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Recent progress in electrochemical sensors for detection and quantification of malaria

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ABSTRACT

Malaria is still a major disease in sub-Saharan Africa and South-East Asia. This is despite different interventions by the World Health Organization (WHO), such as insecticide-treated mosquito net, antimalarial drugs, indoor residual spraying, and rapid diagnostic tools. In 2018, the mortality rate due to malaria was estimated to be 405 000, with children under five years accounting for 67% of all malaria deaths. Malaria can be prevented and treated using different strategies as recommended by WHO. However, the lack of rapid diagnostic tools with good selectivity and sensitivity is still a challenge. Therefore there is a need to develop rapid, low-cost, and portable analytical methods for quantifying malaria. This review focuses on the role of malaria biomarkers (*Plasmodium falciparum* Lactate Dehydrogenase (*Pf*LDH), *Plasmodium* aldolase, *Plasmodium falciparum* Histidine-Rich Protein 2 (*Pf*HRP2), *Plasmodium falciparum* Glutamate dehydrogenase (*Pf*GDH), and Hemozoin) in diagnosis. Recent developments in nanomaterial-based electrochemical and colorimetric biosensors for malaria diagnosis are discussed. Finally, the review concludes with closing remarks and future perspectives of electrochemical biosensors.

1. Introduction

1.1. Overview of malaria cases

Malaria is a parasitic disease that has become a public health problem. This disease is mostly found in tropical and subtropical areas. In 2000, the World Health Organization (WHO) reported approximately 262 million malaria cases, of which 839 000 resulted in death [1–3]. Fifteen years later, in 2015, nearly 214 million malaria cases were reported, of which 469 000 resulted in death [2–4]. From 2000 to 2015, there was a decrease in the number of cases of about 48 million. Although the number of cases decreased, malaria is still a dominant disease in tropical and sub-tropical countries. In 2018 an estimated 228 million malaria cases were reported worldwide; 405 000 cases resulted in death. Most malaria cases are reported in Africa, with 213 million cases of which 380 700 resulted in death. Nineteen countries with the world's biggest malaria problem are in sub-Sahara Africa and India; these two regions account for 85% of the global burden [4,5].

2. Malaria

2.1. The life cycle of malaria

Malaria is caused by a protozoan parasite that belongs to the *Plasmodium genus* [6,7]. Among all the *Plasmodium genus* species, only four are responsible for the presence of malaria in humans; these species include *Plasmodium malariae (P.malariae)*, *Plasmodium ovale (P.ovale)*, *Plasmodium vivax (P.vivax)*, and *Plasmodium falciparum (P.falciprum)* [1]. The most prevalent malaria species globally is *Plasmodium falciparum* which accounts for 99.9% of malaria cases in Africa, 50% in South-East Asia, 71% in the Eastern Mediterranean Region, and 65% in the Western Pacific Region [5]. Malaria cases due to *Plasmodium vivax* are mostly dominant in South-East Asia and the Americas [5]. The other malaria species can cause severe illness with low mortality rate [8]. The four species are transmitted to the human body through a single bite from a female mosquito. Since malaria affects human beings, it is important to understand the life cycle of malaria. The events that occurs in the life cycle of malaria include the exoerythrocytic, erythrocytic, and sporogonic cycle.

The human infection starts in the exoerythrocytic cycle, where the

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mosquito injects the sporozoites during the blood meal. The injected sporozoites travel to the liver cell, where they overcome the liver cells; during this stage, thousands of merozoites are generated by asexual replication. The replication stage is referred to as exoerythrocytic schizogony. Schizogony is defined as a replication process where merozoites are formed. To achieve this, sporozoites undergo many divisions followed by budding or segmentation. The merozoites are released into the bloodstream after they rapture liver cells [1,9,10].

The second stage is the erythrocytic cycle; at this stage, the merozoites defeat the erythrocytes and form trophozoites through asexual replication, here another round of schizogony is initiated. This process takes place repeatedly and in the end causes malaria. As the infection continues, the peripheral blood is concentrated with female and male gametocytes formed by young merozoites. Therefore when the mosquito feeds, it injects the gametocytes into itself [9]. In the sporogonic cycle, the gametocytes develop into microgametes and macrogametes. The gametes are fertilized within the mosquito midgut to form ookinetes. These ookinetes penetrate the gut wall and develop oocytes. The oocytes result in the formation of sporozoites [1,9].

2.2. Role of biomarkers in malaria diagnosis

Since malaria affects most people in developing and tropical countries, early detection is important. Early diagnosis will have several advantages, such as early treatment of malaria. As a result, the spread of the disease will be prevented; thus, the mortality rate will be reduced. Currently, conventional methods such as nucleic acid-based analytical techniques, immunobased rapid diagnostic test kits, and microscopic analysis are being used to diagnose malaria [9]. These conventional methods have some drawbacks, such as multi-step analysis, lack of onsite applicability, and are time-consuming. Due to these drawbacks, there is a need for a simple, rapid, cheap, sensitive, and onsite-applicable point of care device to detect malaria. To achieve this, several malaria biomarkers are used to develop diagnostic sensors.

To develop a selective and sensitive biosensor for the early detection of malaria, it is crucial to understand the various malaria-related biomarkers. A biomarker is defined as a naturally occurring molecule, gene, or characteristic in which a particular pathological or physiological process or disease can be identified [11,12]. The advantage of using biomarkers in diagnostic tools is their sensitivity towards a specific disease pathogen [13]. Biomarkers that are frequently used in malaria-related detection devices include *Plasmodium falciparum* Lactate Dehydrogenase (*Pf*LDH), *Plasmodium* aldolase, *Plasmodium falciparum* Histidine-Rich Protein 2 (*Pf*HRP2), *Plasmodium falciparum* Glutamate dehydrogenase (*Pf*GDH), and Hemozoin.

