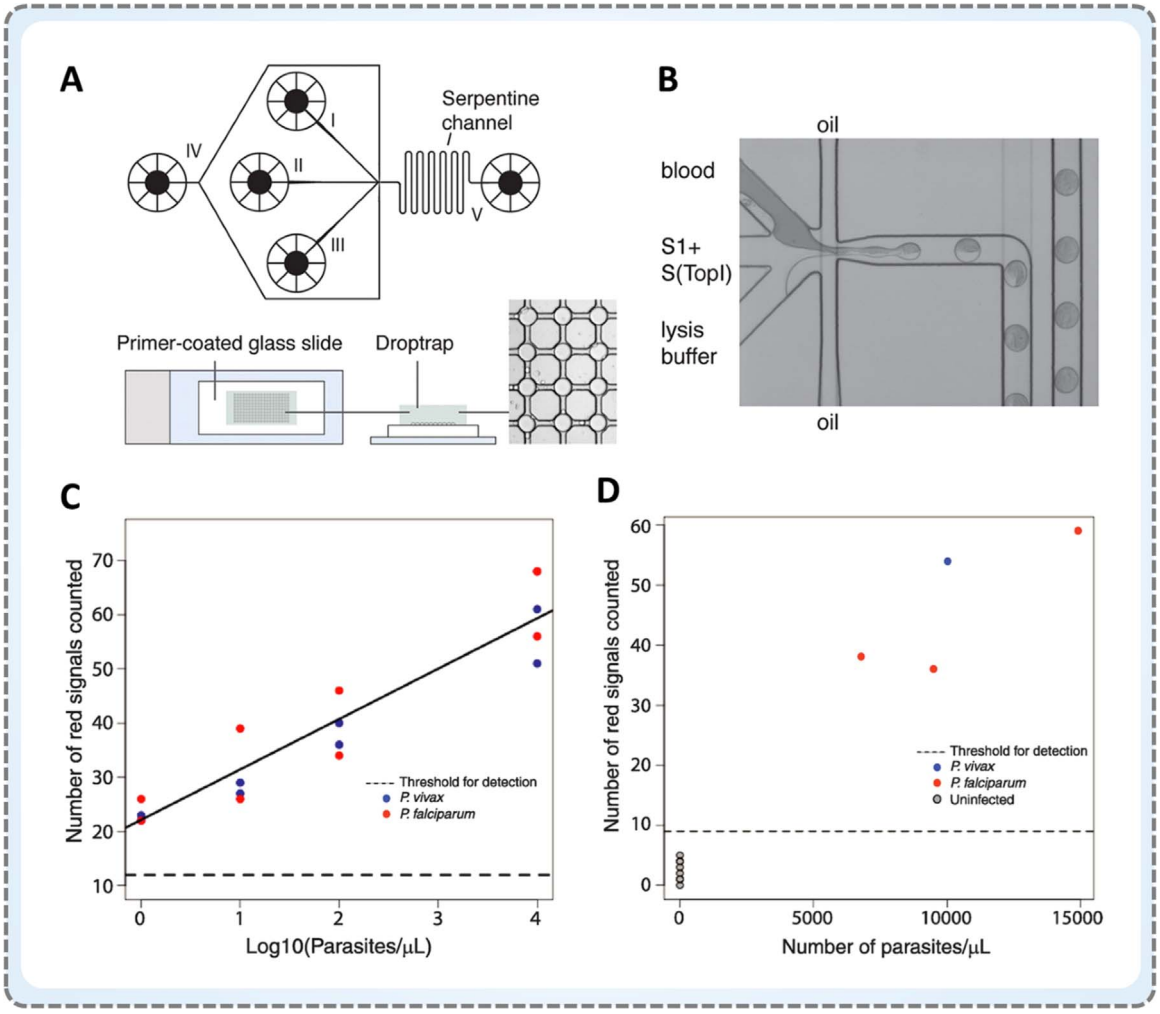

Fig. 13. (A): Schematic representation of Microfluidic lab-on-a-chip device (REEAD-on-a-chip) used for malaria diagnosis (B): Fluid flow inside microfluidic channels observed through light microscope. (C): Signals from REEAD device for different concentrations of parasites in blood samples (D): Signals from REEAD device for different concentrations of parasites in saliva samples. "Reprinted with permission from Juul et al. (2012). Copyright {2012} American Chemical Society".

Multiplexed detection is based on the color development resulting from the concentration of target molecules in the sample (Deraney et al., 2016).

