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REVIEW

Trends in advanced materials for the fabrication of insulin electrochemical immunosensors

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Abstract
Diabetes is one of the main problems of our community that has been the reason for 1.5 million people in 2019. Raising blood sugar or hyperglycemia is an effect of uncontrolled diabetes which can lead to serious and dangerous health issues. Insulin is a hormone that regulates the level of sugar in the human blood. Therefore, reliable and fast quantification of insulin has a key role in the clinics. This review aims to provide a summary of the employed new advanced materials in the fabrication of insulin immunosensors for possible application in clinics. The importance and role of different types of nanomaterials in the fabrication of these types of insulin sensing probes were also highlighted. Carbon-based materials are concurrently the most used and sensitive materials for insulin immunosensor fabrication. Also, the employed techniques for the designing of insulin immunosensors have been discussed and their limitations and beneficial features for accurate and on-time quantification of insulin were explored in detail. Electrochemical-based methods have been widely utilized and usually provide more sensitive approaches than other methods which have been developed for insulin detection.

Keywords Biomedical Analysis · Diabetes · Insulin · Immunosensor · Advanced materials · Clinical analysis

Introduction

Diabetes is one of the main health problems of the world, which results in the death of many people every year (Roglic 2016; Tao et al. 2015; Yu and Suissa 2016). In 2019, diabetes was one of the main reason of death which directly caused to about 1.5 million deaths (WHO 2021). Diabetes disease occurs due to some problems in the production of insulin or the utilization of it by the body. Insulin, a polypeptide hormone, is produced in pancreas by the beta cells which also regulate the metabolism of sugar (Shen et al. 2019). It lifts blood glucose into the liver or other organs to produce glycogen or change into other important nutrition, it can also increase the oxidation of glucose. Disorder in the production of insulin hormone can cause diabetes mellitus, which is the crucial reason for coronary heart disorder, kidney failure, or blindness. Further, insulin is a powerful hypoglycemic medicine for type 2 diabetes patients. Thus, proper determination of blood insulin levels may be very crucial for the recognition of numerous kinds of diabetes. Immunoassays have been extensively used in this case; however, these approaches have a critical disadvantage of binding with other biomolecules in the biological media, which can lead to incorrect detection in Shafiei-Irannejad et al. (2019), Soleymani et al. (2017).

Up to now, numerous analytical methods including various types of liquid chromatography techniques (LC–UV, LC–MS, etc.), surface plasmon resonance (SPR), fluorescence spectroscopy, flow injection analysis and electrochemical techniques have gained attention in the detection of insulin (Shafiei-Irannejad et al. 2019; Luong et al. 2021).

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Among them, the electrochemical-based biosensors are notably selective and sensitive and provide low-cost testing approaches (Karimzadeh et al. 2020; Hasanzadeh et al. 2009; Ghorbani et al. 2019; Ezzati Nazhad Dolatabadi and Guardia 2014; Jouyban et al. 2011). Electrochemiluminescence (ECL), combining the electrochemistry and chemiluminescence analysis, has extensively gained wide attention due to its noticeable selectivity and sensitivity, low background signal, broad dynamic range, and it has been used in many research fields involving biosensing and biodetection technologies (Khalilzadeh et al. 2017; Isildak et al. 2020). ECL avoids the presence of scattered light and luminescent impurities and does not need any extra light source (Chang et al. 2016). Photoelectrochemical (PEC) immunosensors play a key role in the detection of biological targets because of their capabilities in bio-analysis such as low cost, high sensitivity and rapid investigation. Compared to other techniques, PEC is inexpensive, simple and easy to use (Zhang and Zhao 2013). In PEC detection, an electrical signal can be detected while the light illuminates the photoactive materials. Moreover, PEC active species and biological elements are the two important parameters for a PEC detector (Shu and Tang 2020). Various techniques and sensors were fabricated and utilized for the detection of insulin in biological matrixes (Table 1). Considering different types of advanced materials show different physicochemical properties and play diverse roles in the fabrication of immunosensing platforms, we classified the materials into five categories and discussed their characteristic properties in the designing of insulin immunosensors. Besides, several sensing techniques and mechanisms exploited for immunosensing of insulin are discussed along with their beneficial features and limitations.

Advanced materials for immunosensing of insulin

Noble metal nanoparticles

Noble metal-based nanoparticles (NPs), specifically gold (Au NPs) and silver (Ag NPs), have been widely used because of their unique features including large specific