2.2.1. Histidine-rich protein 2

Histidine-rich proteins 2 (HRP2) is a frequently used biomarker in developing malaria diagnostic tools. HRP2 is a unique protein produced by *P. falciparum* [14]. In the total composition of HRP2, 37% of its amino acid sequence is histidine, and a repeat of histidine plus alanine covers 85% of its sequence [11,15]. HRP2 is released from infected erythrocytes as a water-soluble protein into the red blood cells cytosol through a mosquito bite [16]. HRP2 is found in the food vacuole [17], digestive vacuole [18], and membrane surface of the infected red blood cells [19]. It is also found in cerebrospinal fluid, serum plasma, and urine of infected patients [11]. HRP2 is mainly used as a biomarker in the development of antimalarial drugs and rapid diagnostic tests because it shows high sensitivity towards *P. falciparum* compared to other biomarkers such as *P. falciparum lactate dehydrogenase* and *P. Glutamate Dehydrogenase*.

2.2.2. Lactate dehydrogenase

Plasmodium Lactate Dehydrogenase (*p*LDH) is a common biomarker found in all *Plasmodium* species. The primary function of *p*LDH is to convert pyruvate to lactate by using a cofactor reduced nicotinamide adenine dinucleotide (NADH) [13,20]. High levels of *p*LDH are produced during the asexual intraerythrocytic cycle; this is because the *Plasmodium* parasite depends on anaerobic metabolism to generate energy [21,22]. *p*LDH is useful as a malaria biomarker since it has structural features that differ from the human Lactate Dehydrogenase (*h*LDH). The main difference between *p*LDH and *h*LDH is the presence of Leu 163 on *p*LDH instead of Ser 163, which is found in *h*LDH [20,23]. *p*LDH is used in malaria case management because the circulation of this enzyme in the host environment clears within 24 h after successful treatment. Thus false-positive diagnosis after the elimination of the infection is reduced.

2.2.3. Hemozoin

Blood-feeding parasite species such as *Plasmodium* spp. produces an insoluble brown microcrystalline product during the digestion of blood called hemozoin [11,13]. Hemozoin is a crystal structure made up of hemes linked by carboxylate side group oxygen and the central ferric ion. Hemozoin is used as malaria pigment during the development of antimalarial drugs and diagnostic tools; this is because hemozoin is essential for the parasite survival in the host. The red blood cells of the host are infected during the intra-erythrocytic cycle; at this stage, amino acids and toxic-free heme that were released from the digestion of hemoglobin are polymerized to hemozoin [24,25]. 80% of hemoglobin in infected red blood cells is digested by the parasite [26].

2.2.4. Aldolase

Aldolase is a homotetrameric protein with each subunit of approximately 40 kDa [11,27]. This protein is used as a malaria biomarker since it is found in *P. falciparum* and *P. vivax*. Also, the sequence of *Plasmodium* aldolase (*P.* aldolase) is different from the human aldolase. The amino acids sequence of aldolase in *P. vivax* and *P. falciparum* are 369 in length and conserved [28,29]. Aldolase is present in its active and soluble form at the parasite's cytoplasm. In its insoluble form, it is associated with the membrane fraction. During the glycolytic pathway, aldolase act as a catalyst to cleavage fructose-1,6-bisphosphate to form glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. HRP2 is mostly used as a biomarker for detecting *P. falciparum* instead of *P.* aldolase; this is due to the poor sensitivity of aldolase in commercially available rapid diagnostic tools [30,31]. The poor sensitivity is mostly attributed to low antigen concentrations in infected erythrocytes. Another disadvantage of using aldolase is that the *P. falciparum* aldolase shares a 61–68% sequence with eukaryotic aldolase [32].

2.2.5. Plasmodium falciparum glutamate dehydrogenase

The branch point between the carbon and nitrogen metabolism is occupied by ubiquitous enzymes called Glutamate dehydrogenases (GDH). *Plasmodium falciparum* Glutamate dehydrogenase is a common malaria biomarker that is present throughout the intra-erythrocytic cycle of the parasite. This enzyme is absent in the host red blood cells. It has different kinetics, structure, location, and sequence compared to the GDH of the host; thus, it is attracting interest from researchers to be used as a malaria biomarker [33–35]. *Plasmodium falciparum* expresses three different genes encoding potential GDH proteins, namely GDHa (PF 14-0164), GDHb (PF 14-0286), and GDHc (PF08-0132) [36]. GDHa and GDHb are found in chromosome 14, and GDHc is in chromosome 8 [13,36]. The function of glutamate dehydrogenase is to facilitate the conversion of L-glutamate to α-ketoglutarate and ammonia by using NADP (H) or NAD (H) as cofactors [36].

3. Challenges for malaria diagnostic tools

3.1. Conventional methods

Diagnosis of malaria using traditional methods such as light microscopy, empirical/syndromic, and clinical diagnosis is still widely used in malaria-endemic countries. Empirical/syndromic clinical diagnosis is

based on patient medical history, signs, and symptoms such as headache, fever, dizziness, nausea, diarrhea, chills, weakness, vomiting, and myalgia. The World Health Organization (WHO) is against using this approach in areas where adequate laboratory diagnostic tools are available. This is mainly due to some limitations associated with this approach, such as incorrect diagnosis that increases resistance to available antimalarial drugs, non-specificity, and significant clinical overlap with other pyretic diseases.

Therefore microscopic method remains a gold standard in most developing countries since it is cost-effective, readily available in most laboratories, can accurately identify the infecting species and mixed infections. Microscopy can also be used to determine the density of the parasite in the blood [37–39]. However, the following drawbacks are associated with this approach; it is time-consuming, unreliable at low parasite densities, and experts are required to operate the microscopy and interpret the results effectively [8,40,41]. The ability to detect mixed malaria infections at low-level parasitemia using Polymerase chain reaction (PCR)-based diagnostic method (RFLP-dHPLC) was compared with the microscopic method by Steenkeste et al. [42]. The PCR-based method was found to be more sensitive; also, the presence of *Plasmodium falciparum* and *Plasmodium vivax* were found to be approximately 59% and 15%, respectively, while 28% and 5% were obtained for the microscopy method. The PCR-based method detected 11.2% and 1.3% of *Plasmodium ovale* and *Plasmodium malariae,* respectively. No cases were found when the microscopic method was used. In another study, Hopkins et al. [43] used 272 blood samples to compare the sensitivity of a new loop-mediated Isothermal Amplification kit with microscopy and single-well nested PCR. Compared with 3-well nested PCR, the sensitivity of both the new loop-mediated Isothermal Amplification and single-well nested PCR was 90% and 51% for the microscopy method.