The matrix effect is a common problem for precise estimation of target molecules in complex samples such as blood. To overcome the hindrance and concentrate the target molecule from the sample, a Triton X-144-based, aqueous, two-phase sample extraction has been reported. Triton X-144 is a non-ionic surfactant that helps in solubilizing and concentrating *P*LDH without affecting its native state in a blood sample. The concentration step reduces the time required for sample preparation, and the processed sample is analyzed through a gold nanoparticle-based 3D lateral flow paper device. Monoclonal antibodies specific to *P*LDH are coated on the paper, and the same monoclonal antibodies are conjugated to gold nanoparticles to act as a color probe (Fig. 14). The intensity of color on the test line depends on the amount of *P*LDH present in the sample (Table 1) (Pereira et al., 2015). The reported method is an attempt to improve the precise estimation of target molecules with an improved sample-processing step.

4.9. Cellphone-based sensors

Increasing use of cellphones and wireless communication has opened up a new avenue in sensor technology for onsite analysis, point-of-care diagnosis and health monitoring. This technology empowers the end user by overcoming the need for a readable device to analyze the signals in various sensor models with less margin of error. Small devices—primarily containing lenses, circuits and microfluidic devices—are used as add-ins to improve the performance of the cellphone-based sensors (Roda et al., 2016). In malaria diagnosis, they play a major role by empowering people living in low-resource settings with advanced and reliable devices without additional cost. At the same time, this approach enables data collection and analysis through the integration of result parameters from a region or globally through networking with servers/cloud storage. Cellphone-based portable diagnostic devices were demonstrated for effective data integration and follow-up of febrile patients with geo-tagging and data management through servers. The developed reader platform weighs just 65 g and acts as a plugin device capable of reading data from lateral flow immuno-chromatographic assays (Mudanyali et al., 2012).

A compact, handheld electrochemical detector named uMED was fabricated by Whitesides and his coworkers for onsite malaria diagnosis using screen-printed electrodes (SPE) (Nemiroski et al., 2014). The device has the capability to perform five different modes of electrochemical detection, and the results can be integrated by a simple mobile phone lacking smart functions and effectively used with a smartphone as well (Fig. 15). The fabricated sensor was demonstrated for malaria diagnosis through a chronoamperometry-based sandwich immunoassay format. Antibodies specific to *Pf*HRP-II were coated on the SPE surface, which captured *Pf*HRP-II from the sample. In the next step, another antibody conjugated with horseradish peroxidase (HRP) bound with the