Table 1 Reported immunosensors for insulin detection and their figures-of-merit

Material	Technique	LOD	Dynamic range	References
BiOBr/Ag_2S	PEC	0.2 pg/mL	0.001–20 ng/mL	Fan et al. (2017)
AuNPs@MoS_2	EC	50 fM	0.1 pM–1 nM	Sun et al. (2018)
AuPdPt-MoS_2@TiO_2	ECL-RET	0.13 pg/mL	0.5 pg/mL–60 ng/mL	Li et al. (2019a)
Au@Pb-β-CD	ECL-RET	0.042 pg/mL	0.1 pg/mL–10.0 ng/mL	Zhang and Lin (2018)
Au-$ZnCd_{14}S$/NH_2-NMC	ECL	0.03 pg/mL	0.1 pg/mL–30 ng/mL	Zhu et al. (2017)
RGO-ICE	EC	0.086 nM	1 ng/mL–10 µg/mL	Yagati et al. (2016)
PGE/MWNT/Py	EC	15 pM	–	Singh and Krishnan (2015)
OMC-TPS	EC	0.18 fM	1.0 f.–10.0 pM	Amouzadeh Tabrizi et al. (2018)
C-g-C_3N_4	ECL	33 fg/mL	0.1 pg/mL–20.0 ng/mL	Ma et al. (2018)
MWCNT@SnS_2@CdS	PEC	0.03 pg/mL	0.1 pg/mL–5 ng/mL	Liu et al. (2016)
Cu_2O@Au NPs	ECL	40 fg/mL	0.5 pg/mL–50 ng/mL	Xing et al. (2019)
SnO_2/RGO/Au NPs-Lu/SiO_2@PDA	ECL	26 fg/mL	0.0001–50 ng/mL	Xing et al. (2018)
Zn_2SiO_4-Pd NPs	EC	0.25 fg/mL (SWV) 80 fg/mL (CA)	0.1 pg/mL–50 ng/mL	Li et al. (2018a)
Ag/$ZnIn_2S_4$/RGO	ECL-RET	0.034 pg/mL	0.1 pg/mL–80 ng/mL	Khan et al. (2020)
C-TiO_2/CdS	PEC	0.03 pg/mL	0.1 pg/mL–50 ng/mL	Wang et al. (2018)
Cu_7S_4-Au	EC	35.8 fg/mL (DPV) 12.4 fg/mL (CA)	0.1 pg/mL–50 ng/mL	Li et al. (2018b)
Cu_2O@TiO_2-PtCu	EC	0.024 pg/mL	0.1 pg/mL–100 ng/mL	Li et al. (2019b)
Pd NPs@3DMoS_x	EC	3.0 pg/mL	0.01–100 ng/mL	Gao et al. (2019)
NiO/Fe_2O_3/$NiCo_2O_4$	EC	9.1 fg/mL	0.01 pg/mL–100 ng/mL	Gu et al. (2020)
CHN/CCE	EC	0.11 nM	0.5–15 nM	Habibi et al. (2016)
WO_3/CdS/PDA	PEC	2.8 pg/mL	0.01–50 ng/mL	Wang et al. (2017)
HRP/ALP	EC	177 pM	0–3 nM 0–3 nM	Vargas et al. (2020)
PFO dots/PTCA	ECL	3.0×10^{-6} ng/mL	1.0×10^{-5}–1.0×10^{2} ng/mL	Zhang et al. (2018)

PEC Photoelectrochemical, *HCR* hybridization chain reaction, *ECL-RET* electrochemiluminescence resonance energy transfer, *EC* Electrochemical surface area, surface chemistry, morphology, and aggregation behavior (Fratoddi et al. 2017; Azharuddin et al. 2019; Pareek et al. 2017). Furthermore, these nanoparticles have gained scientific and technological interests due to their unique electronic, optical, and thermal properties (Rivero et al. 2017; Shakhgildyan et al. 2020). The size and shape of Au NPs and Ag NPs noticeably affect the properties of these nanoparticles. Moreover, their higher stability, controllable properties and less cytotoxicity make these nanoparticles suitable in different fields-like nanomedicine, biosensing and food analysis (Zhang and Lin 2018; Ferdous and Nemmar 2020).

Especially, electrochemistry-based methods have significant effect in the immunosensing of insulin. Recently, an ultrasensitive PEC immunosensor using BiOBr/Ag_2S was reported for the insulin detection. In this method, the BiOBr/Ag_2S nanocomposite was formed by the in situ growth of Ag_2S nanoparticles onto the BiOBr. Ascorbic acid (AA) was used as an electron donor for regulating of the photoelectrochemical activity of BiOBr/Ag_2S nanocomposite. The important piece of this sensor was a layer of polydopamine (PDA) which was produced by a self-polymerization method on the surface of BiOBr/Ag_2S composite to immobilize the insulin antibody. In comparison with other methods, this platform has favorable limit of detection (LOD) and a wide linear range of detection due to special interaction of insulin and insulin-specific antibody. Moreover, this system presented better stability, so it could be used in various and repeatable assays. The fabricated immunosensor with outstanding properties provides a suitable sensing platform for the sensitive determination of insulin in clinical applications (Fan et al. 2017).

Also, a sandwich-type immunosensing platform was fabricated for insulin recognition using modification the surface of a glassy carbon electrode (GCE) with MoS_2 nanosheets, Au NPs and hybridization chain reaction (HCR). Then, a large amount of the first antibody (Ab_1) was anchored onto the surface of Au NPs. One of the effective signal amplifications in electrochemical techniques is HCR. This reaction was used to trigger the polymerization of DNA via initiator or target molecules. The existence of Au NPs on MoS_2 nanosheets increased charge transport among the nanosheets and improved the catalytic efficiency of hydrogen evolution reactions. The fabricated immunosensor has LOD of 50 fmol/L, and it offers a better analytical range due to the enhanced surface area of Au NP@MoS_2 nanostructure and higher capability of HCR molecules to enhance the electrochemical signal (Sun et al. 2018).

Another technique of the electrochemistry electrochemiluminescence resonance energy transfer (ECL-RET) was employed by Li et al. (2019a). Interestingly, an ECL-RET sensor based on Mn^{2+} and capped carbon nanospheres (MnO_2@C) was developed via the reduction of MnO_2 and superoxide radicals ($O_2^{\cdot-}$). The technique relied on energy transfer between MnO_2@C as an ECL acceptor and luminol as an ECL donor, respectively. Luminol has been referred to as an ECL agent with an outstanding luminescence effect as it can produce ECL signals which are used for biomarker detection sensors. The resulting AuPdPt-MoS_2@TiO_2 nanocomposite was used to bind with Ab_1 and luminol. This specific binding led to excellent selectivity of this sensor. This technique indicated the importance of Mn^{2+} in the determination of insulin. Despite the selectivity, sensitivity and reproducibility, this technique is a time-consuming process (Li et al. 2019a). In another study, an ECL-RET immunosensor was introduced which was based on energy transfer between Au@Pb-β-CD and CRuSi NPs as ECL donor and acceptor for detection of insulin, respectively. In this work, the electrode surface was decorated with Au@Pb-β-CD which was used to immobilize Ab_1 and form a sensing platform for insulin antigen. At the same time, CRuSi NPs which were labeled with secondary antibody solution (Ab_2-CRuSi NPs), produces high ECL signal toward insulin concentrations. The fabricated immunosensor indicates a wider dynamic response range of 0.1 pg/mL–10.0 ng/mL with a lower LOD of about 0.042 pg/mL. Au NPs are a vital key material in the construction of the proposed immunosensor. The presence of Au NPs makes this immunosensor reagent free. Also, high water solubility and biocompatibility make this immunosensor good candidate for various clinical and biological applications (Zhang and Lin 2018).

