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REVIEW ARTICLE

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Biosensors and biomarkers for determining gestational diabetes mellitus and jaundice in children

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Abstract

Gestational diabetes and jaundice are the correlated diseases predominantly found in mother and newborn child. Jaundice is a neonatal complication with an increased risk when mother has gestational diabetes. Mothers with diabetes at an early stage of gestational age are at higher risk for hyperbilirubinemia (jaundice) and hypoglycemia. So, it is mandatory to monitor the condition of diabetes and jaundice during the pregnancy period for a healthy child and safest delivery. On the other hand, nanotechnology has displayed a rapid advancement that can be implemented to overcome these issues. The development of high-performance diagnosis using appropriate biomarkers provides their efficacy in the detection gestational diabetes and jaundice. This review covers the aspects from a fast-developing field to generate nanosensors in the nanosized dimensions for the applications to overcome these complications by coupling diagnostics with biomarkers. Further, the serum-based biomarkers have been discussed for these inborn complications and also the diagnosis with the current trend.

KEYWORDS

blood sugar, glucose biosensor, liver disease, nanobiosensor

1 | INTRODUCTION

Gestational diabetes develops during the pregnancy period, a type of metabolic disorder portrayed by hyperglycemia caused by defects with either secretion of insulin or action of insulin or both to the pregnant mother.[1–4] During the pregnancy period, various hormones are produced at higher rate by placenta, which impairs insulin action in the cells, elevating the blood glucose level. As baby develops, more insulin is counteracting the hormones and is provoked with an increment in blood sugar level and affects the baby. Apart from that, gestational diabetes causes various organ failures, particularly the eyes, kidneys, nerve, heart, and blood vessels are often

Abbreviations: dL, Decilitre; ELISA, Enzyme Linked Immunosorbent Assay; ELASA, Enzyme-linked aptasorbent assay; GOx, Glucose oxidase; MEMS, Microelectromechanical systems; mM, Millimolar; mg, Milligram; NEMS, Nanoelectromechanical systems; pM, Picomolar; PCD, Programmed Cell Death; SPR, Surface plasmon resonance; TMB, 3,3′,5,5′-Tetramethylbenzidine; ZnO, Zinc Oxide

connected to chronic hyperglycemia. Gestational diabetes is also found to increase the complications associated with birth trauma, hyperbilirubinemia, hypoglycemia, stroke, and macrosomia.[5,6] One of the most dangerous processes taking place during the development of diabetes is the programmed cell death (PCD) of the beta cells in pancreas, which then results in insulin deficiency. An individual with diabetes mellitus tends to possess abnormalities in carbohydrate, fat, and protein metabolism due to deficient insulin. Research has shown that approximately 18% women in South Asia and 14% of women in West Africa were diagnosed with gestational diabetes. Gestational diabetes develops during the period of week 24 of pregnancy, and glucose tolerance test is usually conducted during the period of 24–28 weeks.[7–9]

Hyperbilirubinemia (jaundice) and diabetes are highly correlated diseases found with newborn babies and the mother. Hyperbilirubinemia is a life-threatening disease and affects approximately 25% of newborn of mothers with diabetes.[10] Hyperbilirubinemia is generally caused when the liver does not work properly. When the breakdown of red blood cell occurs, the bilirubin chemical is released, making the skin become yellow. Newborn babies with higher rate of bilirubin leads to jaundice. Liver disease during the period of pregnancy and the period of postpartum causes the dysfunction in the biliary system, and leads to an abnormal level of bilirubin.[11,12] This condition is observed in 3%–10% of all pregnancies. As gestational diabetes and hyperbilirubinemia are highly associated, it is mandatory to monitor these two complications to deliver a healthy baby.

Various researches prove that controlled diabetes allows normal perinatal and does not show any complication and side effects, such as hyperbilirubinemia. It is mandatory to follow a proper diet with continuous monitoring for maintaining normal blood sugar level.[13–15] Due to the high variations of glucose level during the pregnancy period, generating a simple monitoring system is mandatory for a healthier pregnancy. Different sensing methods and biomarkers have been utilized to watch the glucose level, and researchers are still experimenting toward an efficient jaundice and glucose identification methods.[16–23] This review discusses about the recent development of biosensor in glucose monitoring and jaundice identification, which are mandatory during the pregnancy period and helpful for healthy pregnancy.

Highlights

- Gestational diabetes and jaundice are correlated diseases predominantly found in mother and newborn child. It is mandatory to monitor the condition of diabetes and jaundice during the pregnancy period for a healthy child and safest delivery. On the other hand, the development of high-performance diagnosis using appropriate biomarkers provides their efficacy in the detection gestational diabetes and jaundice, and this review covers the aspects from the fast-developing field to generate nanosensors to overcome the above complications by coupling diagnostics with biomarkers.

2 | BIOSENSOR FOR GESTATIONAL DIABETES AND JAUNDICE

Biosensor is an analytical device that combines a biological receptor with a physiochemical detector, used to detect the concentration of specific substance in a biological fluid by converting a biological response into an electrical signal. Professor Leland C. Clark Jr. (1918–2005) is the "father of biosensor" and also well known for the invention of Clark electrode. In 1962, he published an experiment that showed that by using a dialysis membrane, glucose oxidase (GOx) can be entrapped at the Clark electrode.[24] A biosensor consists of three main components: (a) a biological element that specifically interacts with target analyte and produces a biological signal, which can be detected by a transducer; (b) transducer transforms one signal to another signal, which is easier to be measured; and (c) output device displays the results in a user-friendly way. Biologics such as enzyme, antibody, nucleic acid, hormone, receptor, even biological cells and microorganisms can be used selectively to interact and recognize the target analyte. Biosensor is classified into different classes based on molecular interaction, biological signal and transducer (Figure 1).[25–29] Four basic types of transducing elements are electrochemical, optical, thermal, piezoelectric, commonly used to identify various biomarkers for diagnosing different diseases.[24,30–34] Applying this receptor and transducer with a suitable biomarker, various diseases have been identified including gestational diabetes and jaundice.

