Review Paper

Nano-carbons in biosensor applications: an overview of carbon nanotubes (CNTs) and fullerenes (C_{60})

Hazal Gergeroglu[1] · Serdar Yildirim[2,3] · Mehmet Faruk Ebeoglugil[2,3]

Received: 12 September 2019 / Accepted: 2 March 2020 / Published online: 10 March 2020

Abstract
Recently, the use of carbon nanotubes (CNTs) and fullerenes in the design of new biosensors have attracted great interest in the development of carbon nanomaterials. Due to the superior properties of CNTs and fullerenes, the use of sensor components allows the development of reliable, accurate and fast biosensors. Depending on the types of target molecules, the development and application areas of the sensors vary. This review summarizes the role of CNTs and fullerenes in the development of biosensors in different application areas. Considering the difference between other members of the nano-carbon family, we explain why CNTs are used more widely in biosensor applications and why fullerenes have high potentials in these areas of application. Moreover, we focused on investigating the function of these nano-carbons in the detection of various analytes in bio-sensing. By discussing the challenges and future expectations, we have put forward a perspective that may help synthesize advanced composites in the development of new generation designs in biosensor applications.

Keywords Carbon nanotubes · Fullerene · Biosensing · Nano-carbons

1 Introduction

Detection of biomolecules has great importance in critical areas, ranging from health medicines, clinical and infectious drugs, food control, homeland security, and monitoring of environmental pollution, to the detection and identification of diseases and the recognition and viewing of new drug molecules. Therefore, the evolvement of reliable and inexpensive devices that high-precision/selective, enable direct, and rapid analysis of biomolecules in the detection of biomolecules can affect human health to have a healthier and more reliable life [1].

A large number of surveys have been carried through around the world to use different biological molecules since Leland C. Clark's first successful study of biosensors in 1962. Nowadays, biosensors with numerous application areas such as food analysis, environmental monitoring, drug distribution, toxicity measurement, genetic analysis, protein engineering, DNA sequencing, disease diagnosis are a class of devices in which the detection of gas molecules has been widely used in real-time monitoring of chemical signals in biological cells. Additionally, biosensors have the potential to significantly affect disease screening, drug discovery, biohazard screening, and fundamental science [2, 3].

Generally, as shown in Fig. 1, a sensor consists of an active sensing constituent and a signal converter and originates an electrical, optical, thermal or magnetic output signal. While the sensor constituent is responsible for the detection of the analyte selectively, the converter transforms a chemical event into a suitable signal, which can be used with or without amplification to detect the

✉ Hazal Gergeroglu, hazal.gerger@gmail.com | [1]Department of Nanoscience and Nanoengineering, Dokuz Eylul University, 35397 Buca, Izmir, Turkey. [2]Department of Metallurgical and Materials Engineering, Dokuz Eylul University, 35390 Buca, Izmir, Turkey. [3]Center for Fabrication and Application of Electronic Materials, Dokuz Eylul University, 35397 Buca, Izmir, Turkey.

SN Applied Sciences (2020) 2:603 | https://doi.org/10.1007/s42452-020-2404-1

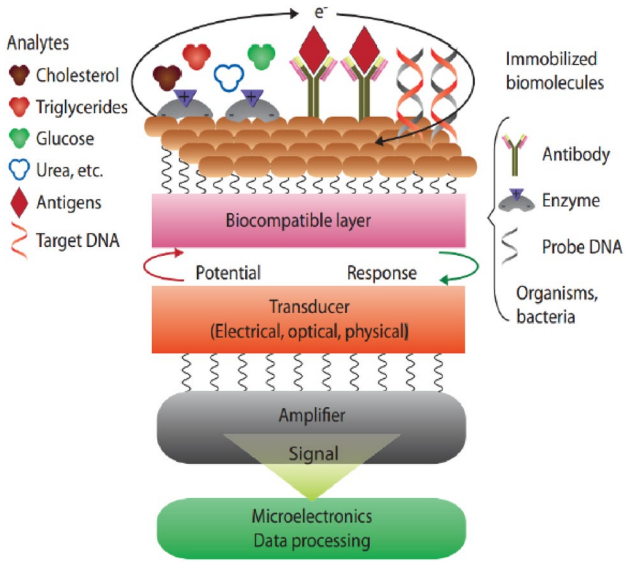


Fig. 1 Basic working principle of biosensors [4]