Another sensitive ECL immunosensor for the sensing of insulin was fabricated by utilizing $ZnCd_{14}S$ and Au–Cu nanocrystals as donor and acceptors, respectively. $ZnCd_{14}S$ provided the ECL emission. Simultaneously, the combination of Au NPs with nitrogen-doped mesoporous carbon (NMC)-NH_2, enhanced the ECL emission of $ZnCd_{14}S$ owing to its special properties such as perfect conductivity and large surface area to volume ratio. The resulting Au-$ZnCd_{14}S$/NH_2-NMCs nanocomposite was used as a core material in the insulin immunosensor, where it presented a wide dynamic linear range of insulin concentration from 0.1 pg/mL to 30 ng/mL with a LOD of 0.03 pg/mL. CdS nanocrystals indicated very low intensity which is ideal and suitable, leading to a highly stable sensor (Zhu et al. 2017).

In conclusion, different techniques of electrochemical methods have been utilized for insulin detection including PEC, voltammetry, ECL, and ECL-RET. The combination of two sensitive techniques i.e., optical and electrochemical not only provides a sensitivity to the methods but also can enhance their specificity of them. The reported works and methods declared important use of ECL in bioanalysis and other clinical fields. These methods have high selectivity and sensitivity by controlling excited states with changing electrode potentials and detecting numerous biomarkers in human samples at low concentrations, respectively. On the other hand, low detection limits, availability of instrumentation, on-time and facile measurements make this method suitable for insulin detection compared with other analytical methods.

Carbon-based materials

Carbon-based nanomaterials have some important beneficial features such as high stability, biocompatibility, high water solubility, excellent photoluminescence properties and economic synthesis process (Massoumi et al. 2020). These materials have been used in many applications such as drug delivery, biosensing, and catalysis (Mahmoudpour et al. 2021; Alizadeh et al. 2019; Azizi et al. 2021; Hasanzadeh et al. 2018; Soleymani et al. 2021, 2018a). Some of the carbon-based nanoparticles are nano-diamonds, fullerenes, graphene, carbon-based quantum dots, and carbon nanotubes. There are different techniques for the synthesis of carbon nanomaterials consisting of hydrothermal, electrochemical carbonization, laser ablation, ashing, arc discharge, and solvothermal synthetic methods (Kalhor and Yahyazadeh 2019).

Recently, an interdigitated chain electrode (ICE) with modification of reduced graphene oxide (RGO) was designed for the quantification of insulin. RGO was deposited on the surface of ICE via an electrochemical method, followed by the attachment of insulin antibodies to the electrode to offer insulin binding sites. Capacitance values and impedance spectroscopy were measured for various concentrations of insulin. By increasing analyte molecules, the concentration gradient is increased between the electrodes which leads to sensitive measurements via increasing of signal to noise ratio by electrode thickness. Overall, this sensor was useful for on-time detection of insulin and could be extended for different biomarkers (Yagati et al. 2016). Despite the sensitive detection of the method, there are need to more sensitive methods to trace the insulin. Using of the multi-walled carbon nanotube (MWNT) with advanced features of large surface area, easy functionalization, etc., is a favorable candidate. Functionalization of carbon nanotubes with pyrenyl compounds could form a conductive and large-surface area substrate for binding of enzymes and proteins. A voltammetric immunosensor with pyrolytic graphite electrodes modified by MWNTs-pyrenebutyric (PGE/MWNT/Py) was introduced for facile detection of diabetic disorders. The surface of the electrode enabled the attachment of anti-insulin antibodies (Fig. 1). The detection process of this method is based on a simple redox signal. This immunosensor can detect insulin molecules at the picomolar levels (as a result of use of MWNT) and also, has a simple modification process (Singh and Krishnan 2015).

To enhance the specificity of the sensing platform, application mesoporous substances play substantial role. These types of materials enhance the selectivity of the probes with antifouling effects on the coexisting interfering molecules with providing a filtering system on the outer layers of the sensing platforms (Mahmoudpour et al. 2022). Ordered mesoporous carbon (OMC) is another shape of the carbon-based nanomaterials which has received large interest because of its high surface area, flexibility, and mechanical stability (Ndamanisha and Guo 2012). OMC can be utilized as the nano-platform to produce various biosensors (Walcarius 2017). An aptamer-based insulin detection method at femtomolar concentrations was developed by modifying the screen-printed carbon electrode (CSPE) with ordered mesoporous carbon-1,3,6,8 pyrenetetra sulfonic acid (OMC-TPS) and aptamer-methylene blue (MB), and it was employed for the quantification of insulin in clinical samples. In this work, TPS, a biocompatible molecule, was linked to the amino-terminated aptamer through reactive sulfonyl chloride groups. In the next step, redox probe MB was anchored into the aptamer and to be bond to the insulin. The determination of insulin was performed via the signal shift of adsorbed MB which is attached onto the OMC-TPS/

