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Graphene-based electrochemical biosensors for monitoring noncommunicable disease biomarkers

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ABSTRACT

Graphene is a 2-dimensional nanomaterial with an atomic thickness has attracted a strong scientific interest owing to their remarkable optical, electronic, thermal, mechanical and electrochemical properties. Graphene-based materials particularly graphene oxide and reduced graphene oxide are widely utilized in various applications ranging from food industry, environmental monitoring and biomedical fields as well as in the development of various types of biosensing devices. The richness in oxygen functional groups in the materials serves as a catalysis for the development of biosensors/electrochemical biosensors which promotes for an attachment of biological recognition elements, surface functionalization and compatible with micro- and nano- bio-environment. In this review, the graphene-based materials application in electrochemical biosensors based on recent advancement (e.g; the surface modification and analytical performances) and the utilization of such biosensors to monitor the noncommunicable diseases are presented. The detection performances of the graphene-based electrochemical biosensors are in the range of ng/mL and have reached up to fg/mL in detecting the targets of NCDs with higher selectivity, sensitivity and stability with good reproducibility attributes. We have discussed the advances while addressing the very specific biomarkers for the NCDs detection. Challenges and possible future research directions for the NCDs detection based on graphene nanocomposite with other 2D nanomaterials are outlined.

1. Introduction

Noncommunicable diseases (NCDs) are the major threat to human health and it becomes the leading cause of deaths accounting for 71% (41 million) of the 57 million of global's deaths estimated in 2016 (World Health Organization, 2018). There are four major classifications of NCDs such as cardiovascular diseases (CVD), cancers, chronic respiratory diseases and diabetes as well as other NCDs. According to the NCDs global status report by World Health Organization (WHO), in 2016 the cardiovascular diseases is ranked top first with the largest proportion of global deaths (31%), followed by cancers (16%), then the chronic respiratory diseases in the third place (7%) and finally diabetes is responsible for 3% of deaths. The mortality burden is very high in low- and middle-income countries where it representing 78% of all NCDs deaths with the Mediterranean countries is ranked at the first place of deaths (24%) and followed by South East Asia region in the second place (23%). Specifically, the mortality rate in Malaysia due to the NCDs which has been estimated to account for 74% of all deaths with CVD representing the highest deaths rate (35%) followed by cancers (16%), then chronic respiratory diseases (4%) and diabetes (3%) as well as other NCDs which account for 16% of deaths (World Health Organization, 2018). In order to rectify the scariest NCDs mortality rate, WHO had released nine action plans to prevent and to control the diseases. The first outlined plan is "*A 25% relative reduction in the overall mortality from cardiovascular diseases, cancer, diabetes or chronic respiratory diseases*" (World Health Organization, 2014). An early stage monitoring of NCDs with a right diagnosis method and a suitable treatment plays a vital role in fighting such deadliest diseases. In addition, rapid and inexpensive screening method with highly reliable test result is the key criteria for the successful treatments and preventions. In this context, electrochemical biosensors are having a great and promising role to monitor the NCDs. This is because the electrochemical biosensors offers potential advantages such as simplicity, cheap, real-time monitoring and analysis, label free, less sample volume requirement as well as hand-held devices. Moreover, it enables to design flexibility where it allows for electrodes modification and

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surface functionalization during sensor fabrication which akin to the device performances in term of sensitivity, specificity, rapid-response and provides multiple functionality as well as easy to use (Chauhan et al., 2017; Haque et al., 2012).

Graphene and its derivatives [graphene oxide (GO) and reduced graphene oxide (rGO)] are the well-accepted nanomaterials for the fabrication of biosensors because of their bio-compatibilities. The graphene-based materials contain a large number of oxygen as the functional groups that are useful for the electrode surface functionalization. Physically, these nanomaterials exhibit a high surface area to volume ratio where it increases the bio-receptor immobilization that leads to improvement in biosensing (Dong et al., 2017). The number of research articles published with graphene-based materials are significantly increased year by years and the major portion of research are devoted to the biomedical applications are ranging from biosensing, tissue engineering, protein, stem cell, drug-delivery and nucleic acid-based researches, toxicity research and imaging (Mao et al., 2013). Graphene is a 2-dimensional nanomaterial where it composed by carbon atoms in honeycomb lattice structure and having an atomic thickness. Graphene was first discovered thru mechanical exfoliation from a highly oriented pyrolitic graphite or known as scotch-tape technique and the material is thermodynamically stable at room temperature at atomic scale (Geim and K. S. N., 2007; Jiang, 2015; Novoselov et al., 2004a). The graphene itself can be wrapped up to 0-dimensional (fullerene) or rolled to 1-dimensional (carbon nanotube) or stacking up to form 3-dimensional layers (graphite). Graphene has many remarkable qualities ranging from electronic spectra, mechanical, optical, thermal as well as electrochemical properties (Singh et al., 2011). The tangible applications of graphene and its derivatives that have been reported until to date are shown in Fig. 1. To name a few, graphene-based materials are utilized in various application ranging from optoelectronic devices, chemical sensors, electrochemical biosensors, as nanocomposites, energy storage devices, aquatic environment, insulation, food analysis and security as well as forensic science (Zhao et al., 2014; Wang et al., 2011; Bonanni et al., 2012).

This critical overview mainly focuses the aptitude of graphene-based materials in bridging the transducer in electrochemical biosensors, specifically to monitor the NCDs (an emerging threat to human), emphasising on recent development and advancement of electrochemical nanodevices. First, we comparatively narrate the graphene-based materials characteristics and their preparation scheme from the recently generated eminent techniques. Then, we summarize the binding strategies and materials synergistic with transducers as well as their performances based on recently developed nanodevices. In addition, we address the very specific biomarkers for the NCDs monitoring. The most common chronic diseases within NCDs (heart disease, lung cancer, asthma and diabetes) are discussed based on the electrochemical detections, where the transducers are mediated with graphene-based materials. Challenges and possible future research directions for NCDs detection based on graphene nanocomposite with other 2D nanomaterials are outlined.

2. Graphene, graphene oxide (GO) and reduced graphene oxide (rGO)

Pristine graphene is defined as a single 2D plane/a flat monolayer of carbon atoms that are tightly packed by covalent bonding (sp^2 hybridization) in the honeycomb lattice structure and more importantly it

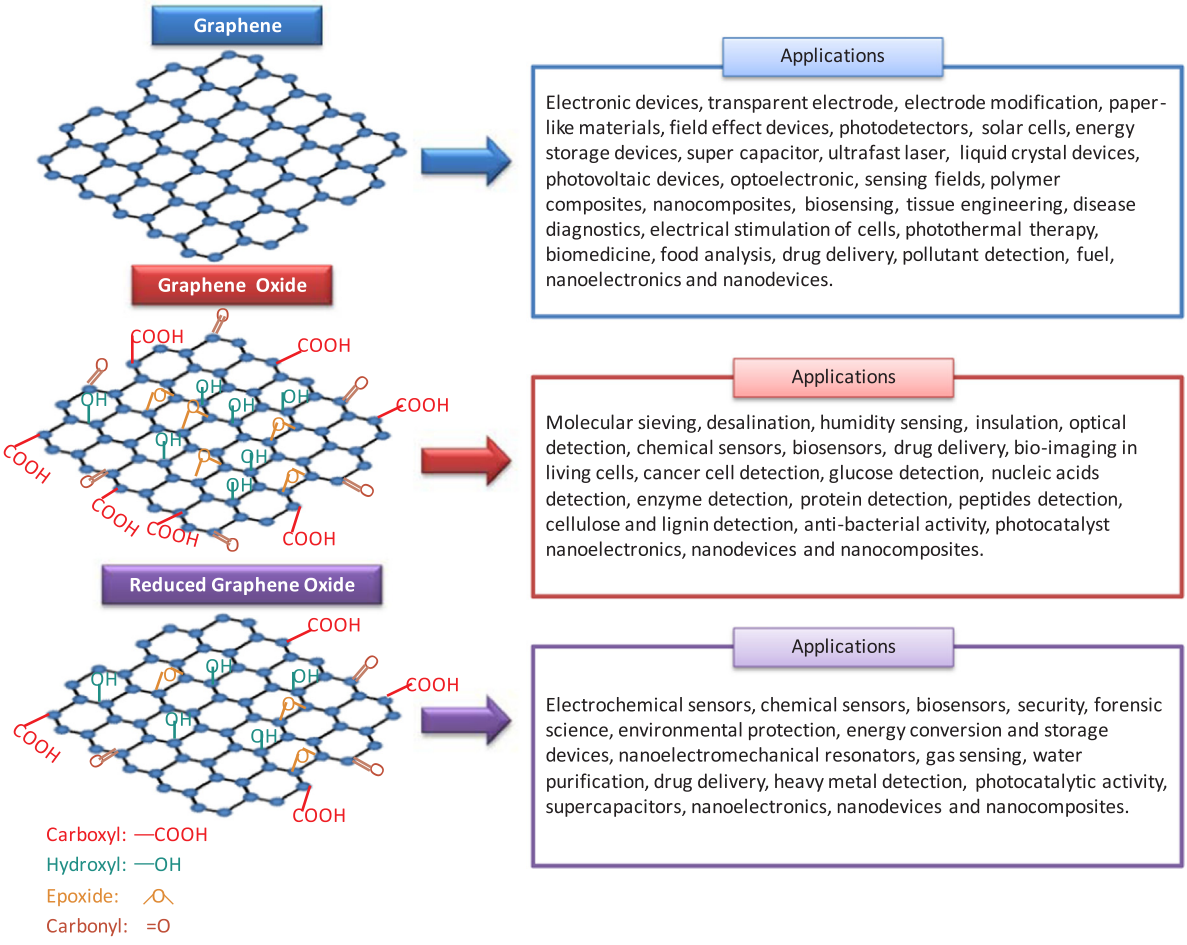

Fig. 1. The applications of graphene and its derivatives (graphene oxide and reduced graphene oxide are displayed).

is synthesized from a high quality of graphite (Geim and K. S. N., 2007). The pristine graphene exhibit a very high crystal quality, strong ambipolar electric field effect and having massless Dirac fermions characteristics because of the valence and the conduction bands touch the Brillouin zone corners (Mao et al., 2013). However, the electronic spectra of pristine graphene are changed when the number of layer is increased. The difficulties and the lack of an international standard method to isolate single sheet graphene makes researches to ignore to state the number of layers used in their research precisely and simply use the term of graphene (which referred to single 2D plane/a flat monolayer of carbon atoms). In general, the material can be called *graphene films or graphene sheets* when it contains 2–10 layers. However, when the graphene sheet is more than 10 layers one can address the material as graphite thin films (GtTF) (Pumera, 2013). Pristine graphene has many remarkable and unique qualities are ranging from electronic, physical, optical and mechanical to electrochemical perspectives. The remarkable properties from electronic perspectives are, it is highly conductive at room temperature when biasing with voltage, charge transport is ballistic at interatomic distance, having linear current-voltage (I-V) characteristics, exhibit strong interatomic bonds, only a few crystal defects during thermal fluctuation, semimetallic nature with a tiny overlap of band gap which producing quantum hall effect and a strong ambipolar electric field effect with high concentration of charge carriers (Mao et al., 2013; Schedin et al., 2007). The details review on the physics of electronic properties of graphene can be found in literature (Castro Neto et al., 2009). Besides the electronic spectra, graphene also exhibits unique mechanical properties such as high mechanical strength, band gap tuneability, a large surface area, high elasticity, superior in heat transfer (Su et al., 2009) and also having hydrophobic characteristic (Liu et al., 2011a). Stoichiometric process (chemical reactions) offers a great potential to use the graphene in various applications and it enables researches to control the electronic properties as well as to enhance the electrochemical activities (Geim, 2009). Oxidizing graphite can alter its chemical structure, forming functional groups at the edges and basal plane of the sheets, shows a better biocompatibility and transform to hydrophilic characteristics (Gilje et al., 2008). Then, the subsequent process of exfoliation of graphite oxide will result in graphene oxide.

