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REVIEW ARTICLE

The overview and perspectives of biosensors and *Mycobacterium tuberculosis*: A systematic review

Kobra Salimiyan Rizi[1] | Ehsan Aryan[1] | Zahra Meshkat[1] | Golnaz Ranjbar[2] | Mojtaba Sankian[3] | Kiarash Ghazvini[1] | Hadi Farsiani[1] | Hamid R. Pourianfar[4] | Majid Rezayi[5,6]

[1]Department of Medical Bacteriology and Virology, School of Medicine, Antimicrobial Resistance Research Center, Qaem University Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

[2]Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[3]Division of Immunobiochemistry, Immunology Research Centre, Bu-Ali Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[4]Research Department of Industrial Fungi Biotechnology, Research Institute for Industrial Biotechnology, Academic Centre for Education, Culture and Research [ACECR]-Khorasan Razavi Province Branch, Mashhad, Iran

[5]Medical Toxicology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[6]Department of Medical Biotechnology and Nanotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence
Majid Rezayi, Medical Toxicology Research Center, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran.
Email: rezaeimj@mums.ac.ir

Abstract

Tuberculosis (TB) is referred to as a "consumption" or phthisis, which has been a fatal human disease for thousands of years. *Mycobacterium tuberculosis* (*M. tb*) might have been responsible for the death of more humans than any other bacterial pathogens. Therefore, the rapid diagnosis of this bacterial infection plays a pivotal role in the timely and appropriate treatment of the patients, as well as the prevention of disease spread. More than 98% of TB cases are reported in developing countries, and due to the lack of well-equipped and specialized diagnostic laboratories, development of effective diagnostic methods based on biosensors is essential for this bacterium. In this review, original articles published in English were retrieved from multiple databases, such as PubMed, Scopus, Google Scholar, Science Direct, and Cochrane Library during January 2010–October 2019. In addition, the reference lists of the articles were also searched. Among 109 electronically searched citations, 42 articles met the inclusion criteria. The highest potential and wide usage of biosensors for the diagnosis of *M. tb* and its drug resistance belonged to DNA electrochemical biosensors (isoniazid and rifampin strains). Use of biosensors is expanding for the detection of resistant strains of anti-TB antibiotics with high sensitivity and accuracy, while the speed of these sensory methods is considered essential as well. Furthermore, the lowest limit of detection (0.9 fg/ml) from an electrochemical DNA biosensor was based on graphene-modified iron-oxide chitosan hybrid deposited on fluorine tin oxide for the MPT64 antigen target. According to the results, the most common methods used for *M. tb* detection include acid-fast staining, cultivation, and polymerase chain reaction (PCR). Although molecular techniques (e.g., PCR and real-time PCR) are rapid and sensitive, they require sophisticated laboratory and apparatuses, as well as skilled personnel and expertise in the commentary of the results. Biosensors are fast, valid, and cost-efficient diagnostic method, and the improvement of their quality is of paramount importance in resource-constrained settings.

KEYWORDS

biosensors, detection, *Mycobacterium tuberculosis*, tuberculosis diagnosis

1 | INTRODUCTION

Tuberculosis (TB) has historically been a widespread disease, affecting various organs of the human body, while mostly causing lung damage (Saleem & Azher, 2013). Most cases of TB are reported in underdeveloped countries, such as Pakistan, where there are 268,000 and 64,000 new TB and mortality cases each year, respectively (Amin et al., 2011). The major concern regarding TB control is the emergence of drug resistance, particularly multidrug resistance (MDR), total drug resistance, and pan-drug resistance. No treatments are available for some resistant bacterial strains, and they may spread rapidly across the world (Palomino, 2005).

Eastern Europe, China, and Iran are the countries with the high prevalence of MDR TB infection (Organization, 2010). The World Health Organization (WHO) has endorsed the strategy of directly observed treatment, short-course, which has proven efficient in blocking the emergence of drug resistance TB (Frieden, 2000). The current methods used for the treatment of pulmonary TB require clinical processing, laboratory materials, and techniques, especially sputum smear microscopy, cultivation methods, X-radiography, and tuberculin skin test. Moreover, the current diagnostic methods for extra pulmonary TB should be performed routinely to vouch for introductory results in cases with extra pulmonary TB; such example is the biopsy of various body tissues (Al-Zamel, 2009). Therefore, development of rapid, easy, accurate, and sensitive detection techniques is critical.

To the best of our knowledge, no systematic reviews have been focused on the sensory detection methods of *Mycobacterium tuberculosis* (*M. tb*). The present study aimed to review the articles published regarding the progress in the biosensory technologies used for human TB, with an emphasis on the recognition of various signal transducer methods and their potential for clinical rendition.

2 | MATERIALS AND METHODS

2.1 | Research questions

The main research question was focused on the most commonly used screening methods for the detection of *M. tb* in the human body, especially in the sputum, as confirmed by culture or polymerase chain reaction (PCR) during January 2010–October 2019.

2.2 | Search strategy

This systematic review was performed via searching in databases such as Web of Science, PubMed, Cochrane Library, Scopus, Science Direct, and Google Scholar for the articles published during January 2010–October 2019. The literature search was limited to the original papers published in English. In the search strategy for the studies focusing on TB detection, various keywords and medical subject headings (MeSH) were used, including *Mycobacterium tuberculosis* OR *M. tb* AND biosensors AND electrochemical biosensor OR optical method OR piezoelectric method OR fluorescent method OR colorimetric method. The search was performed by two independent researchers, and the obtained results were assessed by a third researcher (Figure 1).

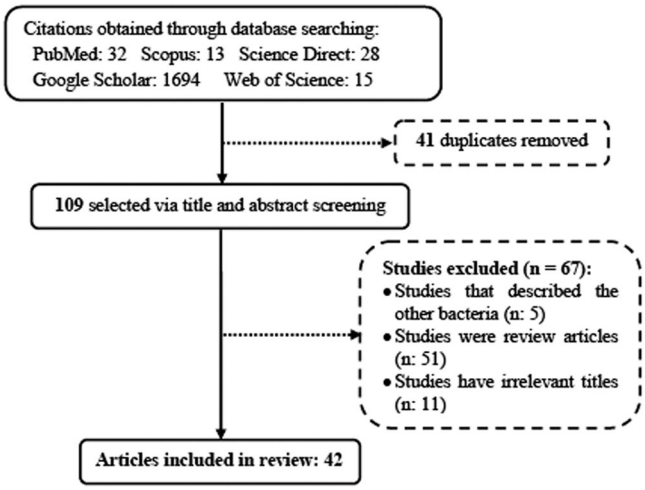

FIGURE 1 Flowchart of search strategy

2.3 | Data extraction

Data were extracted from the selected articles ($n = 42$), including the data on the location, target population, transducer, bio-recognition elements, platform, sensitivity, specificity, limit of detection, detection range, type of samples, and comments.

2.4 | Inclusion and exclusion criteria

The inclusion criteria were the studies published in English, describing the biosensor techniques for the detection of *M. tb* during January 2010–October 2019. The exclusion criteria were the studies on the detection of patients coinfected with other microorganisms (e.g., viruses), nonoriginal articles, and the studies for investigation purposes.

2.5 | Quality assessment

To evaluate the quality of the selected articles, data extraction and quality assessment were performed independently by two reviewers (K. S. and M. R.), and the final results were evaluated by the third researcher (I. I. A.).

2.6 | Detection of *M. tb* using traditional screening methods

Pulmonary TB could be diagnosed based on its symptoms, chest radiography findings, sputum smear microscopy, and cultivation of

M. tb, which is considered to be the "gold standard" technique in this regard (Gholoobi, Masoudi-Kazemabad, Meshkat, & Meshkat, 2014). Furthermore, the Ziehl–Neelsen (ZN) method is routinely used for the detection of acid-fast bacilli (AFB), particularly in low-income countries, owing to its simplicity, cost-efficiency, rapidity, high specificity, and positive predictive value (Palomino, 2005). However, the sensitivity of this approach is directly correlated with the bacterial load per milliliter of sputum. It is also notable that accurate results on acid-fast staining require high bacterial load for sputum (5,000 AFB/ml; Swai, Mugusi, & Mbwambo, 2011). In immunocompromised patients (e.g., HIV infection), extra-pulmonary TB, and pediatric TB, this method has been reported to have poor detection capability and may cause false negative results (Desikan, 2013). On the other hand, acid-fast staining cannot distinguish viable and dead bacilli, as well as *M. tb*, from NTM and resistant/susceptible strains (Srivastava, Van Rijn, & Jongsma, 2016).

Culture-based methods are the second class of techniques that are applied for the detection of *M. tb* in clinical samples. In fact, they are considered to be the "gold standard" methods for TB detection (Asmar & Drancourt, 2015). Culturing could be performed on both solid and broth media; for instance, solid egg-based Lowenstein–Jensen (LJ) medium is used commonly in this regard. The detection limit of culture methods is approximately 10 viable bacilli per milliliter of clinical samples. However, the sensitivity of LJ medium culture is higher compared with acid-fast staining (80–85%). Owing to the long incubation time (4–6 weeks), a long period is required to access the results (Muddaiah, James, & Lingegowda, 2013). Therefore, an alternative tool is required for the rapid and accurate detection of *M. tb*.