To improve the sensitivity of the microscopy method, Davis et al. [44] investigated the effect of passive gravitational sedimentation of peripheral blood on the sensitivity of microscopic detection of malaria. 205 samples were analyzed using three methods; conventional thin smear preparation, centrifuged samples, and gravitational sedimented samples. A sensitivity of 25.39%, 30.24%, and 30.24% was observed for traditional, centrifuged, and sedimented blood, respectively. Thus, the two methods were more sensitive than conventional thin smear preparation. Berzosa et al. [45] compared microscopy, rapid diagnostic test, and PCR for detection of the malaria parasite in representative samples. 1724 blood samples were analyzed, 19.4% and 13.3% false-negative results were obtained for microscopy and rapid diagnostic test, respectively.

Since light microscopy is still considered the gold standard for malaria diagnosis, efforts are being made to overcome some drawbacks, such as lab-based microscopy. A handheld light microscopy for diagnosis of malaria due to *Plasmodium falciparum* was reported by Coulibaly et al. [46]. 223 samples were used, the sensitivity and specificity was found to be 80.2% (95% Confidence interval [Cl]: 73.1–85.9%) and 100% (95% Cl: 92.6–100%) respectively. Several innovative strategies to improve the selectivity and sensitivity of light microscopy for malaria diagnosis have been reported, as shown in Table 1.

Table 1
Some of the innovative light microscopy for detection of malaria.

Technique	Sensitivity	Benefits	Ref
Handheld light microscopy with mobile phone attachment	80.2% (95% Confidence interval [Cl]: 73.1–85.9%)	Portable quality laboratory testing of malaria in remote settings	[46]
Light Emission Diode fluorescence microscopy	Sensitivity and specificity of 71.2% and 96.3%, respectively	highly specific in comparison to Light microscopy	[47]
Polarized microscope designed using a cell phone.	Device Resolution is sufficient for observing birefringence from hemozoin crystals	Low cost, and it is adaptable to multiple mobile devices	[48]
Mobile phone mounted light microscopy	Device resolution is sufficient to accurately capture images of malaria-infected red blood cells from both thick and thin blood smears	Cheap, fast, and field applicable microscopic evaluation of malaria patients.	[49]

3.2. Electrochemical biosensors

A biosensor is a device made up of a biological receptor, transducer, signal amplification, and output unit [39]. Biosensors can be classified as electrochemical, optical, magnetic, thermometric, and piezoelectric. Ideal biosensors consist of 12 key features; high sensitivity, high selectivity, reproducibility, rapid response time, multiplexing, multimode, high stability, easy to use, disposable, easily manufactured, cost-effectiveness, and autonomous [50,51]. In recent years several studies have reported the application of biosensors in malaria diagnosis. Most of the reported biosensors use nanocomposites to improve their sensitivity, selectivity, and reproducibility. Nanocomposites are solid materials that consist of multiple phase domains, and at least one of these domains has nanoscale structures. Nanocomposites material have been studied in recent years because of their unique and fascinating properties. These unique properties arise from the synergistic effect of the individual components that make up the composite. The application of nanocomposites in the fabrication of sensors has some advantages such as high surface to volume ratio, reactive capacity, biocompatibility, and high adsorption [52,53]. Nanocomposites are responsible for catalysis of electrochemical reactions, easy immobilization of biomolecules, labelling of biomolecules, and enhancement of electron transfer rate [54–57]. Nanocomposites that are mostly used to modify the surface of the electrode are made up of conducting polymers (CP), metal-organic frameworks (MOFs), graphene (G), nanofibers (Nf), carbon nanotubes (CNTs), and nanoparticles (Nps).

A tri-inlet device integrated with an electrode, used as a diagnostic tool for electrochemical detection of *Plasmodium vivax* in human whole blood samples, was reported by Singh et al. [58], as shown in Fig. 1. Reduced graphene oxide (RGO) gold nanocomposite was used to modify the surface of the electrode, followed by conjugation with *Plasmodium vivax* antibody. The interaction of the electrode with the infected red blood cells (RBCs) resulted in a decrease in current charge density. The sensor showed good selectivity and sensitivity with a detection limit of 40 vivax infected RBCs/10 μl blood. This study demonstrated the use of a disposable type sensor kit for the onsite analysis of *Plasmodium vivax* within 5 min.

Since most malaria cases in Africa are due to *Plasmodium falciparum*, it is important to develop diagnostic tools that are sensitive and selective to this malaria species. It is important to note that DNA aptamers and antibodies are usually used to improve the selectivity of the biosensor. DNA aptamers are defined as short oligonucleotide chains that can bind to a target with high specificity and affinity. DNA aptamers have higher stability at elevated temperatures and humidity than conventional antibodies; thus, they are suitable for point-of-care devices in tropical areas. Gabriel et al. [59] reported an aptamer-based electrochemical biosensor for malaria with an adjustable dynamic response range of up to 10 nM under variable environmental conditions. 2008s aptamer was used as a recognition molecule and *Pf*LDH as the target protein. Ferri/Ferro cyanide ($Fe(CN)_6^{3-/4-}$) was used as a redox probe. The adjustable dynamic response range was made possible by the isoelectric point (pI) of *Pf*LDH (Fig. 2). At pH < pI, a decrease in interface impendence was observed since the negative $Fe(CN)_6^{3-/4-}$ was attracted towards the surface. However, at pH > pI, the interface impendence increased since $Fe(CN)_6^{3-/4-}$ was repealed. A detection limit of 0.84 pM was obtained. This was attributed to the electrostatic properties of the protein and the excellent selectivity of the 2008s aptamer. The sensor was selective to