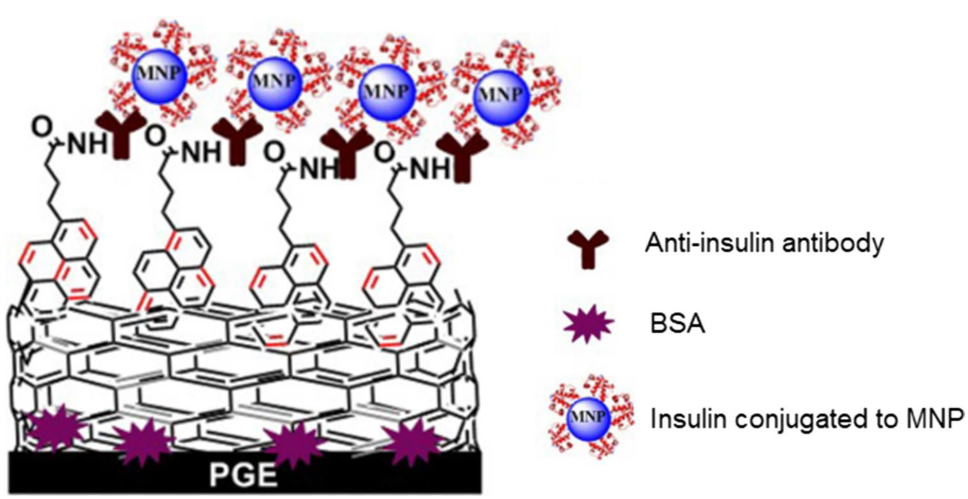

Fig. 1 The schematic demonstration of fabricated immunosensor for quantification of insulin. [Reprinted with permission from Singh and Krishnan (2015). Copyright 2021 American Chemical Society]

aptamer modified screen-printed electrode. When the concentration of insulin increased, the electrochemical signal of the OMC-TPS-aptamer-MB modified electrode decreased. Despite high selectivity, reproducibility and wide linear range, this immunosensor has some disadvantages such as non-continuous detection of insulin, and serum samples must be diluted many times for the quantification of insulin (Amouzadeh Tabrizi et al. 2018).

In another work, an ECL immunosensor for quantitative recognition of insulin with carboxyl-modified graphite-carbon nitride (C-g-C_3N_4) was developed, where C-g-C_3N_4 was employed as the surface for binding capture antibody (Ab_1), while G-quadruplex/hemin DNAzyme (NiPd-DNAzyme) macromolecule was used as a probe to attach detection antibodies (Ab_2). The NiPd-DNAzyme platform was placed onto the immunosensor surface to catalyze the H_2O_2 reduction, which caused a decrease in the ECL signal. High electrocatalytic activity of NiPd-DNAzyme, repeatability and stability of this immunosensor led to accurate quantification of insulin (Ma et al. 2018). The reported method is mainly suffered from sophisticated sensor preparation steps and usually clinician prefer simple and single-step operation method to analysis the analytes. In this problem is largely solved in the PEC-based method reported by Liu et al. (2016). Due to its ability to suppress background signals, PEC methods have higher sensitivity than other electrochemical techniques (Shu and Tang 2020). Besides, PEC instruments are small, cheap and easy to use. A simple PEC immunosensor nanocomposite for the quantification of insulin was fabricated with MWCNT and used as a sensing substrate for insulin quantification. The MWCNTs@SnS_2@CdS nanocomposite has been extensively used as a sensing platform in immunosensors owing to its unique properties like thermal stability and higher electronic conductivity. Upon any change in the concentration of insulin, a decrease in the photocurrent is provided. This decrease happens when steric hindrances increase by antigen–antibody immunocomplexes. This immunosensor showed a linear dynamic range of insulin concentration from 0.1 pg/mL to 5 ng/mL with a LOD of 0.03 pg/mL. The binding of CdS with SnS_2 and using MWCNTs efficiently enhanced the photocurrent by facilitating electron transfer through surface of the electrodes, which makes this immunosensor an ideal candidate for the concentration measurements of numerous biomarkers (Liu et al. 2016).

The same LOD was obtained by a metal/MWCNTs-based immunosensor. Cuprous oxide (Cu_2O) has gained increasing attention in immunosensors because of its properties such as adequate mobility, excellent conductivity and high electrocatalytic activity (Xing et al. 2019). It was reported that octahedral Cu_2O nanocrystals have excellent electrocatalytic activity (Liu et al. 2018). An octahedral Cu_2O-Au-based ECL immunosensing platform was reported recently for the measurement of insulin levels. The probe was based on MWCNT/RGO nanoribbons-CdS and Eu-based nanocomposite was employed as the sensing surface, while Cu_2O and Au NPs were applied as a quencher on the sensing surface. Au NPs can easily bind to antibody Ab_2 by the amino groups. In the presence of insulin, the ECL signal of the probe is proportionally enhanced in the insulin concentration range of 0.5 pg/mL–50 ng/mL and a LOD of 40 fg/mL. Despite the excellent analytical features of the developed method, the application of the developed sensor was not tested in real media (Xing et al. 2019).

In conclusion, carbon-based nanomaterials with different functional groups were used to functionalize with various antibodies or nanomaterials for the quantification of different biomarkers. This quantification happens with different methods and processes, and each method has its advantages and disadvantages. Carbon nanomaterials have an important role in the portability of biosensors aside from their effective electrocatalytic performance. Combining carbon-based with other nanomaterials has indicated a huge impact on the specificity and sensitivity of biosensors.