3 | BIOMARKERS FOR GESTATIONAL DIABETES AND JAUNDICE

Glucose monitoring is mainly involved with three enzymes, namely, hexokinase, dehydrogenase, and GOx. The hexokinase assay was commonly used in spectrophotometry in clinical laboratories.[35] In addition, various

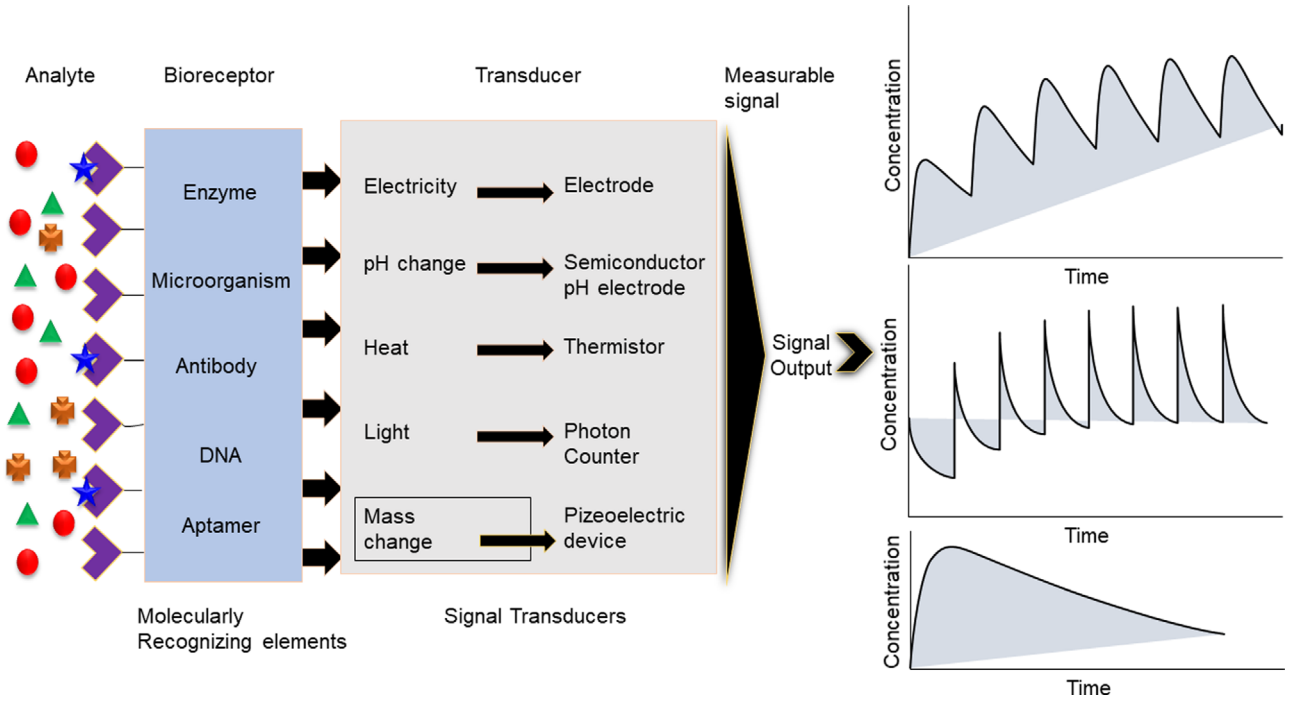

FIGURE 1 Basic principle of biosensing system. Different essential elements for biosensors and their displaying signal modes

researches are being carried out to develop a glucose biosensor using glucose dehydrogenase.[36–38] GOx is the common enzyme used by all traditional sensors due to its higher selectivity with glucose. Apart from that GOx brings out other positive features, such as cheaper, high ionic strength stability at all pH conditions and high temperature tolerance than other enzymes.[39] GOx can reduce the oxygen into hydrogen peroxide (H_2O_2) and transform glucose into 5-lactone and d-glucono-1; identifying glucose based on the production of hydrogen peroxide and the oxygen consumption, which is commonly used to create a glucose biosensor to monitor the glucose level.[40] These overall advantages of GOx were considered by researchers and were used to create various types glucose sensors.

Along with glucose monitoring, identifying the infant jaundice with a suitable biomarker is also mandatory to give the appropriate treatment and improve the condition of the infant. Bilirubin is the orange-yellow color product of red blood cell, which plays a major pharmacological and physiological role for anti-lipid peroxidation and anti-oxygen free radicals. The accumulated bilirubin can pass through the liver and removed by bile. At the same time higher level of bilirubin (over 50 mol/ml) is toxic to the body causing jaundice, liver damage, and can even lead to death of newborns. So, bilirubin serves as a suitable clinical biomarker for identifying the neonatal jaundice and evaluating the function of liver.[41–43] Recently, different biosensors have been developed with specific biomarkers for identifying gestational diabetes and jaundice (Tables 1 and 2) as elaborated below.

3.1 | Electrochemical sensor

Electrochemical sensor is one of the promising biosensors, having various positive features such as easier to use, fast response, reliability, portability, higher selectivity and sensitivity. Thus, electrochemical sensor is a widely accepted promising technique to monitor glucose level.[44,45] With the electrochemical sensor, three main components such as electrical transducer, recognition element, and the signal processing to record the electric changes are used to identify the biomolecular interaction on the sensing surfaces. Most of the electrochemical biosensors are based on nanomaterials to enhance the signal amplification process. Gold nanoparticle, carbon nanotube, zeolite, silica, aluminum, graphene, and metallic oxide are the common nanomaterials used in electrochemical sensors to improve the electric activities and help to identify the various diseases at earlier stages.[28,46–49] Metallic and non-metallic nano- and microparticles have a great potential in biosensor development. Silica, aluminum, and gold are very commonly used as the base of biosensing due to their appealing properties and biocompatibility in varied dimensions. Metallic oxides are more amenable for surface chemical functionalization to link the

TABLE 1 Glucose identification by the currently available sensing strategies

Sensor	Probe	Sensing substrate	Detection limit/sensitivity	Linear range	Status	Ref
Electrochemical	GOx	Gold nanoporous	1.02 μM	50 μM–10 mM	Under Dev.	50
Electrochemical	GOx	Multiwalled carbon nanotube (MWCN)	3.4 μA/mM	–	Under Dev.	52
Electrochemical	GOx	Gold nanoparticle/single-WCN	28.6 mA/M/cm^2	–	Under Dev.	51
SPR	Glucose-binding protein	Carboxymethyl dextran	0.5 mM (dissociation constant)	1–30 mM	Commercial source	65
SPR	–	Gold, MoS_2, graphene, h-BN	0–15 mg/dl	–	Under Dev.	66
SPR	Glucose membrane	Gold sheet	0–160 mg/dl	0–200 mg/dl	Under Dev.	67
Colorimetric	H_2O_2	MnO_2	12.8 μM	0–100 μM	Commercial source	74
Ambient light sensor	H_2O_2	–	0.005 mg/ml	0.039–10 mg/ml	Under Dev.	75
Colorimetric assay	GOx	Microzone plate	0.6 mmol/L	0–10 mmol/L		51
Current–volt	GOx	ZnO nanowire-SiO_2	0.03 mg/dl	0.03–30,000 mg/dl	Clinical	78
Current–volt	GOx	Graphene	0.02–0.03 mg/ml	0.03–0.25 mg/ml	Under Dev.	79
Current–volt	GOx	Silica-alumina	0.03 mg/ml	0.03–0.5 mg/ml	Under Dev.	24