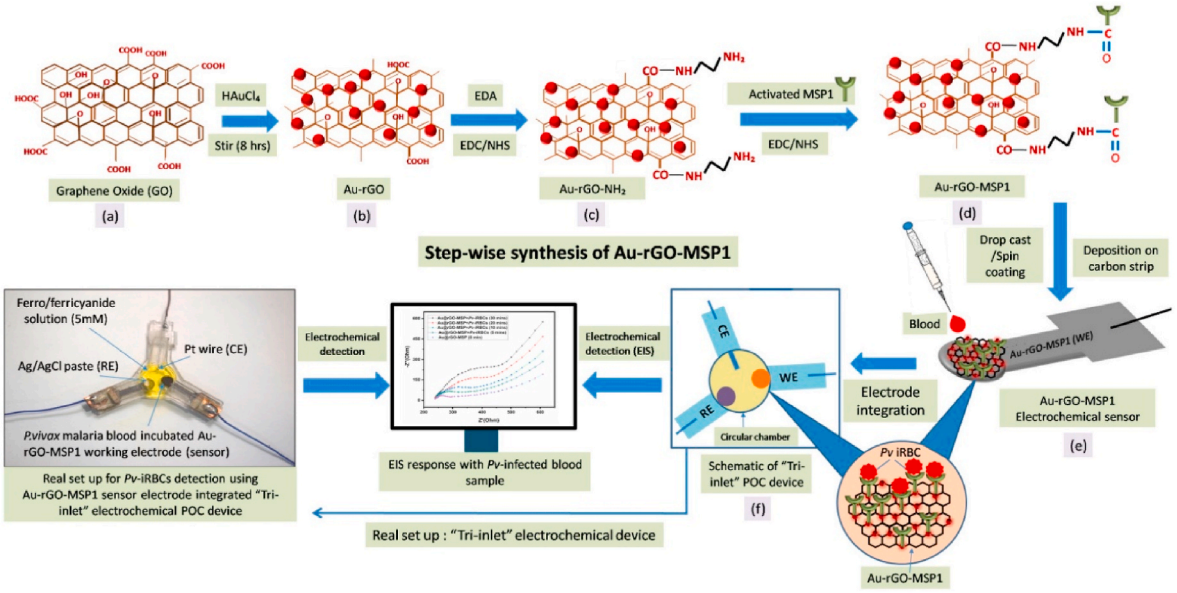

Fig. 1. Electrochemical detection of *Plasmodium vivax*-infected RBCs in whole blood using a tri-inlet device integrated with the modified electrode [58].

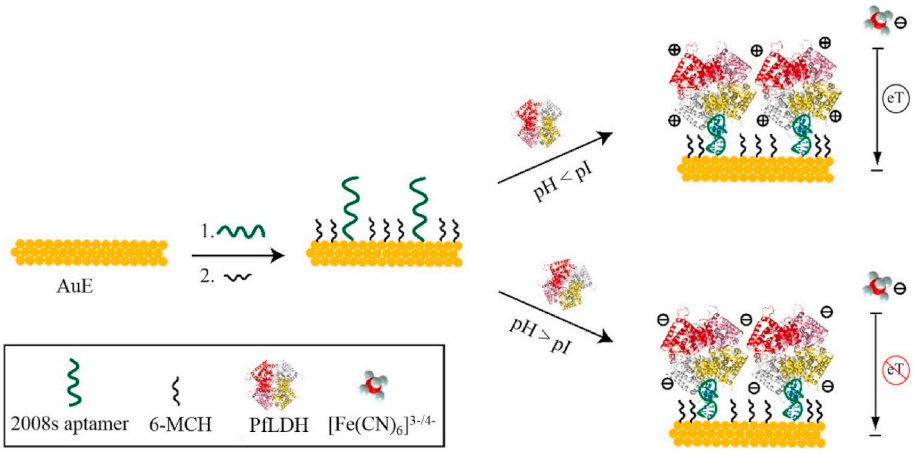

Fig. 2. Stepwise fabrication of an aptasensor for detection of *Pf*LDH in two different pH environments [59].

*Pf*LDH when compared with other proteins such as L-LDH from muse muscle and human LDH, HAS, and bovine serum albumin (BSA). The main advantage of this biosensor is its low detection limit and its reusability since it can be reused by simply rinsing it with 6 M urea. Jain et al. [60] reported an aptamer-graphene oxide sensor for dual electrochemical detection of *Plasmodium falciparum* lactate dehydrogenase (*Pf*LDH). The dual detection was carried out using electrochemical impedance spectroscopy (EIS) and differential pulse voltammetry (DPV). During the EIS measurement, the charge resistance transfer (Rct) was directly proportional to the concentration of (*Pf*LDH). The lowest detectable concentration was found to be 0.5 fM. DPV was used to confirm the specificity of the sensor; HAS, BSA, and lysozyme were used. No current response was obtained for the three proteins. While Singh et al. [33] used *Plasmodium falciparum* glutamate dehydrogenase as a biomarker to develop a capacitive malaria aptasensor (Fig. 3). A limit of detection of 0.77 pM with a dynamic range of 100 fM- 100 nM in human serum was obtained. Also, because of the specificity of the thiolated ssDNA aptamer (NG_3) to *Pf*GDH, interference from LDH and HRP2 was negligible.

Another study by Paul et al. [6] fabricated an ultrasensitive biosensor to detect *Plasmodium falciparum* histidine-rich protein-2 (Fig. 4). The sensor was found to have a limit of detection of 6.8 ag/mL. This low detection limit is due to the complementary effect of copper doped zinc oxide and mercaptopropylphosphonic acid. The acid increases the functional groups required for immobilizing antibodies, while the doped metal oxide enhances the conductivity and pre-concentrates the target analyte.

Diagnostic tools requiring little user intervention are needed in low resource settings for rapid and accurate malaria diagnosis. One such device was reported by Vega et al. [61] in this study a fast and simple point of care (POC) electrochemical sensor for detection and quantification of *Plasmodium falciparum* lactate dehydrogenase (*Pf*LDH) in lysed whole blood was reported. The POC device was made up of the following components; single microfluidic paper, double-sided screen-printed carbon electrode (MP-dsSPCE), a magnet, a whole-blood filtration unit, and an adsorbent, as shown in Fig. 5. The sensitivity of this device was evaluated, with a detection limit of 200 ng/mL. This is close to the WHO recommendation for clinical diagnosis of malaria. Also, this method is fast since the *Pf*LDH was detected in lysed whole blood in less than 20 min.