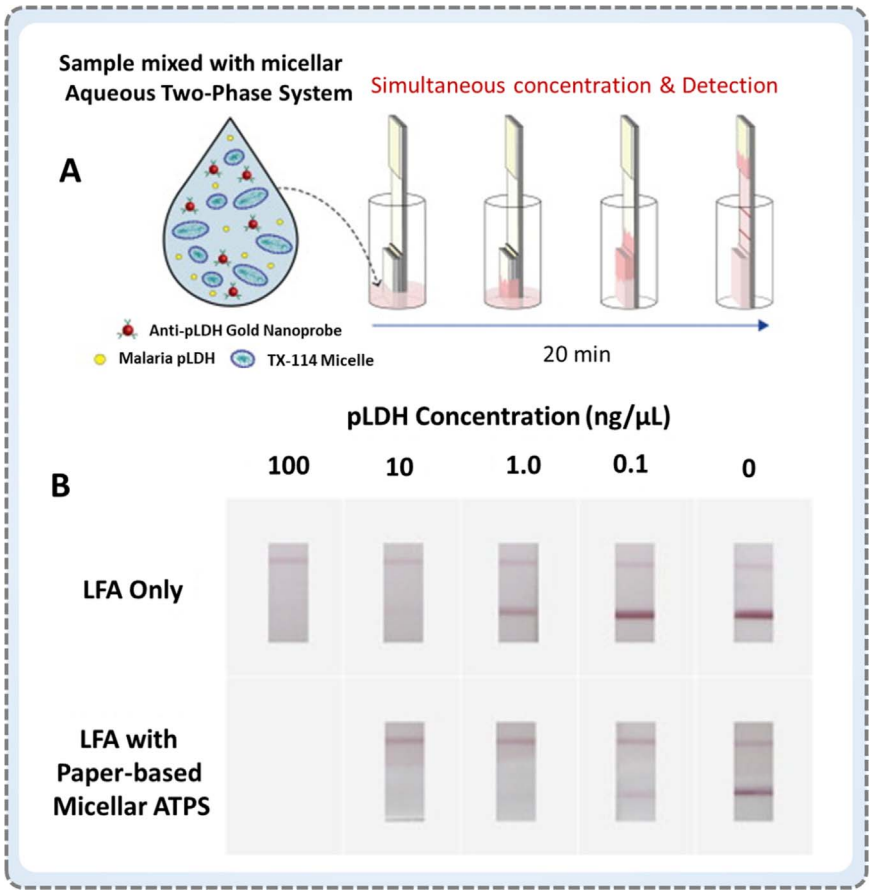

Fig. 14. (A): Working principle of the APTS based simultaneous concentration and detection assay for malaria diagnosis. (B): Performance of the lateral flow assay alone and in combination with APTS (Pereira et al., 2015).

antigen–antibody complex. HRP oxidized the chromogenic substrate 3,3′,5,5′-tetramethylbenzidine (TMB), which generated current signals proportional to the amount of malaria parasite in the sample with a detection limit of 20 ng/mL. The fabricated device cost 25 USD, with the advantage of portability and reliable onsite malaria diagnosis in low-resource settings.

Another device working on the same principle was fabricated containing microfluidic channels embedded with internal electric circuits to reduce the complexity in sample handling (Table 1). Due to the capillary forces, the sample flows through the micro channels, overcoming the need for peristaltic pumps (Lillehoj et al., 2013). The miniaturization of a microscope into a small device that can work with mobile phones has been demonstrated. The fabricated device has the same features as a laboratory microscope and can effectively be used for malaria detection in low-resource settings with a cost of 1 USD per analysis (Pirnstill and Coté, 2015).

4.10. Optical imaging

Optical imaging is a relatively new technique applied to malaria diagnosis based on the changes in the biophysical properties of RBC during the parasite infection. The biophysical properties of cell include electrical (conductivity, impedance and resistivity), mechanical (elasticity, adhesiveness and deformation) and optical (absorption, refractive index and scattering) properties (P. Y. Liu et al., 2016). In the course of the *Plasmodium* infection, hemoglobin in the infected RBC is broken down into heme and peptides. Heme is subsequently oxidized and crystallizes into micro-sized, brown-colored hemozoin crystals, a change that directly impacts the refractive index of RBC. At the same time, a loss in RBC deformability and an increased adherence toward circulatory endothelial and RBC cells is observed. Among the biophysical properties, the refractive index of a cell is measured and interpreted in terms of average, effective, 2D and 3D refractive index of the cell, all of which provide useful information toward malaria diagnosis. Refractive index methods offer the advantage of temporal and spatial resolution and the ability to determine the onset and the succession of the pathological state of malaria infection (Haldar et al., 2006; Park et al., 2008; Weissbuch and Leiserowitz, 2008). Another avenue is the advancement in optical imaging and image processing systems for diagnosis by incorporating algorithms, electronics, cellphones and microfluidics for relatively simple malaria diagnosis (Bishara et al., 2011; Mas et al., 2015).

A microfluidic chip-based microscopic device known as a sub-pixel resolving optofluidic microscope (SROFM) was fabricated for malaria diagnosis (Fig. 16). The device consists of RGB LEDs with illumination at 625, 525 and 475 nm and a CMOS sensor capable of high-resolution color imaging with sub-pixel resolution of blood samples at 0.66 µm. Blood samples were stained with toluidine blue solution, which binds with the parasite similar to a Giemsa stain and discriminates the parasite-infected RBCs from healthier ones. Toluidine blue does not require sample fixation and washing steps to remove the excess dye and therefore has low background noise during imaging (Lee et al., 2011). The proposed method is simple to operate, compact and sensitive, and can serve as an alternative to conventional optical imaging techniques.