For decades, serological techniques based on the detection of antibodies against *M. tb* antigens have been available although no international guidelines have recommended their use (Steingart, Ramsay, Dowdy, & Pai, 2012). For instance, enzyme-linked immunosorbent assay (ELISA) is a commercial method applied to detect the immunoglobulin G against the antigen 85 complex (Ag85 complex) in serum samples (Imaz, Schmelling, Kaempfer, Spallek, & Singh, 2008). PCR-based techniques are diagnostic molecular tests, which include real-time PCR, strand-displacement amplification methods, line probe assay, and loop-mediated isothermal amplification; these techniques have high accuracy, as well as limitations such as high cost. Moreover, they require complicated instruments, and expert personnel have prohibited their performance on a common basis, particularly in low-income countries (Table 1; Foulds & O'brien, 1998; Palomino, 2005).

2.7 | Biosensing methods as alternative tools for *M. tb* detection

Most of the diagnostic methods that are currently available for the detection of TB lack adequate efficiency for the early detection of the disease. In addition, they have insufficient sensitivity and/or specificity and are unable to discriminate between the active and latent forms of TB. Some of the main limitations of most TB detection methods include the time-consuming growth period of *M. tb* (minimum of 17 days), emergence of symptoms only in the advanced stages of the disease (pulmonary TB), and low bacterial load of sputum even in the active form of TB (Srivastava, 2014). Therefore, there is an urgent need for rapid, cost-efficient, simple, and sensitive techniques, which are able to differentiate between the active and latent TB forms, perform the assay of drug susceptibility, and be implemented in deprived areas.

Reports have been published on the development of point-of-care testing strips using biosensors for the detection of microorganisms in

TABLE 1 Comparison of nucleic acid-based techniques for pulmonary *Mycobacterium tuberculosis* detection

Technique	Specificity	Sensitivity	Limit of detection	Assay time	References
GTMD	~58%	~97%	NM	up to 3 hour	(De Luna, Ruiz, Gutierrez, & Casal, 2006; Neonakis et al., 2009)
q real-time PCR	62.5%	97.02%	NM	up to 2 h	(Lv, Zhang, Zhang, & Lu, 2017)
Xpert MTB/RIF (Cepheid, USA)	99% (Adults) 62% (Children)	89% (Adults) 98% (Children)	50-150 cfu/ml	2 h	(Detjen et al., 2015; Steingart et al., 2012)
Conventional PCR	71.4% (pulmonary) 28.6% (Extra-pulmonary)	91.7% (pulmonary) 82.2% (Extra-pulmonary)	NM	120 min	(Chawla, Johar, Vishwanath, & Mukhopadhyay, 2015; Sarmiento, Weigle, Alexander, Weber, & Miller, 2003)
Line probe assays	99.2%	100% (smear-positive) 68.6% (smear-negative)	10000 cfu/ml	up to 150 min	(Farooqi, Qamar, Ali, Jabeen, & Hasan, 2015; Luetkemeyer et al., 2014; Singh et al., 2017)
LAMP	100%	~99%	NM	<1 h	(Sharma et al., 2019)

Abbreviations: cfu, colony-forming unit; GTMD assay, GenoType Mycobacteria Direct assay; LAMP, loop-mediated isothermal amplification; q real-time PCR, quantitative real-time PCR.

clinical and biological samples (Fani, Rezayi, et al., 2019; Khorasani, Langari, Sany, Rezayi, & Sahebkar, 2019; Rezayi, Ghayour-Mobarhan, et al., 2018; Rezayi, Ghasemi, Karazhian, Sookhakian, & Alias, 2014; Said et al., 2016; Said, Rezayi, Narimani, Manan, & Alias, 2015; Sany et al., 2016). Recently, biosensors have been developed for the diagnosis of bacterial infectious disease agents, such as TB (Table 2; Kanayeva, Bekniyazov, & Ashikbayeva, 2013). Various types of TB biosensors have been proposed in this review, such as electrochemical, fluorescent, colorimetric, piezoelectric, optical, and magnetic biosensors (Figure 2).

2.8 | Electrochemical biosensors

In electrochemical biosensors, a solid electrode acts as the basic electrode to transmit the signal throughout the detection process, converting the produced signal into electrical signals, including current, potential, impedance, and coulometry signals (Abraham et al., 2015; Ahmadzadeh, Rezayi, Faghih-Mirzaei, Yoosefian, & Kassim, 2015; Ahmadzadeh, Rezayi, Kassim, & Aghasi, 2015; Rezayi, Karazhian, et al., 2014; Rezayi, Gholami, Said, & Alias, 2016; Said et al., 2015). Due to the various biological targets of *M. tb* detection, the reported electrochemical biosensors for *M. tb* diagnosis have been divided into two categories of electrochemical DNA and immune biosensors (Fani et al., 2018; Mahmoodi et al., 2019; Rasouli et al., 2018; Rezayi, Farjami, Hosseini, Ebrahimi, & Abouzari-Lotf, 2018). Electrochemical biosensors (especially electrochemical DNA biosensors) have the most common application for the detection of infectious agents, such as *M. tb* (Huang, Xu, Liu, Wang, & Chen, 2017; Ronkainen, Halsall, & Heineman, 2010). In a study in this regard, Torres-Chavolla and Alocilja (2011) developed an electrochemical DNA biosensor for *M. tb* detection, which consisted of a complex target sandwich formation process. In this biosensor, the thermophilic helicase-dependent isothermal primers acted as the DNA target amplification, and a 190-bp fragment of the *IS6110* gene was designed for the *M. tb* complex. In addition, the dextrin-coated gold nanoparticles and amine-coated magnetic particles were functionalized with two different thiolated DNA probes, respectively. After the formation of the hybridized sandwich complex between the two functionalized probes, it was pulled and separated using a magnet and transferred to a SPCE. Through reducing the current of the gold ions, the differential pulse voltammograms [Au^{3+}] was produced by adding the HCl solution to dissolve the gold nanoparticles, which was achieved within the potential range of 0.00-1.25 V. Moreover, the proposed biosensor had a detection limit of 0.01 ng/μl of an amplified target (105 bp).

In another research, Zhang, Chai, Xu, and Zhou (2011) introduced an immunosensor chip based on modified graphene oxide TB-specific antigens onto the gold electrode for the detection of TB in human sera samples. According to the findings, graphene oxide was modified for protein attachment with *N*-ethyl-*N*′-(3-dimethylaminopropyl) carbodiimide hydrochloride/*N*-hydroxysuccinimide.

In another study, Mogha, Sahu, Sharma, and Masram (2018) presented an electrochemical DNA biosensor based on reduced graphene oxide nanoribbons (RGONPs) and gold nanoparticles for the detection of the target DNA of *M. tb* (Figure 3). In the mentioned research, the electrode was constructed by the immobilization of the gold nanoparticles, which had been immobilized over the RGONPs, followed by the covalent modification of the gold nanoparticles with 5′-SH-ssDNA (ssDNA/Au/RGONR). Cyclic voltammetry and chronoamperometric methods were used throughout the experiments. The DNA biosensor had acceptable selectivity and sensitivity (up to 0.1 fM) toward DNA *M. tb*.

As is depicted in Figure 4, the mechanism response of the proposed biosensor was clearly described during the immobilization and hybridization of the ssDNA probe. The attachment of ssDNA onto the Au/RGO bioelectrode and its hybridization with complementary target ssDNA to form dsDNA led to the reduction of the electron transfer kinetics due to the repulsion between the $[Fe[CN]6]^{3-/4-}$ ions in the solution and phosphate backbone of DNA. In addition to decreasing the treatment duration from 9 to 6 months of bacterial inspections (e.g., TB), several antibiotics (e.g., rifampicin; Miodek, Mejri, Gomgnimbou, Sola, & Korri-Youssoufi, 2015; Zribi et al., 2016) and pyrazinamide (PZA; Rueda et al., 2018) were used. In case of PZA, only susceptible *M. tb* strains released pyrazinoic acid (POA; Figure 5). In this process, the quantitative measurement of POA is considered to be an indicator of PZA resistance.

In a research in this regard, Rueda et al. (2018) introduced two electrochemical biosensors based on gold and platinum wires by measuring the resulted current with a potential difference applied to various concentrations of POA (Figure 6).

POA is an active form of a prodrug of pyrazinamide mediated by pyrazinamidase (PZase), which is an enzyme encoded by the *pncA* of *M. tb*. If a mutation occurs in the *pncA* gene of *M. tb*, the activity of the pyrazinamidase enzyme is disrupted, and the bacterium shows resistance to prodrug PZA. In the mentioned study, these biosensors were tested on the supernatant of a negative liquid-based microscopically, and drug susceptibility culture was observed for the detection of POA, PZA, and their combination. Moreover, the obtained detection limits of the proposed biosensors were estimated at 40 and 1 μM of POA for the gold and platinum working electrodes, respectively. The fabrication costs of each biosensor were calculated to be approximately 80 dollars.