Lillehoj et al. [62] reported the onsite diagnosis of *Plasmodium falciparum* histidine-rich 2 protein (*Pf*HRP2) using an electrochemical platform integrated with a mobile phone (Fig. 6). The system was made up of several components such as the capillary flow, which was used for

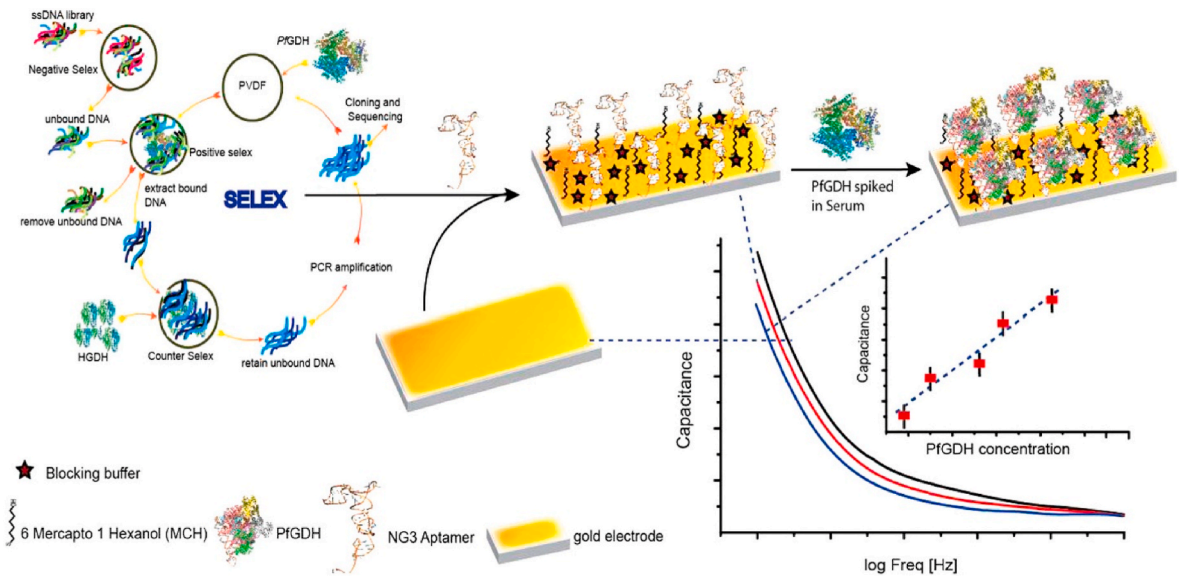

Fig. 3. Development of aptamer through SELEX for electrochemical detection of *Pf*GDH [33].

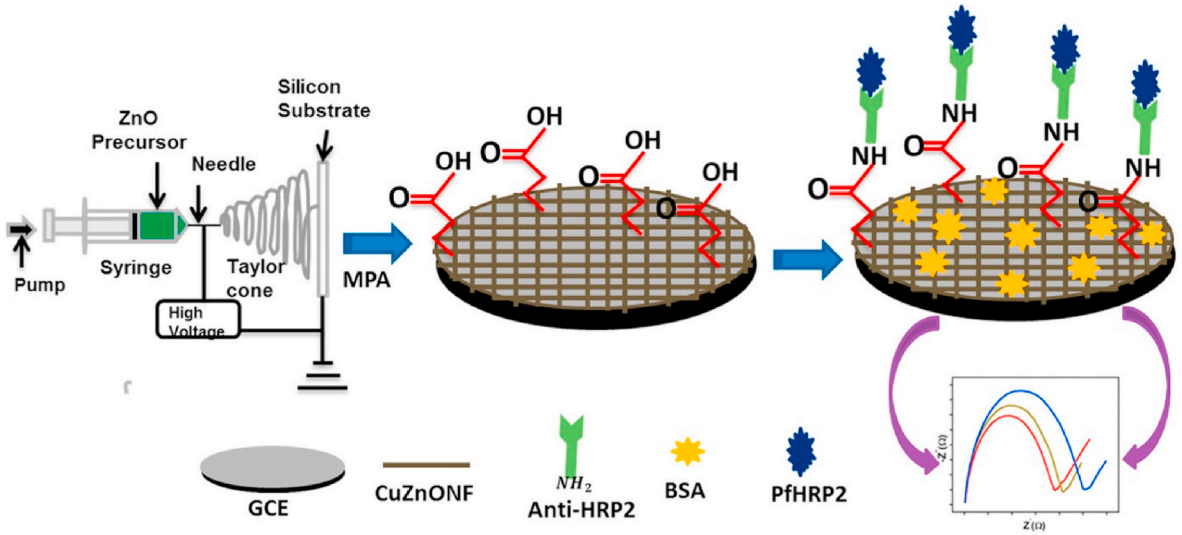

Fig. 4. Stepwise fabrication of electrochemical sensor for detection of *Plasmodium falciparum* histidine-rich protein-2 using Copper doped zinc oxide nanofiber [6].

sample loading, processing, and pumping; microfluidic chips, which are responsible for fluidic handling and biosensing; and a circuit for signal processing and data analysis. *Plasmodium falciparum* histidine-rich 2 protein was successfully detected in human serum within 15 min, a detection limit of 16 ng/mL was obtained. The device was also found to be specific to *Pf*HRP2 in the presence of 5 different proteins. This device can be used in remote and rural areas because of its compact size and good selectivity and sensitivity. Some of the recently reported electrochemical biosensors for the detection of malaria are listed in Table 2.

3.3. Colorimetric biosensors

Recently, several studies have reported developing colorimetric biosensors that meet the WHO recommendations for point of care devices. According to the WHO, the world needs diagnostic tools that are affordable, sensitive, specific, user friendly, robust, rapid, equipment-free, and deliverable to end-user (ASSURED) [73,74]. Therefore several colorimetric malaria biosensors are being reported. These biosensors use the change in color that the naked human eye can identify to confirm the presence of a malaria biomarker. It also uses optical detectors for quantitative measurements. To improve the performance of these biosensors, nanomaterials such as nanoparticles and quantum dots are being used. This is due to their unique physical and chemical properties, such as high surface-to-volume ratio, excellent capacity for reaction catalysis, visual color transition, and optical properties [75,76]. It is essential to note that the properties of nanomaterials depend on their size, shape, and degree of aggregation. Cationic polymers and gold nanoparticles were used to develop a colorimetric aptasensor for malaria diagnosis by Jeon et al. [77] *Plasmodium falciparum* lactate dehydrogenase and pL_1 were used as biomarker and aptamer, respectively. The principle of this biosensor was based on cationic polymers (poly (diallyldimethylammonium chloride) and poly (allylamine hydrochloride)), which aggregate gold nanoparticles (AuNps); thus, a color change was observed from red to blue. This color change depends on the concentration of *Plasmodium falciparum* lactate dehydrogenase (Fig. 7).