Non-invasive diagnosis is preferred by patients for its painless procedures, safety (overcomes the need to draw blood) and rapidity. Hemozoin nanocrystals formed by the parasite in the infected RBCs have high optical absorbance, which is used as a parameter to assess the infection in suspects. A laser pulse in the near-infrared region (672 nm) is passed through the micro blood vessels of the suspects for a short duration. Hemozoin nanocrystals in the infected RBCs absorb the light selectively and effectively convert it into heat in the localized regions around nanocrystal, producing vapor nanobubbles. These vapor nanobubbles generate acoustic signals that are highly selective from the

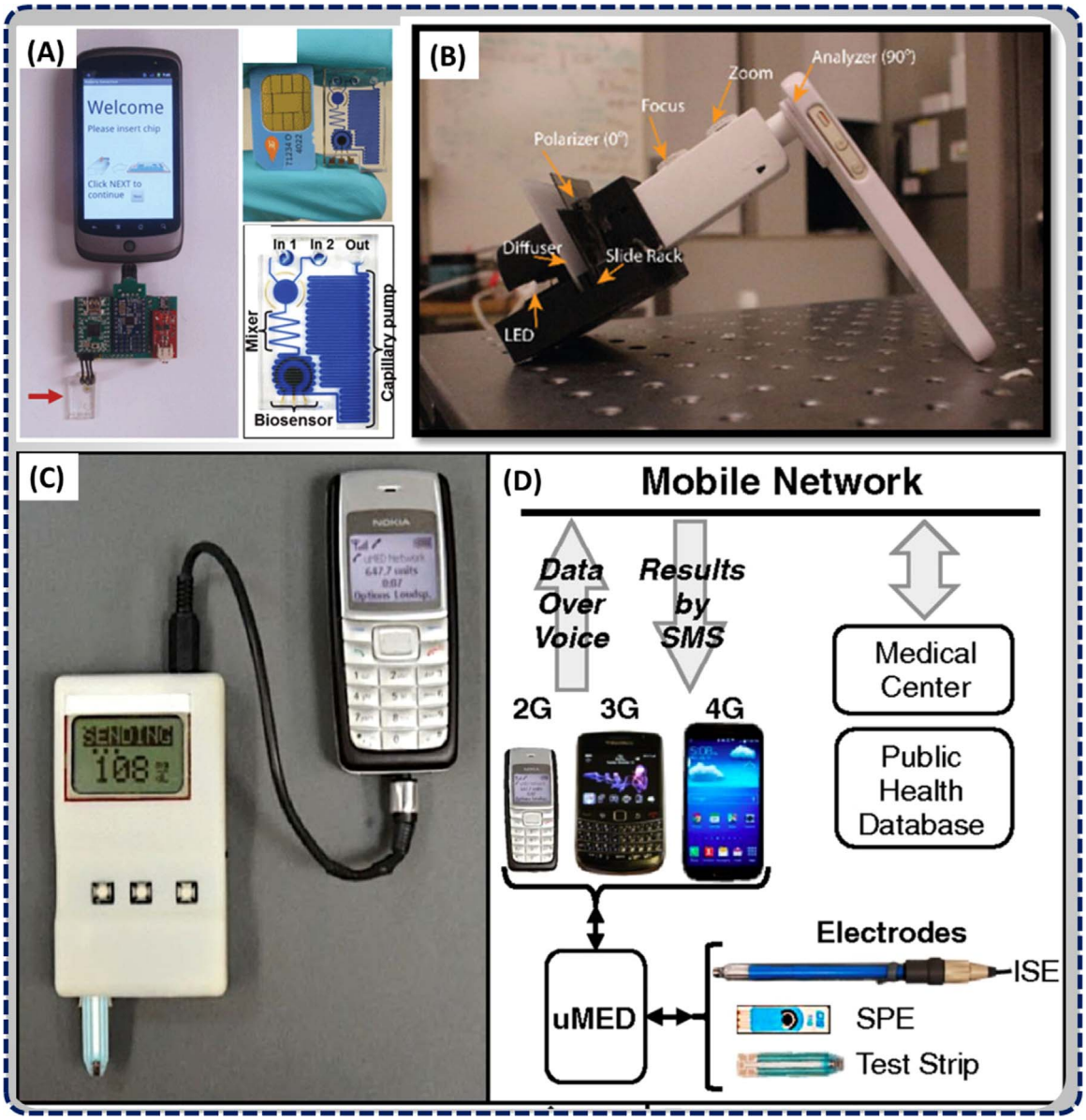

Fig. 15. (A): Miniaturized microfluidic prototype device integrated with mobile phone (Lillehoj et al., 2013). (B): Mobile based polarized light microscope for malaria diagnosis using an iphone (Pirnstill and Coté, 2015) (CC BY 4.0.). (C): Universal mobile based electrochemical detector. (D): Data management and compatibility of the detector with different generation of mobile phones (Nemiroski et al., 2014).

hemozoin nanocrystals, not from any other components in the infected cell. With the highly rapid, non-invasive, optical and acoustic-based method, it was possible to detect malaria infection at a low level of 0.00034% without the requirement of sampling blood and reagents (Table 1). Similar non-invasive methods with simple and compact instrumentation are highly preferred for early malaria diagnosis and malaria eradication (Lukianova-Hleb et al., 2014).

