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Recent Progress on Fabrication of Zinc Oxide Nanorod-Based Field Effect Transistor Biosensors

(Kemajuan Terkini Fabrikasi Biosensor Berasaskan Nanorod Kesan Medan Transistor Zink Oksida)

SITI SHAFURA A KARIM, CHANG-FU DEE, BURHANUDDIN YEOP MAJLIS & MOHD AMBRI MOHAMED*

ABSTRACT

Zinc oxide is a unique n-type semiconducting material, owing to wide bandgap of ~3.37 eV, non-toxic, bio-safe and biocompatible with high isoelectric point of ~9.5, make it as promising biomaterial to be utilized as sensing matrix in biosensor applications. In addition, ZnO that possess high electron affinity provide a good conduction pathway for the electrons hence result in significant electrical signal change upon detection to target biomolecules. Moreover, high surface area of ZnO nanorod enhance immobilization of enzymes, hence, increase the device performance. Field effect transistor (FET)-based biosensor offer simplicity in handling and label-free, has also become research topic among researchers for novel biosensor development. This review aims to explore the preparation of ZnO nanorod using hydrothermal method and investigate the fabrication of ZnO nanorod-based FET biosensor. Thus, contribute to enhance understanding towards biosensor development for health monitoring, especially based on FETs structure devices.

Keywords: Biosensor; field effect transistor; hydrothermal method; zinc oxide nanorod

ABSTRAK

Zink oksida adalah bahan semikonduktor jenis-n yang unik, disebabkan oleh ketinggian selebar ~3.37 eV, tidak toksik, selamat dan bioserasi dengan titik isoelektrik yang tinggi ~9.5, menjadikan ia sebagai biobahan yang sesuai digunakan sebagai matriks penderia dalam aplikasi biosensor. Di samping itu, ZnO yang mempunyai keafinan elektron yang tinggi memberikan laluan konduksi yang baik untuk elektron dan mengakibatkan perubahan isyarat elektrik yang signifikan apabila pengesanan kepada biomolekul sasaran. Tambahan pula, kawasan permukaan ZnO nanorod yang tinggi meningkatkan immobilisasi enzim, seterusnya meningkatkan prestasi peranti. Biosensor berasaskan kesan medan transistor (FET) adalah mudah dikendalikan dan bebas label, juga menjadi topik penyelidikan dalam kalangan penyelidik untuk pembangunan biosensor yang novel. Kajian ini bertujuan untuk meneroka penyediaan ZnO nanorod menggunakan kaedah hidroterma dan mengkaji fabrikasi biosensor FET yang berasaskan ZnO nanorod. Sekaligus menyumbang kepada kefahaman tentang pembangunan biosensor untuk memantau kesihatan, terutamanya yang berasaskan struktur FETs.

Kata kunci: Biosensor; kaedah hidroterma; kesan medan transistor; zink oksida nanorod

INTRODUCTION

The first creation breakthrough of the biosensor development was reported in 1962 by Clark and Lyons with the discovery of detecting glucose using an enzyme electrode. Since then the understanding towards biosensor development has been exponentially expanded. However, the low efficiency of enzyme immobilization on a solid electrode is one of main challenge. Thus, nanomaterial-mediated biosensor has aroused much attention as sensing matrix for biosensor development. This is due to that nanomaterials offer extremely interesting morphological, functional biocompatible, non-toxic and catalytic properties which allowed many new signal transductions and resulting in enhanced performance (Arya et al. 2012; Cheng et al. 2015; Mohammed et al. 2017). The studies on utilizing nanomaterial to fabricate and design novel devices are also keep arising due to many advantages such as miniaturization of device, enhanced performance and cost-effective (Ahmad et al. 2018; Bakar et al. 2018; Sihar et al. 2018).

Biosensor is an analytical tool that monitor the presence of specific biomolecules when biorecognition event generates the signal. Biosensor offers application particularly to detect target biomolecules or to monitor diseases at early stage in many fields such as food industry, medical and health. A typical biosensor consists of four main components: probe molecule, linker, transducer and signal processing and display component (Figure 1). A probe molecule is a biological molecule that specifically recognizes the analyte in sample. For example, DNA probe can make a specific interaction with its target complementary DNA (Galdamez et al. 2019; Kim et al. 2018). Meanwhile, a linker plays a role to immobilize probe molecule onto the device. A suitable linker ensures the signal obtained from biorecognition event transfer to the transducer. Next, a transducer used to transduce signal from the biorecognition event to measurable signal. A transducer which also called as a sensing matrix helps to immobilize biomolecules with retained activity and enhance signal transduction. The physico-chemical properties of the sensing matrix control the method of immobilization and the performance of the biosensors. Signal processing and display used to collect and measure the signal and display them for further analyzation.