TABLE 2 Bilirubin identification by the currently available sensing strategies

Sensor	Sensing substrate	Detection limit/sensitivity	Linear range	Status	Ref
Electrochemical	Graphene	30 nA/μM/cm^2	0.1–600 μM	Under Dev.	58
Electrochemical	MWCN	15 nA/μM/cm^2	0.5–500 μM	Under Dev.	58
Electrochemical	Iron-doped antimony oxide nanorod	16.5 pM	0.1 nM–0.01 M	Under Dev.	59
Amperometry	Graphite-epoxy	–	4×10^{-6} to $\times 10^{-4}$ M	Under Dev.	81
Colorimetry	Gold nanoclusters	248 nM	0–50 μM	Commercial source	77
UV-luminescence	Gold nanoclusters	3.1×10^{-2} mg/ml	0.2–0.8 mg/dl	Under Dev.	69
Potentiometry	Polymeric membrane	–	5–10 mM	Under Dev.	82

biomarkers. In particular, nanomaterial-modified electrode surface exhibits excellent electrocatalytic activity toward the process of glucose oxidation, which improves the detection strategy of glucose quantification.[40] In general, GOx is attached on the electrode surface through chemical modification and quantified by glucose (Figure 2). Wu et al. conducted an experiment with the combination of gold and enzymes to identify the glucose level. They immobilized GOx on the 12-carat gold-modified carbon electrode, and the three-dimensional porous gold gave an excellent interface between the electrode and the enzyme active sites, which helped to

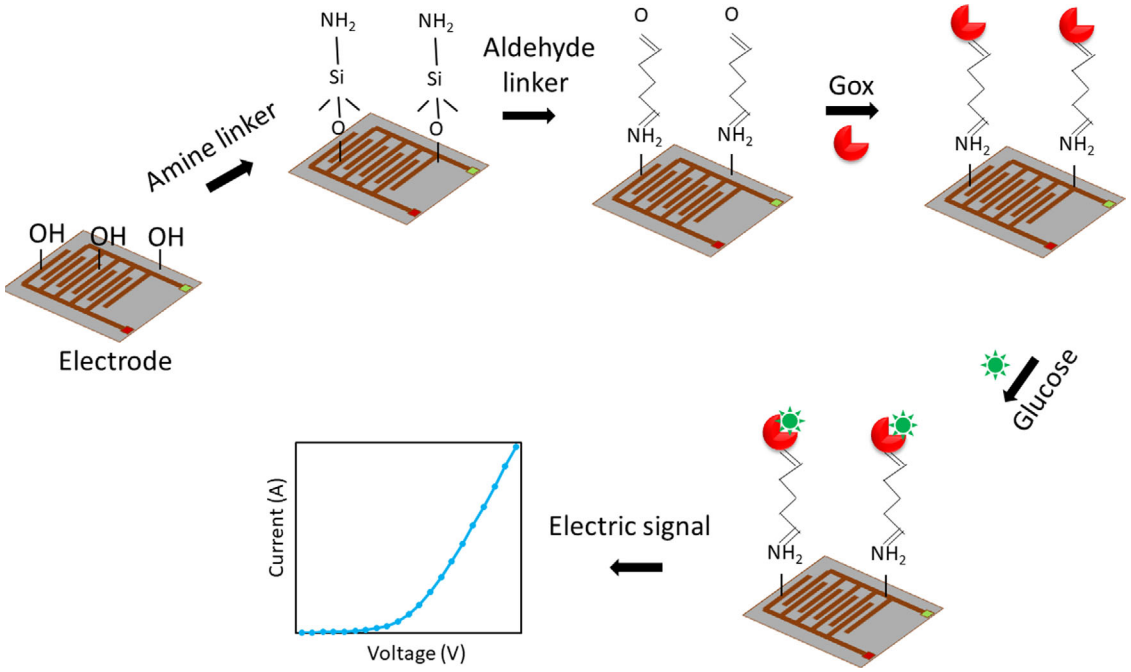

FIGURE 2 Electrochemical sensing. Electrochemical-based interdigitated electrode system is displayed for glucose sensing

reach the detection limit of glucose to 1.02 μM.[50] Similarly, another research was conducted to immobilize GOx on gold nanoparticles with single-walled carbon nanotube-modified carbon electrode and reached the sensitivity of glucose to 28.6 mA/M/cm^2.[51] Graphene-based electrochemical sensor is also popular to identify the glucose level; high immobilization of GOx on graphite nanosheet was achieved and reached at 3.4 μA/mM.[52] Graphene plays an essential role in various fields due to its attractive physio-chemical properties. Graphene has high charge mobility, as it is well established in sensing systems and their downstream applications. The structure and behavior of graphene reveals wonderful electronic properties and bond structure. Graphene exhibits high active sites for charge interactions, which allows various techniques in functionalizing graphene on sensing surface. There are plenty of approaches to integrate graphene on sensing surfaces. It is very important to understand the interaction between graphene and sensing surface for generating a potential graphene-modified sensor. There are several emerging graphene materials in different dimensions to fulfill the graphene-based requirements, such as for anti-corrosion coatings, high-volume applications in energy storage, thermal heat spreaders, and conductive inks. The development of graphene by modified Hummer's method with the above properties also anchors the sensing applications and provides the room for developing new sensing approaches. Further, the competitive bottom-up approach in developing beyond 2D-graphene materials and conductive graphene accelerates the development of micro- and nanoelectromechanical systems (MEMS and NEMS).[53,54] Similarly, other materials such as copper foam, titanium oxide nanotube, zinc oxide nanorods are utilized to attach GOx on the sensing electrode to reach the lower detection level of glucose.[55–57]

Like glucose identification, various researches have shown efficient detection of jaundice biomarker bilirubin through electrochemical sensors. Carbon nanotube and graphene-modified electrodes have been utilized to identify the bilirubin and found the sensitivity to be 15 nA/μM/cm^2.[58] Iron-doped antimony oxide nanorod-modified electrode was utilized for the efficient detection of bilirubin and detection limit was reached at 16.5 pM.[59]

3.2 | Enzyme-linked immunosorbent assay (ELISA)

Developing a sensing strategy that is highly suitable and reliable for the clinical purpose is very important in the field of medical diagnosis. ELISA is the gold standard assay to identify and detect the wide range of major diseases. ELISA is the immunoassay involved with antibody-based detection system (Figure 3).[60,61] Until now the identification and screening of major diseases are done by ELISA due to its high sensitivity and selectivity without involving the dangerous chemicals such as radioisotope. Single-step capillary ELISA was conducted by researchers to identify the enzyme reaction using the combination