analyte concentration in a given test sample [4, 5]. On the other hand, the biosensors, which play an important role in critical application areas, need to carry multiple characteristics such as high sensitivity, high selectivity, service life, reproducibility, stability, simplicity and cheapness, scalability, sterilizable, wide measurement range. The development and performance of biosensors is largely dependent on the properties of the material from which they are made. It also depends on the physicochemical properties of the materials used for the construction of the transducer, matrices used for enzyme immobilization, stabilizers and mediators. One of the factors that hinder the large-scale employment of biosensors is low reproducibility and poor signal stability. The main reason for these obstacles is the inability to control the material used in the construction of the transducer and biosensor. To overcome these problems, using nanomaterials in biosensor applications can be an effective solution. For this reason, over the last decade, nanomaterials have a tremendous interest in catalysis, sensors and biosensors, energy conversion and energy storage devices. Nanomaterials are produced by well-controlled physicochemical properties, surface load, controlled shape and size and variety via significant advances in synthetic methodologies. Nano biosensors based on nanomaterials have significant advantages, including improved physical, chemical and biological properties, depending on the high surface area and small particle size [6]. Especially carbon nanomaterials offering a serious potential as a support matrix in the design of biosensors have simple procedures such as low background flow, surface regeneration capability, low-cost synthesis [7, 8]. For this reason, in the past two years, we know that different carbon allotropes such as primarily CNTs [9–11], graphene [12, 13], fullerenes [14, 15], carbon dots [16, 17], carbon black [18], and nano-diamonds [19, 20] play a very important role in the provision of the specific properties desired features in biosensors.

In the years to come, the nano-carbon family (Fig. 2) may become an indispensable phenomenon in the development of biosensors equipped with the new generation and advanced properties. This predict can be confirmed by the numbers of publications about the biosensor applications of the nano-carbon family (Fig. 2), using keywords such as 'biosensing', 'biosensors', 'bio-sensing' in the Scopus database and Fig. 3 shows the distribution of these areas for the period from 2009 to 12th February 2019. However, before understanding the importance of nano-carbons in biosensor devices and mechanisms, there is a need to classify the nano-carbon family and to be aware

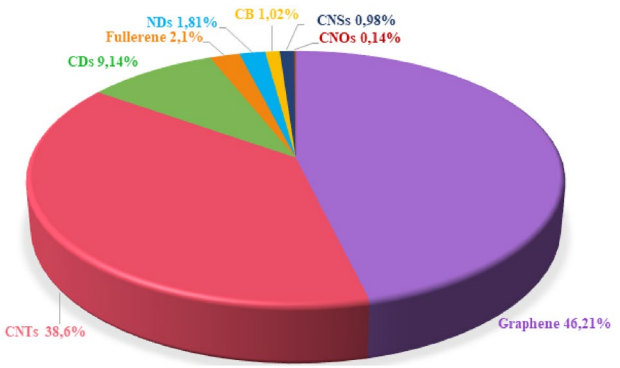
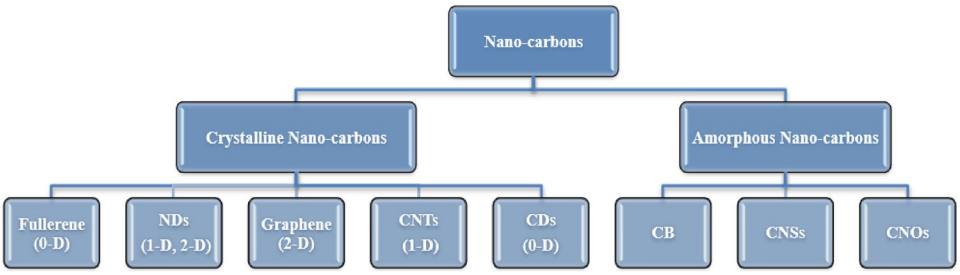


Fig. 3 Pie chart showing the distribution of nano-carbon family in biosensor applications

Fig. 2 Main scheme of a family of nano-carbons widely used as biosensor component



of the distinction within themselves. The basic pedigree in Fig. 2 was prepared considering the basic structural differences of the nano-carbon family used or proposed in biosensor applications.