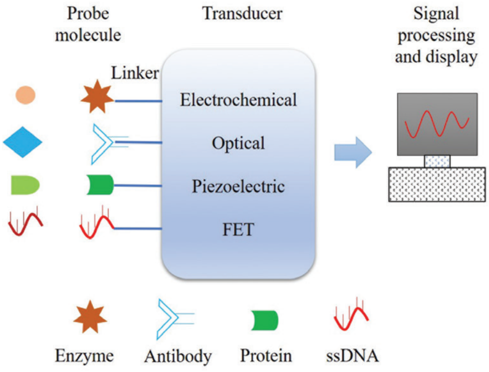

FIGURE 1. Schematic structure of typical biosensor

Zinc oxide (ZnO) is an attractive biomaterial for its versatile properties such as semiconducting (wide bandgap of 3.37 eV), bio-safe and biocompatible with high isoelectric point of ~9.5. ZnO nanostructures can be prepared using various methods such as spin-coating (Bangbai et al. 2013; Mahmood et al. 2019), hydrothermal (Shafura et al. 2018; Zhang et al. 2019), spray pyrolysis (Dedova et al. 2019), radio frequency (RF) magnetron sputtering (Baratto 2018; Ching et al. 2014), chemical vapor deposition (CVD) (Mohammed & Hassan 2019). For instance, Saranya et al. (2017) have synthesized flower-like ZnO nanoflakes using hydrothermal method. Various ZnO nanostructures also has been obtained by hydrothermal method, as shown in Figure 2. Meanwhile, Baratto (2018) was successfully deposited ZnO nanorod by RF magnetron sputtering method. In addition, four kinds of ZnO nanostructures, nanorods, nanopencils, nanotowers and nanoneedles have been successfully deposited using CVD by manipulating the growth parameters (He et al. 2018).

Interestingly, previous studies have also reported that morphologies of ZnO greatly influence their material properties and device performances compared to bulk ZnO films (Ahmad et al. 2017; Gaiardo et al. 2016; Gao et al. 2018; Khayatian et al. 2017; Zong et al. 2018). Due to their high surface-to-volume ratio and strong binding properties, ZnO nanostructures can achieve single-molecule detection. The high isoelectric points (~9.5) of ZnO facilitates the physical immobilization of biomolecules specially to capture target biomolecules that has low isoelectric points. In addition, ZnO that possess high electron affinity provide a good conduction pathway for the electrons that generated from enzymatic reactions on its surface to the electrode, hence results in significant current change upon detection towards target biomolecules. At neutral pH, ZnO possesses a positive charge, whereas enzymes with low isoelectric points (IEPs) behave like a negative charged species, which leads to an electrostatic interaction between them and caused physical binding.

Many studies on biosensors has utilizing on different morphologies of ZnO nanostructures, such as nanoparticles (Mahmoud et al. 2019; Medawar-Aguilar et al. 2019), nanofilms (Agarwal et al. 2019; Zhai et al.

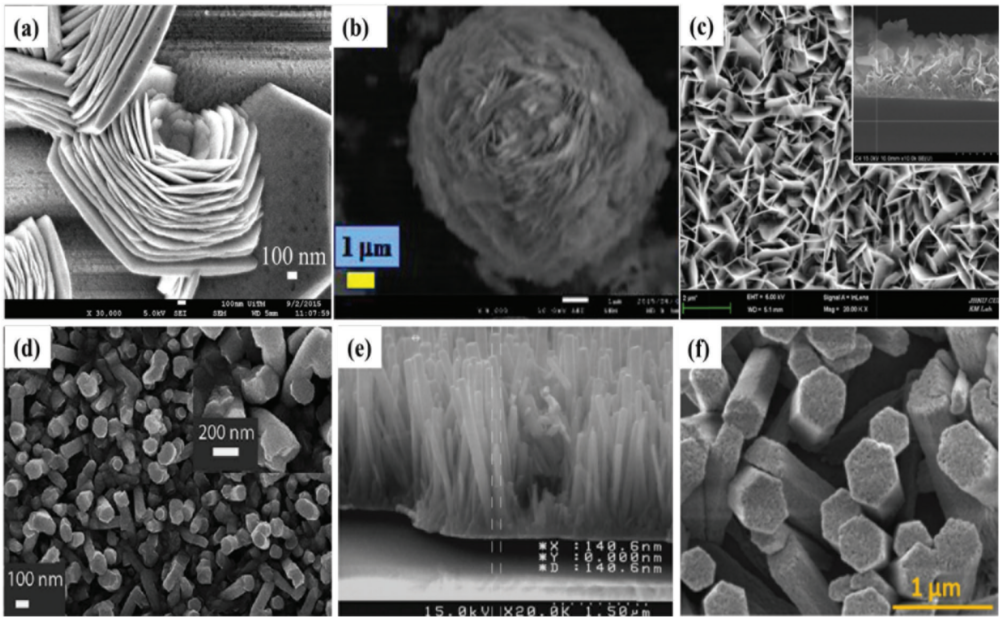

FIGURE 2. Various ZnO nanostructures obtained by hydrothermal method such as flower-like (Saranya et al. 2017; Shafura et al. 2018), nanosheets (Ahmad et al. 2015) and nanorods (Baratto et al. 2018; Fathollahzadeh et al. 2018; Mahmood et al. 2019)