Graphene oxide (GO) is a precursor material in the efforts to synthesis pristine graphene and widely used in micro- and nano-environments especially in biosensors and bioelectronics fields due to its large number of oxygen-containing groups. GO is defined as an oxygenated monolayer of carbon atoms (2D network of sp^2 and sp^3 bonded atoms), produced through oxidation process (Stankovich et al., 2007; Paredes et al., 2008). In 1860, Brodie (Gilje et al., 2007) has successfully synthesized graphite oxide (GtO) and then the same idea has been adopted to synthesis GO after the discovery of graphene. It is really important to address and to standardize the nomenclature for graphite oxide as GtO (Liu et al., 2011b) is more appropriate rather than GO. This is because the terminology usage itself indicates the graphene-based materials having completely different characteristics from its physical structure to physiochemical properties. The presence of oxygenated groups such as hydroxyl and epoxy on the basal plane and carboxyls groups at the edges has its own advantages and disadvantages (Bagri et al., 2010). On one hand, the oxygen-containing groups are really useful to develop the chemical and electrochemical biosensors which promote to the attachment of biological recognition element and ease for surface functionalization. On the other hand, the oxygenated groups also limit the electrical conductivity due to its insulating nature compared to pristine graphene. The level of insulation of GO is highly dependent on the oxidation methods and the degree of oxidation (Wilson et al., 2009). GO exhibits an outstanding and unique characteristics such as exhibits strong hydrophilic traits which give a better dispersibility in many solvents, photoluminescence, an excellent biocompatible material that enhances electrochemical activity and accommodate electron transfers in biomolecules (Chen et al., 2012; Choi et al., 2017). It is worth to mention that the above GO characteristics are based on GO that has been produced via Hummer methods. For more information on the chemistry of GO, interested readers are directed to the critically reviewed literature elsewhere (Dreyer, 2010; Eigler and Hirsch, 2014).

Reduced graphene oxide (rGO) has been introduced to mitigate the known fact of GO that it suffers from electrical conductivity (insulating behaviour) because of the high degree of oxygenated groups. Thus, various approaches have been employed to reduce the oxygen-containing groups by chemically, thermally, hydrothermally, electrochemically to photocatalytic treatment, to name a few (Lightcap et al., 2010). In general, rGO is a monolayer (2D) composed of carbon atoms where a large number of oxygenated groups in it have been removed. After a reduction process, rGO shows an improvement in electrical conductivity although there are some remaining oxygen groups, which are still useful in developing biosensors (Gilje et al., 2007). Further removal of oxygenated groups from rGO can lead to achieving a pristine graphene layer. The electrical conductivity of rGO is highly dependent on the reduction methods and the sample preparation procedures (Khan et al., 2017). Apart from that, the optical properties and the hydrophobic traits (chemical character) of rGO also can be tuned thru the reduction methods (Yang et al., 2009). Other characteristics of rGO such as capable for catalytic activities (Lightcap et al., 2010), exhibit strong antibacterial activity (Liu et al., 2011b), enhanced microwave absorption (Wang et al., 2011) and increase in capacitance (Chen et al., 2011b). Besides that, the reduction of GO sheets in water with hydrazine resulting graphitic characteristics with randomly aggregated, thin and crumpled sheets that are comparable to those of pristine graphite (Stankovich et al., 2007). To give a quick idea about the values of remarkable characteristics of graphene-based materials for the aforementioned electronic spectra, physical and mechanical are shown in Table 1.

3. Graphene-based materials preparation strategies

There are various strategies that have been reported over the past decade to synthesis graphene and its derivatives (GO and rGO). To make it simple and clear, the synthesis techniques to produce single or few layers graphene which exist up to date can be categorised into four main strategies, methodologically known as (1) isolation (Bonanni et al., 2012) (mechanically or chemically exfoliations of graphite), (2) epitaxial growth (Bonanni et al., 2012) (thermally by CVD protocols), (3) unzipping carbon nanotubes (CNTs) (Wei and Liu, 2010), (4) reduction methods (by chemically (Xu et al., 2015) thermally (Luo et al., 2011), solvothermal (Luo et al., 2011), electrochemically (Yang et al., 2011) photocatalytically (Tan et al., 2017), microwave (Voiry et al., 2016) or voltage induce (Faucett et al., 2017)) as shown in Fig. 2. Each strategy mentioned above has their advantages and disadvantages. For instance, mechanical isolation from the bulk graphite could produce a high quality of graphene sheet but the method is only suitable for laboratories research and is not practical for a large scale production because the probability of finding individual graphene sheet is often very low. The mechanical exfoliation usually results in graphene sheet with undesirable sizes, shapes and layers (Wei and Liu, 2010). This method could only produce a sheet with lateral dimension up to several hundreds of micronmeters (Huang et al., 2015). Nevertheless, the isolation by chemical approaches has paved a promising path to produce graphene because of facile technique, inexpensive and also suitable for a large scale production even though it produces some defects and functional groups (Loryuenyong et al., 2013). Other strategies, such as epitaxial growth and unzipping of carbon nanotubes requires the use of expensive gaseous, high vacuum condition, high temperature, intricate procedures as well as the need for highly controlled microfabrication environment which resulting in low yield too, besides the uniformity in growth and to obtain the desired sizes remains as a challenge (Bonanni et al., 2012; Compton and Nguyen, 2010).

Table 1
The characteristics of graphene-based materials - a comparison.

Properties	Graphene	Graphene Oxide	Reduced Graphene Oxide
Surface area *Theoretical	*2630 m^2 g^{-1} (Mao et al., 2013; Chen et al., 2012)	736.6 m^2 g^{-1} (Montes-Navajas et al., 2013)	466 – 758 m^2 g^{-1} (Stankovich et al., 2007; Khan et al., 2015)
Electron mobility at room temperature	~200,000–250,000 cm^2 V^{-1} s^{-1} (Mao et al., 2013; Singh et al., 2011)	0.1–10 cm^2 V^{-1} s^{-1} (Ding et al., 2015)	2–200 cm^2 V^{-1} s^{-1} (Gómez-Navarro et al., 2007)
Visible light absorption	~ 2.3% (Mao et al., 2013)	~ 25% (Goumri et al., 2016)	~ 20% (Goumri et al., 2016)
Thermal conductivity	~ 5000 W m^{-1} K^{-1} (Mao et al., 2013; Singh et al., 2011)	0.5–18 W m^{-1} K^{-1} (Renteria et al., 2015; Mahanta and Abramson, 2012)	1390–2275 W m^{-1} K^{-1} (Kumar et al., 2015a, 2015b; Mahanta and Abramson, 2012)
Young's modulus	~ 1–1.1 TPa (Mao et al., 2013; Singh et al., 2011)	207.6 ± 23.4 GPa (Benchirouf et al., 2016)	6.3 GPa (Kumar et al., 2015a)
Carbon-carbon bond length	0.142 nm (Singh et al., 2011; Castro Neto et al., 2009)	–	–
Thickness	~ 0.4 nm (Novoselov et al., 2004b)	~0.44 – 1 nm (Chen et al., 2012; Akhavan, 2010)	~ 0.9 nm (Khan et al., 2015)
Interlayer distance	~ 0.335 nm (Novoselov et al., 2004b)	~0.61 – 1.2 nm (Stankovich et al., 2007; Fan et al., 2010)	~0.375–0.77 nm (Fan et al., 2010; Chen et al., 2011b; Toan et al., 2016)
Specific capacitance *(*Varies based on cyclic voltammetry)*	550 F g^{-1} (Zhao et al., 2017)	215–255 F g^{-1} (Kasinath Ojha and Biomass, 2017; Rani et al., 2016)	210–425 F g^{-1} (Chen et al., 2011b; Zhao et al., 2017; Ke et al., 2014)
Electrical conductivity *(*varies based on reduction technique)*	~ 6×10^{8} S m^{-1} (Yun et al., 2016; Khan et al., 2015)	5.7×10^{-6} S m^{-1} (Chen et al., 2011b)	10^{2}–10^{5} S m^{-1} (Benchirouf et al., 2016; Chen et al., 2010; Goumri et al., 2016)
Sheet resistance	200 Ω sq^{-1} (De and Coleman, 2010)	~10^{10}–10^{12} Ω sq^{-1} (Gilje et al., 2007; Lee et al., 2016)	~10^{2}–10^{6} Ω s^{-1} (Gilje et al., 2007; Goumri et al., 2016)
Dispersibility in water	Hydrophobic (Liu et al., 2011a)	High (Akkarachanchainon et al., 2017)	Less (Casero et al., 2012)

Note: *Remark.