2.9 | Fluorescent biosensors

These biosensors are usually based on fluorescent organic molecules, nanoparticles, proteins, or their combinations (VanEngelenburg & Palmer, 2008). Some of the key advantages of these biosensors are allowing image and quantification of protein activities and small-molecule signals in living cells with high spatial and temporal resolution (Newman, Fosbrink, & Zhang, 2011). Usually, the receptor or binding molecules are not fluorescent and need to be combined; such example is green fluorescent protein (GFP; Bajar, Wang, Zhang, Lin, & Chu, 2016; Newman et al., 2011; Vacaru, Vitale, Nieves, & Baron, 2014). Fluorescent labels are commonly employed in fluorescence

TABLE 2 A brief window of current biosensor methods for TB and *Mycobacterium tuberculosis* drug resistance detection

Location	Target	Transducer	Biorecognition elements	Platform	Sensitivity	Specificity	Reported limit of detection	Detection range	Type of sample	Comments & limitations	References
USA	DNA [190 bp from IS6110]	Electrochemical	DNA probe	SPCE chip	–	–	0.01 ng/μl	0.01–10 mag ng/μL	–	• Bacterial DNA and biological samples [e.g. sputum] are need order for testing	(Torres-Chavolla & Alocilja, 2011)
Malaysia	N.S.	Electrochemical	DNA probe	SPCE	–	–	7.853×10^{-7} M	10^{-6}–10^{-9} M	–	• Increased of sensitivity & sensitivity with target using PANI/GP composite nanofibers	(Mohamad et al., 2017)
Australia	ESAT-6 gene	Electrochemical	DNA probe	SPCE	High	High	–	–	–	• Detection of isothermally amplified *M.tb* DNA by colorimetrically method	(Ng, Wee, West, & Trau, 2015)
Malaysia	Genomic DNA of *M. tb*	Electrochemical	DNA probe	SPCE	–	–	–	–	–	• Methylene Blue as a suitable label for DNA electrochemical biosensors	(Issa, Hamdan, & Noh, 2010)
China	IS6110 sequence	Electrochemical	DNA probe	GCE/rGO-AuNPs	–	–	N.S.	1×10^{-15}–1×10^{-9} M	–	• Good consistency • Wasn't testing on real samples	(C. Liu et al., 2014)
China	Antigenic proteins of *M. tb* cells	Electrochemical	Antibodies	Graphene oxide	–	–	–	–	Serum sample of a TB patient tested	• High sensitivity due to the usage of Graphene oxide • High sensitivity • Very limited sample size	(P. Zhang, Chai, Xu, & Zhou, 2011)
India	Genomic DNA of *M. tb*	Electrochemical	DNA probe	RGONRs	–	92%	0.1 fM	0.1 fM to 10-6 M	–	• The ssDNA/Au/RGONR bio-electrode that using the DNA target of *M.tb* in this work is the first time • Wasn't testing on real samples	(Mogha, Sahu, Sharma, & Masram, 2018)
Indonesia	Not mentioned in the reference	Electrochemical	DNA probe	GE	–	High	3.47 $\mu g.mL^{-1}$	–	–	• A label-free electrochemical DNA biosensor • Wasn't testing on real samples	(Nurmalasari, Gaffar, & Hartati, 2015)

(Continues)

TABLE 2 (Continued)

Location	Target	Transducer	Biorecognition elements	Platform	Sensitivity	Specificity	Reported limit of detection	Detection range	Type of sample	Comments & limitations	References
France	*rpoB* gene	Electrochemical	DNA probe	GE	–	–	0.3 fM	–	–	• low sample size is need • Effective for usage in clinical setting	(Miodek et al., 2015)
Tunisia, Saudi Arabia	*M. tb* [ESAT-6] Ag	Electrochemical	Anti-ESAT-6 monoclonal Abs	Bare gold electrode	–	–	7 ng/mL	–	BCG culture filtrate	• Differentiation culture filtrate proteins from pathogenic mycobacteria and BCG vaccine strains • Wasn't testing on real samples	(Diouani et al., 2017)
Malaysia	CFP10 Antigen	Electrochemical	polyclonal anti-CFP10 Abs	GP/PANI-modified SPGE	–	–	15 ng/mL	20–100 ng/mL	–	• GP/PANI nanocomposite allows to significantly increase of electrochemical immunosensors performance by suitable direct coating of the biolayer • ELISA is still a more appropriate and sensitive method for detecting CFP10 antigen compared to the sensory methods	(Mohd Azmi et al., 2018)
Perú, USA	POA concentration	Electrochemical	–	Gold -Platinum	–	–	1 μM	1 to 70 μM	–	• Suitable method for source-limited settings • It is qualitative method that is as a limitation • Simple, cost-effective method	(Rueda et al., 2018)
Korea	Not mentioned in the reference	Electrochemical	DNA probe	Gold nanotubes array electrode	–	–	0.05 ng/μL	0.01 ng/μL to 100 ng/μL	–	• A labeled DNA electrochemical biosensor	(Torati, Reddy, Yoon, & Kim, 2016)
China	N.S.	Electrochemical	DNA probe	GCE/AuNPs	–	–	8.7×10^{-15} M	1×10^{-14}–1×10^{-9} M	–	• High selectivity for discriminatory of mismatch DNA sequences	(C. Zhang, Lou, Tu, Bao, & Dai, 2015)

TABLE 2 (Continued)

Location	Target	Transducer	Biorecognition elements	Platform	Sensitivity	Specificity	Reported limit of detection	Detection range	Type of sample	Comments & limitations	References
France	*rpoB* gene	Electrochemical	DNA probe	PDMS/glass	–	–	0. 1 fM	0.1 fM to 1 pM	–	• Having the potential for point-of-care application with multiple target	(Zribi et al., 2016)
India	MPT64 Ag [23 kDa]	Electrochemical	DNA aptamer	Graphene CHIT-IO-GR deposited on FTO	–	–	0.9 fg·mL^{-1}	–	–	• Very fast response [20 min] • MPT64 Ag as a dominant secretory protein in active TB	(Thakur, Kaur, Sabherwal, Sareen, & Prabhakar, 2017)
India	MPT64 Ag	Electrochemical	DNA aptamer sequence	PEDOT-CNT/FTO film	–	–	0.5 ± 0.2 fg mL^{-1}	–	–	• An effective sensing method for detection of *M.tb* in active TB phase • Fast response	(Thakur, Kaur, Sareen, & Prabhakar, 2017)
Colombia	ESAT6 Ag	Electro-immuno-sensors	polyclonal anti-ESAT6 Abs	PCB platform	–	–	–	–	–	• Good precision • Fast response [1h]	(Sepulveda, Aroca, Varela, Del Portillo, & Osma, 2017)
California, Ka-zakhstan	IFN-γ	Electrochemical	DNA aptamer	GE	–	–	0.06 nM	0.06 nM to 10 nM	–	• Conventional IFN-γ ELISA is 5 to 10 times more sensitive • This method responds directly to the IFN-γ • Appropriate for dynamic scouting of IFN-γ	(Y. Liu, Tuleouva, Ramanculov, & Revzin, 2010)
India	16s rRNA spacer region	Electrochemical	DNA probe	ITO-coated glass plate [Nanowire/ nanotubes]	–	–	–	–	–	• A new step towards designing nano-biochips & ultrasensitive bioelectric-systems	(Das et al., 2011)
Turkey	Genomic DNA of *M. tb*	Electrochemical	DNA probe	PGA/PGE	–	–	1.3 nM	1.5–12.5 nM	–	• Good selectivity • Usage of polymerized amino acids for designing modified platform	(Yesil, Donmez, & Arslan, 2016)

(Continues)

TABLE 2 (Continued)

Location	Target	Transducer	Biorecognition elements	Platform	Sensitivity	Specificity	Reported limit of detection	Detection range	Type of sample	Comments & limitations	References
India	Genomic DNA of *M. tb*	Electrochemical	PNA probe	GOPS/ITO & Fe3O4-GOPS/ITO films onto gold electrode	-	-	PNA/Fe3O4-GOPS/ITO platform: 0.1 fM PNA-GOPS/ITO platform: 0.1 pM	PNA/Fe3O4-GOPS/ITO:0.1 fM to 100.0 fM PNA-GOPS/ITO:0.1pM to 50.0 pM	-	• The good reusability [14–15 times] • A PCR-free sensory method • The long Shelf Life	(Prabhakar, Solanki, Kaushik, Pandey, & Malhotra,2010)
Taiwan	IS6110, 16S ribosomal RNA, 85B, Rv3130c and Rv3133c	Optical	DNA probe	GE	0.26 μg/mL	–	115 ng/mL	1–10 μg/mL	–	• *MTB* DNA was successfully detected without immobilization	(Hsu et al., 2013)
Canada, Ukraine	*rpoB* gene	Optical genosensor	DNA probe	GE	N.S.	–	–	N.S.	–	• Good accuracy • Sensitive test	(Rachkov, Patskovsky, Soldatkin, & Meunier, 2013)
Turkey	16 s–23 s rRNA spacer region	Optical[SPR]	DNA probe	GE	–	–	30 ng μl^{-1}	0.05-0.5 μM	–	• Simultaneously detection of *M. tb* complex & *M. gordonae* by a genosensor • Reduced false-positive results of *M. tb* detection in water sources in compared with many conventional TB tests • Wasn't testing on real samples	(Duman & Piskin, 2010)
USA	*M. tuberculosis* whole cells	Optical	Genus-specific Abs[anti-BCG polyclonal IgY]	Immunofluorescence functionalized micro tip	–	–	200 CFU mL^{-1}	–	Sputum samples	• Detection of *M. tb* complex cells in sputum in 25 minutes • Low cost	(Kim et al., 2012)
USA	Anti-HspX Abs	Optical	Hsp-X Ag	local evanescent array coupled LEAC	–	–	87–108 pmdue to mouse IgG and Ag detection	–	–	• Detection of the specific antibodies	(Yan et al., 2011)