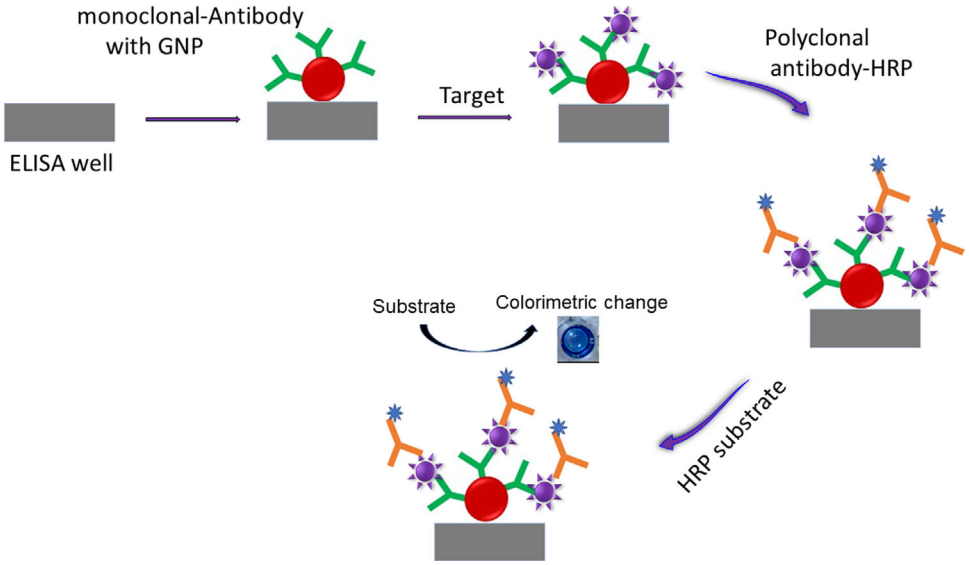

FIGURE 3 Enzyme-linked immunosorbent assay. Involvement of antibodies with different steps are shown with the conventional ELISA

of GOx, antibody and polyethylene glycol containing peroxidase-labeled antibody in a single capillary.[62] Liu et al. (2013) experimented with the electrochemical-based ELISA to identify the glucose level by using multienzyme and nanoparticle-based amplification method.[63] These kinds of ELISAs can be further modified/expanded by aptamer-mediated assays, "so-called" enzyme-linked aptasorbent assay (ELASA), which involves aptamer (an artificial antibody) with/without the involvement of antibody.[64]

3.3 | Surface plasmon resonance (SPR)

SPR is a device/strategy that can monitor consciously the level of glucose and is highly valuable to manage the gestational diabetes. SPR is refractive index-based biosensing platform, which demonstrates the real-time monitoring of analyte–ligand interaction[65] (Figure 4). The covalent attachment of glucose-binding protein was performed on the SPR sensing substrate and it identified the glucose by using the refractive detection method; the dissociation constant of glucose was identified as 0.5 mM. Modeling with a highly sensitive SPR-based biosensor was constructed by researchers to identify the glucose level. Sensing substrate was modified with four layers of metals, namely, graphene, hexagonal boron nitride (h-BN), molybdenum (MoS_2), and gold to reach out to the glucose detection to 0–15 mg/dl.[66] MoS_2 is one of the recent popular material used in sensing applications due to its analogous nature to the graphene. Further, broad range of SPR-based glucose sensing was conducted with improved glucose membranes. The membrane was immobilized on the gold sheet to perform the SPR sensing for glucose identification, and found the sensitivity range of 0–160 mg/dl.[67] Like diabetes, jaundice is also identified by various sensors by operating with the surface plasmon principle. Maity et al. (2014) have demonstrated the bilirubin interaction on a gold-modified sensing substrate by using the shifting of plasmon resonance band.[68] In another research, UV-luminescence assay was conducted on gold nanoclusters to identify the bilirubin and reach the limit of detection 3.1×10^{-2} mg/ml.[69]

3.4 | Colorimetric assay

Colorimetric assay is very attractive in biosensors, with lots of positive features such as it is cheaper, easier with visual detection, and does not need any prior experience, requires lesser time, and has high sensitivity.[70–72] In particular, gold is the popular material for colorimetric assay due to its color changes of red (dispersed condition) to purple (aggregated state). Gold nanoparticle-conjugated DNA, RNA, or aptamer were utilized as the probe to diagnose various diseases.[32,73] Gold nanoparticle-mediated colorimetry assay has attained the proper optimal level, as performed by several researchers, due to easier steps involved in the methodology. In the presence of target, GNP color changes to purple due to aggregation, while remains red in the absence of target (Figure 5). MnO_2 nanosheets with yellow color were utilized to identify the glucose level by using colorimetric assay. Identification of glucose corresponds to different absorbance of MnO_2 being achieved and reached the detection limit of glucose to 12.8 μM.[74] Similarly, colorimetric assay was performed with the combination of hydrogen peroxide, horseradish peroxidase, and the TMB

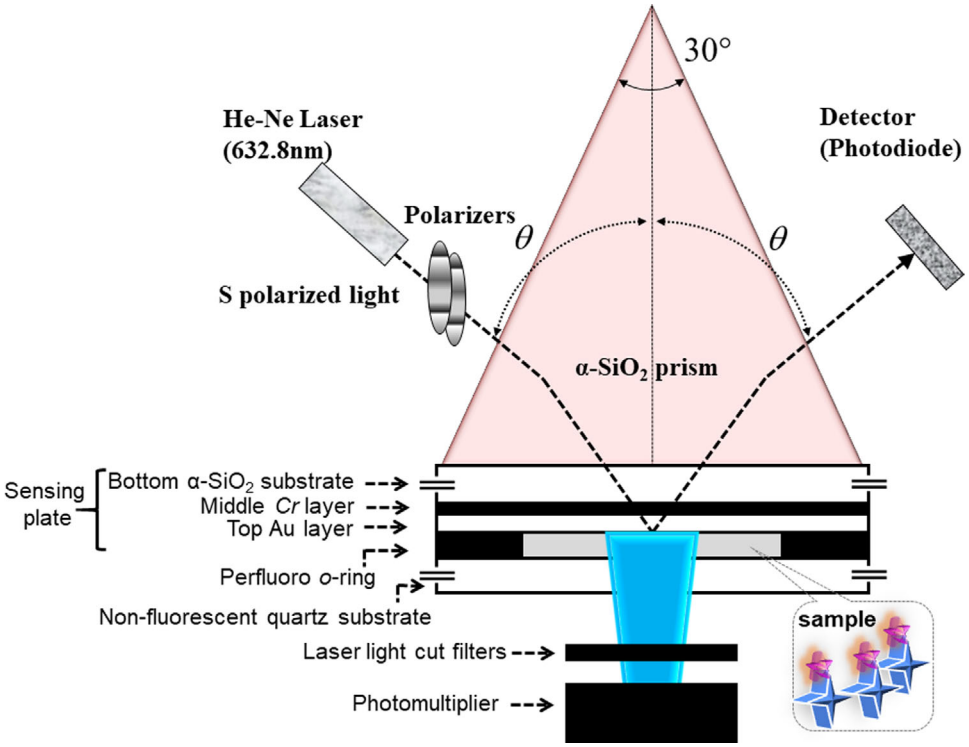

FIGURE 4 Surface plasmon resonance. Modified SPR with the involvement of fluorescent molecules