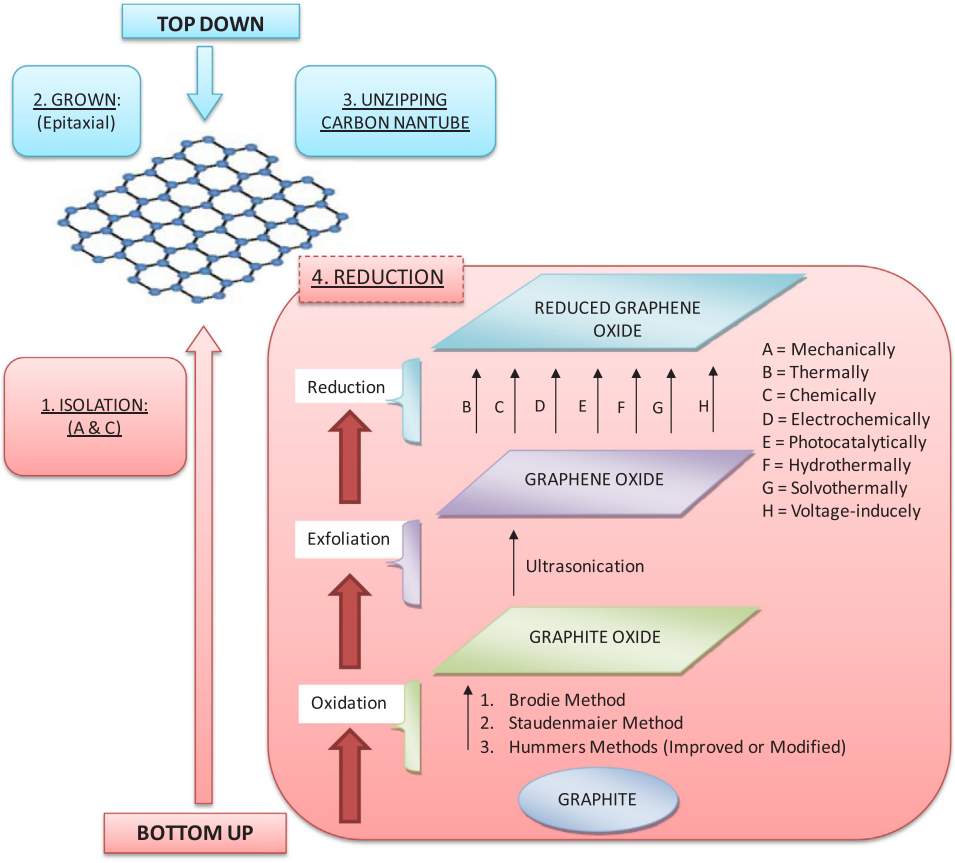

Fig. 2. Graphene, GO and rGO synthesis strategies.

Table 2
Oxidation methods to produce graphite oxide.

	Brodie	*Staudenmaier*	*Hummers*	*Modified Hummers*	Improved Hummers	Modified Hummers
Year	*1859*	*1898*	*1958*	*2004*	2010 (Marcano et al., 2010)	2017 (Muzyka et al., 2017)
Oxidants	*$KClO_3$, HNO_3*	*$KClO_3$ (or $NaClO_3$), HNO_3, H_2SO_4*	*$NaNO_3$, $KMnO_4$, H_2SO_4*	*$NaNO_3$, $KMnO_4$, H_2SO_4*	Graphite (3 g) $KMnO_4$ (18 g), H_2SO_4:H_3PO_4 (360:40 mL)	Graphite (1 g) $NaNO_3$ (3 g); $KMnO_4$ (3 g), H_2SO_4 (30 mL);
C:O ratio	*2.16*	*N/A*	*2.25*	*1.8*	Oxidized carbon, 69%	1.35
	2.28	*1.85*	*2.17*			
Reaction time	*3–4 days*	*1–2 days*	*≈ 2 h*	*≈ 5 days*	~ 12 h	< 3 h
	10 h	*10 days*	*9 − 10 h*			
Intersheet spacing [Å]	*5.95*	*6.23*	*6.67*	*8.3*	~9.5	~7.8

Note: *Italic letters in* Table 2 are the adaptation from the reference (Compton and Nguyen, 2010).

Reduction of GO has received a large attention from researches and industrialist recently to produce graphene-like material (e.g. rGO) because the reduction process is less complicate, consume fewer cost, can produce the bulk amount of graphene-like sheets, highly processable and easy to transfer onto substrates compared to other aforementioned methods. The rGO exhibits a very good balance of electronic properties between GO and pristine graphene which is highly suitable for biosensing applications. The electrical conductivity of rGO is enhanced compared to GO and the remaining functional groups in rGO are advantageous for biosensing applications compared to the pristine graphene. Briefly, there are three main steps to synthesis rGO: (1) incept with oxidation process, (2) exfoliation and (3) reduction process (Fig. 2). The modified Hummers method is widely accepted for the oxidation process to date. This is due to the reaction time where it takes only few hours (< 3 h) when compared to the other oxidation methods that required up to 12 h or several days (Table 2). Next, the exfoliation process is carried out using ultrasonication technique and then followed by reduction process (Niu et al., 2016; Shao et al., 2010). The fundamental information on reduction methods can be found elsewhere (Pei and Cheng, 2012). In addition, the exfoliation and the reduction processes can be carried out simultaneously (Benchirouf et al., 2016; Abdolhosseinzadeh et al., 2015). The simultaneous process can significantly enhance the yields of few-layer of rGO (Abdolhosseinzadeh et al., 2015). The entire scheme of synthesis can be called as 'bottom-up approach' when one is using graphite as a starting material to synthesis graphene (referring to the end-material) (Stankovich et al., 2006). However, the same scheme could also be called 'top-down approach' (Cheng et al., 2017; Xu et al., 2017). These discrepancies in referring are due to either one is referring to the end-material (graphene) or the processes itself.

4. Monitoring noncommunicable diseases via graphene-based electrochemical biosensors

A biosensor is an integrated device that contains two main components namely a biological recognition element (bio-receptor) and a transducer (electrode) with an electronic reader to sense specific biomolecule (analyte/biomarker) that should operate at high sensitivity and specificity. Choosing a right bio-receptor for a sensor will determine the degree of a high specificity and leads towards an accurate detection. The function of a transducer is to transfer the non-electrical signal (chemical event) to an electrical signal which provides bi-directional communication during the analyte-bioreceptor-electrode interaction. The physical transducers may vary from spectroscopic, electrochemical, piezoelectric, thermal and surface acoustic wave (Gerard et al., 2002). The output signal from a transducer is quantifiable which will give a cue to an observer about the interaction event.

An 'electrochemical biosensor' is a self-contained integrated device which is capable of providing a specific quantitative or semi-quantitative analytical information using a bio-receptor retained in direct spatial contact and it can be classified based on the transduction modes (Thevenot et al., 2001). The transduction mode is a type of measurement for the electrochemical biosensor and it could be based on potentiometric, amperometric, conductometric, impedimetric or field effects transistor (Labib et al., 2016). Each type of measurements has a specific role, for instance, potentiometric is based on potential difference measurement, amperometric is based on current measurement from the electrochemical redox activity, impedimetric is based on impedance measurement of analyte/target binding event, conductometric is based on based on current conduction measurement during bio-recognition event and the field effects transistor operates based on carrier mobility between source and drain due to electric field effect controls from biasing gate terminal (Luo et al., 2013; Paper, 2008). The integration of graphene-based materials with transducers have shown a remarkable improvement in physicochemical properties such as it enhances electrical conductivity, electron transfer rate and electro-active surface area to volume ratio owing to their ultra-thin 2D characteristic, which provide an important solution for higher sensing sensitivity (Dong et al., 2017). The high surface area of graphene ≈ 2630 $m^2 g^{-1}$ (see Table 1) extremely increases biosensor's sensing areas, analytes loading and their 2D nanostructure flat surface becomes ultra sensitive to any changes on its surface which is important to capture a biological event at nano-scale environments (Wang et al., 2016b). The technology to integrate 2D nanomaterials with transducers have brought a great opportunity in medical fields for disease detection because of their end-product exhibits a high selectivity and sensitivity to detect a variety of biological analytes (Yang et al., 2015). The analytical summary of graphene-based materials that bridges transducers for heart disease, lung cancer, asthma and diabetes detection in term of the target molecule, immobilization matrixes, deposition technique, electrochemical principle as well as their performances are shown in Table 3. Further elucidation of each disease and the development of transducers using graphene-based materials as well as their performance can be found below sub-sections.

In electrochemical sensing, the graphene-based transducers have been demonstrated on various device structure configuration such as glassy carbon electrode (GCE) (Wang et al., 2014; Pan et al., 2015), the screen-printed electrode (SPE) (Martín et al., 2015; Yang et al., 2013), interdigitated electrode (IDE) (Tuteja et al., 2015, 2014), field effect transistor (FET) (Mukherjee et al., 2015; Farid et al., 2015) and paper-based electrode (PBE) (Sun et al., 2015; Ruecha et al., 2014) (Fig. 3). The concept and the working principle can be found in other literatures (Hayat and Marty, 2014; Zhan et al., 2014; Desmet et al., 2016) and it is beyond the scope of this paper. GCE modified with graphene-based materials have been used very widely in electrochemical biosensors to detect various analytes (see Table 3). Such a modification have shown an excellent conductivity, promotes sensitivity, increases the electrochemical active sites, shows anti-interference ability, promotes stability, shows reproducibility and enhances an electro-catalytic activity (Wang et al., 2014; Raj and John, 2013; Chen et al., 2011a). This phenomenon could be due to the adhesion/bonding of graphene-based materials onto carbon electrode is quite straightforward and achievable compared to other types of electrode materials with/without the use of a linker. Meanwhile, screen printed electrodes offer numerous benefits

Table 3
An analytical summary of graphene-based materials bridges transducers for NCDs.