2019), nanosheets (Yue et al. 2019a), nanoflowers (Yue et al. 2019b), nanorods (Ahmad et al. 2017; Ridhuan et al. 2018; Singh et al. 2019a) and nanowires (Ditshego 2018). For instance, ZnO nanosheets has been utilized for biosensing matrix to detect uric acid (Ahmad et al. 2015a). The fabricated biosensor exhibited sensitivity of 129.81 μA mM^{-1} cm^{-2} in wide-linear range of 0.05-2.0 mM. Meanwhile, Ahmad et al. (2015) has reported ZnO nanorod-based biosensor for simultaneously detect multi-analyte that are glucose, cholesterol and urea. It was found that the ZnO nanorods that acted as sensing matrix shown high selectivity without any interference towards those targeted bio-molecules. These attractive findings make ZnO as a promising sensing matrix for novel biosensor development.

GROWTH OF ZINC OXIDE NANOROD USING HYDROTHERMAL METHOD

ZnO has received enormous attention for device fabrication, drug delivery, biomedical applications and so on, due to many favorable properties. Directly grown vertical ZnO nanorods would be the most promising properties for designing biosensor devices due to its high surface-to-volume ratio and biocompatible by nature. Among solution-based deposition methods, hydrothermal method is the most commonly used for ZnO nanorod synthesis (Ahmad et al. 2017; Fathollahzadeh et al. 2018; Resmini et al. 2016). This approach offers simplest preparation set-up, least energy consuming and low production cost where the ZnO nanorod can be grown under mild synthesis condition (such as normal pressure and low growth temperature), simple facility, good repeatability and high reliability (Gao et al. 2010; Ismail et al. 2016; Zhang et al. 2019).

ZnO seed layer is needed in order to grow ZnO nanorod/nanowire using hydrothermal method (Cheng et al. 2016; Hassanpour et al. 2017; Park et al. 2016). Usually, ZnO seed layer are prepared using zinc acetate dehydrate as the precursor (Greene et al. 2005; Park et al. 2016; Shafura et al. 2018). Well seed alignment significantly influences the growth of ZnO nanorod (Yu et al. 2017). In order to obtain well seed alignment, thermal treatment is needed at range of 150°C to 200°C for complete decomposition of zinc acetate to ZnO. Meanwhile, annealing at temperature between 200°C to 500°C will promotes higher crystallinity and growth of seed. In addition, Greene et al. (2005) has confirmed that acetate-derived seed layer significantly improves vertical alignment of grown ZnO nanorod compared to unseeded and zinc nitrate-derived seed layer. Increasing the number of coating layers will reduce their grain boundaries hence providing path for electrons to move and result in increased conductivity, also shown in Figure 3 (Khan et al. 2017; Shafura et al. 2018).

In hydrothermal method, precursor play important role to determine the morphology of ZnO. Different precursors may result in different morphology and shape which may be attributed to different reaction pathways, solubility of the precursor, and basicity of the solution which influenced the crystal nucleation and growth of ZnO nanorod (Yun et al. 2010). Moreover, it can be predicted that the diameter of nanorod strongly depends on diameter of seed and the length of nanorod depends on the growth time and temperature (Hassanpour et al. 2017; Jeong et al. 2011; Park et al. 2016; Yu et al. 2017). Additive of ethylene glycol (EG) assists the crystal of ZnO nanorod to grow homogenously attributed to its good dispersibility and glutinosity (Long et al. 2008). In addition, ammonia solution has been used to significantly control the aspect ratio and growth rate of ZnO nanorod (Li et al. 2019; Zhang et al. 2019). Ammonia solution can inhibit the homogeneous nucleation and promote heterogeneous nucleation in the zinc acetate-derived precursor solution. The precursor and condition used to grow ZnO nanorod has been summarized in Table 1. The observed ZnO nanorod trend grown using hydrothermal method also were presented in Figure 4.