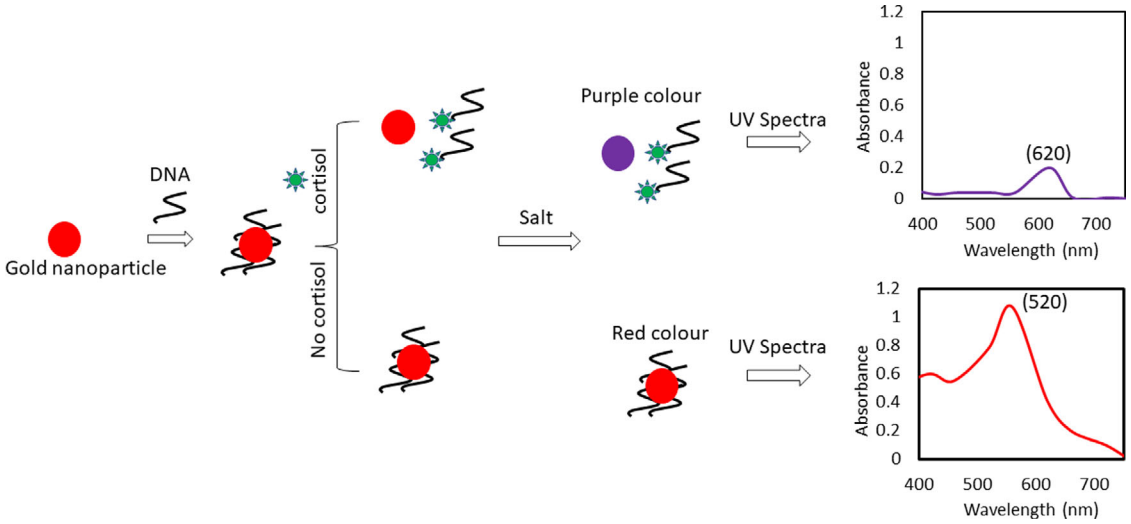

FIGURE 5 Colorimetry assay. Gold nanoparticle-based colorimetry assay with aggregation and dispersion states are indicated

substrate for glucose identification. They utilized the ambient light sensor-based smartphone assay and the detection limit of glucose was calculated as 0.005 mg/ml.[75] Further, toner-based microzone plate was used as the substrate for colorimetric assay and the researchers used GOx and H_2O_2 for color changes to identify the glucose to reach the lower sensitivity of 0.6 mmol/L.[76] Colorimetric sensor was also utilized to identify the lower level of bilirubin, human serum albumin stabilized gold clusters were used as the fluorescent probe to identify the bilirubin and the detection limit was found as 248 nM. The fluorescence from the nanoclusters was quenched by bilirubin in a concentration-dependent manner by virtue of the inherent interaction between human serum and bilirubin. This method was used to quantify the bilirubin level in the blood serum sample.[77]

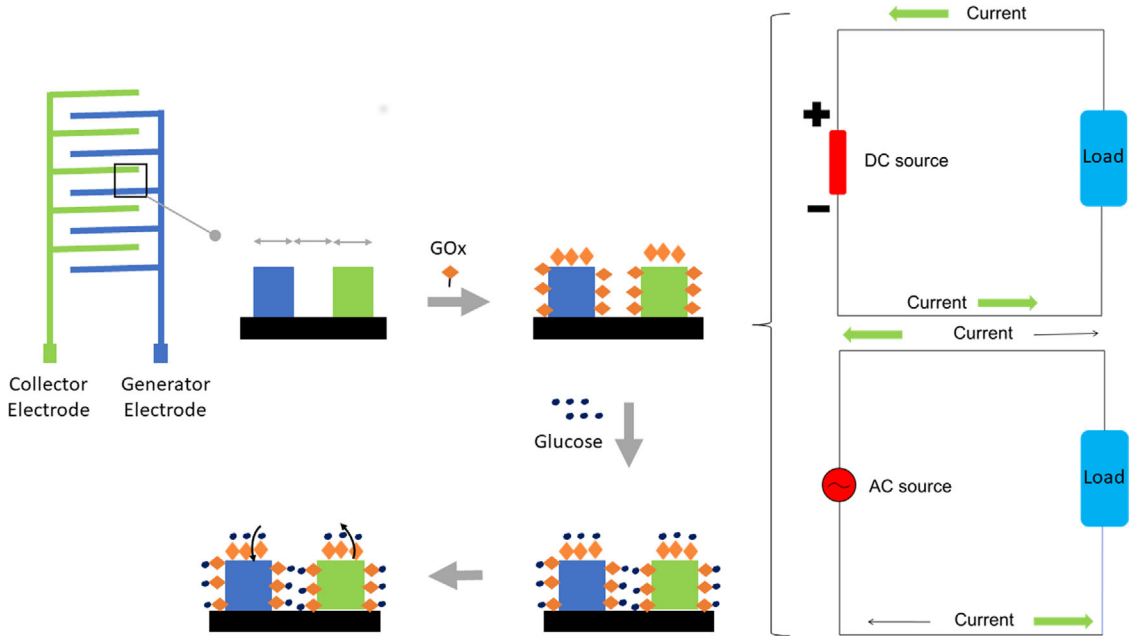

FIGURE 6 Current–volt measurement. A dielectrode measurement system for biosensor is shown. Both alternate and direct currents are displayed as insets

3.5 | Current–volt measurements

Current–volt measurements are the popularized label-free approaches established with currently available micro- and nanobiosensors. Due to the appealing label-free current–volt measurements, analyses have been performed with intact molecules and avoid structural changes in molecules with labeling. Apart from that, the current–volt measurements can be carried out by both alternate and direct currents to be used for the point-of-care analysis (Figure 6). With these set-ups, several portable and wireless sensors are available in the market. Haarindraprasad et al. (2016) made a sensing system for determining the blood glucose level on zinc oxide (ZnO)-based nanowire on the silica substrate and attained the limit of detection at 0.03 mg/dl with the linear range of 0.03–0.25 mg/dl.[78] Their research output is comparable with the conventional glucose portable monitor and suitable for high-throughput analysis. ZnO used in this research is found to have good electric conductivity and can be used in other available semiconductor-based sensors. By using similar current–volt measurement, Ge et al. (2019) have produced a dielectric sensor, which is able to sense 10-fold higher sensitivity of the above report by using the graphene surface on the linearity of 0.03–0.25 mg/ml.[79] On the other hand, recent report on silica-alumina surface has also reached similar detection level as a complement study to the report by Ge and group.[80] There are plenty of patterns/designs of sensing surfaces that can be made to expand/promote the above current–volt measurements. The new developments with the current–volt system might help to overcome several problems associated with clinical management of blood sugar and other diseases.