4.11. Miscellaneous sensors

In the following section, miscellaneous and novel sensor platforms that do not fit the earlier categories are discussed. Nucleic acid–based diagnostic methods are highly reliable for malaria diagnosis; however, they require many reagents, strict temperature control and much time. To overcome these disadvantages, a Mach–Zehnder Interferometer-Isothermal solid-phase DNA Amplification (MZI-IDA) sensing method is reported. DNA from the sample was extracted using microfluidic channels in the dimethyl adipimidate (DMA)/thin film sample processing (DTS) closed system. The extracted DNA was transferred to the MZI-IDA sensor for amplification at an isothermal temperature of 37 °C using polymerase, recombinase and three different probes of the target DNA. The real-time phase changes of the DNA obtained from the system were correlated for the infection levels. This method does not require centrifuges or solvents, and detection was possible within 60 min with a sensitivity of less than one parasite per μL (Q. Liu et al., 2016).

A new type of coffee-ring pattern-based sensor for the detection of *Pf*HRP-II using gold-plated polystyrene particles has been reported. In this detection method, amine-capped polystyrene micro-particles were coated with gold and further functionalized with Ni(II)nitrilotriacetic acid (NTA) for the interaction of the target compound on particles and a glass slide. The presence of *Pf*HRP-II in the sample caused the particles to aggregate in the solution, and the solution was dropped on the functionalized glass slide. Due to the interaction of Ni(II)NTA and the aggregate, they adhered to the glass surface. On evaporation, these aggregates migrated toward the edges, and a ring-like pattern appeared, similar to coffee rings on a cup (Fig. 17). The intensity of the rings was proportional to the concentration of *Pf*HRP-II in the sample and was visible to the naked eye even at a low concentration of 10 pM (Table 1).

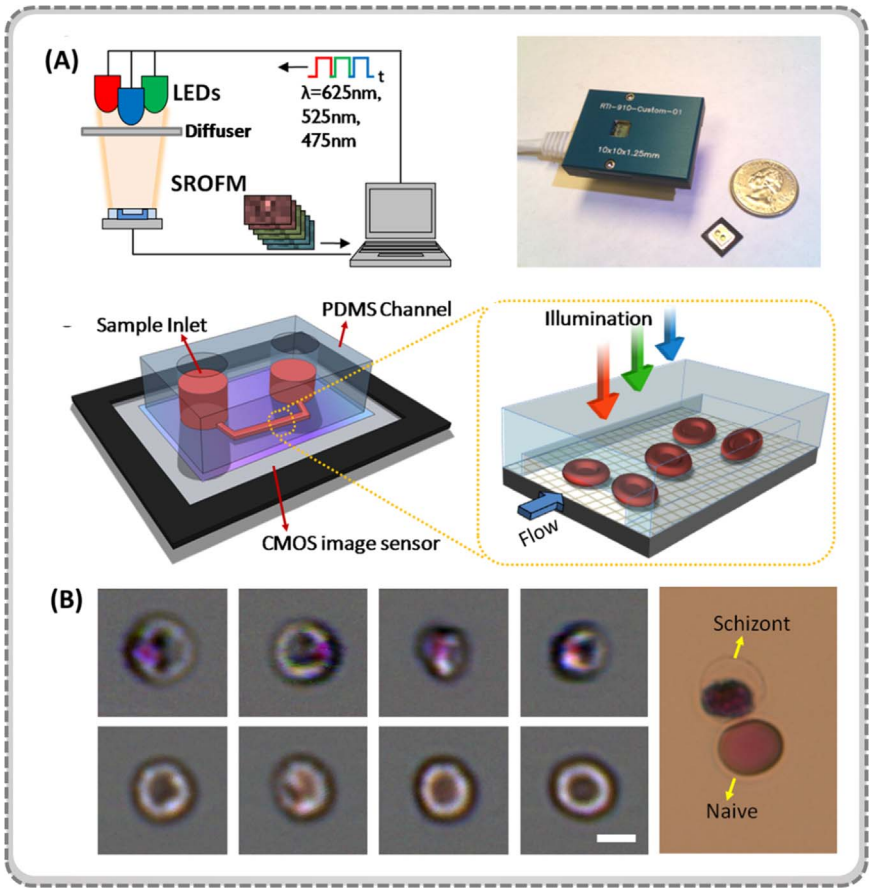

Fig. 16. (A): Configuration and working principle of microfluidic chip based sub-pixel resolving optofluidic microscope (SROFM) device. (B): Color images of malaria infected (Schizont stage) and healthy RBC (Lee et al., 2011) Creative Commons Attribution License.