FABRICATION OF ZnO NANOROD-BASED FIELD EFFECT TRANSISTOR BIOSENSOR

Field effect transistor (FET) has become promising platform for the fabrication of biosensors since it has drawn much attentions among scientist all over the world due to their attractive features, such as ultra-sensitive

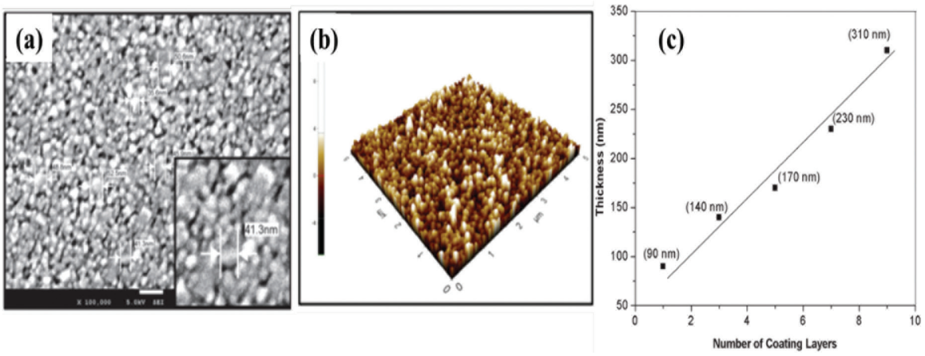

FIGURE 3. (a) The morphology and (b) AFM topography of ZnO seed layer prepared using acetate-derived precursor solution (c) The thicknesses obtained by increasing the number of coating layer from 1 to 9 layers (Shafura et al. 2018)

TABLE 1. Summary of precursor and condition used to deposit ZnO seed layer and to grow ZnO nanorod using hydrothermal method

Morphology	Precursor	Condition	Dimension	Ref.
Seedlayer:				
nanoparticle	Zinc acetate (5 mM), ethyl alcohol	Pre-heat: 120°C Anneal: 200-400°C Time: 30 min	D: ~10 nm	Hassanpour et al. (2017)
nanoparticle	Zinc acetate dehydrate (10 mM), MEA (10 mM), 2-methoxyethanol	Anneal: 400°C	D: ~5 nm	Cheng et al. (2016)
nanoparticle	Zinc acetate dehydrate (30 mM), ethanol	UVO treatment Anneal: 80-180°C Time: 1 h	Thickness: 38-50 nm	Park et al. (2016)
nanoparticle	Zinc acetate dehydrate (5 mM), ethanol	Anneal: 350°C for 20 min	D: ~10 nm	Greene et al. (2005)
nanoparticle	Zinc acetate dehydrate (0.4 M), MEA, 2-methoxyethanol	Anneal: 500°C for 1 h	D: less than 50 nm Thickness: 90-310 nm	Shafura et al. (2018)
Grown ZnO:				
nanorod	Zinc nitrate hexahydrate (50 mM), HMTA (50 mM), DI water	Growth temp.: 85°C Time: 2 h	D: 103 nm L: 175 nm	Hassanpour et al. (2017)
nanowire	Zinc nitrate hexahydrate (25 mM), HMTA (25 mM), DI water	Growth temp.: 92°C Time: 3 h Anneal: 200°C Time: 10 min	Aspect ratio: 14 L: ~1 µm	Park et al. (2016)
nanowire	Zinc nitrate hexahydrate (2.5 mM), HMTA (2.5 mM), polyethyleneimine (PEI, 20 mg), DI water (3 mL)	Growth temp.: 90°C Time: 1.5 h	L: ~1.2 µm	(Cheng et al. 2016) Cheng et al. (2016)
nanorod	Zinc nitrate hexahydrate (100 mM), HMT (100 mM), DI water	Growth temp.: 95°C Time: 1-5 h Anneal: 70°C Time: 30 min	D: 60-148 nm L: ~0.7-3 µm	(Jeong et al. 2011) Jeong et al. (2011)
nanorod	Zinc nitrate hexahydrate (30 mM), DI water, ammonium hydroxide (28 wt.%)	Dope: 5 mM Aluminium nitrate Growth temp.: 60°C Time: 6 h	Density: 108 nanorod per µm^2	Yun et al. (2010)
nanowire	Zinc nitrate hexahydrate (25 mM), methenamine or diethylenetriamine (25 mM)	Growth temp.: 90°C Time: 1.5 h	D: 40-80 nm L: 1.5-2.0 µm	(Greene et al. 2003) Greene et al. (2003)
nanorod	Zinc acetate dihydrate (40 mM), DI water, ammonium hydroxide (28 wt.%)	Dope: 5 mM Aluminium nitrate Growth temp.: 60°C Time: 6 h	Density: 186 nanorod per µm^2	Yun et al. (2010)
nanorod	Zinc chloride (50mM), HMT (50 mM), EG (50 vol.%), DI water	Growth temp.: 95°C Time:12 h Dry: 80°C Time: 1 h	D:~2 µm L:~7 µm	Long et al. (2008)

D= diameter, L= length, MEA= monoethanolamine, HMTA= hexamethylenetretramine

detection, fast measurement ability, mass production capability and low-cost manufacturing (Syu et al. 2018). Furthermore, FET based biosensor offer simplicity in handling and label-free, which mainly use electric fields to control the performance of fabricated device (Garrote et al. 2019; Singh et al. 2019).