4 | CONCLUSION

Gestational diabetes and jaundice are highly related diseases and affect pregnant mother and the newborn. Pregnant women with diabetes are at high risk for getting hyperbilirubinemia (jaundice). Thus, identifying and monitoring these two diseases and their conditions are mandatory for healthy pregnancy and delivery. This review discusses the potential biosensors and biomarkers involved for high-performance analysis in determining gestational diabetes and jaundice. Further, various methods/strategies generated for earlier identification of diabetes and jaundice were discussed, as they explore the recent developments with gestational diabetes and jaundice identification. These biomarkers aided biosensors acquired the nanotechnological approaches to accelerate the conventional set-ups. Biosensors are more amenable toward this direction for the production of high-performance and user-friendly sensing systems for a wide range of clinical diagnoses. Revealing additional biomarkers for the desired disease diagnosis aids to demonstrate the high sensitivity of the developed sensors. At present, several hand-held sensors are available in the clinics; however, implementation

of current–volt based label-free micro- and nanobiosensors can help in advancing our research in the field way ahead.

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REFERENCES

1. Liu B, Xu Y, Zhang Y, Cai J, Deng L, Yang J, et al. Early diagnosis of gestational diabetes mellitus (EDoGDM) study: a protocol for a prospective, longitudinal cohort study. BMJ Open. 2016;6:e012315.
2. Spaight C, Gross J, Horsch A, Puder JJ. Gestational diabetes mellitus. Endocr Dev. 2016;31:163–78.
3. Diabetes P, Mellitus GD. Management of diabetes in pregnancy. Diabetes Care. 2017;40:S114–9.
4. Meyer WJ, Carbone J, Gauthier DW, Gottmann DA. Early gestational glucose screening and gestational diabetes. J Reprod Med. 1996;41:675–9.
5. Berger H, Gagnon R, Sermer M, Basso M, Bos H, Brown RN, et al. Diabetes in pregnancy. J Obstet Gynaecol Can. 2016;38:667–79.
6. Rashad NM, Ahmed HS, Ashour WMR, Yousef MS. Association of vaspin gene expression and its serum level on the risk of ischemic stroke in type 2 diabetic Egyptian patients: prospective case-control study. Biotechnol Appl Biochem. 2020;67:912–9.
7. Lefkovits YR, Stewart ZA, Murphy HR. Gestational diabetes. Medicine (United Kingdom). 2019;47:114–8.
8. Russell MA, Carpenter MW, Coustan DR. Screening and diagnosis of gestational diabetes mellitus. Clin Obstet Gynecol. 2007;10:QE01–4.
9. Catalano PM. Trying to understand gestational diabetes. Diabetes Med. 2014;31:273–81.
10. Ullah S, Rahman K, Hedayati M. Hyperbilirubinemia in neonates: types, causes, clinical examinations, preventive measures and treatments: a narrative review article. Iran J Public Health. 2016;45:558–68.
11. Shoham B, Migron Y, Riklin A, Willner I, Tartakovsky B. A bilirubin biosensor based on a multilayer network enzyme electrode. Biosens Bioelectron. 1995;10:341–52.
12. Ngashangva L, Bachu V, Goswami P. Development of new methods for determination of bilirubin. J Pharm Biomed Anal. 2019;162:272–85.
13. Utz B, Delamou A, Belaid L, De Brouwere V. Detection and management of diabetes during pregnancy in low resource settings: insights into past and present clinical practices. J Diabetes Res. 2016;2016:3217098.
14. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352:2477–86.
15. American Diabetes Association. 12. Management of diabetes in pregnancy. Diabetes Care. 2016;39:S94–8.
16. Kim NY, Adhikari KK, Dhakal R, Chuluunbaatar Z, Wang C, Kim E-S. Rapid, sensitive, and reusable detection of glucose by a robust radiofrequency integrated passive device biosensor chip. Sci Rep. 2015;5:7807.
17. Yusan S, Rahman MM, Mohamad N, Arrif TM, Latif AZA, Aznan M, et al. Development of an amperometric glucose biosensor based on the immobilization of glucose oxidase on the Se-MCM-41 mesoporous composite. J Anal Methods Chem. 2018;2018:2687341.
18. Sharma S, Huang Z, Rogers M, Boutelle M, Cass AEG. Evaluation of a minimally invasive glucose biosensor for continuous tissue monitoring. Anal Bioanal Chem. 2016;408:8427–35.
19. Zhang W, Du Y, Wang ML. Noninvasive glucose monitoring using saliva nano-biosensor. Sens Biosensing Res. 2015;4:23–9.
20. Geelhoed-Duijvestijn P, Vegelyte D, Kownacka A, Anton N, Joosse M, Wilson C. Performance of the prototype noviosense noninvasive biosensor for tear glucose in type 1 diabetes. J Diabetes Sci Technol. 2020. https://doi.org/10.1177/1932296820964844
21. Wiorek A, Parrilla M, Cuartero M, Crespo GA. Epidermal patch with glucose biosensor: PH and temperature correction toward more accurate sweat analysis during sport practice. Anal Chem. 2020;92:10153–61.
22. Halder A, Adhikari A, Ghosh R, Singh S, Banerjee A, Ghosh N, et al. Large scale validation of a new non-invasive and non-contact bilirubinometer in neonates with risk factors. Sci Rep. 2020;10:11149.
23. Iwatani S, Yamana K, Nakamura H, Nishida K, Morisawa T, Mizobuchi M, et al. A novel method for measuring serum unbound bilirubin levels using glucose oxidase–peroxidase and bilirubin-inducible fluorescent protein (UnaG): no influence of direct bilirubin. Int J Mol Sci. 2020;21:1–11.
24. Chen L, Xie W, Luo Y, Ding X, Fu B, Gopinath SCB, et al. Sensitive silica-alumina modified capacitive non-Faradaic glucose sensor for gestational diabetes. Biotechnol Appl Biochem. 2021. https://doi.org/10.1002/bab.2155
25. Centi S, Sanmartin LB, Tombelli S, Palchetti I, Mascini M. Detection of C reactive protein (CRP) in serum by an electrochemical aptamer-based sandwich assay. Electroanalysis. 2009;21:1309–15.
26. Jang HJ, Lee T, Song J, Russell L, Li H, Dailey J, et al. Electronic cortisol detection using an antibody-embedded polymer coupled to a field-effect transistor. ACS Appl Mater Interfaces. 2018;10:16233–7.
27. Filippo E, Serra A, Manno D. Poly(vinyl alcohol) capped silver nanoparticles as localized surface plasmon resonance-based hydrogen peroxide sensor. Sens Actuators B Chem. 2009;138:625–30.
28. Lu B, Liu L, Wang J, Chen Y, Li Z Gopinath SCB, et al. Detection of microRNA-335-5p on an interdigitated electrode surface for determination of the severity of abdominal aortic aneurysms. Nanoscale Res Lett. 2020;15:105.
29. Gopinath SCB, Shikamoto Y, Mizuno H, Kumar PKR. A potent anti-coagulant RNA aptamer inhibits blood coagulation by specifically blocking the extrinsic clotting pathway. Thromb Haemost. 2006;95:767–71.
30. Yoo E, Lee S. Glucose biosensors: an overview of use in clinical practice. Sensors (Basel). 2010;10:4558–76.
31. Wang H, Lakshmipriya T, Chen Y, Gopinath SCB. Squamous cell carcinoma biomarker sensing on a strontium oxide-modified interdigitated electrode surface for the diagnosis of cervical cancer. Biomed Res Int. 2019;2019:1–7.