Silica-based materials

Silica nanoparticles (SiO_2 NPs) were extensively used in many clinical fields because of their good stability, enhanced specific surface area and high biocompatibility (Bitar et al. 2012; Soleymani et al. 2018b; Polshettiwar et al. 2010; Jaafariasl et al. 2011). SiO_2 NPs can easily bind to the detection antibodies (Ab_2), and this can cause signal amplification. In a recent investigation on an ECL immunosensor for detection, a nanocomposite of SnO_2/RGO/AuNPs was modified with the luminol molecules. The resulting SnO_2/RGO/Au NPs-Lu nanocomposite with large surface area increased the intensity of ECL signal. Functionalized Au NPs are important for the growth of Ab_1. Meanwhile, Ab_2 immobilized SiO_2@polydopamine (SiO_2@PDA) nanomaterials were employed as the sensing platform of ECL. The constructed immunosensor had great potential in biological applications with higher specificity, wide linear dynamic range and promoted electron transferring rate (Xing et al. 2018). PDA particles are originally low stable materials and may be in influence the final stability of the probe. To increase the stability of the probe, the silica-based materials are combined with the metal-based particles. Li et al. (2018a) used zinc silicate spheres-palladium nanoparticle-based electrochemical immunosensor which acted as a dual-function label for insulin detection. First, icosahedral gold nanocrystals (Au INCs) were incubated with Ab_1 molecules to produce Au INCs–Ab_1. Later, Zn_2SiO_4-Pd NCs were incubated with Ab_2. These nanocomposites were able to increase the speed of electron transfer and the probe signal, resulting in the enhanced analytical performance of the fabricated sensor. By increasing the concentration of insulin, the surface antigen can reduce the electron transfer, thus a decrease in electrochemical signal occurs. Favorable analytical performance of this immunosensor was provided by Au INCs with high surface area and many spots linked strongly to the biomolecules (Li et al. 2018a).

Khan et al. reported an ECL-RET immunosensor using Au@SiO_2 NPs and Ag/$ZnIn_2S_4$/RGO as an ECL acceptor and donor, respectively. First, insulin antibodies were attached on the surface of Ag/$ZnIn_2S_4$/RGO (Ab_1), then Au@SiO_2 NPs, as ECL acceptor, were used to label the detection antibodies (Ab_2). Au@SiO_2 spheres promote the efficiency of ECL-RET due to the spectral overlap between Au@SiO_2 and Ag/$ZnIn_2S_4$/RGO (Khan et al. 2020). Another Collaboration of electrochemical and optical methods was introduced based on the PEC technique for insulin detection. In this method, C-TiO_2/CdS was fabricated as a sensing agent, while CuS-SiO_2 complex was employed as a signal hindering element. Because of its synergistic effect, this complex could efficiently decrease the photocurrent. Besides, the reported immunosensor provided an effective, simple, and low cost way of signal amplification (Wang et al. 2018). PEC-based sensors provide low background detection with the capability to easily miniature the fabricated probe.

SiO_2 NPs can make ideal biological probes because of their low toxicity, leading to an infallible method for the detection of different biomarkers. Combination of the unique properties of SiO_2 NPs with the other nanomaterials can offer various opportunities to improve the effectiveness of sensing platforms for clinical applications and individual therapies.

Metal-based materials

Metal-based materials are good candidates for the fabrication of electrochemical immunosensors due to their enhanced catalytic activity and excellent electrocatalytic activity toward different compounds (Soleymani et al. 2020; Liu et al. 2020; Kumar et al. 2020). For instance, an electrochemical insulin immunosensor was reported based on Cu_7S_4-Au nanoparticles. Here, polyaniline (PANI) was covalently grafted on the surface of graphene sheets and then linked to Au NPs (GS-PANI-Au NPs) (Fig. 2). Following, the nanocomposites were combined with Cu_7S_4 to form the sensing platform and double signal indicator. The developed immunosensor exhibited good performance for insulin detection and provided a rapid and facile determination of insulin (Li et al. 2018b).

In another work, the same technique was performed by utilizing MoS_2/Au NPs as a substrate to coat onto the surface of a GCE electrode to provide a large specific area. This coating process improved the loading capacity of primary antibodies. Furthermore, Cu_2O@TiO_2-NH_2 was prepared to attain signal amplification. The synthesized nanocomposite showed a favorable electrocatalytic activity for the reduction of H_2O_2 molecules, which presents a strategy of signal amplification (Fig. 3). The immunosensor was used to accurately quantify insulin in human serum, and it displayed a linear dynamic range of 0.1 pg/mL–100 ng/mL with a LOD of 0.024 pg/mL (Li et al. 2019b). Despite the sensitivity, the developed method is an indirect method with limited ability to selective the target analyte. Molybdenum disulfide (MoS_2) has attracted wide attention because of its useful properties