A detection limit of 8.7 pM and 8.3 pM was obtained for *Plasmodium vivax* lactate dehydrogenase when (poly (diallyldimethylammonium chloride) and poly (allylamine hydrochloride)) were used, respectively.

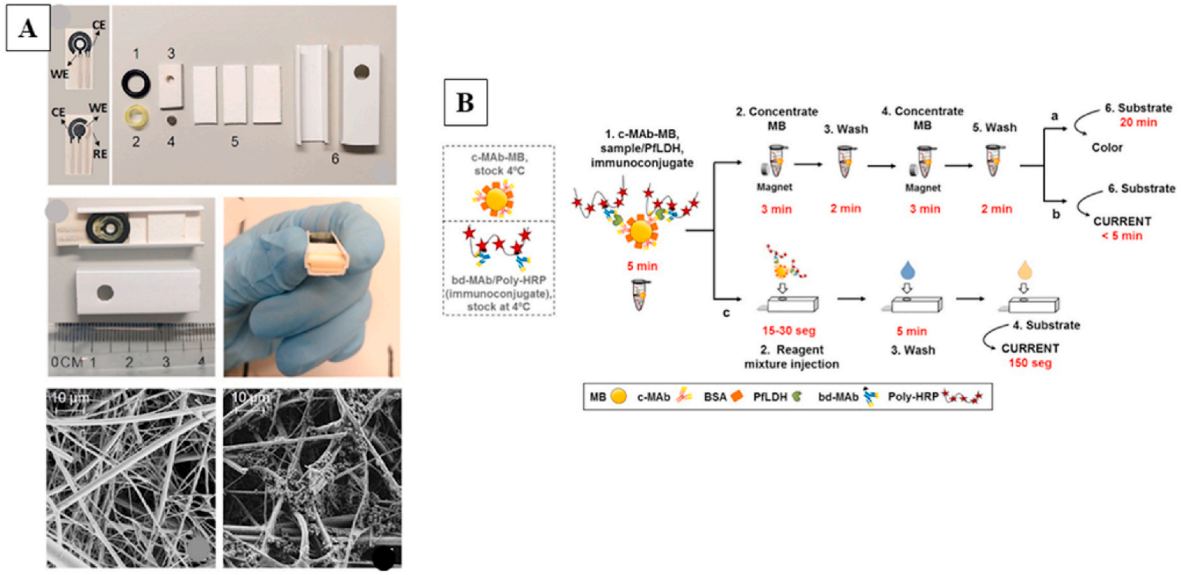

Fig. 5. (A) Production of the MP-dsSPCE POC device, (B) Different formats of the single-step magneto-immunoassay [61].

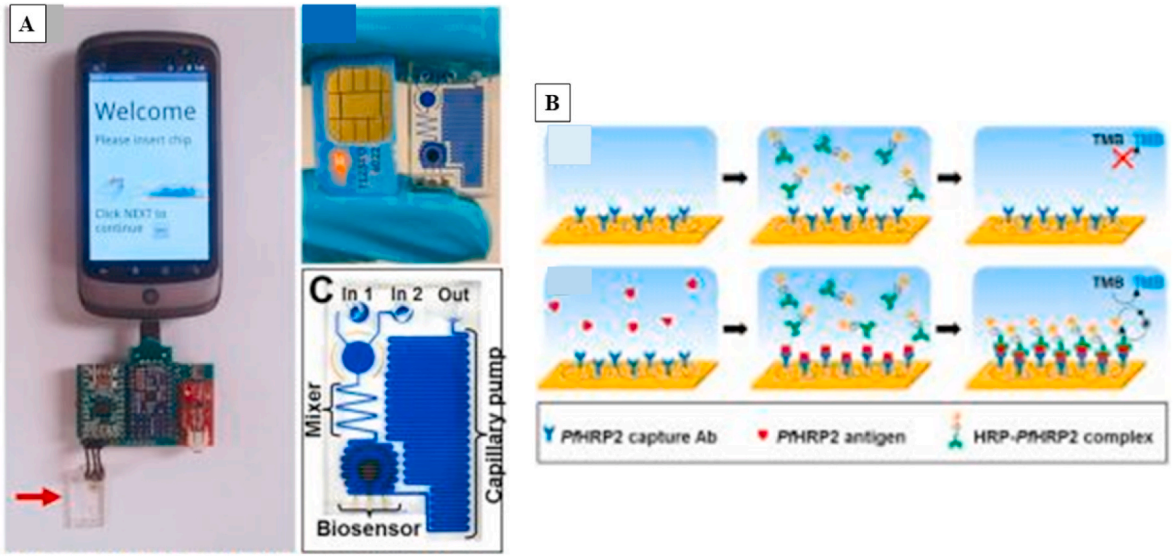

Fig. 6. (A) Image of the designed prototype device. (B) Scheme for electrochemical detection of *Pf*HRP2 [62].

The same sensor was used for the measure *Plasmodium falciparum* lactate dehydrogenase, and a detection limit of 125 pM and 10.3 pM was obtained for poly (allylamine hydrochloride)) and (poly (diallyldimethylammonium chloride) respectively. A similar study was conducted by Lee et al. [78], where a cationic surfactant was used as shown in Fig. 8. A detection limit of 2.94 pM and 1.25 pM was obtained for *Pf*LDH and *Pv*LDH, respectively. While Jain et al. [79] reported the use of aromatic surfactant (benzalkonium chloride) as aggregating agent for aptamer (P38) gold nanoparticles based detection of *Plasmodium* lactate dehydrogenase. A detection limit of 281 ± 11 pM was obtained.