Acute myocardial infarction detection (Graphene, GO, rGO based electrochemical Immunosensors)

Target molecule	Device Structure	Immobilization step	Deposition technique	Linear range	LOD	Sensitivity	Electrochemical principle	Sample	Reference
Troponin-I	Glassy Carbon Electrode	GCE/ G-MWCNT film/ 1-pyrene butyric acid N-hydroxysuccinimide ester (PyBuNHS) in DMF/ anti-cTnI in PBS/BSA	Scoop and transfer	0.001–10 ng/mL	0.94 pg/mL	63.5 Ω cm^2 per decade	cyclic voltammetry and Impedimetric	human serum	(Singal et al., 2015)
Troponin-I	Interdigitated Electrode	Si/SiO2/titanium/ Au/graphene in n-methyl pyrrolidone / 2-ABA/ anti-cTnI in 2-morpholino ethanesulfonic acid (MES buffer)/ sodium cyanoborohydride/BSA	Drop casting and annealed for 1 h a t 120 °C	0.01–1 ng/mL	10 pg/mL	–	I–V characteristic and linear sweep voltammetry	commercial analyte, cTnl	(Tuteja et al., 2015)
Troponin-I	Glassy Carbon Electrode	GCE/ PrGO in dimethyl formamide (DMF) /anti-cTnI in PBS	Drop casting and incubated for 1 h at 80 °C.	0.1–10 ng/mL	70 pg/mL	–	Impedimetric and cyclic voltammograms	commercial analyte, cTnl and human serum	(Habib et al., 2016)
Troponin-I	3-Electrode System	Au/ PDDA-ethanol/PDDA-rGO/ anti-cTnl/ glycine	Drop casting and dried for 20 min at 50 °C	0.1–10 ng/mL	24 pg/mL	–	cyclic voltammetry and amperometric	commercial analyte, cTnl	(Li et al., 2017b)
Troponin-I	Screen Printed Electrode	SPE-Au/4-ATP solution/(GQD in EDC, NHS and PBS) /PAMAM/ (anti-cTnI in EDC, NHS and PBS)	Drop casting	–	20 fg/mL	109.23 μA cm^{-2} $μg^{-1}$	cyclic voltammetry and differential pulse voltammetry	commercial analyte, cTnl and human serum	(Bhatnagar et al., 2017)

Lung cancer detection (Graphene, GO, rGO based electrochemical Immunosensors)

Target molecule	Device Structure	Immobilization step	Deposition Technique	Detection/ Linear range	LOD	Sensitivity	Electrochemical principle	Sample	Reference
Carcinoembryonic antigen (CEA)	Paper Electrode	Paper/ (PEDOT: PSS in ethylene glycol)/(rGO in PEDOT: PSS)/EG/anti-CEA	Dip coating	2–8 ng/mL	–	25.8 μA ng^{-1}mL cm^{-2}	Impedimetric, chronoamperometric	human serum	(Kumar et al., 2015b)
Carcinoembryonic antigen (CEA)	Glassy Carbon Electrode	GCE/ (PPYGR)/ AuNPs /anti-CEA/ BSA	Drop casting, dried for 20 min under infrared lamp	0.1–1000 ng/mL	0.06 ng/mL	–	Impedimetric and cyclic voltammetry	commercial analyte, CEA	(Li et al., 2017a)
Carcinoembryonic antigen (CEA)	Glassy Carbon Electrode	GCE/(AgPt NRs-rGO)/ anti-CEA/ PBS/BSA	Drop casting, and dried in air	5 fg/ mL - 50 ng/ mL	1.43 fg/mL	–	Impedimetric, cyclic voltammetry	–	(Wang et al., 2018)
Human telomerase reverse transcriptase (hTERT),	–	Glass /ITO/GO/(EDC + NHS)/anti-hTERT/PBS/ ethanolamine	Spin coating	100 fg/mL - 10 ng/mL	100 fg/mL	–	Differential pulse voltammetry	Human sputum	(Choudhary et al., 2013)

Asthma detection (rGO based non-enzymatic electrochemical sensor)

Target molecule	Device Structure	Immobilization step	Deposition technique	Detection/Linear range	LOD	Sensitivity	Electrochemical Principle	Sample/analyte	Reference
Nitrite	Screen Printed electrode	Glass/SPE microchip/rGO	Drop casting, dried at room temp.	20–100 μM	830 nM	0.21 μA $μM^{-1}$ cm^{-2}	cyclic voltammetry, square wave voltammetry	exhaled breath condensate (EBC)	(Gholizadeh et al., 2017)

Diabetes detection (rGO based non-enzymatic electrochemical biosensors)

Target molecule	Device Structure	Electrode modification	Deposition Technique	Detection//Linear range	LOD	Sensitivity (mA mM^{-1} cm^{-2})	Electrochemical principle	Sample	Reference
Glucose	Glassy Carbon Electrode	GCE/NiCo2O4/N-rGO/IL	Drop casting, dried at room temperature	0.001–4.555 Mm at working potential of + 0.5 V.	0.18 μM	3.76	cyclic voltammograms	real human blood serum	(Rao et al., 2017)
Glucose	Glassy Carbon Electrode	GCE/$(Ni(OH)_2$/N-rGO	Electrodeposition (0 ~ −1.1 V vs. Ag/AgCl, 20 scans, 100 mV s − 1)	0. 5 μM - 0.0115 mM,at an applied potential of + 0.45 V	0.12 μM	3.214	cyclic voltammetry and amperometry	real human blood serum	(Zhang et al., 2017)
Glucose	Glassy Carbon Electrode	GCE/Cu_{53} @Ni_{47} CSNPs/rGO	Coating, dried in air	0.001–4.1 mM), At an applied potential of + 0.575 V	0.5 μM	0.780	cyclic voltammetry and amperometry	purchased glucose	(Wu et al., 2017)

(*continued on next page*)

Table 3 (*continued*)

	Diabetes detection (rGO based non-enzymatic electrochemical biosensors)								
Target molecule	**Device Structure**	**Electrode modification**	**Deposition Technique**	**Detection//Linear range**	**LOD**	**Sensitivity (mA mM^{-1} cm^{-2})**	**Electrochemical principle**	**Sample**	**Reference**
Glucose	Glassy Carbon Electrode	GCE/Ni-MoS_2/rGO	Drop casting, dried in air	0.005–8.2 mM At an applied potential of + 0.575 V 0.55	2.7 μM	0.2566	cyclic voltammetry and amperometric	purchased glucose	(Geng et al., 2017)

such as disposability, portability, low fabrication cost, reproducibility and easy for mass production when compared to traditional electrodes. The graphene inks/paste composition plays a crucial role in defining the printed electrode characteristics whether to have a slow or fast in electron transfer for electrochemical response (Randviir et al., 2014; Karuwan et al., 2017). Nevertheless, IDE is more facile transducer than any kind of transducers because it only uses two electrode systems, eliminates the reference electrode compared to the three electrodes systems (GCE and SPE). One material is sufficient to fabricate the anodic and cathodic electrodes of IDE thus facile, inexpensive and favourable for mass production (Ohno et al., 2013). IDE modified with graphene-based materials has promoted for rapid detection of analytes hence promises for fast diagnosis. FET modified with graphene is a versatile structure and has been reported in various applications ranging from biological (Kakatkar et al., 2015), chemical (Lee et al., 2016a), gas (Pearce et al., 2011) and mechanical (Trung et al., 2013) for sensors development. The FET modified with graphene-based materials especially in electrochemical sensing have shown the sensor exhibits characteristics like ultrasensitive, high specificity, rapid response, enhanced stability and applicable for real-time monitoring indicating its potentiality for disease diagnostics (Cai et al., 2014, 2015; Park et al., 2014; You and Pak, 2014). The paper-based electrodes with graphene modification are suitable to develop bendable, disposable and lightweight electrochemical sensors which involve a relatively simple fabrication process and fewer cost (Lee et al., 2017). A direct writing method using a ball pen and custom made conductive ink explains its simplicity of fabrication process compared to other types of electrode's fabrication. The paper-based electrodes have shown a good selectivity in detecting hydrogen peroxide in wastewater (Ghosale et al., 2017). Apart from that, it has shown a simultaneous detection capability towards of alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) (cancer markers) with high sensitivity and specificity in real human serum (Li et al., 2014). In addition, we note that gold is the most widely adopted material to fabricate most of the electrodes because the material exhibits a good electron transfer and good in electrical conductivity compared to other conductive materials. In general, the advantages of the aforementioned device structures are label-free, handheld device, cheap, smaller in size, showing high performance and hold a great promise towards the point-of-care testing and analytical application.

4.1. Acute myocardial infarction detection

Cardiovascular disease (CVD) is one of the instances lives threatening disease that can cause a sudden death without any major symptoms for some patients and it is the top first ranked as the leading cause of death of all NCDs. The abnormalities of blood flow in arteries due to plaques build-up in blood vessels are the major causes of CVD. This blockage condition is commonly called as 'heart attack' or in the clinical term as acute myocardial infarction (AMI). An early stage detection or point-of-care testing (POCT) plays a vital role to prevent this fatal disease (Negahdary et al., 2017; Fathil et al., 2015). The gold standard biomarker for AMI detection is cardiac troponin I (cTnI) (molecular weight is about ~29 kDa) (Singal et al., 2014) because the biomarker is released from myocardial cells upon cardiac injury and has higher specificity compared to other biomarkers such as creatin kinase-MB isoenzyme and myoglobin (Mgb) (Tuteja et al., 2014; Wu et al., 2017). The normal concentrations level of cTnI for healthy human are normally lower than 0.4 ng/mL (Wang et al., 2016a). Technically, upon minor cardiac injury the cTnI biomarker will be released in the bloodstream and the concentration level in human blood serum increases up to 0.2–1.4 ng/mL within 3–6 h. Further injuries can increase up to a level of 100 ng/mL and the elevation in the blood can remain up to 5–9 days (Tuteja et al., 2014; Singal et al., 2015; Kumar et al., 2017).

Various diagnosis methods have been reported over the past years to capture the cTnI biomarker which known as colorimetric fluorescence,