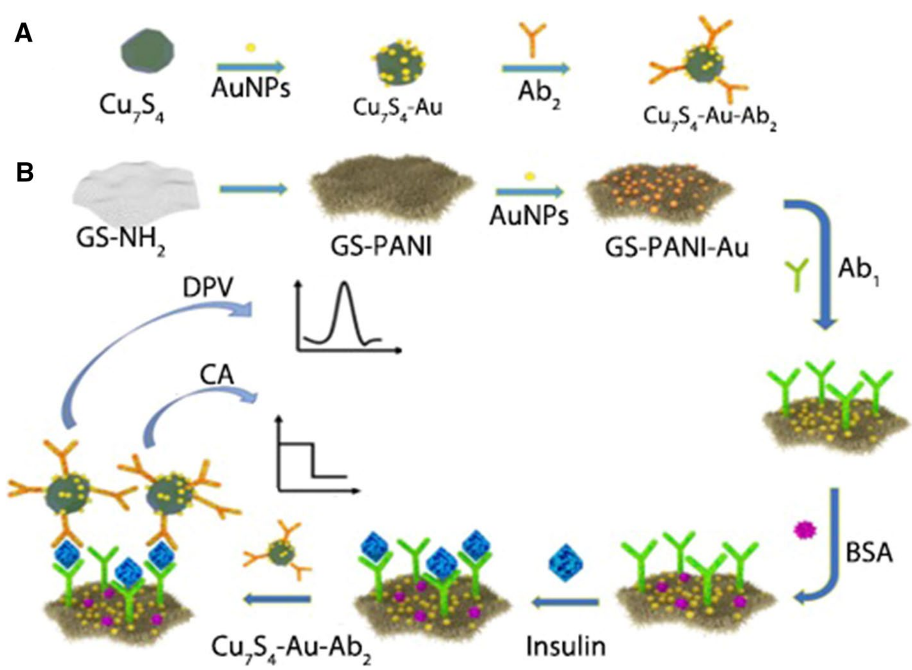

Fig. 2 **A** Preparation steps of Cu_7S_4–Au–Ab_2, and **B** schematic representation for the development of the immunosensor. [Reprinted with permission from Li et al. (2018b). Copyright 2021 American Chemical Society]

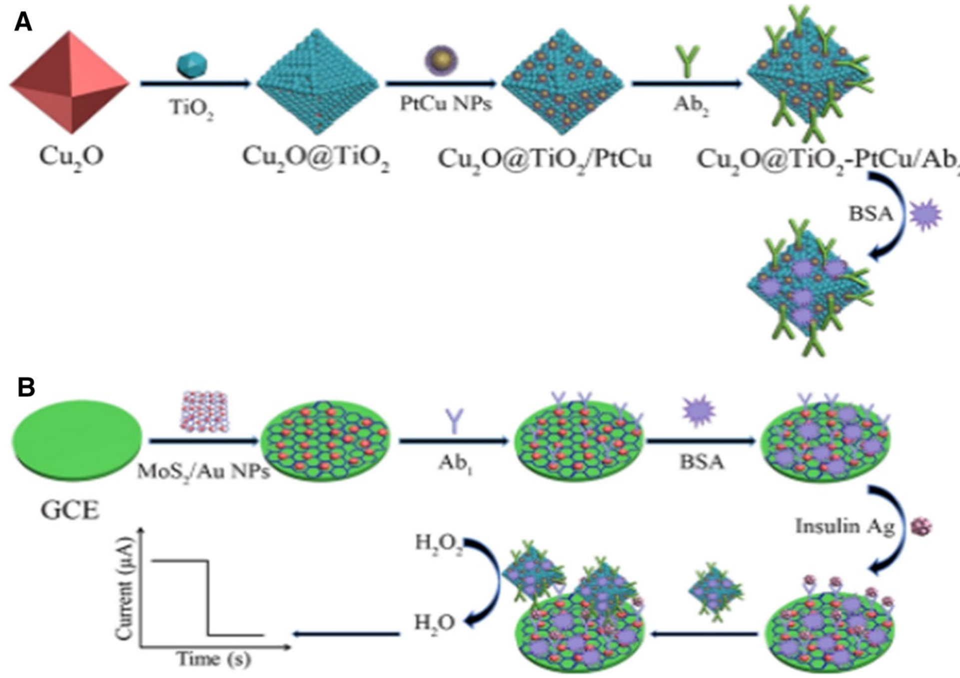

Fig. 3 **A** Preparation of Cu_2O@TiO_2–PtCu/Ab_2 and **B** Fabrication process of the proposed immunosensor. [Reprinted with permission from Li et al. (2019b). Copyright 2021 American Chemical Society]

and applications in electronic fields and clinical sensors (Jain et al. 2019; Zhang et al. 2020; Gupta et al. 2020). Besides, it can bind with other nanomaterials to form compounds with unique features (Wu et al. 2020). An efficient immunosensor based on Pd NPs@3D MoS_x was fabricated for the detection of insulin. Pd NPs were immobilized on 3D MoS_x by in situ reduction, forming Pd NPs@3D MoS_x. The fabricated immunosensor provided high signal responses in clinical analysis (Gao et al. 2019).

Owing to the large specific area, tenability and chemical tolerability, metal–organic frameworks (MOFs) are widely used in sensor fabrication (Bieniek et al. 2021; Shahat et al. 2013). An effective platform for sensitive detection of insulin by using MOF-on-MOF was reported by Gu et al. (2020). In this sensor, CoNi-zeolitic imidazolate nanosheets (CoNi-ZIF) were produced around the CoFe/PB analog to produce a MOF-on-MOF structure (Fig. 4). This makes a perfect sensing platform for the measurement of insulin level in clinical samples. Tunable physicochemical properties of MOFs make these materials as efficient ones in the fabrication of both electrochemical and optical sensors (Gu et al. 2020). Although, in the developing of the electrochemical platforms, it is necessary to supplement metal ions to regulate the electrical property of the probe.

Analytical methods could be improved by flow or other chromatographic instruments for the detection of insulin. However, due to slow heterogeneous electron transfer mechanism, utilizing standard electrodes for electrochemical oxidation of insulin molecules is not desirable. To solve this problem, the surface of electrodes is improved with various chemical modifiers. Modifiers such as nickel powder, nanocarbon black and carbon nanotube layers have been employed. A carbon-ceramic electrode is modified with cobalt hydroxide nanoparticles via the cyclic voltammetry (CV) technique. Electrocatalytic activity of the fabricated carbon ceramic electrode (CHN|CCE) against insulin oxidation was examined through numerous electrochemical techniques. Electrocatalytic activity of the electrode was used to increase the flow injection method for the quantification of insulin. This sensor provided high sensitivity, stability and easy functionalization (Trojanowicz and Kołacińska 2016; Chen et al. 2007).