FET based biosensors typically consist of three electrodes; source, drain and gate (Chen et al. 2017; Cheng et al. 2015; Ditshego 2018), as shown in Figure 5. The detection mechanism of the FET based biosensors is when the changes in electrical signal on the surface of sensing channel is detected during the target biomolecule is being captured. The output electrical signal is normally correlated to the concentration of analyte. The transfer curve determines the threshold voltage of fabricated device. In addition, the depletion layer can be controlled

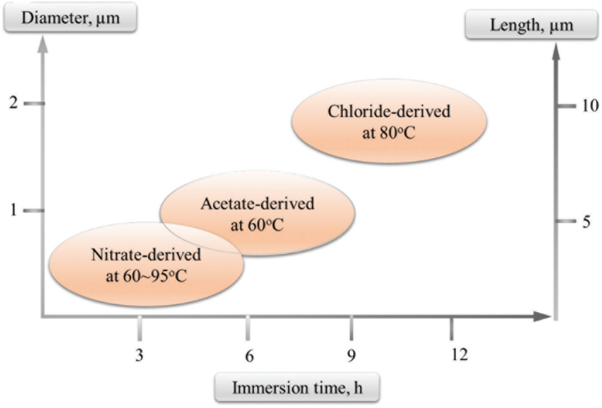

FIGURE 4. Observed ZnO nanorod trend grown using hydrothermal method

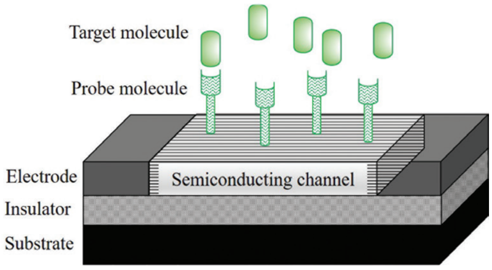

FIGURE 5. Schematic structure of a field effect transistor (FET) biosensor

by applying voltage gate, thus the sensitivity of biosensor can be controlled. High uniformity and high surface-to-volume ratio with high immobilization efficiencies and bioactivity retainment can be achieved by utilizing nanomaterials that act as the sensing channel in FET biosensor devices (Bhat et al. 2017; Kaisti 2017). This due to that high surface-to-volume ratio of nanomaterials provide greater interconnection between the device and biomolecules and thus enhance electron transfer between them. Hence it become considerable demand for health monitoring in the near future.

Recently, ZnO nanostructures have aroused attention among researchers due to their potential to be utilized as a sensing matrix for biosensor applications. ZnO nanostructures with unique morphological, structural and electrical properties provide an effective bio-interfacing platform for immobilization, biological recognition events and signal amplification. Moreover, high surface-to-volume ratio of ZnO nanostructures enables enhanced immobilization of enzymes onto its active surface and thus lead to more target biomolecules being recognized and captured. Moreover, ZnO has high chemical stability with high isoelectric point (~9.4) which makes it an attractive sensing matrix for biosensor applications (Ahmad et al. 2017; Tripathy et al. 2018). In addition, the ease of fabrication using low cost processes (hydrothermal method) offer promising way for large scale production. Therefore, many efforts and attempts has been made to explore and enhance the performance of ZnO nanostructures for biosensor applications.

FET based phosphate biosensor has been developed by utilizing ZnO nanorod arrays as the sensing matrix, as shown in Figure 6 (Ahmad et al. 2017). Silver (Ag) as source-drain electrode were deposited using RF magnetron sputtering at 60 W to obtain approximately 100 nm of thickness. Then, ZnO seedlayer (~60 nm) were sputtered between the Ag source-drain electrode. Zinc nitrate hexahydrate (40 mM), hexamethylenetetramine (HMTA, 40 mM) and deionized water were used to prepare ZnO solution. Then, ZnO nanorod arrays were grown on SiO_2/Si substrates using hydrothermal method at 85°C for 4 h. They obtained ZnO nanorod with length of approximately 1.2 µm and diameter of approximately 80-90 nm. The ZnO nanorod based FET biosensor exhibited higher current response compared to bare FET biosensor. This were due to vertically grown nanorod arrays has exhibited higher surface area which enhanced the immobilization of pyruvate oxidase (PyO) to detect the presence of phosphate. As a result, higher specificity and sensitivity (80.57 $\mu A\ mM^{-1}\ cm^{-2}$) were obtained to detect phosphate in range of 0.1 µM–7.0 mM.