32. Ramanathan S, Gopinath SCB, Arshad MKM, Poopalan P, Anbu P. A DNA based visual and colorimetric aggregation assay for the early growth factor receptor (EGFR) mutation by using unmodified gold nanoparticles. Microchim Acta. 2019;186:546.
33. Lv Q, Wang Y, Su C, Lakshmipriya T, Gopinath SCB, Pandian K, et al. Human papilloma virus DNA-biomarker analysis for cervical cancer: signal enhancement by gold nanoparticle-coupled tetravalent streptavidin-biotin strategy. Int J Biol Macromol. 2019;134:354–60.
34. Letchumanan I, Gopinath SCB, Md Arshad MK, Anbu P, Lakshmipriya T. Gold nano-urchin integrated label-free amperometric aptasensing human blood clotting factor IX: a prognostic approach for "Royal disease." Biosens Bioelectron. 2019;131:128–35.
35. Zhang R, Wang S, Huang X, Yang Y, Fan H, Yang F, et al. Gold-nanourchin seeded single-walled carbon nanotube on voltammetry sensor for diagnosing neurogenerative Parkinson's disease. Anal Chim Acta. 2020;1094:142–50.
36. Bollella P, Sharma S, Cass AEG, Tasca F, Antiochia R. Minimally invasive glucose monitoring using a highly porous gold microneedles-based biosensor: characterization and application in artificial interstitial fluid. Catalysts. 2019;9:550.
37. Liang B, Zhang S, Lang Q, Song J, Han L, Liu A. Amperometric L-glutamate biosensor based on bacterial cell-surface displayed glutamate dehydrogenase. Anal Chim Acta. 2015;884:83–9.
38. Matos-Peralta Y, Antuch M, Abradelo DG, Bazán-Bravo L, Hernández KR, De la Luz K. Glutamate dehydrogenase-based electrochemical biosensors: the immobilization method defines sensor selectivity. J Electrochem Soc. 2019;166:1146–50.
39. Liu J, Wang J. Remarkable thermostability of bioelectrodes based on enzymes immobilized within hydrophobic semi-solid matrices. Biotechnol Appl Biochem. 1999;30(Pt 2):177–83.
40. Nery EW, Kundys M, Jeleń PS, Jönsson-Niedziólka M. Electrochemical glucose sensing: is there still room for improvement? Anal Chem. 2016;88:11271–82.
41. Xu P, Yang HW, Shi JL, Ding B, Zhao X-J, Yang E-C. Efficient detection of a biomarker for infant jaundice by a europium(III)-organic framework luminescence sensor. RSC Adv. 2019;9:37584–93.
42. López-Velázquez JA, Chávez-Tapia NC, Ponciano-Rodríguez G, Sánchez-Valle V, Caldwell S, Uribe M, et al. Bilirubin alone as a biomarker for short-term mortality in acute-on-chronic liver failure: an important prognostic indicator. Ann Hepatol. 2014;268:30910.
43. Hooda V, Gahlaut A, Gothwal A, Hooda V. Bilirubin enzyme biosensor: potentiality and recent advances towards clinical bioanalysis. Biotechnol Lett. 2017;39:1453–62.
44. Baingane A, Shankara Narayanan J, Slaughter G. Sensitive electrochemical detection of glucose via a hybrid self-powered biosensing system. Sens Biosensing Res. 2018;20:41–6.
45. Kong L, Ren Z, Du S, Wu J, Fu H. Co2Nx/nitrogen-doped reduced graphene oxide for enzymeless glucose detection. Chem Commun (Camb). 2014;38:4921–3.
46. Zhang J, Gopinath SCB. Quantification of cortisol for the medical diagnosis of multiple pregnancy-related diseases. 3 Biotech. 2020;10:35.
47. Letchumanan I, Md Arshad MK, Gopinath SCB, Rajapaksha RDAA, Balakrishnan SR. Comparative analysis on dielectric gold and aluminium triangular junctions: impact of ionic strength and background electrolyte by pH variations. Sci Rep. 2020;10:6783.
48. Ramanathan S, Jusoh M, Sabapathy T, Yasin MN, Gopinath SCB, ARahim H, et al. Elastomeric polydimethylsiloxane polymer on conductive interdigitated electrode for analyzing skin hydration dynamics. Appl Phys A. 2020;126:756.
49. Donmez S, Arslan F, Sarı N, Hasanoğlu Özkan E, Arslan H. Glucose biosensor based on immobilization of glucose oxidase on a carbon paste electrode modified with microsphere-attached l-glycine. Biotechnol Appl Biochem. 2017;64:745–53.
50. Wu C, Sun H, Li Y, Liu X, Du X, Wang X, et al. Biosensor based on glucose oxidase-nanoporous gold co-catalysis for glucose detection. Biosens Bioelectron. 2015;66:350–5.
51. Parlak O, İncel A, Uzun L, Turner APF, Tiwari A. Structuring Au nanoparticles on two-dimensional MoS2 nanosheets for electrochemical glucose biosensors. Biosens Bioelectron. 2017;89:545–50.
52. Fu C, Yang W, Chen X, Evans DG. Direct electrochemistry of glucose oxidase on a graphite nanosheet-Nafion composite film modified electrode. Electrochem Commun. 2009;11:997–1000.
53. Weiss NO, Zhou H, Liao L, Liu Y, Jiang S, Huang Y, et al. Graphene: an emerging electronic material. Adv Mater. 2012;24:5782–825.
54. Castrignanò S, Valetti F, Gilardi G, Sadeghi SJ. Graphene oxide-mediated electrochemistry of glucose oxidase on glassy carbon electrodes. Biotechnol Appl Biochem. 2016;63:157–62.
55. Juska VB, Walcarius A, Pemble ME. Cu nanodendrite foams on integrated band array electrodes for the nonenzymatic detection of glucose. ACS Appl Nano Mater. 2019;2:5878–89.
56. Ahmad R, Tripathy N, Ahn MS, Bhat KS, Mahmoudi T, Wang Y, et al. Highly efficient non-enzymatic glucose sensor based on CuO modified vertically-grown ZnO nanorods on Electrode. Sci Rep. 2017;7:5715.
57. Yang Q, Long M, Tan L, Zhang Y, Ouyang J, Liu P, et al. Helical TiO2 nanotube arrays modified by Cu-Cu2O with ultrahigh sensitivity for the nonenzymatic electro-oxidation of Glucose. ACS Appl Mater Interfaces. 2015;7:12719–30.
58. Thangamuthu M, Gabriel WE, Santschi C, Martin OJF. Electrochemical sensor for bilirubin detection using screen printed electrodes functionalized with carbon nanotubes and graphene. Sensors (Basel). 2018;18:800.
59. Rahman MM, Ahmed J, Asiri AM. Selective bilirubin sensor fabrication based on doped IAO nanorods for environmental remediation. New J Chem. 2019;43:19298–307.
60. Cione E, Piegari E, Gallelli G, Caroleo MC, Lamirata E, Curcio F, et al. Expression of MMP-2, MMP-9, and NGAL in tissue and serum of patients with vascular aneurysms and their modulation by statin treatment: a pilot study. Biomolecules. 2020;10:359.
61. Yan C, Teng J, Liu F, Yao B, Xu Z, Yao L, et al. Signal amplified enzyme-linked immunosorbent assay with gold nanoparticles for sensitive detection of trace furaltadone metabolite. Microchem J. 2020;159:105414.
62. Henares TG, Tsutsumi E, Yoshimura H, Kawamura K, Yao T, Hisamoto H. Single-step ELISA capillary sensor based on surface-bonded glucose oxidase, antibody, and physically-adsorbed PEG membrane containing peroxidase-labeled antibody. Sens Actuators B Chem. 2010;149:319–24.
63. Liu QL, Yan XH, Yin XM, Situ B, Zhou HK, Lin L, et al. Electrochemical enzyme-linked immunosorbent assay (ELISA) for