TABLE 2 (Continued)

Location	Target	Transducer	Biorecognition elements	Platform	Sensitivity	Specificity	Reported limit of detection	Detection range	Type of sample	Comments & limitations	References
Korea	CFP-10 Ag	Optical [SPR]	Monoclonal CFP-10 Abs	Cystamine – modified gold chip	–	–	100 ng/mL	100 ng mL^{-1} to 1μg mL^{-1}	–	• Reduction of the non-specific reactions due to cystamine blocking • Wasn't testing on real samples	(Hong et al., 2011)
China	16 s–23 s rRNA spacer region	Optical genosensor	DNA probe	GCE/AuNPs	–	–	10^4 CFU mL^{-1}	10^4–10^8 CFU mL^{-1}	–	• A qualitative method	(Xiang, Zhu, Huang, Zheng, & Fu, 2015)
USA	Ag85, ESAT6, and LAM	Optical(SPR)	Antibodies	optical waveguide	–	–	–	0.5 pM(Ag85), 1 pM (LAM), 100 pM (ESAT-6)	Spiked sputum and urine samples	• Detection of LAM, ESAT6 and Ag85 TB-specific biomarkers • Very high selectivity & sensitivity	(Mukundan et al., 2012)
Taiwan	Antigenic proteins of *M. tb* cells	Optical(SPR)	Console of 9 Ags	–	14-79% (single Ag) & 100% (multiple Ags)	93-100% (single Ag) & 89% (multiple Ags)	–	–	Serum samples of TB patients & healthy individuals	• A qualitative detection method • label-free sensor method	(Hsieh et al., 2012)
Italy, Germany	rAg85B recombinant protein	Optical(SPR)	*M.tb* Ag85 monoclonal antibody	Two electrode:GE & carboxymethyl dextran hydrogel	High	High				• Good selectivity • The ability to determine the affinity binding index of the Ag-Ab interaction • The possibility of usage real sera TB samples was not due to the low amount of specific Abs	(Rinaldi et al., 2019)
Malaysia, Iran	Genomic regions of ESAT-6	FRET	DNA probe	AuNPs	94.2 %	86.6 %	10 fg	–	Sputum samples	• Detection of *M.tb* complex • Can discriminate M.tb and BCG simultaneously • Small amount of sample is needed	(Shojaei et al., 2014)

(Continues)

TABLE 2 (Continued)

Location	Target	Transducer	Biorecognition elements	Platform	Sensitivity	Specificity	Reported limit of detection	Detection range	Type of sample	Comments & limitations	References
Thailand	DNA (178 bp from IS6110)	Colorimetric DNA based with LAMP	Gold nanoparti-cle (AuNPs) DNA probe	–	High	High	5 pg	–	–	• Combining of LAMP method with a gold nanoparticle [AuNPs] probes to detect *M.tb* DNA • **Read by the naked eye**	(Kaewphinit, Santiwatana-kul, & Chansiri, 2013)
Thailand	mutant *katG* gene	Colorimetric method	–	In-house turbidity	–	–	–	–	–	• Limited sample size • Quantitative detection	(Ckumdee, Santiwatana-kul, & Kaewphinit, 2017)
Washington	*M. tuberculosis* whole cells	Amperometric	Biotinylated IgY Abs	Functionalized the micro tip silicon nitride [Si3N4] film	–	–	100 CFU/mL	10^2–10^5 CFU/mL	Sputum samples	• Good selectivity & sensing • Low cost	(Hiraiwa et al., 2015)
China	DNA (IS6110)	Amperometric	DNA probe	Functionalized fullerene (C60) nanoparticles (FC60)	High	–	1 fM	1 fM–10 nM	Sputum samples	• Fabrication of the ultrasensitive platform with CNTs and fullerene • It has potential application for monitoring of TB treatment in more early stage	(Chen et al., 2018)
China	*M. tuberculosis* whole cells	Piezoelectrical	–	MSPQC	89 %	95 %	100 cfu/mL	10^1–10^4 cfu/mL	–	• This method is faster & more economical compared with BACTEC960 MGIT • A relatively long detection time	(Mi, He, Xiang, Lian, & Yi, 2011)
Thailand	DNA (IS6110)	Piezoelectrical	DNA probe	GE	High	High	0.25 μM	0-2.0 μM	150 ZN-positive & 50 ZN-negative samples that were suspected to tubercu-losis	• Based on non-Amplified DNA detection • High specificity of IS*6110* gene sensor with DNA probe	(Kaewphinit, Santiwatanakul, Promptmas, & Chansiri, 2010)

TABLE 2 (Continued)

Location	Target	Transducer	Biorecognition elements	Platform	Sensitivity	Specificity	Reported limit of detection	Detection range	Type of sample	Comments & limitations	References
China	*M.tb* drug resistant strains	Piezoelectrical	–	–	–	–	–	–	Sputum samples	• An indirect series piezoelectric (ISP) • Simultaneously detection of *M. tb* resistant strains to eight drugs of the first- & second lines anti-tuberculosis drugs • Good sensitivity	(Ren, Ma, Li, Huang, & Yi, 2013)
Portugal	*M. tuberculosis* whole cells	Magnetic	polyclonal antibodies	GE	–	–	–	–	–	• As a potential for point-of-care strip tests • Large sample need to improve the result of this study	(Barroso et al., 2016)
Harvard	16s rRNA spacer region	Magnetic	DNA probe	Magnetic nanoparticles on glass slide	–	High	100 CFU mL^{-1}	–	Sputum samples	• Low-cost method • Good sensitivity • Large sample need to improve the result of this study	(Liong et al., 2013)

Abbreviations: Ab, antibody; Ag, antigen; aM, attomolar; AuNP, gold nanoparticle; cfu, colony-forming unit; CHIT-IO-GR, graphene-modified iron-oxide chitosan hybrid; ESAT-6, early secretory antigen target-6; PEDOT-CNT/FTO, polymer 3,4-ethylenedioxythiophene (EDOT)-carbon nanotubes (CNTs)/fluorine-doped tin-oxide (FTO); Fe3O4, iron oxide; FTO, fluorine tin oxide; GCE, glassy carbon electrode; GE, gold electrode; GOPS, glycidoxypropyltrimethoxy silane; GP/PANI, graphene powder (GP)/aniline-poly methyl vinyl ether-alt-maleic acid; ITO, indium-tin-oxide; LAM, lipoarabinomannan; LAMP, loop-mediated isothermal amplification; MSPQC, multichannel series piezoelectric quartz crystal; N.S., not specified; PCB, printed circuit board; PDMS, polydimethylsiloxanes; PGA/PGE, poly(l-glutamic) acid-coated pencil graphite electrode; PNA, peptide nucleic acid; POA, pyrazinoic acid; RGONR, reduced graphene oxide nanoribbon; RM, resonant mirror; SPCE, screen-printed carbon electrode chip; SPGE, screen-printed gold electrode; SPR, surface plasmon resonance; ZN, Ziehl—Neelsen.

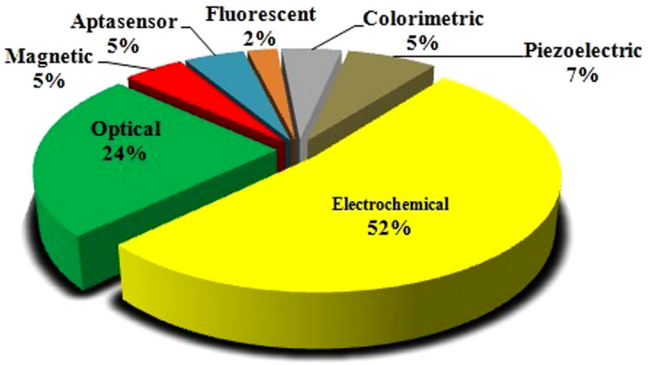

FIGURE 2 Frequency of reported biosensors for *Mycobacterium tuberculosis* detection (electrochemical, optical, piezoelectric, magnetic, aptamer, and immunosensors)

spectroscopy (Gaddam, Narayan, & Raju, 2016). Three aromatic amino acids (tyrosine, tryptophan, and phenylalanine) and the proteins containing these elements (GFP, nucleic acids, flavin nucleotides, and NADH) are reactive species, while most saccharides and lipids are nonfluorescent (Stich, Fischer, & Wolfbeis, 2010).