In another study, a simple colorimetric point of care device for diagnosing malaria was reported by Dirkzwager et al. [80]. This POC device was made of a paper-based syringe test and a magnetic bead-based well test. *Pf*LDH and 2008s-biotin were used as a biomarker and aptamer, respectively. Both methods were found to be sensitive to *Pf*LDH. However, the syringe method was more sensitive with a wider linear range and a detection limit of 4.9 ng/mL. A novel and sensitive carbon nanofibers grown on glass micro balloons immunosensor was reported by Gikunoo et al. [81] to detect *Pf*HRP2, a detection limit of 0.025 ng/mL was obtained.

4. Conclusion and future perspectives

Several electroanalytical methods have been reported for the detection and quantification of malaria. To diagnose malaria, WHO recommends using parasite-based diagnostic testing such as microscopy or rapid diagnostic tests. The selectivity and sensitivity of some of these analytical methods are poor. Therefore, there is a need to develop diagnostic tools that are affordable, sensitive, specific, user-friendly, robust, rapid, equipment-free, and deliverable to the end-user (ASSURED). More studies still need to be done to improve electrochemical biosensors' analytical performance in real-world malaria samples. Also, the application of various nanomaterials to fabricate electrochemical sensors for diagnosing malaria is limited; thus, more research focus is needed.

Table 2
Some of the selected electrochemical biosensors for malaria diagnosis.

Biosensor description	Biomarker/malaria species	Detection limit	Advantages	Future work/disadvantages	Ref
A tri-inlet device integrated with nanocomposite (reduced graphene oxide gold nanoparticles) and *Plasmodium vivax* modified electrode	*Plasmodium vivax*	40 vivax infected RBCs/10 μl blood	Rapid (5 min) and sensitive. Showed low detection limit under the point of care settings.	With the technological advances, this biosensor could be further developed to a disposable type sensor kit for the onsite analysis of *Plasmodium vivax*	[58]
4-mercaptobenzoic acid-modified gold SPR chip immobilized with Ag and malaria antibodies	*Pf*HRP2	5.6 pg	High sensitivity due to the use of 4-mercaptobenzoic acid, which has a lesser thickness and fast electron transfer compared to dextain	The developed biosensor still needs to be tested in samples collected from malaria-infected patients.	[63]
Dual electrochemical analysis of malaria using aptamer-graphene oxide biosensor	*Plasmodium falciparum* lactate dehydrogenase (PfLDH)	0.5 fM	dual electrochemical detection of *Pf*LDH	More technological innovations could develop this biosensor into a handheld device that can be used in resource-limited environments.	[60]
Magneto immunoassay strategy for detection of malaria based on magnetic nanoparticles	*Pf*HRP2	0.36 ng/mL	The use of nanoparticles resulted in a low detection limit and improved washing and separation steps. Application for onsite diagnosis of malaria and it uses disposable screen-printed magneto electrodes	Future studies still need to be conducted on malaria-infected patients to correlate patients' samples with clinical status.	[64]
aptamer-based electrochemical biosensor for malaria with an adjustable dynamic response range	*Pf*LDH	0.84 pM	High selectivity, low detection limit, and it is reusable.	Since the detection of malaria was done in 10 fold diluted human serum, more experiments still need to be conducted in clinical samples. After that, this work can be modified for an innovative reusable design of a microfluidic malaria device.	[59]
Electrochemical immunosensor based on methylene blue and the electro-oxidation of hydrazine on Pt nanoparticles	*Pf*HRP2	2.2 pg/mL	High sensitivity and ability to detect PfHRP2 in unadulterated saliva samples	The detection of *Pf*HRP2 was done as proof of concept. There are more possibilities for this immunosensor to detect other important protein biomarkers.	[65]
Malara Immunosensor based on chronoamperometry	*Pf*HRP2	2.14 ng/mL and 2.95 ng/mL	Cost-effective, sensitive, and easy to use. Ideal for onsite application.	More experiments still need to be conducted in patient serum samples.	[66]
Electrochemical impendence spectroscopy-based malaria aptasensor	*Pf*HRP2	3.15 pM	High sensitivity and selectivity because of the novel ssDNA aptamer	The developed aptasenser was used to detect *PF*HRP2 in mimicked blood serum. More experiments still need to be conducted in malaria-infected patients.	[67]
Copper-doped zinc oxide nanofibers modified electrode for the detection of malaria.	*Pf*HRP2	6.8 ag/mL	High sensitivity and a new surface modification method for adding functional groups that improve the selectivity of the biosensor.	The developed biosensor still needs to be tested in samples collected from malaria-infected patients.	[6]
capacitive malaria aptasensor	*Pf*GDH	0.77 pM	High selectivity due to specificity of the thiolated ssDNA aptamer (NG_3) to PfGDH. This is the first study to report an aptasensor exploiting non-Faradaic impedance as a sensing signal to detect *Pf*GDH.	More technological innovations could develop this aptasensor into a handheld device that can be used in resource-limited environments.	[33]
Electrochemical detection of malaria in whole blood using a wash-free, label-free immunoassay	*Pf*HRP2	Not available however detection range from 100ng/mL- 100 μg/mL was given	Wash-free and label-free immunoassay that uses two liquid dispensing steps. The immunoassay is rapid (5 min) with excellent specificity and reproducibility.	The detection of *Pf*HRP2 was done as a proof of concept assay. There are more possibilities of this label-free immunoassay to be used for multiple protein detection.	[68]
Detection of *Plasmodium* lactate dehydrogenase using an aptasensor.	*Pf*LDH *Pv*LDH	120,1 fM and 108.5 fM for *Pf*LDH and *Pv*LDH respectively	Simple rapid and highly sensitive sensor with an aptamer that selectively bound to both *Pf*LDH and *Pv*LDH	With technological advances, this biosensor can be developed to meet the requirements for point of care testing.	[69]
Gold nanoparticles based biosensor for detection of malaria	*Pf*LDH	19 pg/mL 23 pg/mL	Rapid (2 h) and cost-effective point of care immunoassay with high sensitivity and reproducibility.	Future experiments still need to be performed in clinically relevant samples before the biosensor can be used in real-world	[70]
Screen-printed electrode modified with gold nanoparticles-multi-wall carbon nanotubes, and *Pf*-HRP2 antibody	*Pf*HRP2	8 ng/mL	Disposable Amperometric immunosensor with high sensitivity compared to commercial Paracheck Pf test	This biosensor has the potential to be packaged into a handheld potentiostat device.	[10]
Point of care (POC) electrochemical sensor for detection and quantification of malaria in lysed whole blood	*Pf*LDH	200 ng/mL	Rapid (20 min) Quantitation in lysed whole blood. Single-step magneto-immunoassay for PfLDH.	With technological advancement, this biosensor can be developed to meet the requirements for point of care testing.	[61]
Mobile-based electrochemical biosensor for quantification of malaria in low resource settings.	*Pf*HRP2	20 ng/mL	Simple and cost-effective hands held device that transmits data automatically to the cloud.	#	[71]
electrochemical platform integrated with a mobile phone	*Pf*HRP2	16 ng/mL	This device is rapid (15 min) and can be used in remote and rural areas because		[62]