The most striking member of the family in biosensor applications can be 2-Dimensional (2-D) graphene when considering the pioneering studies in previous years (see Fig. 3) [21, 22]. The physical, optical, and electrochemical advantages offering by graphene, known as a hexagonal, sp^2 bonded carbon atom with a single atomic thickness, have led to the design of new products that have improved sensitivity and selectivity to biosensor applications. In recent years, there have been numerous studies on the contribution of graphene's superior electronic and physical properties to biosensor applications [13, 22]. Nevertheless, there are some problems to be overcome in graphene-based biosensor applications. For instance, a different method is required for each electrode modification. This results in an inconsistent comparison in graphene-based biosensors. Additionally, there is no standardization in production and there are difficulties due to the high agglomeration tendency of graphene during production. Moreover, graphene-based biosensors cannot benefit from the superior properties of graphene in full efficiency. Furthermore, the physical stability of the graphene in the biological environment and the toxicity assessment for the cells is controversial [21–24].

In contrast to graphene, other nano-carbon crystalline family member carbon dots (CDs) have superior biocompatibility and low toxicity. CDs which consist of synchronized sp^2 and sp^3 hybridized carbon atoms are expressed as zero-dimensional (0-D) nanoparticles below 10 nm (Fig. 4). CDs have been shown to be generally non-toxic by in vitro studies [16, 25]. Additionally, their potential for use as an electron donor and receiver made them a suitable candidate for biosensor components [25, 26]. For this reason, CDs are the members of the nano-carbon family with the highest number of publications after graphene and CNTs in biosensor applications (Fig. 3). However, they cannot provide long-term stabilization, which is one of the most important features desired in a biosensor design [25, 26]. Therefore, it is clear that the future of CDs in electrochemical biosensor applications depends on the development of stabilization.

On the other hand, another biocompatible cousin of CDs is nano-diamonds (NDs) (Fig. 2), have superior cellular adhesion, and have a mixture of sp^2 and sp^3 hybridized carbon atoms like CDs [33, 34]. NDs with the average radius of

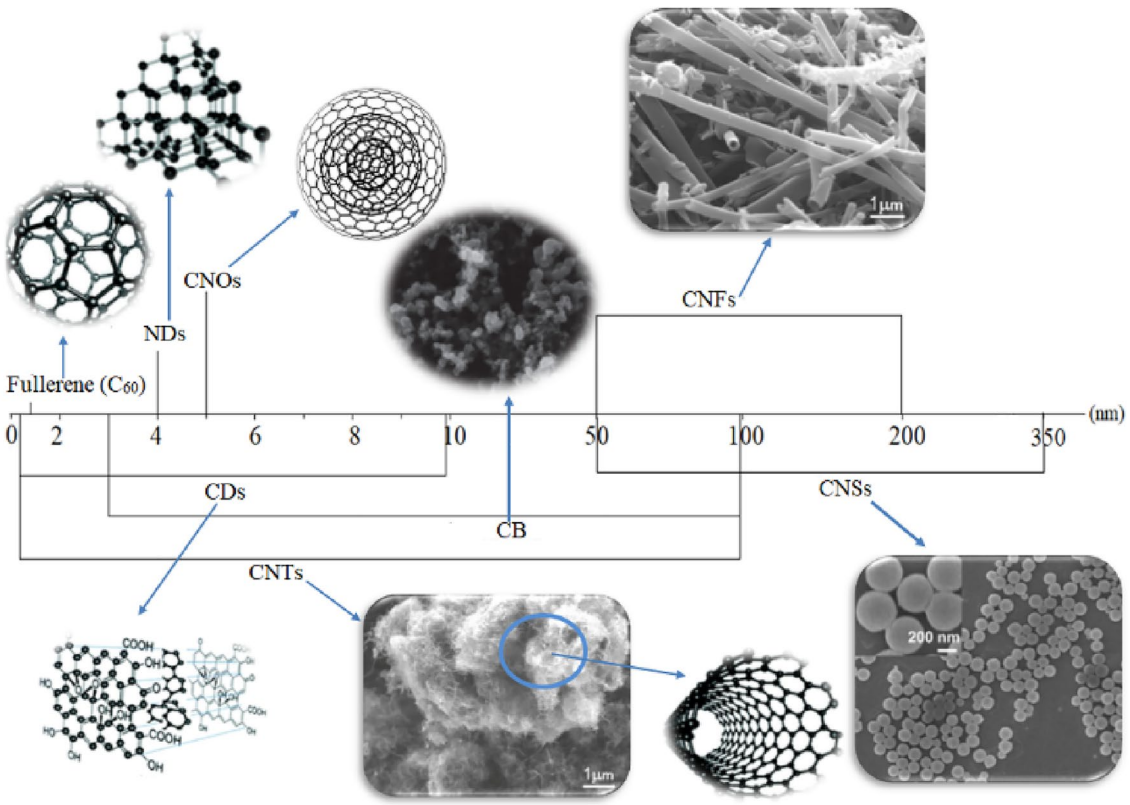


Fig. 4 Classification of nano-carbons according to their average diameters; Fullerene (1.4 nm) [27, 28], NDs (4–5 nm) [28, 29], CNOs (5–6 nm) [30], CDs (below 10 nm) [25, 28], CB (3 to 100 nm) [18], CNTs (1 to 100 nm) [27, 28, 31], CNFs (50 to 200 nm) [27, 31], CNSs (50 to 350 nm) [32]