Fluorescence resonance energy transfer (FRET) biosensors are based on the physical FRET process, involving the less energy radiation transfer from a donor fluorophore to an acceptor fluorophore; these biosensors are widely applied for the detection of viral and bacterial infections, showing strong potential for these purposes (Lu et al., 2013; Villalobos et al., 2012; Zadran et al., 2012). As an ongoing research subject, fluorescent nanomaterials with a minimum of one dimension (≤100 nm) and organic dyes could be used for the better design and fabrication of fluorescent biosensors (Manasreh, 2011). In a research

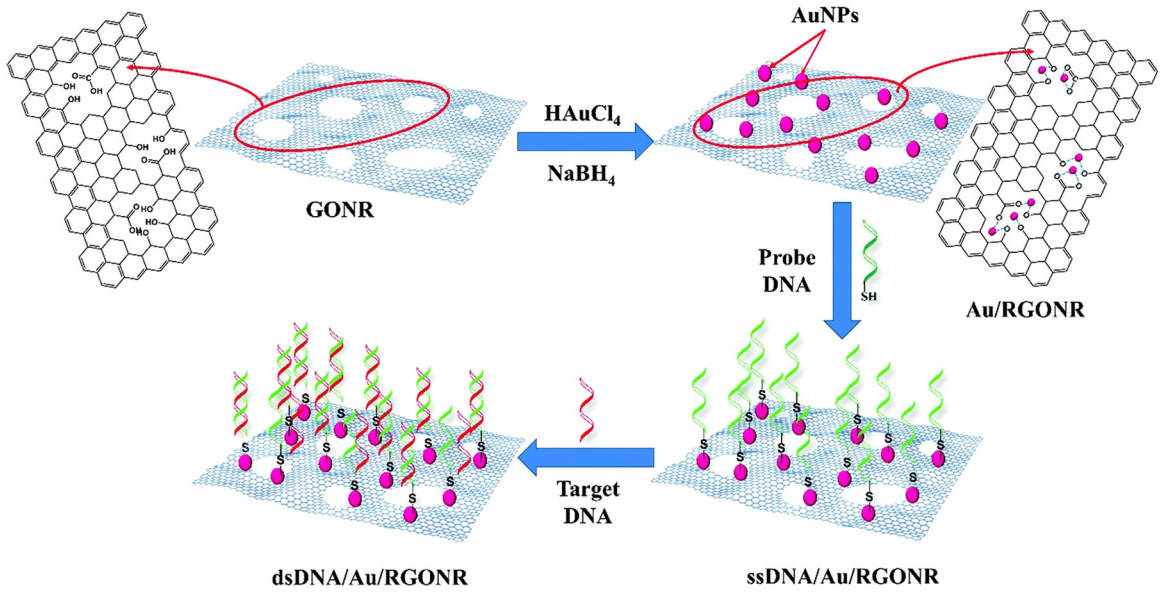

FIGURE 3 Schematic view of synthetic procedure of reduced graphene oxide nanoribbons (RGONRs) and gold nanoparticles for detection of the target DNA of *Mycobacterium tuberculosis*. It is reproduced with permission from Elsevier (Mogha et al., 2018)

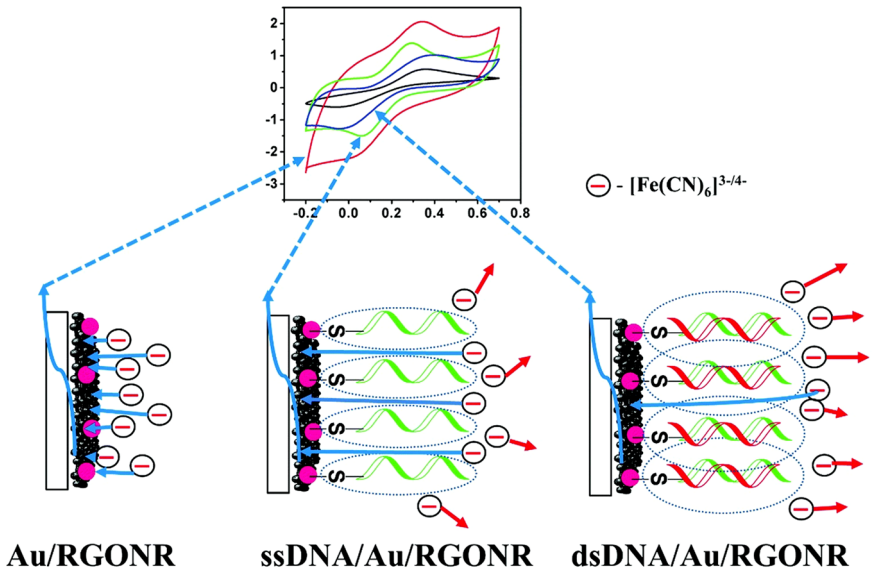

FIGURE 4 Mechanism of detection by ssDNA/Au/RGONR bio-electrode. It is reproduced with permission from Elsevier (Mogha et al., 2018). dsDNA, double-stranded DNA; RGONR, reduced graphene oxide nanoribbon; ssDNA, single-stranded DNA

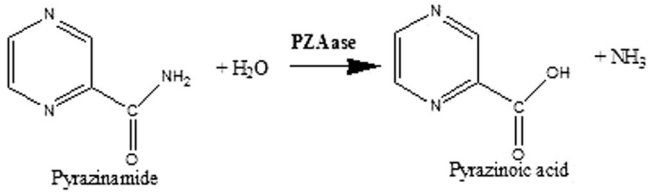

FIGURE 5 Conversion of pyrazinamide and water (H_2O) into pyrazinoic acid and ammonia (NH_3) by pyrazinamidase enzyme

in this regard, Shojaei et al. (2014) introduced a nanobiosensor detection method with the advantages of cadmium-telluride quantum dots (CdTeQDs) and gold nanoparticles onto the platform surface connected with two probes based on the conserved genomic regions of the ESAT-6 antigen. As is illustrated in Figure 7, QDs and AuNPs were conducted with two sequence-specific oligonucleotides probes (p1 and p2) to obtain a selective and sensitive sandwich form the FRET-based biosensor, respectively. To validate the proposed biosensor, the method was compared with the PCR, culture, and nested PCR techniques.

This conjunction led to a sandwich-form fluorescence resonance energy transfer sensory method with the detection limit of 10. The purpose of these probes was the simultaneous discriminatively detection of bacillus Calmette-Guerin (BCG) and other *Mycobacterium* species, which could cause false positive and cross-reactivity results during the detection process.

2.10 | Colorimetric biosensors

Colorimetric biosensors have been fabricated on rigid surfaces (e.g., glass substrate, plastic, and polymer) using photoresist etching techniques, which often have a high refractive index, and a dielectric thin film is deposited on the glass substrate

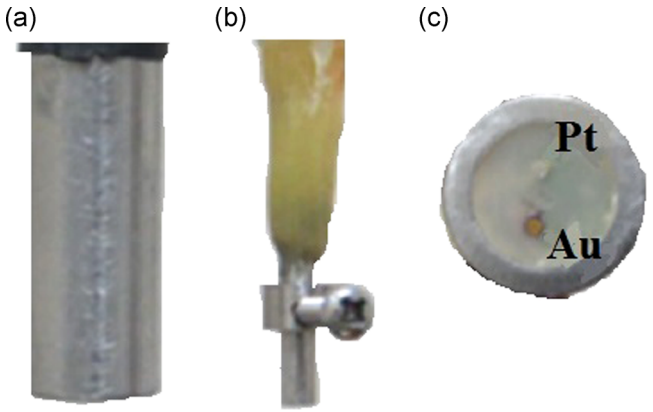

FIGURE 6 (a) Large electrochemical sensor with 13.2-mm external diameter, (b) small electrochemical sensor with 4-mm external diameter, (c) end-on view of large (13.2 mm) electrochemical sensor showing gold (Au) and platinum (Pt) working electrodes (Torres-Chavolla & Alocilja, 2011)

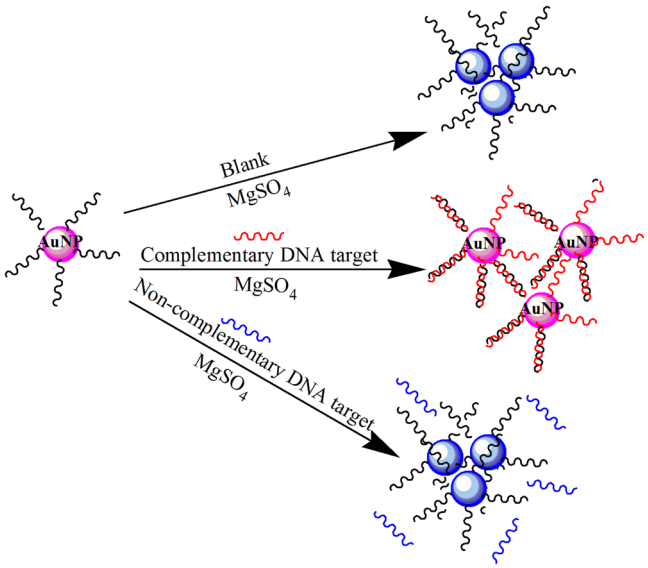

FIGURE 7 Sandwich-form FRET-based biosensor schematic. In the presence of the target, the AuNPs/P2 moiety optically quenched the QDs/P1 moiety; the presence of the target molecules turned the AuNPs/P2 into fluorescence acceptor close enough to the QDs/P1 resulting in a FRET signal (Shojaei et al., 2014). AuNP, gold nanoparticle; FRET, fluorescence resonance energy transfer; QD, quantum dot

(Cunningham et al., 2006). It is also notable that a photoresist material is defined as a material that is sensitive to light. Although colorimetric biosensors have attracted great attention, they have relatively low sensitivity, and their applications in clinical detection are limited (Xiao et al., 2017).