α-fetoprotein based on glucose detection with multienzyme-nanoparticle amplification. Molecules. 2013;18:12675–86.
64. Toh SY, Citartan M, Gopinath SCB, Tang T-H. Aptamers as a replacement for antibodies in enzyme-linked immunosorbent assay. Biosens Bioelectron. 2015;64:392–403.
65. Hsieh HV, Pfeiffer ZA, Amiss TJ, Sherman DB, Pitner JB. Direct detection of glucose by surface plasmon resonance with bacterial glucose/galactose-binding protein. Biosens Bioelectron. 2004;19:653–60.
66. Mudgal N, Saharia A, Agarwal A, Ali J, Yupapin P, Singh G. Modeling of highly sensitive surface plasmon resonance (SPR) sensor for urine glucose detection. Opt Quantum Electron. 2020;52:1–14.
67. Yuan Y, Yuan N, Gong D, Yang M. A high-sensitivity and broad-range SPR glucose sensor based on improved glucose sensitive membranes. Photonic Sens. 2019;9:309–16.
68. Maity M, Das S, Maiti NC. Stability and binding interaction of bilirubin on a gold nano-surface: steady state fluorescence and FT-IR investigation. Phys Chem Chem Phys. 2014;16:20013–22.
69. Basu S, Sahoo AK, Paul A, Chattopadhyay A, Thumb imprint based detection of hyperbilirubinemia using luminescent gold nanoclusters. Sci Rep. 2016;6:39005.
70. Guo S, Lakshmipriya T, Gopinath SCB, Anbu P, Feng Y. Complementation of ELISA and an interdigitated electrode surface in gold nanoparticle functionalization for effective detection of human blood clotting defects. Nanoscale Res Lett. 2019;14:222.
71. Pandana H, Aschenbach KH, Gomez RD. Systematic aptamer-gold nanoparticle colorimetry for protein detection: thrombin. IEEE Sens J. 2008;8:661–6.
72. Gong Y, Hu J, Choi JR, You M, Zheng Y, Xu B, et al. Improved LFIAs for highly sensitive detection of BNP at point-of-care. Int J Nanomed. 2017;12:4455–66.
73. Gopinath SCB, Lakshmipriya T, Awazu K. Colorimetric detection of controlled assembly and disassembly of aptamers on unmodified gold nanoparticles. Biosens Bioelectron. 2014;51:115–23.
74. Huang Z, Zheng L, Feng F, Chen Y, Wang Z, Lin Z, et al. A simple and effective colorimetric assay for glucose based on MnO2 nanosheets. Sensors (Basel). 2018;18:2525.
75. Wang TT, Guo K, Hu XM, Liang J, Li X-D, Zhang Z-F, et al. Label-free colorimetric detection of urine glucose based on color fading using smartphone ambient-light sensor. Chemosensors. 2020;8:6–8.
76. Silva PBM, Oliveira KA, Coltro WKT. Colorimetric detection of glucose in biological fluids using toner-based microzone plates. J Braz Chem Soc. 2017;28:197–201.
77. Santhosh M, Chinnadayyala SR, Kakoti A, Goswami P. Selective and sensitive detection of free bilirubin in blood serum using human serum albumin stabilized gold nanoclusters as fluorometric and colorimetric probe. Biosens Bioelectron. 2014;15:370–6.
78. Haarindraprasad R, Hashim U, Gopinath SCB, Perumal V, Liu WW, Balakrishnan SR. Fabrication of interdigitated high-performance zinc oxide nanowire modified electrodes for glucose sensing. Anal Chim Acta. 2016;925:70–81.
79. Ge Y, Lakshmipriya T, Gopinath SCB, Anbu P, Chen Y, Hariri F, et al. Glucose oxidase complexed gold-graphene nanocomposite on a dielectric surface for glucose detection: a strategy for gestational diabetes mellitus. Int J Nanomed. 2019;14:7851–60.
80. Wang J, Ozsoz M. A polishable amperometric biosensor for bilirubin. Electroanalysis. 1990;2:647–50.
81. Bell JG, Mousavi MPS, Abd El-Rahman MK, Tan EKW, Homer-Vanniasinkam S, Whitesides GM. Paper-based potentiometric sensing of free bilirubin in blood serum. Biosens Bioelectron. 2019;126:115–21.

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