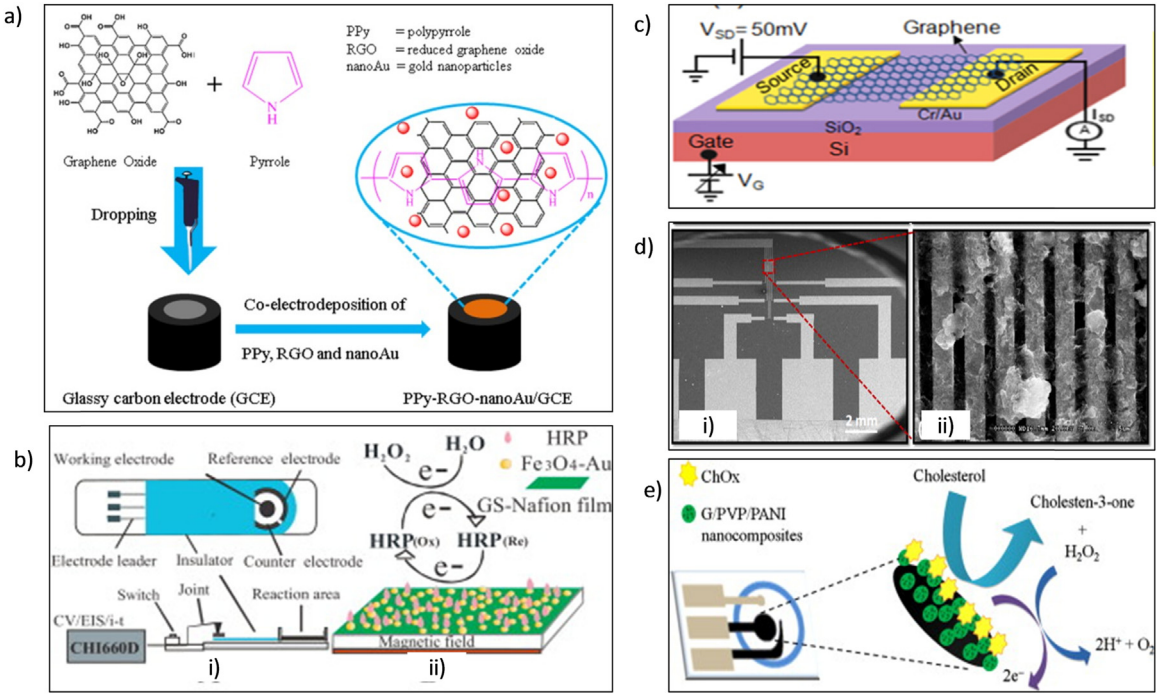

Fig. 3. (a) Polypyrrole-reduced graphene oxide-gold nanoparticles (PPy-RGO-AuNPs) biocomposite modified onto glassy carbon electrode (GCE) for hydrogen peroxide detection. Reproduced with permission from (Wu et al., 2016) Copyright 2016 MDPI. (b) Schematic diagram of (i) the screen-printed carbon electrode (SPE) sensor apparatus and (ii) the surface of graphene sheets (GS) nafion film modified working electrode for hydrogen peroxide detection. Reproduced with permission from (Xin et al., 2013) Copyright 2013 Elsevier B.V. (c) Graphene on field effect transistor (FET) device structure and the circuit diagram corresponding to the measurement of I_{SD} (V_G). Reproduced with permission from (Kakatkar et al., 2015) Copyright 2015 IOP Publishing. (d) FE-SEM images (i and ii) of the amine functionalized graphene (f-GN) on interdigitated electrodes (IDEs). Reproduced with permission from (Tuteja et al., 2015) Copyright 2015 Elsevier B.V. (e) Schematic diagram of enzymatic reaction between cholesterol and cholesterol oxidase (ChOx) on graphene/PVP/PANI modified paper-based electrode (PBE). Reproduced with permission from (Ruecha et al., 2014) Copyright 2014 Elsevier B.V.

electrochemical, surface plasmon resonance and paramagnetic methods (Bhatnagar et al., 2016). However, electrochemical biosensors are considered as simple, label-free, rapid in detection, cheap as well as miniaturized in which it has the ability to detect the biomarker at a very low concentration with higher specificity and sensitivity compared to other aforementioned methods (Negahdary et al., 2017; Xiong et al., 2017). The electrochemical biosensor's sensitivity and selectivity can be further improved by modifying the electrode structure, material, dimension, immobilization methods, or without immobilization method ('which will serve as a novel method'), fabrication procedure or by chemical usage (Abdorahim et al., 2016). Thus, in this review specific attention is given on recently developed electrochemical biosensors that utilize graphene-based materials to capture cTnI. Clearly, the detection limits of cTnI have reached up to pg/mL and even up to fg/mL when using graphene-based materials (Table 3). Various electrochemical transduction modes have been demonstrated in detecting cTnI as shown in Fig. 4. For example, Tuteja et al. (2015) reported a simple approach to functionalize graphene by electrochemically with 2-aminobenzyl amine (2-ABA) to develop an immunosensor for cTnI detection. They used a silicon substrate to construct gold IDE and followed by graphene deposition by drop casting. After that, 2-ABA was deposited electrochemically onto the graphene for the functionalization followed by anti-cTnI immobilization step which takes about 3 h to complete at room temperature. They found the I-V response for the immunosensor has a wider linear range for antigen detection (0.01–1 ng/mL) with the detection limit of 10 pg/mL (Fig. 4a). They also tested the sensor with real human serum sample and the sensor's performance is almost similar compared to synthetic antigen in buffer media with reaction time is only takes about 10 min. Singal et al. (2015) developed an immunosensor using electroactive graphene-multi walled carbon nanotube (G-MWCNT) hybrid film to construct a bioelectrode for capture cTnI in human serum. The G-MWCNT hybrid film (as a biomolecular immobilization material) was synthesized by chemical vapor deposition (CVD) method and transferred the film onto a GCE by scooping technique. Then, G-MWCNT/GCE was covalently immobilized with human cardiac troponin antibody (anti-cTnI) through bi-linker, 1-pyrene butyric acid N-hydroxysuccinimide ester (PyBuNHS). They reported the sensor exhibits a wide range of 0.001–10 ng/mL of cTnI detection in human serum with a low detection limit of 0.94 pg/mL (Fig. 4b). However, the immobilization procedure rather involves extensive washing steps with the usage of nitrogen gas as a drying agent besides the fact of needing the expensive tools for G-MWCNT synthesization. Habib et al. (2016) fabricated a biosensor by using porous graphene oxide (PrGO) nanostructures onto glassy carbon electrode for the cTnI detection and the graphene oxide have been reduced partially. They reported that the immobilization efficiency is increased due to the employed porosity of rGO nanosheets in which it gives a large surface to volume ratio. The immobilization step is carried out by immersing the electrode in anti-cTnI antibody mixed with 0.1 M phosphate buffer saline (PBS) solution (pH 7.4) containing 0.25 mg of sulfo-NHS and 0.5 mg of EDC for about 3 h performed at room temperature. They used amide covalent bonding technique for the immobilization with a very simple procedure as explained above and found the immunosensor has a detection limit of 70 pg/mL with a linear range of 0.1–10 ng/mL based on calculation (Fig. 4c). They also tested the fabricated immunosensor with real clinical samples and observed the results are in good agreement with standard enzyme-linked fluorescence assay (ELFA) method. Very recently, Li et al. (2017b) have prepared poly-(diallyldimethylammonium chloride) (PDDA) and rGO nanocomposite to construct an electrochemical immunosensor for cTnl detection. They deposited the as-prepared nanocomposite onto the gold electrode. The immobilization steps are carried out by pouring 5 μL of PDDA ethanol solution onto a gold electrode followed by drying it at 45 °C for 10 min; which results in a uniform polymer layer. Then the polymer layer was

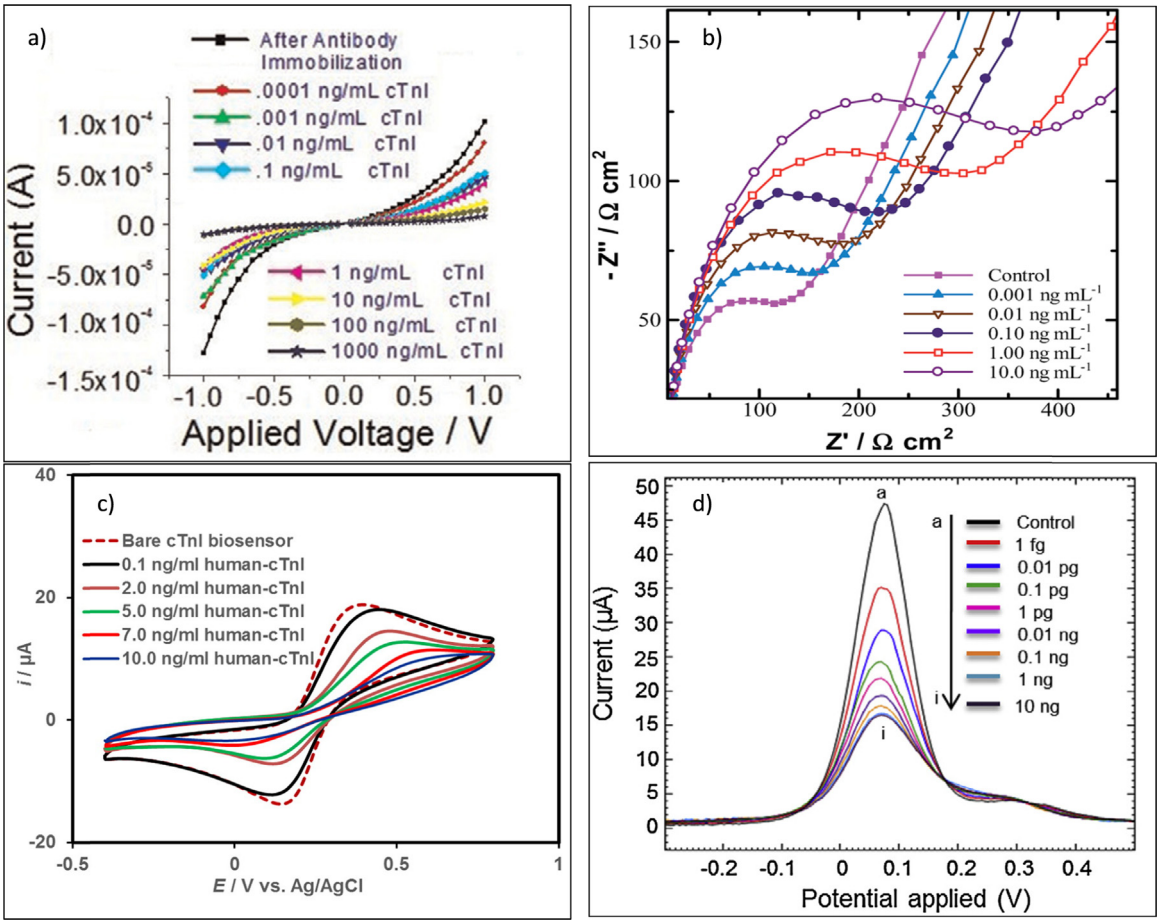

Fig. 4. a) I–V response of 2-aminobenzyl amine (2-ABA) functionalised graphene on interdigitated electrode (IDE) for cTnI detection with different concentrations (0.01–1 ng/mL) of antigen cTnI. Reproduced with permission from (Tuteja et al., 2015) Copyright 2015 Elsevier B.V. b) The impedance response of graphene-multi walled carbon nanotube (G-MWCNT) hybrid film on glassy carbon electrode (GCE) before (control) and after incubation with different concentrations (0.001–10 ng/mL) of cTnI-spiked human serum. Reproduced with permission from (Singal et al., 2015) Copyright 2015 The Royal Society of Chemistry. c) The cyclic voltammograms response (CV) of porous graphene oxide (PrGO) nanostructures onto glassy carbon electrode (GCE) for detection of human-cTnI of various concentration (0.1–10 ng/mL). Reproduced with permission from (Habib et al., 2016) Copyright 2016 Elsevier B.V. d) The differential pulse voltammetry (DPV) of graphene quantum dots GQD modified with polyamidoamine (PAMAM) dendrimer onto screen-printed electrode (SPE) for ultra-low detection limit (20 fg/mL) with wider range of 10^{-6}–10 ng/6 µL of cTnI in human blood serum(a to i). Reproduced with permission from (Bhatnagar et al., 2017) Copyright 2017 Elsevier B.V.