WO_3 is one of the wide band-gap semiconductors that has gained broad interest because of its chemical stability and high mobility (Enesca et al. 2007). A PEC immunosensor was designed based on PDA@carbon nanotubes (CNT) and WO_3/CdS/PDA for the immunosensing of insulin in serum media. WO_3/CdS/PDA structure was formed as a matrix and PDA was employed to attach the primary antibodies (Ab_1) and reduce the toxicity of CdS. At the same time, for signal improvement, PDA@CNT conjugates were grown onto the secondary antibodies (Ab_2) (Fig. 5). The band edges of WO_3 are well matched with CdS nanoparticles which can ease the electron–hole pairs apart and therefore decrease the possibility of their recombination, resulting in the enhanced PEC signal. The immunosensor indicated a dynamic range of 0.01 ng/mL–50 ng/mL with a LOD of 2.8 pg/mL (Wang et al. 2017).

Metal-based nanomaterials have been largely used in many clinical fields due to their unique features such as size-tunable properties (Takamura et al. 2015; Baghban et al. 2021). Although metal-based materials are the first

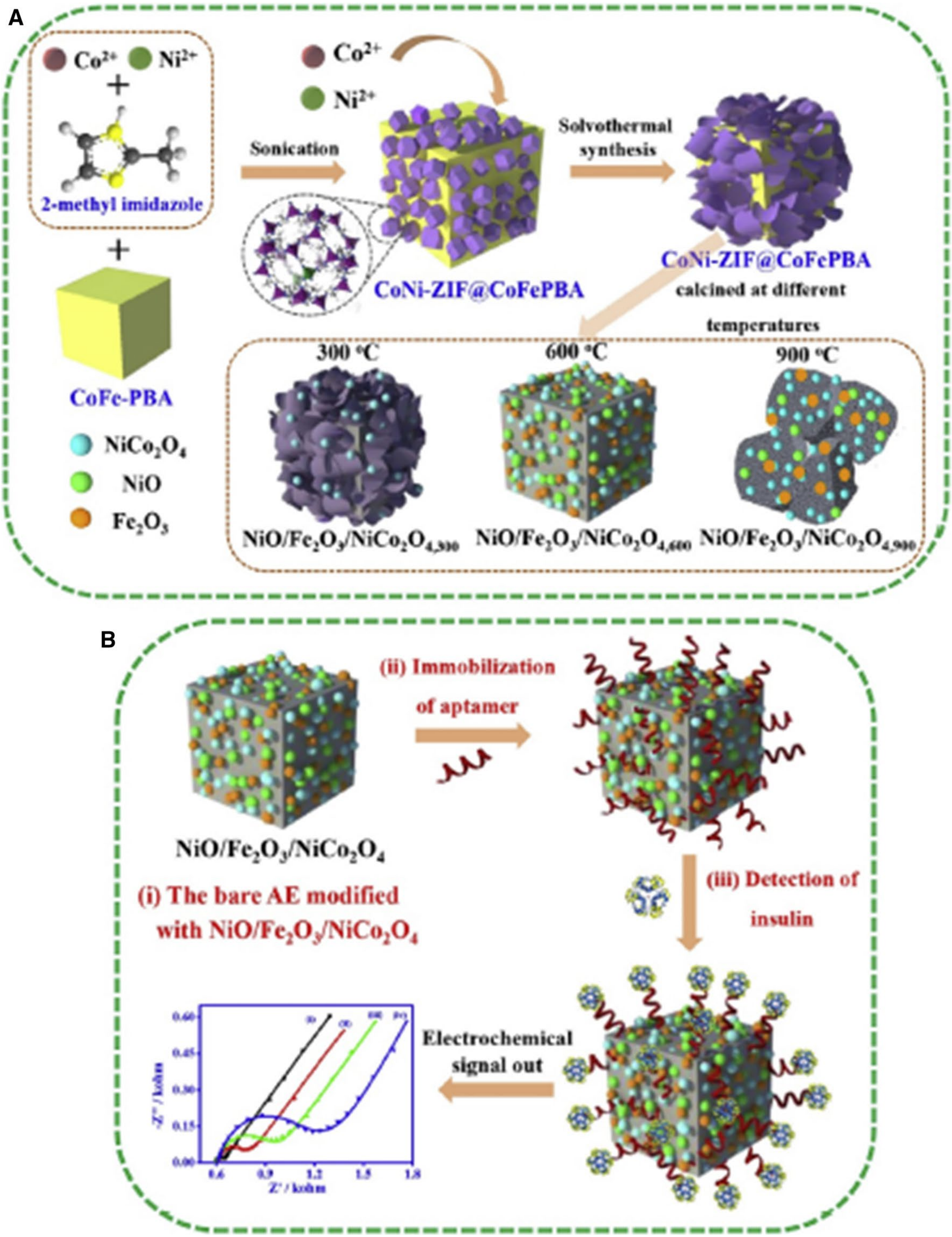

Fig. 4 **A** Schematic diagrams for preparation of $NiO/Fe_2O_3/NiCo_2O_4$ nanohybrids and **B** Development of $NiO/Fe_2O_3/NiCo_2O_4$-based aptasensor for insulin detection. [Reprinted from Gu et al. (2020) with permission of Elsevier with license code of 5367430110398]

choice for the fabrication of the electrochemical sensing platform, however, in the use of this material should regard some considerations (Takamura et al. 2015). First, the stability of these materials is limited and they are usually stored in condition-controlled rooms. Second, the aggregation process may be started during the surface functionalization process and after completing this process,