With respect to *M. tb* diagnosis, colorimetric biosensors are not widely used and are often employed in combination with other methods, such as a loop-mediated isothermal amplification (LAMP), to increase their sensitivity (Ckumdee, Kaewphinit, Chansiri, & Santiwatanakul, 2016). In a study in this regard, two DNA probes were hybridized with the target on the gold nanoparticle layer, resulting in a polymeric network close to the gold nanoparticles, as well as colorimetric changes from pink to purple only within 15 min in a single tube. If a complementary target had existed in the reaction medium, it could have inhibited aggregation, and the color would have remained pink. In the absence of a complementary target strand, the color changes to violet. The detection limit of the proposed DNA biosensor was 18.75 ng in a diluted sample volume of 10 µl of mycobacterial DNA.

In another research, Kaewphinit, Santiwatanakul, and Chansiri (2013) improved another colorimetric DNA biosensor for *M. tb* detection based on LAMP products using gold nanoparticles attached to a thiol-modified, single-stranded DNA probe based on the IS*6110* gene of *M. tb* in optimal conditions (63°C for 5 min). As is shown in Figure 8, a positive reaction occurred by the color change from red to purple, and the aggregation of gold nanoparticles caused the color to change from red to blue/purple.

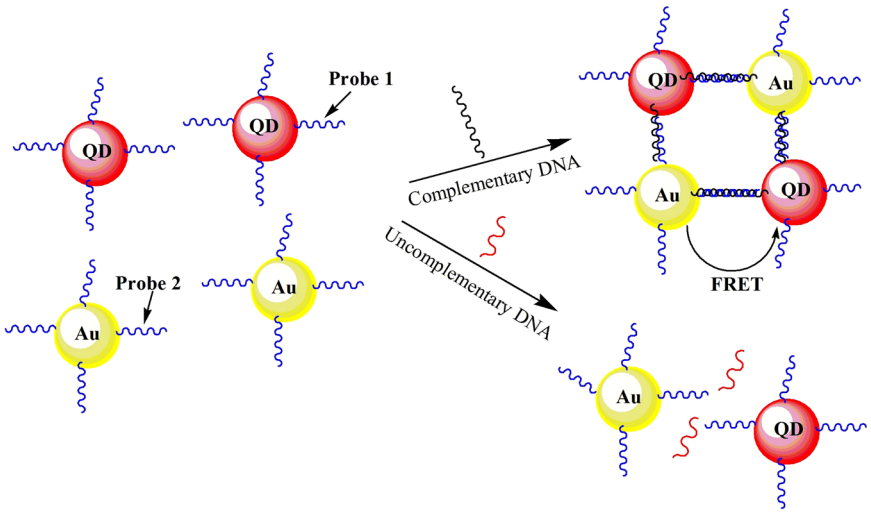

FIGURE 8 Experimental schematic representation LAMP-AuNPs probes based colorimetric assay in this study. The assay consists of visual comparison of test solutions before and after $MgSO_4$-induced AuNPs probes aggregation: (a) AuNPs probes alone as blank; (b) AuNPs probes in the presence of a noncomplementary DNA sample as negative; (c) AuNPs probes in the presence of a complementary DNA sample as positive (Shojaei et al., 2014). AuNP, gold nanoparticle; LAMP, loop-mediated isothermal amplification; QD, quantum dot

The proposed LAMP-AuNPs assay presented a limit of detection of 5 pg for genomic DNA. In another research, Ckumdee, Santiwatanakul, and Kaewphinit (2017) introduced a LAMP DNA turbidity biosensor to identify isoniazid-resistant *M. tb* strains with a point mutation at *katG* gene position 315 (G → C). The proposed LAMP biosensor was applied in real samples, such as MDR-TB DNA, confirming 100% of the samples by the LAMP amplification system at <60 min.

2.11 | Piezoelectric biosensors

Piezoelectric biosensors could operate in direct, label-free, and interaction models, with the analyte generating the maximal use of the benefits through the piezoelectric platform (Pohanka, 2018; Williams & Brown, 1948). A piezoelectric DNA biosensor was designed by Kaewphinit in 2010, which consisted of genomic *IS6110*-specific DNA sequences of *M. tb*, which had been digested by the *BtgI* enzyme and hybridized with a complementary DNA probe immobilized onto a quartz crystal (Kaewphinit, Santiwatanakul, Promptmas, & Chansiri, 2010). The assay using the biosensor was performed on 200 clinical samples, and the obtained results were similar to the PCR-based technique. In addition, the biosensor showed high specificity when tested onto microorganisms such as the *Mycobacterium avium* complex and *Escherichia coli*. Another strength of the biosensor was its proper reproducibility (minimum of 10 times), which was achieved by applying the biosensor.

In another study, Mi, He, Xiang, Lian, and Yi (2011) presented a multichannel series piezoelectric quartz crystal (MSPQC) biosensor for *M. tb* detection, which had sensitive conductivity response to the normal growth of *M. smegmatis*. When *M. smegmatis* showed the normal growth caused by the killing of the phage D29 due to ferrous ammonium sulfate (FAS) action in the detection medium. In this case, the *M. tb* cell was not in the detection medium. Figure 9 shows the schematic diagram of the detection principle of *M. tb*. Phase D29 was added to the sample solution containing *M. tb* and incubated for 1 hr. Following that, 4% FAS solution was added to the inactive phase D29 outsized *M. tb*. to eliminate the role of FAS, the sample solution was diluted 10-fold and transferred to the detection cell containing *M. smegmatis* in the detection medium. Afterward, the sample solution with nil *M. tb* led to no phage D29 in the detection medium, and the MSPQC was applied for the recording of the frequency curve.

This biosensor would be able to assay the initial microbial concentration of *M. tb* up to 10^2 cfu/ml in a clinical sample with turnaround time <30 hr. Ren, Ma, Li, Huang, and Yi (2013) introduced an indirect series piezoelectric (ISP) system to detect drug-resistant *M. tb* cells. The ISP system was marked in three sections of I, II, and III; the first section was composed of an array of 32 sensors to generate the reactions to *M. tb* growth, as well as a culture chamber and piezoelectric quartz crystal, the second section consisted of a device for obtaining information, and the third section had a control chamber and data production system (Figure 10).

The first section in the mentioned biosensor acted as the sensitive key of the ISP system due to its responsiveness to the changes in the electrical parameters from the broth medium where *M. tb* had grown. In the third section, the control chamber was without anti-TB drugs and contained 1% of *M. tb* isolates. The critical and standard concentrations of antituberculosis antibiotics included isoniazid, rifampin, ethambutol hydrochloride, streptomycin, capreomycin, *p*-amino salicylic acid, rifabutin, and ethionamide, which were provided by the Clinical & Laboratory Standards Institute. With the growth of the *Mtb* cells in the detection media, the NH_3 and CO_2 products were generated, absorbed by the detection compartment, and detected by the ISP system sensitively.