modified with the as-prepared 5 µL of PDDA-rGO composite suspension onto the polymer and then dried at 50 °C for 20 min followed by washing the electrode to remove the unbound PDDA-rGO. Finally, 5 µL anti-cTnI solution with the concentration of 1 µg/mL is pipetted and followed by incubation at 4 °C for 60 min. They found the developed immunosensor shows an excellent performance in detecting cTnI with a low detection limit of 24 pg/mL and wider linear response in the range of 0.1–10 ng/mL. Bhatnagar et al. (2017) developed an ultrasensitive immunosensor by embedding polyamidoamine (PAMAM) dendrimer on graphene quantum dots (GQD) deposited onto screen-printed gold electrode for rapid detection of cTnI. The hybridization between GQD and PAMAM dendrimer provides an ultrahigh surface area for the antibody immobilization. The immobilization step is carried out by functionalizing the Au electrode with 4-aminothiophenol (ATP) of amino groups followed by depositing the GQD solution that mixed with carbodiimide (EDC) and N-hydroxysuccinimide (NHS) solution to create carboxyl functionalities group and subsequently with PAMAM deposition. For the final step of immobilization, a mixture of anti-cTnI antibody, EDC and NHS was deposited on the Au/GQD/PAMAM working electrode for 3 h at room temperature. They reported the developed immunosensor exhibits characteristics such as can detect cTnI biomarker in just 10 min with very high electrode sensitivity (109.23 µA cm^{-2} $µg^{-1}$), ultra-low detection limit (20 fg/mL) with wider range of 10^{-6}–10 ng/6 µL of cTnI in human blood serum (Fig. 4d) and specific only to the target antigen cTnI.

A patient with type-2 diabetes mellitus is potential for coronary risk where the patient will have a high risk of 2–4 fold to increase the cardiovascular disease depending upon the disease duration, severity and concomitant risk factors. Recently, Leeuw et al. (2016) evaluated 23 novel biomarkers related to cardiovascular disease to predict the cardiovascular risk in 1290 patients with type-2 diabetes mellitus by using Cox proportional hazards model. They reported that the Natriuretic peptide, osteopontin and Matrix Metalloproteinase biomarkers and their combination are the only biomarkers significantly associated with risk of the cardiovascular event which resulted in the largest improvement to predict the risk beyond traditional risk factors compared to other 20 biomarkers. Interested readers can refer recently published review articles in electrochemical sensing of cardiac troponin that uses other nanomaterials apart from graphene-based materials (Abdorahim et al., 2016; Sheng et al., 2017; Fathil et al., 2016).

4.2. Lung cancer detection

According to the world cancer report by WHO, in 2012, the estimated numbers of new cases for all types of cancer that affects all ages including male and female around the globe were reported reached

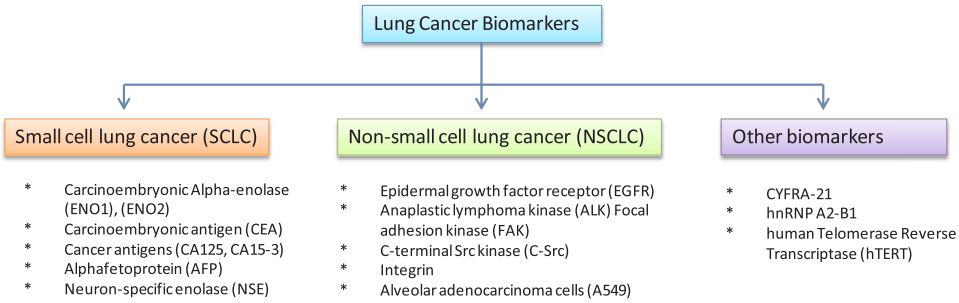

Fig. 5. Highly related biomarkers for lung cancer detection.

more than 14 million and 8 million alone for cancer-related deaths. Among all types of new cases, lung cancer is ranked number one with 13% followed by breast cancer with 11.9% of the total new cases (International Agency for Research on Cancer, 2014). Lung cancer is defined as an uncontrollable growth of abnormal cells in one or both lungs. The abnormal growth of cells (dysfunction cells) in the lung will lead to the formation a lump like tissue/mass that generally called as tumor and the cancer cells spreads to other parts of the body is called metastasis. The highly related lung cancer biomarkers are shown in Fig. 5. According to the American Cancer Society, there are two most common types of lung cancer known as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Among both types, NSCLC accounts for approximately 80–85% of the lung malignancies meanwhile SCLC represent about 10–15% malignant (Ho et al., 2010; Zhao et al., 2017). The carcinoembryonic antigen (CEA) is widely accepted as a tumor biomarker and the marker is highly associated with diseases such as lung cancer, ovarian cancer, colon cancer, breast cancer and pancreatic cancer. CEA is a glycoprotein with molecular mass of ~200 kDa and categorised as SCLC (Kumar et al., 2015b; Li et al., 2017a; Wang et al., 2018).

We overview the development of electrochemical sensors based on graphene-based transducers for carcinoembryonic antigen (CEA) detection that associated with lung cancer. Kumar et al. (2015b) developed a flexible electrochemical paper-based biosensor by using poly (3,4 ethylenedioxythiophene): poly(styrenesulfonate) (PEDOT: PSS) and reduced graphene oxide (rGO) composite for CEA detection. They prepared (PEDOT: PSS + ethylene glycol + rGO) aqueous suspension and dipped the Whatman paper into the solution for 1 h and then dried at 100 °C in a hot air oven followed by the treatment with ethylene glycol for 20 min and drying the paper at 100 °C for about 1 h. Finally, they immobilized the CEA antibodies thru physical absorption onto PEDOT: PSS/rGO based electroactive paper. They found the sensor has high sensitivity of 25.8 μA ng^{-1} mL cm^{-2} with a detection range of 2–8 ng/mL. The hybridization between the polymer and rGO enhances the electrical conductivity and improved electrochemical performance as well as signal stability. Recently Li et al. (2017a) developed a label-free impedimetric immunosensor based on a water dispersible graphene/amphiphilic pyrene derivative modified with gold nanoparticles (AuNPs) nanocomposite for sensitive detection of CEA. They presented a strategic to functionalize the graphene through non-covalent attachment by using water-soluble 4-armed poly(ethylene glycol)-NH2 (PEG) and pyrenebutyric acid (PY) to produce graphene/amphiphilic pyrene (PPYGR) nanocomposite. The as-prepared PPYGR nanocomposite shows an improvement in graphene hydrophilicity and loading capacity of AuNPs. This strategic also shows efficiency in immobilizing the CEA antibodies onto the AuNPs/PPYGR nanocomposite. Thus, the monoclonal CEA antibody (anti-CEA) was immobilized onto the AuNPs/PPYGR nanocomposite using drop casts technique and followed by incubation for 12 h at 35 °C as for the immunosensing platform. The as-fabricated sensor exhibits an excellent detection performance with a wider range of response (0.1–1000 ng/mL) to detect CEA with a detection limit of 0.06 ng/mL. Wang et al. (2018) fabricated an electrochemical immunosensor based on bimetallic (AgPt) nanorings modified with rGO forming (AgPt NRs-rGO) nanocomposite for CEA detection. The immobilization step starts with the AgPt NRs-rGO suspension deposition onto glassy carbon electrode using drop a cast technique and followed by drying it in the air. Then, they coated anti-CEA on the electrode surface followed by drying the electrode at 4 °C in the refrigerator. The final step is by washing the electrode with a phosphate buffer solution (PSA) and immersion into the bovine serum album (BSA) solution. The BSA is used as blocking agent molecules to fill undesired spaces where no antibody is occupied. The developed immunosensor shows very good performance for the detection of CEA with a wide linear range of 5 fg/mL - 50 ng/mL, the low detection limit of 1.43 fg/mL, improved stability, enhanced reproducibility and selectivity.

From the aforementioned statistic, lung cancer has the highest mortality rate within all types of NCD cancers. This is because most of the lung cancer cases (about 70%) are detected at advance stage and it can be detected through high-end equipments or invasive procedure like positron-emission tomography (PET) scan, computed tomography (CT) scan, magnetic resonance imaging (MRI), fluorescence bronchoscopy, mediastinoscopy, sputum cytology, needle biopsy (fine needle aspiration), blood tests, pulmonary function tests, immunological methods, however, the survival chances are often too low. Furthermore, these methods are only available at the selected hospital because of the expensiveness and required trained personnel (Choudhary et al., 2013).

A noninvasive method via electrochemical biosensors by using saliva has paved a new opportunity and avenue for the for lung cancer detection. Salivary based biomarker has been considered recently to develop an electrochemical biosensor for lung cancer detection. For example, (Choudhary et al., 2013) for the first time fabricated an ultrasensitive label free electrochemical immunosensor based on graphene oxide (GO) to detect lung cancer based on human telomerase reverse transcriptase (hTERT) biomarker found in spiked sputum samples. They fabricated the sensor by covalently immobilized the rabbit anti-hTERT antibodies onto GO film whereby the GO film was first deposited through spin coats technique onto indium titanium oxide (ITO) electrode coated on a glass substrate. They reported, the as-fabricated immunosensor shows an ultrasensitive and the fast detection response (30 s) for hTERT determination with high specificity and low detection up to 0.01 fg/mL in the wide linear range of 100 fg/mL - 50 ng/mL, suggesting the potential usage in real biological fluid samples. The excellent performance is due to the fast electron transfer and efficient loading of antibodies on large surface area supported by the uniform distribution of GO nanosheets.

4.3. Asthma detection

According to the global status report by WHO on 2018, the respiratory diseases (asthmatic and chronic obstructive pulmonary disease) are in third-ranked behind heart attack and lung cancer nearly 3.8 million deaths alone was estimated on 2016 (World Health Organization, 2018). The asthmatic condition is more prevalence than

the chronic obstructive pulmonary disease (COPD) where 235 million asthmatic cases were estimated compared to COPD with 200 million cases globally on 2013 (Ferkol and Schraufnagel, 2014). The asthmatic condition is a chronic heterogeneous disease that involving the airways in lungs such as bronchial tubes and is usually characterized by the inflammation, swollen and/or muscle tightness in the airways (Corlateanu et al., 2017; Tang et al., 2017). We noted that not much work on non invasive detection method has been done to detect an asthmatic condition. This is due to the lack of gold standard biomarker for this disease. Only very recently and for the first time, Gholizadeh et al. (2017) developed a label-free and non-enzymatic graphene-based electrochemical biosensor to detect nitrite biomarker thru exhaled breath condensate (EBC), a non-invasive method for asthmatic condition detection. They fabricated the biosensor using rGO suspension and screen printed electrode for nitrite detection in exhaled breath condensate sample. They observed the developed sensor showed a sensitivity of 0.21 μA $\mu M^{-1} cm^{-2}$ in the range of 20–100 μM and of 0.1 μA $\mu M^{-1} cm^{-2}$ in the range of 100–1000 μM nitrite concentration with a low detection limit of 830 nM. They also suggested further improvement such as detection limit at a very low concentration level or enhancing sensor sensitivity can be done by utilizing other nanomaterials composite modified electrodes.