(*continued on next page*)

Table 2 (*continued*)

Biosensor description	Biomarker/malaria species	Detection limit	Advantages	Future work/disadvantages	Ref
			of its compact size, good selectivity, and sensitivity.	Field testing and wireless data transmission functionality implementation still need to be done.	
Chemiresistive biosensor for detection of malaria using multi-walled carbon nanotubes-zinc oxide nanofibers	*Pf*HRP2	0.97 fg/mL	Good reproducibility and specificity with a sensitivity of 8.29 $K\Omega g^{-1}$ mL. This is the first study to report a flexible chemiresistive biosensor for the detection of malaria.	The developed chemiresistive platform can be modified to detect other important biomarkers.	[72]

No future work is recommended.

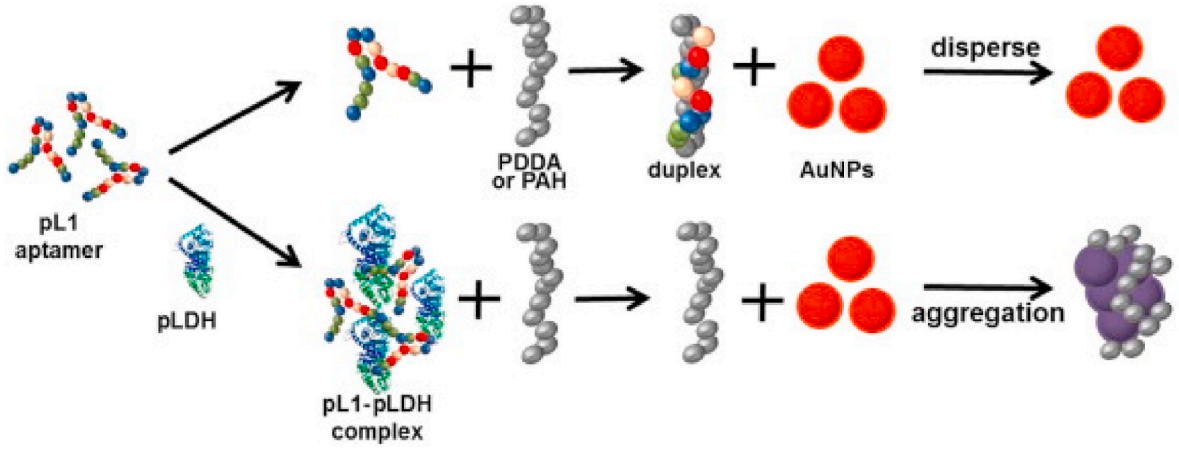

Fig. 7. Representation of the aptasensor for pLDH detection [77].

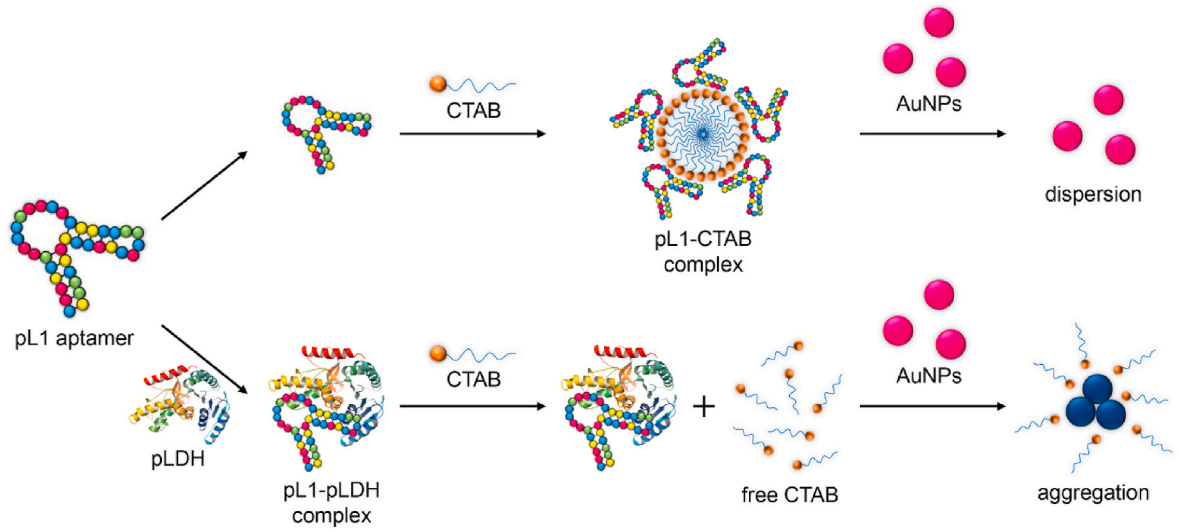

Fig. 8. Detection of pLDH based on the surfactant-induced aggregation of AuNPs [78].

CRediT authorship contribution statement

Zondi Nate: Conceptualization, Writing – original draft. **Atal A.S. Gill:** Writing – review & editing. **Ruchika Chauhan:** Writing – review & editing. **Rajshekhar Karpoormath:** Supervision, Funding acquisition, Resources.

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