Additives such as tween and glycerol were found to improve the stability of particles and led to reproducible results. The method does not contain any biomolecules as a component and thus has strong potential for low-cost, onsite malaria diagnosis (Gulka et al., 2014).

5. Perspectives and conclusions

A wide range of biosensors with various novel elements for malaria diagnosis has been reported. Each of them attempts to solve one or more of the existing challenges of malaria diagnosis in low-resource settings. Advancements in the biosensor field are a cumulative effect stemming from novel nanomaterials, bio-recognition elements and detection platforms. Among them, nanomaterials such as TMDCs, graphene, up-conversion nanoparticles, quantum dots and composites with interesting properties such as surface plasmon resonance, catalytic activity, magnetism, superior electrical and electrochemical behaviour, optical properties (light absorption, fluorescence emission and quenching) and large surface area have significantly improved the performance of sensors, especially their sensitivity. As a result, detection of malaria infection in the early stages has been made possible, which was not the case with conventional techniques. However, better understanding and control of nanomaterial properties are desired for device fabrication at an industrial scale. Interestingly, nanomaterials also offer the potential for direct antimalarial activity by inhibiting malaria parasite invasion and controlling the parasite's growth (Kenry et al., 2017).

An important reason for the advanced biosensor system is the development and use of novel recognition elements for the fabrication of sensors, devices and kits for malaria diagnosis. Even though antibodies are currently the preferred recognition element in sensors, they are rapidly being replaced by aptamers, receptors, proteins and enzymes. Aptamers are particularly anticipated to be the preferred recognition element due to the former's better stability, higher sensitivity and greater ease of functionalization in sensor fabrication. Notably, aptamer-based colorimetric assays are suitable for onsite, simple, qualitative-based malaria diagnosis in low-resource settings, if the existing issues such as nonspecific interaction, nanoparticle stability and cost are resolved. Affordable aptamer-based diagnostic kits are a likely development in the near future. Surprisingly, enzyme-based biosensors for malaria diagnosis are not common, though they were the molecules of choice for the fabrication of biosensors until the 21st century. Recombinant enzymes with improved specific ligand-binding capacity can play a great role in malaria diagnosis. One of the emerging challenges with respect to bio-recognition elements is the change in structural homology of protein-based malarial biomarkers, often leading to false positive results and lowered sensitivity in RDTs (Mouatcho and Goldring, 2013).

In devices and kits, an important emerging aspect is paper and screen-printed electrode-based colorimetric, fluorescence and electrochemical sensors integrated with mobile phones. These platforms empower the suspects living with limited medical access to diagnose themselves and seek medical attention through data integration with available resources (mobile phones and network) at a low cost. Acoustic and optical imaging techniques based on tracking the biophysical parameters for malaria diagnosis are a clear example of an interdisciplinary approach to label-free diagnosis, which is a bright prospect if the background noise and signal enhancement options are discovered. Boosted by the novel nanomaterials, SERS and SPR based biosensor platforms have progressed as a highly sensitive technique for early-stage malaria diagnosis. However, the miniaturization of the current instrumentation into a portable device is necessary for onsite malaria diagnosis. Advancement in the sample processing steps to reduce the matrix effect and the concentration of target molecules has a great impact on the outcome of the sensing platform. It contributes to