The invasive contemporary methods to detect asthmatic condition are thru induced sputum (IS) and bronchoscopic alveolar lavage fluid (BALF). However, exhaled breath condensate (EBC) is a non-invasive, emerging diagnosis strategic to detect chronics respiratory diseases. The technical aspect, limitation and collection procedure of EBC samples can be found in these articles (Carter et al., 2012; Konstantinidi et al., 2015). EBC substance contains various biomarkers that related to pulmonary diseases such as asthma, chronic obstructive pulmonary disease, chronic bronchitis, bronchiecstasis and cystic fibrosis. Several biomarkers from EBC substance have been identified and reported to have a correlation with an asthmatic condition such as hydrogen peroxide, nitrotyrosine, peroxynitrite, leukotrienes, nitrite, 8-isoprostane, prostaglandin-E2, interleukins and malondialdehyde (Konstantinidi et al., 2015; Mutlu et al., 2001; Bajaj and Ishmael, 2013). Among these biomarkers, hydrogen peroxide is widely researched and many electrochemical sensors have been developed to detect hydrogen peroxide from various samples (eg: extrinsic H_2O_2 (Sophia and Muralidharan, 2015), human urine (Devasenathipathy et al., 2016), humidity (Komkova et al., 2013) and honey (Majidi et al., 2015)) but the hydrogen peroxide detection from EBC sample is not done yet to the best of author's knowledge (2017). Thus, this finding would enlighten research community to develop an electrochemical biosensor to detect hydrogen peroxide from the real EBC substance which has a higher specificity for asthmatic detection. However, Dorp (2012) have developed an electrochemical sensor to show a proof-of-concept for hydrogen peroxide detection in the gaseous phase that mimicking the exhale breath system. The developed system shows achievable detection limits of hydrogen peroxide were in the tens of parts per billion and the system response time was 5 min. Similarly, Komkova et al. (2013) developed electroanalytical system using Prussian Blue with Salt-Bridged electrodes for hydrogen peroxide detection in wet air (humidity) that mimicking exhaled human breath condition. For other biomarkers detection, very recently Peel et al. (2017) had assessed the use of 8-isoprostane from EBC as a biomarker in adult asthma. From their assessment they concluded the clinical value of 8-isoprostane from EBC as a quantitative assessment of oxidative stress for asthma remains unclear due to variability in results and methodological heterogeneity. Apart from that, the nitrates and nitrites can be detected in EBC and the levels of nitric oxide (NO) will increase during inflammatory conditions. NO and their related molecules are may be useful in monitoring various inflammatory pathologies of lower airways (Bajaj and Ishmael, 2013). More recently (Tang et al., 2017) a team from 'The First Affiliated Hospital of Huzhou University Zhejiang, China' have conducted an observation to test on NO content level for ICU warded patients (102 adults) with severe acute respiratory distress syndrome (ARDS). They used the commercially available kit to test NO concentration in EBC. The normal level of nitric oxide in EBC for a healthy person is recorded and about 15.65 ± 4.43 μmol/L compared to ARDS patients about 47.81 ± 6.05 μmol/L. They concluded measuring NO content in EBC can directly correlate to observe pulmonary hypoxia condition and disease course in ARDS patients. They also suggested the NO element from EBC can work as one index for ARDS detection because the observatory results between EBC and human serum samples show a satisfactory correlation thus can replace the use of human blood serum. Further quantification of NO level in EBC can help to evaluate treatment efficacy and determining better prognosis. Nonetheless, the small number of patients as a test subject would limit for the final conclusion thus a larger cohort of patients indeed required for further evaluation to identify a specific marker for the asthmatic condition.

4.4. Diabetes detection

Diabetes is a chronic disease, a metabolic disorder and a life-threatening condition in this 21st century because the epidemic is not only affecting adults but children too regardless of their gender or age and it becomes one of the major caused of death among the other NCDs (IDF, 2015). For example, in 2017, children (0–19 years) that affected by type 1 diabetes is already more than one million (1,106,500) recorded for the first time with USA and India ranked as the top two countries with 169,900 and 128,500 affected children, respectively. In the same year, the number of people that diagnosed with diabetes worldwide is expected to grow on a daily basis from 425 million to 629 million people by 2045 estimated by International Diabetes Federation (IDF) (IDF, 2017). There are three main types of diabetes namely type 1, type 2 and gestational diabetes. Diabetes is normally diagnosed by monitoring the elevated levels of glucose in blood and this condition occurs when the body is unable to produce/react with insulin hormone (IDF, 2015). The normal range of glucose level in blood is about 3.9–6.2 mM measured on an empty stomach and 3.9–7.8 mM after 2 h of food consumption. Above this range a hyperglycemia condition will be reflected in the blood (Online et al., 2013). The continuous persistence of higher levels of glucose in the blood can lead to other serious life-threatening diseases such as nervous, cerebral, renal, cardiac, ocular, and peripheral vascular diseases and finally death (Abbas and Shin, 2016).

Biosensors can play a significant role in home-healthcare as a medical kit for a regular check-up. Of overall biosensors market, about 85% (~US$ 8.5 billion) belongs to glucose sensors (Vashist et al., 2011). There are two types of glucose sensors known as enzymatic and non-enzymatic. The enzymatic glucose sensor is the first commercially successful biosensor available in the market for the past 50 years because of their good selectivity and high sensitivity. The sensor is developed based on immobilization of glucose oxidase enzyme onto an electrode surface (Zheng et al., 2015; Labib et al., 2016). This sensor has several disadvantages such as lack of long-term stability, involving multi-step in immobilization procedures, need costly enzyme and influenced by external environment (temperature and humidity). For this reason, a non-enzymatic glucose sensor has attracted a considerable amount of interest in recent years due to low cost in fabrication, prompt response, high stability and capable for a low level of detection. Furthermore, the advents of nanotechnology and nanomaterials have offered new opportunities to construct non-enzymatic glucose sensors (Geng et al., 2017; Zhu et al., 2016; Lu et al., 2014). There are plenty of studies have been reported in the past on developing highly sensitive non-enzymatic biosensors using graphene-based materials. For example, recently Rao et al. (2017) studied the biosensing properties of $NiCo_2O_4$/nitrogen-doped rGO/ionic liquid ($NiCo_2O_4$/N-rGO/IL) nanocomposite towards glucose detection on a GCE without any enzymes. They found the $NiCo_2O_4$/N-rGO/IL nanocomposite exhibits an excellent electrocatalytic activity towards glucose detection, with a sensitivity of