Continuous glucose monitoring is crucial for diabetic patients to prevent diabetes complications. Zong et al. (2018) has successfully fabricated glucose FET biosensor for continuously detect glucose by utilizing ZnO nanorod as the sensing matrix to transduce glucose concentrations to measurable current signal, also can be observed in Figure 7. The ZnO nanorod were grown between Cr/Au source-drain electrode (100 nm) using electric-field assisted hydrothermal method at 75°C for

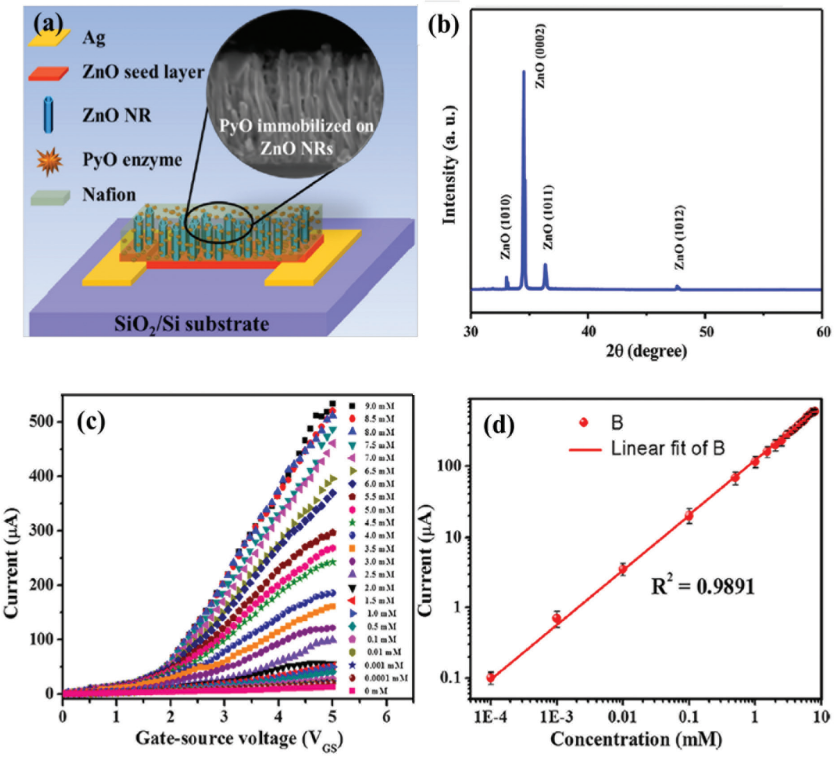

FIGURE 6. (a) Schematic view of ZnO-based FET biosensor and cross-sectional image of ZnO nanorod arrays (inset) (b) XRD pattern of ZnO nanorod grown on SiO_2/Si substrate (c) transfer curve of the device at increasing phosphate concentrations from 0.1 µM to 9.0 mM in 0.02 M HEPES buffer (pH7.0) and (d) the device corresponding calibration curve (Ahmad et al. 2017)

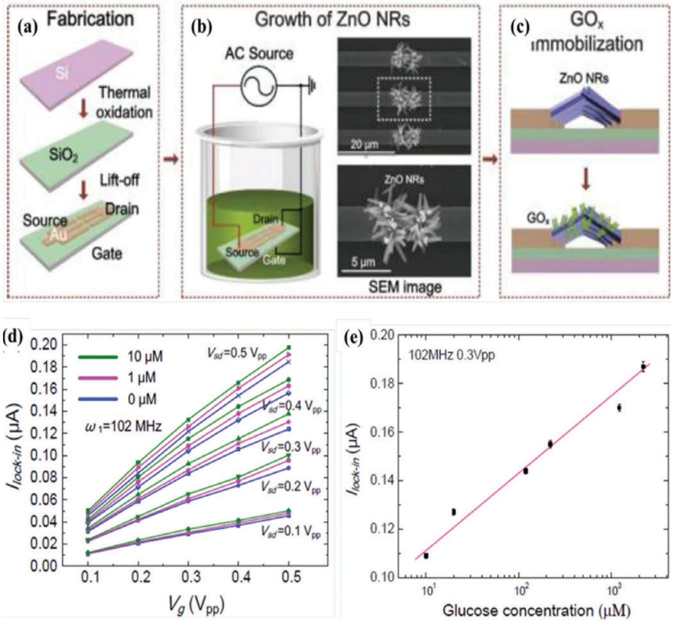

FIGURE 7. (a) Fabrication of source-drain electrodes of FET biosensor, (b) electric field-assisted hydrothermal method used to grow ZnO nanorod, (c) schematic view of ZnO nanorod based FET biosensor, (d) current-voltage (I-V) measurement at glucose concentrations from 0 to 10 µM by varying the source-drain voltage (V_{sd}) and (e) the device corresponding calibration curve (Zhong et al. 2018)