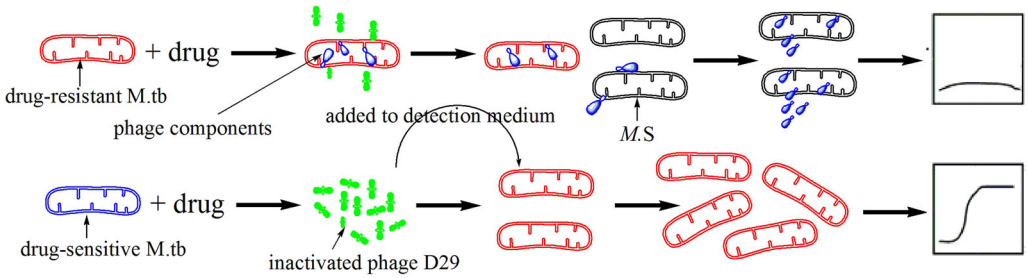

FIGURE 9 Flowchart of PA MSPQC for *Mycobacterium tuberculosis* detection (Yan et al., 2011)

2.12 | Optical biosensors

This class of biosensors are most commonly applied and use light as a detection source, which could react with target analytes. Optical biosensors and their connection with the bio-electronic field as a nano-bio molecular device could broaden the horizons of biomedical research (Dey & Goswami, 2011). They are more extensively used compared with other biosensors as they require no large sample volumes and sample preparation processes (Ligler & Taitt, 2011). Optical biosensor systems include evanescent wave fluorescence, surface plasmon resonance (SPR)-based biosensors, bioluminescent optical fiber biosensors, and reflectometric interference spectroscopy (RIfS; Martins et al., 2013). Label-free and label-based optical biosensors are also another sorting scheme of optical biosensors (Heydari et al., 2019). In label-free optical biosensors, the signal is generated due to the direct interaction between the analyte and transducer, and if the optical signal is generated by a colorimetric, fluorescent, or luminescent method, an optical label is used (Damborský, Švitel, & Katrlík, 2016; Fani, Mahmoodi, et al., 2019).

In a study in this regard, H. Mukundan et al. (2012) presented a planar waveguide-based optical biosensor for the detection of TB antigens (Ag85, ESAT6, and LAM) in spiked sputum and urine, respectively. Furthermore, a biotinylated capture antibody, antigen, and a fluorophore-labeled reporter antibody were applied on the surface of the biosensor. By combining ELISA and optical sensors, diagnostic sensitivity and reliability were obtained. In another study by Hong, Chen, et al. (2011) an SPR optical biosensor was used for the detection of the recombinant TB antigen (CFP10), which was developed in the tissue fluids of TB patients. Direct chemisorption of a monoclonal antibody (anti-CFP10) was performed through cystamine for immobilization on bare gold. The limit of detection of 100 ng/ml was obtained via observing a correlation between the SPR angle shift and CFP10 concentrations (range, 0.1–1.0 μg/ml). The proposed optical biosensor was further employed in clinical urine samples for the CFP10 concentration level assay of TB patients (Hong, Lee, et al., 2011). All the 55 patients were classified at the stages of 0–4 (AFB stages) based on the severity of the infection. Following that, the quantitative correlation between the SPR angle shift and AFB stages was investigated by drawing a calibration curve among different studies for recombinant CFP10. According to the results, there was a significant difference between healthy and infected samples, and a linear correlation was also denoted between

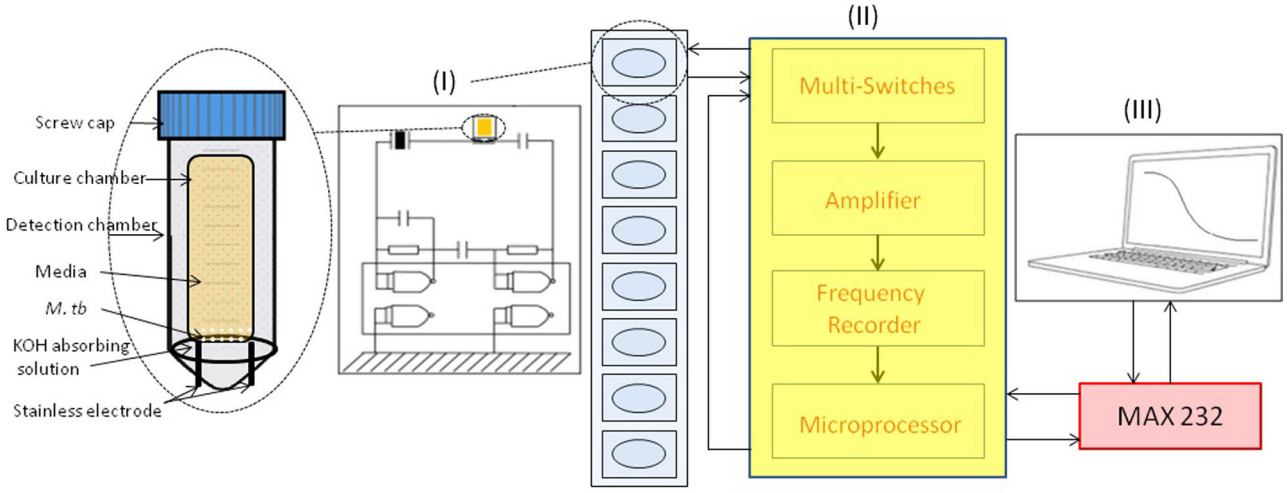

FIGURE 10 Block diagram of an indirect series piezoelectric system (system consisted of three major components: (I) 32 samples of detection system (circuit of single oscillator); 1, detection cell; 2, 9 MHz AT-cut piezoelectric quartz crystal), (II) microprocessor system, and (III) data output and control system (Xiang, Zhu, Huang, Zheng, & Fu, 2015)

the bacterial counts in AFB staining and CFP10 concentrations. Therefore, the grouping of TB patients based on disease severity was a major strength of the mentioned study.

In a similar research, Duman and Piskin (2010) introduced a portable multichannel SPR biosensor system based on the oligo-deoxynucleotides (probe-ssODNs) with the ability to detect DNA sequences from *Mtb* complex cells and *M. gordonae* simultaneously (target-ssODNs). The detection limit of the proposed biosensor was achieved in 30 ng/μl, and the sensor could detect DNA hybridization up to 0.05 μM. Therefore, it could be concluded that the performance of the SPR assay was better than ELISA.

In a study, Yan et al. (2011) presented a photodetector as a waveguide biosensor for the detection of TB-specific antibodies. By the interaction of the TB antigens and their specific antibodies, changes in evanescent field distribution were caused and sensed by the photodetector. In addition, the detection limit of the proposed DNA biosensor was estimated at 30 ng/μl (Yan et al., 2011). Rachkov, Patskovsky, Soldatkin, and Meunier (2013) described an optical SPR genosensor for the detection of rifampin-resistant *M. tb* oligonucleotide strains due to a specific point mutation of the *rpoB* gene. The hybridization efficiency and detection limit of the genosensor were estimated at 5×10^{12} molecules/cm^{-2} (30%) and 10 nM, respectively. On the other hand, Rinaldi et al. (2019) published an original research based on the use of the SPR sensory method to determine the affinity binding index of the recombinant Ag85B and specific monoclonal antibody interaction to identify the epitope regions on this antigen. The SPR biosensors are considered to be viable options for label-free and on-line assays (Ren et al., 2013). Therefore, optical biosensors could be used in the development and design of new and specific vaccines based on the new biomarkers of various pathogens.

2.13 | Magnetic biosensors

Nanoparticles with magnetic properties could be used variably for the detection of the etiology of infectious diseases, including *M. tb* (Wang, Yu, Kong, & Sun, 2017). A specific bio-probe has been immobilized onto the surface of magnetic compounds, which reacts with its complement in a sample dubious to contain biologic traces of *M. tb* (Vargas et al., 2018). Barroso et al. (2016) developed a biomolecular detection system, which combined the technology of sandwich-immunoassay and a magnetoresistive biochip. Streptavidin-coated magnetic nanoparticles were used for the labeling of the anti-*M. tb* biotinylated antibodies, and *Mycobacterium bovis* BCG cells were used for the surrogating of *M. tb* (Barroso et al., 2016). When magnetic capturing occurred, the target bacteria were carried in the clash with the surface of the functionalized biochip, and the *Mtb* cells that were labeled magnetically were detected on the surface of the magnetoresistive biochip by the functionalized sensor with the anti-*M. tb* antibodies through a sandwich-type immunoassay method (Figure 11).

Liong et al. (2013) presented a magnetic biosensor to identify the nucleic acids of *M. tb*, as well as rifampin-resistance and wild-type strains, based on a magnetic barcoding strategy. In the mentioned

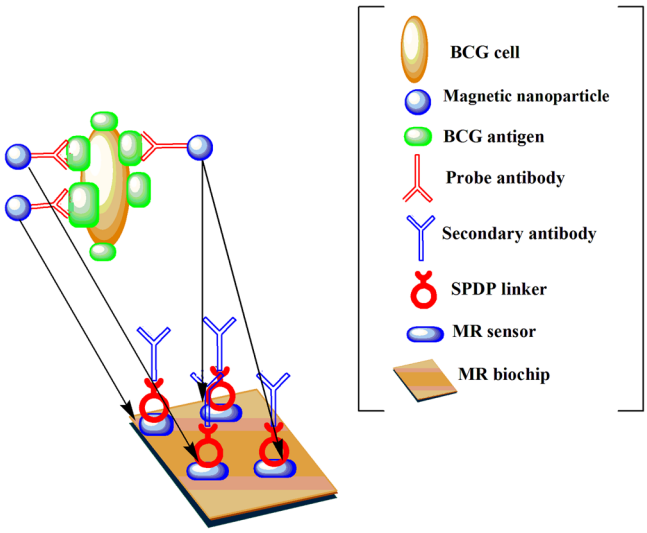

FIGURE 11 Schematic exemplification of enzyme-linked immunosorbent assay (ELISA) sandwich assay in magnetoresistive biochip used in the experiment work (Barroso et al., 2016)

study, the analyzed sample was the total RNA obtained from the *M. tb* cells. Asymmetric real time-PCR was performed to amplify the 16S rRNA sequence, and the single-strand DNAs were immobilized onto the conjugated beads, followed by interaction with magnetic nanoparticles, and covered by a detection probe to make a magnetic sandwich compound. By passing through the microfluidic tubes, the detection process of these complexes was completed, and the cost-efficiency of the method was remarkable (Liong et al., 2013).