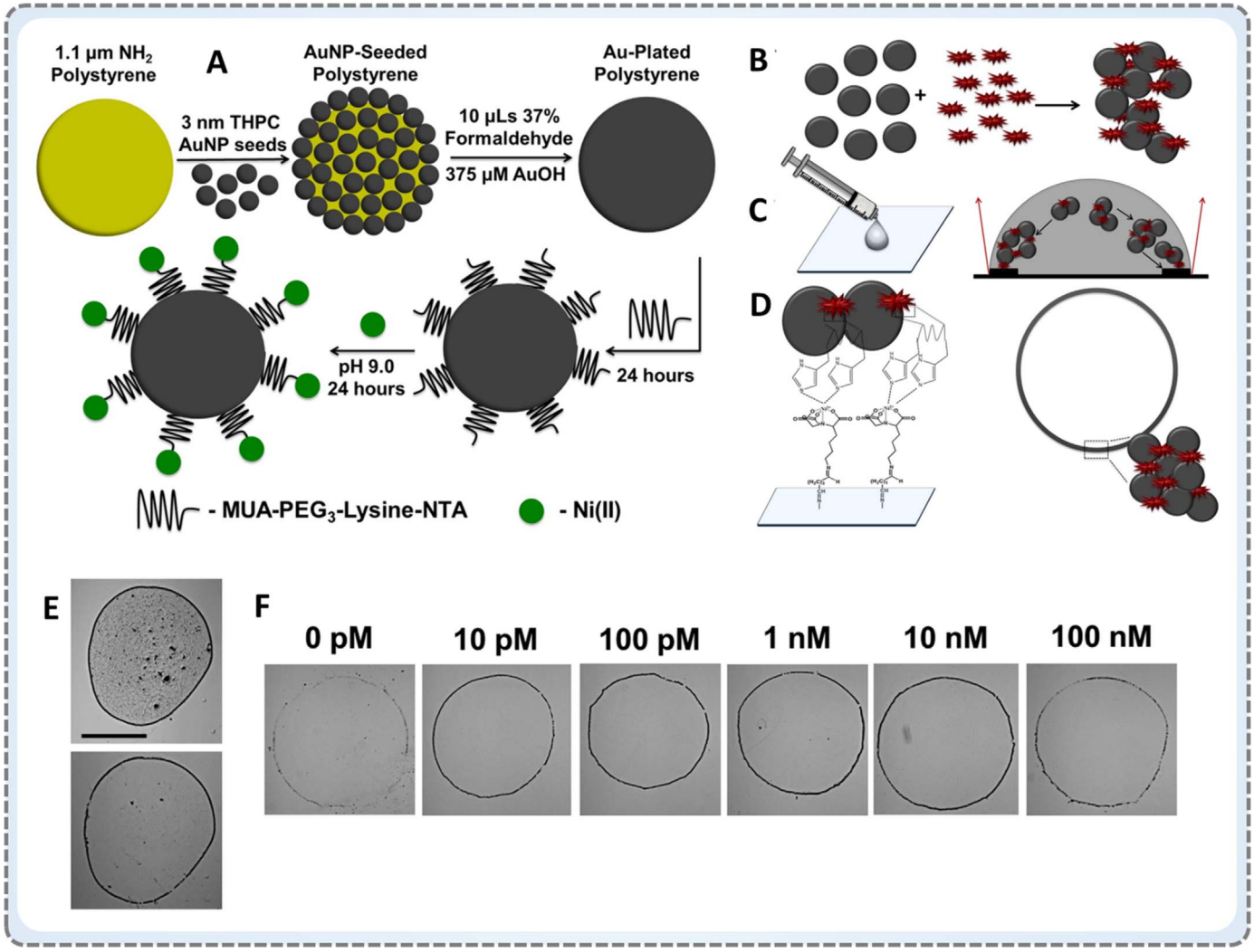

Fig. 17. (A): Steps involved in the synthesis of AuPS particles. (B): Aggregation of AuPS particles in presence of rcHRP-II. (C): Aggregation of protein and particles leading to their movement towards the edges of the drop due to tension gradient during evaporation of liquid (D): Interaction of sensor components in enzyme linked immunoassay format for the formation of rings on the glass slide. (E): Image showing the formation of rings in the presence of rcHRP-II before and after washing the slides. (F): Intensity of rings respective to different concentrations of rcHRP-II. "Reprinted with permission from Gulka et al. (2014). Copyright {2014} American Chemical Society".

accurate and precise measurement with simple sample processing steps. Further progress in similar aspects will improve the overall performance of biosensors.

Clearly, much progress has been achieved in the field of biosensors for malaria diagnosis, in terms of sensitivity, easy to use, multi-species diagnosis, cost, tracking patient's pathological condition and onsite applicability. However, from the above discussion, it is evident that appropriate solutions to challenges such as sample preparation, reproducibility and miniaturization are expected before these novel biosensor systems can replace conventional diagnostic kits. With the continuous interdisciplinary efforts, biosensors will become indispensable tools for disease management and diagnosis.

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