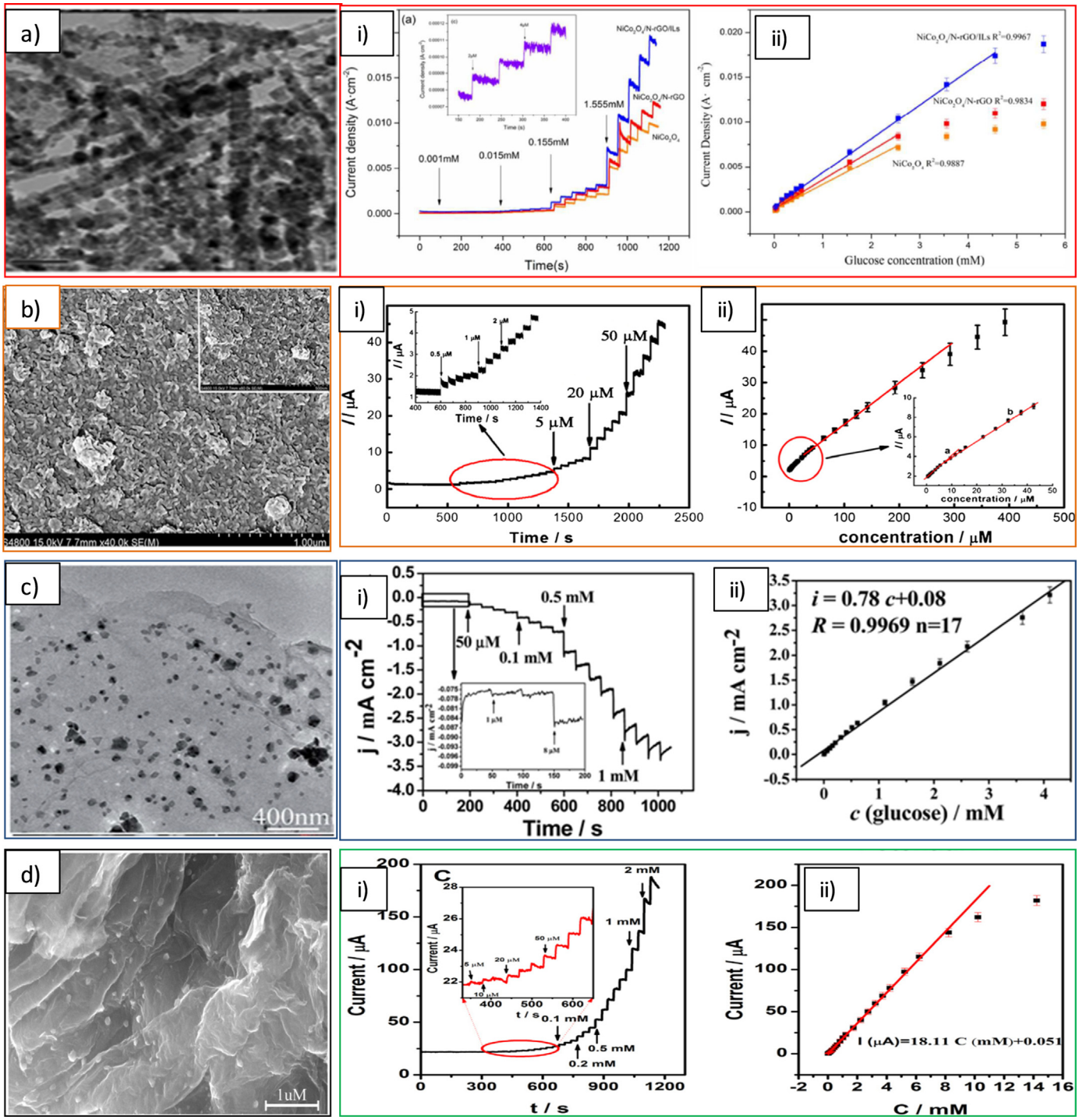

Fig. 6. a)TEM image of $NiCo_2O_4$/ N-rGO/IL nanocomposite on GCE and (i) Amperometric current response for glucose detection and (ii) corresponding concentration of glucose in 0.1 M KOH. Reproduced with permission from (Rao et al., 2017) Copyright 2017 The Royal Society of Chemistry. b) SEM image of $Ni(OH)_2$/N-rGO on GCE and (i) Amperometric current response for glucose concentration detection, (ii) electrocatalytic current of glucose vs. the corresponding concentration. Reproduced with permission from (Zhang et al., 2017) Copyright 2017 Springer. c) TEM image of Cu_{53} @Ni_{47} CSNPs/rGO nanocomposite on GCE and (i) Amperometric current response for glucose concentration detection and (ii) the linear relationship between catalytic current and glucose concentration. Reproduced with permission from (Wu et al., 2017) Copyright 2017 The Royal Society of Chemistry. d) SEM image of Ni-MoS2/rGO nanocomposite on GCE and (i) Amperometric current response for glucose concentration detection. (ii) The corresponding calibration plots between the concentration of glucose and the current signal. Reproduced with permission from (Geng et al., 2017) Copyright 2017 Elsevier B.V.

3.76 mA mM^{-1} cm^{-2} and a good linear response from 0.001 mM to 4.555 mM [Fig. 6a(i and ii)]. They reported that the synergistic effect of the metal oxides, rGO and an ionic liquid as a nanocomposite shows significant electrochemical sensitivity, long-term stability and reproducibility. Very recently Zhang et al. (2017) developed a low-cost non-enzymatic glucose sensor with nickel hydroxide nanorods and nitrogen-doped reduced graphene oxide ($Ni(OH)_2$/N-rGO) nanocomposite deposited onto a GCE. They reported the nitrogen doped rGO has wrinkles and it increases the electrical conductivity, electrocatalytic activity, the surface area and the stability. The sensor with ($Ni(OH)_2$/N-

rGO) nanocomposite shows a high sensitivity to detect glucose level with sensitivity of 3.214 mA mM^{-1} cm^{-2} and exhibit a low detection limit down to 0.12 μM when compared to the other sensors based on Ni $(OH)_2$ developed in their study (Fig. 6b (i and ii)). They reported the as-fabricated sensor possesses a good reproducibility, having long-term stability and high selectivity over sucrose, lactose and fructose. Wu et al. (2017) demonstrated the sensitivity of the non-enzymatic glucose sensor can be lower down to 0.780 mA mM^{-1} cm^{-2} by utilizing bi-metallic core-shell nanoparticles (CSNPs) with right composition and supported by rGO sheets (Fig. 6c (i and ii)). They fabricated the sensor by employing Cu_{53}@Ni_{47} CSNPs/rGO nanocomposite onto GCE and found to be enhanced in electrocatalytic activity (fast response, within 3 s). This is due to the synergetic effects from their specific core-shell structures, bimetallic compositions and interactions from the bimetallic CSNPs and supported by rGO sheets. The interference species such as uric acid (UA), dopamine (DA), ascorbic acid (AA) shows insignificant to the current response when they added 0.1 mM of UA, DA, AA into 0.5 mM glucose in 0.1MNaOH; concludes that the sensor has a high selectivity for glucose detection. Geng et al. (2017) developed a more sensitive non-enzymatic glucose sensor based on Ni-doped molybdenum disulfide nanoparticles/reduced graphene oxide (Ni-MoS_2/rGO) nanocomposite with the sensor sensitivity reached to a level of 0.2566 mA mM^{-1} cm^{-2} (Fig. 6d (i and ii)). They found the Ni-MoS_2/rGO nanocomposite shows highly exposed catalytic sites, favourable for conductivity and having excellent electron transport rates due to large surface area and modification with rGO, as a supporter.

Clearly, the non-enzymatic graphene-based glucose sensors have the ability to detect the glucose concentration approximately ~8000 folds lower level than the normal range of glucose concentrations in human blood. The sensors also show a very high electrocatalytic activity, fast response within 3 s, having long term stability and able to be reproduced which fills the gaps of enzymatic-based sensors. However, the linear range of glucose detection (Fig. 6a(ii)-c(ii)) is not in the normal range of detection where the practicality of the sensor is appreciated at the range of 3.9–6.2 mM.

The non-invasive detection method of glucose level through saliva, sweat, tears and urine are definitely painless way which can be used to diagnose diabetes mellitus. Recently, Shanbhag et al. (2016) published a mini review discussing the role of graphene in detecting glucose thru saliva. They summarized the glucose biosensors based on graphene and its derivatives especially solution gated graphene transistor and flexible organic electrochemical transistor shows a promising traits for glucose detection through saliva.

Apart from that, detecting a006E insulin level in the human body is an alternative approach to measure its abnormalities that can be considered for alarming diabetes condition. This approach rather needs the use of immobilization of insulin antibodies onto the electrode surface. The normal concentration of insulin in blood under fasting conditions is 0.86 ng/mL (Kumar et al., 2016). For example, Yagati et al. (2016) have demonstrated a reduced graphene oxide deposited on Indium tin oxide (ITO) interdigitated chain electrodes patterned on a slide glass substrate to detect insulin level by immobilizing insulin antibodies onto the electrode surface. The immobilization of insulin antibodies was carried out by immersing the sensor onto APTES solution, followed by drop-casting of (GA + PBS solution) onto the sensing electrodes and finally drop-cast with insulin antibody (IgG) for binding. The fabricated sensor shows a good response to capacitance change varies with insulin concentration in human serum that is ranging from 1 ng/mL to 10 μg/mL with a detection limit of 0.086 nM. They were proposing the as-fabricated sensor for real-time monitoring of type-2 diabetes which is akin to insulin level and as a label-free biosensor.

5. Conclusion and perspectives

In this critical overview, we have summarized and addressed the graphene-based materials aptitudes in bridging the transducer in electrochemical biosensors based on recent progression especially in detecting the noncommunicable diseases (an emerging peril). The diseases such as heart disease, lung cancer, asthma and diabetes silently develop over a period of time without any major symptoms or indication to human. Electrochemical biosensors have a promising role in NCDs detection and the biosensors commercialization are still in its early stage for all aforementioned diseases except for diabetes. This is because the glucose sensors are widely commercialized and largely available in the market. Nowadays, the non-enzymatic glucose sensors with graphene-based transducers are the most researched than enzymatic glucose sensors because of the high sensitivity and less expensive. Meanwhile, the development of electrochemical biosensors to monitor heart disease, lung cancer and asthmatic condition are still in its infancy stage. A lot of investigations based on real sample/analyte need to be carried out especially for cardiac troponin I detection and the identification of potential prognostic biomarkers for lung cancer and the asthmatic condition is at utmost required. A facile biomolecule immobilization and material's functionalization strategies can bring forth to practicality and commercialization at cheaper cost.

The utilization of nanomaterials incorporating with graphene-based materials in transducer fabrication has shown a good performance in various analytes detection, mostly the limit of detection in the range of ng/mL with higher selectivity, sensitivity, stability, electrocatalytical activity and a good reproducibility attributes. Such high electrochemical performances are attributed to the fact of fast electron transfer and an efficient immobilization of bioreceptors on a large surface area (synergistic effects of nanocomposite hybridization) supported by the uniform distribution of graphene nanosheets. However, there are few challenges that currently remains and expecting for the best solution such as (1) an universal method to synthesis graphene-based materials with desired size and layers, (2) the production of a high quality graphene layer with zero defect, (3) the best performing nanocomposite for electrode modification on diabetes detection, (4) the best functionalization method for immunosensors development considering less cost, (5) the identification of gold standard biomarkers for lung cancer and asthmatic condition detection and (6) to develop electrochemical biosensors based on non-invasive analytes.

Nevertheless, other quasi-2D nanomaterials such as hexagonal boron nitride (h-BN) and transition metal dichalcogenides like molybdenum disulfide (MoS_2), niobium selenide ($NbSe_2$), tungsten disulfide (WS_2) are widely studied for biosensors development. Particularly, the MoS_2 gets a large attention among researches to develop electrochemical biosensors, in recent years. This is because the material has unique physical and chemical characteristics that are similar to pristine graphene with additional advantages such as the ability to tune band gap and easiness in exfoliation into a single layer-due to weak Van der Waals bonding force. The hybridization between graphene and MoS_2 would bring an extra high surface area and also expected to have an excellent electrocatalytic activity that is suitable for electrochemical applications.

Currently, biosensing platform is directed towards the point-of-care testing (POCT) where it brings huge benefits to personnel and healthcare. POCT offers numerous benefits such as rapid detection, reliable test results, simple to use, portable, miniaturized and more importantly it can be used for bed-side analysis. All these advantages are actually reflecting the fabrication procedures of nanodevices/biosensors starting from the choice of electrode materials, chemicals preparation, biological recognition element and immobilization procedures as well as 2D materials functionalization strategies. In general, POCT has two types of classes namely small hand-held devices (Fig. 7) and large bench-top devices where the small hand-held devices are the results from the advancement of microfabrication and nanotechnology (Syedmoradi et al., 2017). The qualitative and quantities measurement for a wide range of analytes is also made possible with such small hand-held devices in disease diagnostics and it can optimize the diagnosis procedures as well. Besides that, the integration of biosensors and the

Fig. 7. Commercial readout devices; (A) iPhone rapid diagnostic lateral flow reader. (B) Android-based lateral flow reader. (C) Novarum reader. (D) iBGstar. Reproduced with permission from (Syedmoradi et al., 2017) Copyright 2017 Elsevier B.V.

readout software with a real-time display by using a smartphone can further simplify the disease diagnosis procedures, thus expediting treatments. Hence, cost-effective biosensors can be afforded in every home as POCT for a regular health monitoring and management.

CRediT authorship contribution statement

S. Taniselass: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **M.K. Md Arshad:** Conceptualization, Data curation, Funding acquisition, Project administration, Supervision, Validation, Writing - review & editing. **Subash C.B. Gopinath:** Data curation, Supervision, Validation, Writing - review & editing.

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Declaration of interest statement

None.

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