5 h. They prepared equimolar aqueous solution (15 mM) using zinc nitrate hexahydrate and HMTA. Then, the ZnO nanorod were immobilized using glucose oxidase (GOx) for glucose detection. The ZnO nanorod has diameter of ~300-500 nm and length of ~1-2 µm. High surface area of nanorod enhanced immobilization of GOx and resulted

higher sensitivity of 1.6 mA μM^{-1} cm^{-2} towards 1 μM of glucose concentration. In addition, Fathollahzadeh et al. (2018) has demonstrated ZnO nanorod-based liquid-gated FET biosensor to specifically detect glucose, as shown in Figure 8. Ti/ Au (100 nm/200 nm) source-drain electrode was used for FET device fabrication. Meanwhile, ZnO nanorod were grown using hydrothermal method at 90°C for 3 h. The equimolar aqueous solution (10 mM) of zinc nitrate hexahydrate and HMTA were used to grown ZnO nanorod with diameter and length of approximately 150 nm and 1 μm, respectively. The device has detection limit up to 3.8 μM and showed fast response time of 10 s.

Monitoring cholesterol is important to manage and plan a treatment for many diseases such as coronary heart diseases, stroke, hypertension and arteriosclerosis etc. High sensitivity, long-term stability and high repeatability of cholesterol biosensor is needed. Therefore, Ahmad et al. (2013) has developed high performance ZnO nanorod-based FET biosensor to specifically detect cholesterol. Hydrothermal method was used to grow highly crystalline (0002) plane of ZnO nanorod. ZnO that owing to high surface area has enhanced the immobilization of cholesterol oxidase (ChOx). The device exhibited sensitivity of 10 mA mM^{-1} cm^{-2} for wide-linear range of cholesterol concentration (0.001-45 mM). Interestingly, by utilizing ZnO nanorod as sensing matrix has discover its properties to simultaneously detect multi-analyte as has been discovered by Ahmad et al. (2015b) as shown in Figure 9. The device exhibited high selectivity towards detection of glucose, cholesterol and urea. The comparative results from the previous works has been summarized in Table 2.

CONCLUSION

Nanotechnology offers advantageous approaches for miniaturization and novel device development. Field effect transistor-based biosensor is one of promising devices for biosensor development due to easy in handling and label-free with high sensitivity towards detection of target biomolecules. By utilizing zinc oxide (ZnO) nanorod as the sensing matrix, enhanced performance of FET based biosensor can be obtained. High surface-to-volume ratio, high electron affinity and high electron mobility of ZnO nanorod attribute to enhance the device performance. Among solution-based approach, hydrothermal method is the most favorable method due to its many advantages such as simple, least energy consuming and high repeatability. However, it is still a challenge to obtain tunable ZnO nanorod using hydrothermal method. Thus, there is a need to further studies on control the growth of ZnO nanorod using hydrothermal method in development of novel FET based biosensor.