2.14 | DNA biosensors and *M. tb* detection

DNA biosensors are a type of biosensors that are easily operated and have high sensitivity and low costs, with wide applications in the diagnosis of infectious diseases (Su et al., 2011). There has been growing demand for automated, inexpensive test devices that could cope with the miniaturization of the test platform stimulated the extensive development of DNA biosensors (Ozsoz, 2012). They are based on DNA hybridization recognition and are classified as label-free and labeled DNA biosensors (Ozsoz, 2012). In fact, electroactive labels, dye molecules (e.g., methylene blue), and nanoparticles could be used as labels in DNA biosensors (Ozsoz, 2012). Label-free DNA biosensors could also use adenine or guanine oxidation signals (Dutta et al., 2018), while electrochemical DNA biosensors between another DNA biosensor have more frequent applications (Ozsoz, 2012).

In this systematic review, we analyzed the probe sequences of *M. tb* detection based on the DNA biosensors, observing that the conserved regions of IS6110 insertion sequence of MTB are the most important diagnostic aim for researchers to design probes that could be used in this field. IS6110 is 1361-bp long and applied for the *in-vitro* identification of *M. tb* by PCR. Different regions of this sequence act as diagnostic targets, and the sequence is common among

TABLE 3 Genes and sequences of DNA probes for *Mycobacterium tuberculosis* bio-sensory detection

Genes	Sequences [5′-3′]	References
IS6110 sequence	18 mer: 5′-GAG CGT AGG CGT CGG TGA-3′	(Torres-Chavolla & Alocilja, 2011)
Genomic DNA of *M. tb*	20 mer: 5′-CTC GTC CAG CGC CGC TTC GG-3′	(Mohamad et al., 2017)
Genomic DNA of *M. tb*	20 mer: 5′-CTC GTC CAG CGC CGC TTC GG-3′	(Ng et al., 2015)
Not mentioned in the reference	20 mer: 5′-CTC GTC CAG CGC CGC TTC GG-3′	(Issa et al., 2010)
IS6110 sequence	10 mer: 5′-GGTGAGGTCT-3′	(C. Liu et al., 2014)
Not mentioned in the reference	21 mer: 5′-GGTCTTCGTGGCCGGCGTTCA-3′	(Mogha et al., 2018)
Not mentioned in the reference	21 mer: 5′-IAC III CAA TCC AII IC-3′	(Nurmalasari et al., 2015)
rpoB gene	15 mer: 5′-GATACTTCTATCACC-3′	(Miodek et al., 2015)
Not mentioned in the reference	21 mer: 5′-GGT CTT CGT GGC CGG CGT TCA-3′	(Torati et al., 2016)
Not mentioned in the reference	15 mer: 5′--GATACTTCTATCACC-3′	(Zribi et al., 2016)
MPT64 antigen	77 bp aptamer: 5′- [Btn]GTACAAACGACGGCCAGTCCTTGGGATGATTCAAGCAAAG CCTCACGCCTACGGCTAAGTCATAGCTGTCTCTCCTG-3′	(Thakur, Kaur, Sareen, et al., 2017)
IFN-γ	37 bp aptamer: 5′- GGGGTTGGTTGTGTTGGGTGTTGTGTCCAACCCCCCC-3′	(Y. Liu et al., 2010)
Genomic DNA of *M. tb*	25 mer: 5′- biotin GACCAAATAGGTATCGGCGTGTTCA-3′	(Yesil et al., 2016)
Not mentioned in the reference	21 mer: 5′- GGT CTT CGT GGC CGG CGT TCA-3′	(Prabhakar et al., 2010)
Genomic DNA of *M. tb*	24 mer: 5′-CGG TGG CGT GTT CTT TGT GCA ATA-3′	(Hsu et al., 2013)
rpoB gene	21 mer: 5′- ACCCACAAGCGCCGACTGTTG-3′	(Rachkov et al., 2013)
Genomic DNA of *M. tb*	22 mer: 5′- CCAACTTTGTTGTCATGCACCC-3′	(Duman & Piskin, 2010)
Genomic region of ESAT-6 antigen	Probe 1: 5′-NH2 [CH2]6-GTAAGTAAGGGAGGAAC-3′Probe2: 5′- TGCTCCCCT TCGTCAGG-[CH2]6-SH-3′	(Shojaei et al., 2014)
IS6110 sequence	15 mer: 5′-ATCCGGCCACAGCCC-3′	(Kaewphinit et al., 2013)
IS6110 sequence	5′-SH-$[CH2]_6$-TTTTTTGTGGCCATCGTGGAAGCGA-3′	(Kaewphinit et al., 2010)

all *M. tb* complex species (Gonzalo-Asensio et al., 2018; Sankar, Kuppanan, Balakrishnan, & Nandagopal, 2011). Table 3 shows these sequences based on this review study.

2.15 | Biosensors and antibiotic resistance of *M. tb*

An important principle of antimicrobial stewardship is the detection of resistant strains to design proper and standardized therapy regimens for patients. With regard to *M. tb*, the conventional and user-friendly drug-susceptibility test methods are commonly employed for antibiotic susceptibility testing (e.g., proportion and solid culture media-based methods) in high-burden TB regions across the world, especially in low- and middle-income countries (Miotto et al., 2017; Morency-Potvin, Schwartz, & Weinstein, 2017). Therefore, cost-efficient, rapid, and accurate methods with potential multiuse features are essential to the detection of resistant strains. In addition, prolonged TB antimicrobial treatment is required to prevent the clinical complications of TB. TB treatment has been a curative confusion not only due to the intrinsic high resistance level of *M. tb* to antibiotics, but also the recently obtained mutations that allow further resistance (Nguyen, 2016). The new platforms in the sensory methods such as magnetic barcoding strategy have a high potential for the detection of drug-resistant *M. tb* strains (Liong et al., 2013). Designing and fabrication of biocomponent recognizer components as a detector of single-nucleotide mutations could offer high sensitivity and specificity, while also determining the antibiotic susceptibility pattern of *M. tb* in the clinical setting at a high speed using specific probes for the common native drug resistance mutations.

Today, the detection systems based on sensory methods are applied to identify resistance to isoniazid (Ckumdee et al., 2017), rifampin (Miodek et al., 2015; Rachkov et al., 2013; Zribi et al., 2016), pyrazinamide (Rueda et al., 2018), and first- and second-line drugs, including anti-TB antibiotics (e.g., isoniazid, rifampin, ethambutol

hydrochloride, streptomycin, capreomycin, *p*-amino salicylic acid, rifabutin, and ethionamide; Ren et al., 2013), in the hopes that these systems continue to improve.

3 | CONCLUSION

According to the report by the WHO, more than 95% of all TB cases and morbidity rates occur in developing countries, where there are poor resource settings and high risk of acquired TB infection (especially in children), as well as the high risk of drug-resistant strain transmission in the community. As such, affordable biosensors should be provided as routine detection and analytical tests since they have significant benefits in the prevention of such risks.

This review study aimed to assess the traditional and recent *M. tb* assays for the detection of *M. tb* and resistance of the bacterium against isoniazid and rifampin as first-line anti-TB drugs. According to the findings, the traditional methods lack the capability to meet the needs and address the turbulences of rapid detection in *M. tb* analysis.

The most frequent methods used for *M. tb* detection are acid-fast staining, cultivation, and PCR. However, previous studies have denoted that molecular techniques (e.g., PCR and real-time PCR) are rapid and sensitive, while they require sophisticated laboratory and apparatuses. Moreover, these techniques require skilled personnel and expertise in the commentary of the results.

As alternative devices, biosensors must have high specificity and sensitivity toward the targets so as to successfully compete with other detection methods. Overall, it is expected that a multidisciplinary approach and integration of sciences and technologies (physical sciences, chemistry, biology, medicine, and engineering disciplines) are essential to the proper use of TB bio-sensing techniques and improvement of point of care diagnostic tests. In fact, according to the limitations and complex problems in the road of rapid and accurate tuberculosis diagnosis and anti-tuberculosis drug resistance of *M. tb*, the accurate, simple, and rapid diagnostic tests for *M. tb* detection are needed. So scientific, research, and industrial investment in biosensor techniques is a necessary and essential part of our world.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study.

ORCID

Hadi Farsiani http://orcid.org/0000-0002-4738-0245
Hamid R. Pourianfar http://orcid.org/0000-0003-3541-7618
Majid Rezayi http://orcid.org/0000-0003-1024-3906

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