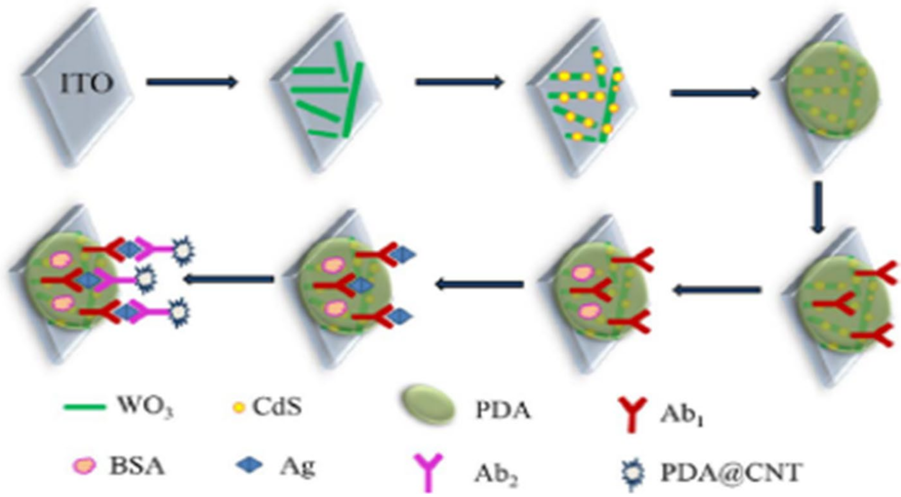

Fig. 5 Schematic demonstration for preparation of PDA@CNT PEC immunosensor. [Reprinted from Wang et al. (2017) with permission of Elsevier with license code of 5367430341394]

the resultant particles must be dialyzed against the proper solvent to remove unreacted materials.

Other materials

Polymeric materials were also used because of their high photostability and fluorescence brightness (Tian et al. 2013). An insulin biosensor based on the ECL method was presented recently in which two polymers of carboxyl poly(9,9-dioctyfluorenyl-2,7-diyl) (PFO) and 3,4,9,10-perylenetetracar-boxylic acid (PTCA) were used as ECL donor and acceptor, respectively. Then, Ab_1 and Ab_2 labeled ECL donor and ECL acceptor was utilized to form the immunosensing platform. By increasing the concentration of insulin, the ECL signal of PFO decreased, and finally, insulin detection started. Combining the ability of the PTCA with different luminescent materials is an important part of this method which led to formation of many other ECL-RET systems for biological analysis (Zhang et al. 2018).

Microchips can provide on-time, accurate and facile detection of insulin without any delay. In a recent work, a microchip was produced for simultaneous detection of insulin and cortisol in human serum samples (Vargas et al. 2020). Cortisol is a biomarker which can attach to hypoglycemia in stressful situations or control the glucose levels in blood. Therefore, it has great impact on the secretion of insulin. The reported method is based on an enzyme tagging method in which the detection of insulin relies on a peroxidase (HRP)-labeled assay, while detection of cortisol depends on alkaline phosphatase (ALP)-labeled immunoassay. Besides on-the-spot detection of insulin, this technique provides the facility to simultaneous detection with tagging of two enzymes in a single substrate which can further develop for the detection of various biomarkers (Vargas et al. 2020).

Different analytical techniques have been employed for insulin detection involving chromatography, enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA), however these methods are slow and expensive.

Impact of the material on the performance of the immunosensors for insulin

There have been employed several materials for the fabrication of insulin immunosensors. However, these materials must show some features to be a usual material for designing of possible future immunosensor. The first property is the stability of the produced materials. Despite the superior analytical performance of some of the materials, they are not stable in the mid- or long term storing time till used for testing. The second feature is the toxicity of the materials which must not be harmful to the biological media. Although by using modification processes, the toxicity of material could be regulated, these processes may have resulted in the diminishing of the overall stability of the materials and sometimes leaching of the material may occur during the processes. The last feature is the sensitivity of the fabricated sensor which is provided by the materials. Generally, carbon-based materials are low-toxic materials with high stability. They could be employed as a favorable material for the development of various immunosensing platforms, however, in some cases, their toxicity may be controlled by surface modifications. Metallic materials are the first candidates for the fabrication electrochemical platform, however, their aggregation could be the main problem. There are some ways to solve this problem such as functionalization of the surface of metal-based nanoparticles with modifiers, in situ synthesis of them with electrochemical techniques such as CV, chronoamperometry, etc., on-demand synthesis, etc. (Soleymani et al. 2020). Silica-based materials provide an excellent substrate to combine one or more to exploit their properties of them to enhance the function of the developed sensor.

Conclusions and future outlooks

Diabetes is a matter of public health with more than tens of millions of cases every year worldwide. On-time, facile, specific and sensitive quantification of insulin is crucial in improving the glucose management and managing the diabetes. In this review, summarized reports of immunosensing platforms of insulin have been provided with useful details for the research community to guide them to direct the future works for the development of advanced insulin immunosensors. We introduced several nanomaterials including gold, metallic, carbon, silica and also polymer-based materials with various amplifying methods such as ECL, SWV and immunoassays for the detection of insulin. Integrating nanotechnology with optical, electrochemical or any other methods leads to the improvement of various ultrasensitive devices, microchips and systems for the detection of insulin as an important biomarker. Among many techniques, aptamer-based biosensors are interesting for many applications. By using nanomaterials in aptamer-based biosensors, devices that are inexpensive, small and easy to use can be produced. Overall, the development of new methods for insulin detection should continue to simplify the sensing process and provide rapid detection.

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Declarations

Conflict of interest We have no conflict of interest to declare.

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