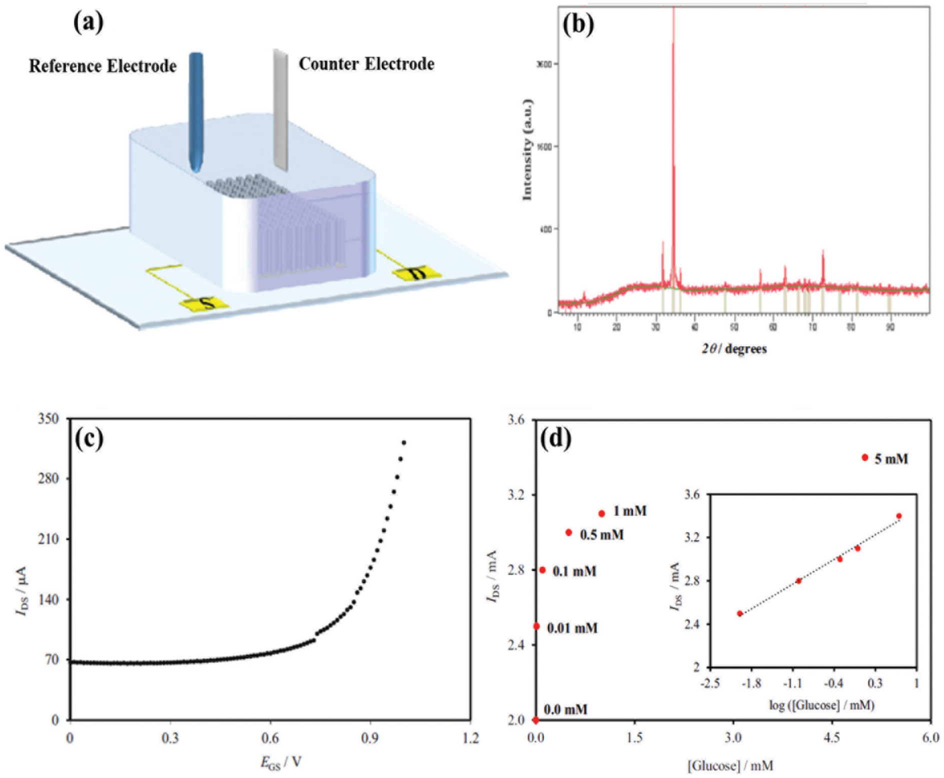

FIGURE 8. (a) Schematic view of glass-based liquid-gated FET biosensor (b) XRD pattern of grown ZnO nanorod (c) transfer curve of GOx/ZnO nanorods based FET biosensor in 0.01 M PBS (pH7.4) at 0.1 mM glucose and (d) their corresponding calibration curve for glucose (Fathollahzadeh et al. 2018)

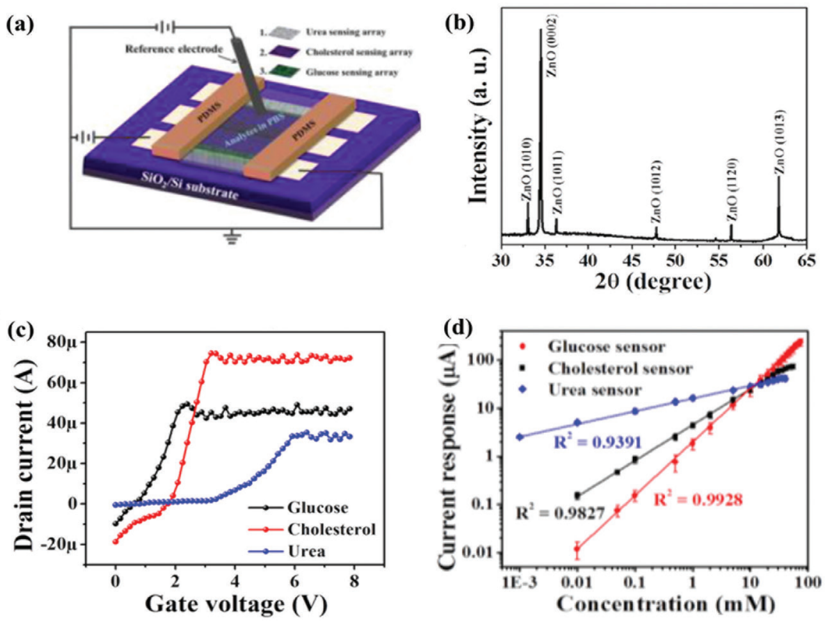

FIGURE 9. (a) Schematic view of FET device measurement to simultaneously detect multi-analyte (b) XRD pattern of deposited ZnO nanorod using hydrothermal method (c) transfer curve of fabricated device and (d) the corresponding calibration curve for glucose, cholesterol and urea detection, respectively (Ahmad et al. 2015b)

TABLE 2. Comparative results of ZnO nanorod-based FET biosensors

Morphology	Electrode	Enzyme	Target	Sensitivity	Ref.
D: ~80-90 nm L: ~1.2 μm	Ag (100 nm)	PyO	phosphate	80.57 μA mM^{-1} cm^{-2}	Ahmad et al. (2017)
D: ~300-500 nm L: ~1-2 μm	Cr/Au (100 nm)	GOx	glucose	1.6 mA μM^{-1} cm^{-2}	Zong et al. (2018)
D: ~150 nm L: ~1 μm	Ti (100 nm)/ Au (200 nm)	GOx	glucose	Not reported	Fathollahzadeh et al. (2018)
D: ~100 nm L: ~2 μm	Ag/AgCl	ChOx	cholesterol	10 mA mM^{-1} cm^{-2}	Ahmad et al. (2013)
D: ~50 nm L: ~1 μm	Ag	GOx ChOx urease	glucose cholesterol urea	32.27 μA mM^{-1} cm^{-2} 17.10 μA mM^{-1} cm^{-2} 14.23 μA mM^{-1} cm^{-2}	Ahmad et al. (2015b)

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Institute of Microengineering and Nanoelectronics (IMEN)
Universiti Kebangsaan Malaysia
43600 UKM Bangi, Selangor Darul Ehsan
Malaysia

*Corresponding author; email: ambri@ukm.edu.my

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