approximately 4–5 nm (Fig. 4) and having 1-Dimensional (1-D) (diamond nanorods) and 2-D (diamond nanoplatelets) forms; shows the highest biocompatibility reported compared to other alternative carbon allotropes [29, 34, 35]. Additionally, cheap cost, high fluorescence capabilities, low cytotoxicity, the ability to transfer target molecules to target cells, and the ability to interact with specific cells make NDs a remarkable bio-sensing platform [19, 28]. However, some issues need to be clarified regarding the bio-electrochemical behavior of NDs such as conductivity, local capacitive behavior, and electrochemical activity. Furthermore, these nano-carbon structures in biosensor applications need to be functionalized with stable and electroactive modifiers to achieve an effective yield [36]. Moreover, studies on NDs, especially in biosensing applications, should be developed due to the high tendency of agglomeration, the difficulties in such as producing particles smaller than 4 nm, preparing large volumes of colloidal solutions, and the inability to control the surface chemistry [34].

Compared to nano-carbons that are remarkable in biosensor applications (Fig. 3), carbon black (CB), can be classified in amorphous nano-carbon family (Fig. 2) with the ranging in average diameter from 3 to 100 nm (Fig. 4), is a young member for use in bio-sensing applications. It is a promising nano-carbon for biosensing applications due to its features such as inexpensive cost, high analytical sensitivity, experimental simplicity, portability, high selectivity [18, 37]. Moreover, CB, due to its high conductivity property, has been reported to can be used as an alternative to other members of the family such as graphene and graphene-like structures, fullerenes and CNTs, and increases activity in enzymatic biosensors [18, 38]. On the other hand, the physical properties of CB which are composed of sp^2 and sp^3 hybridized carbon atoms depend on particle size, porosity, chemical properties of the surface, aggregate morphology and surface area. Additionally, CB is generally present as loosely bonded agglomerates on one another [27, 38, 39]. This makes it difficult to obtain consistent and rigorous data comparable to standardization and final products in the production procedures of biomolecular applications of CB, as in graphene and graphene-like structures. Furthermore, there is also a need to develop characterization methods of these structures, each of which is a few unit cell size [27]. However, easily characterizations can be carried out in the case of another member of the amorphous nano-carbon family (Fig. 2) with the big average diameter (50–350 nm) (Fig. 4) which called carbon nanospheres (CNSs). Carbon spheres are classified as graphitic carbon onions with diameters between 2 and 20 nm, less graphitic carbon spheres with diameters in the range of 50 nm to 1 micron, and carbon particles having diameters from one to several microns [40]. In this study, CNSs are expressed as an amorphous structure with a size range of 50–350 nm (see Fig. 4). We know that carbon is bonded in different ways to create structures with different characteristics [27]. CNSs may be formed by the matching of pentagonal and heptagonal carbon rings, in other words, by rearranging graphene structures [27, 40]. Due to this bond structure, CNSs exhibit similar structural, physical and electrical properties as fullerene which will be mentioned in detail in the further stages of this work. Because of its unusual features, CNSs have offered a potential in a wide range of application areas such as drug delivery, excellent catalyst support materials, lubricating features, heterogeneous catalysis, capacitor, energy storage, encapsulation of support and electrode materials, and rubber reinforcement [27, 41, 42]. However, about the biosensor applications of CNSs, it was seen that very few publications were performed compared to the other nano-carbons (Fig. 3). This may be due to the economic difficulties of the production of a large amount of CNSs under reasonable experimental conditions. In future studies, areas such as photoluminescence and multi-photon-biological imaging may be promising areas for CNSs, but no improvement has been made on a commercial scale yet [27, 41]. A similar problem is seen in carbon nano-onions (CNOs) that are a member of another amorphous nanocarbon family. The challenge of high-quality industrial-scale production of CNOs has caused to be of the least interest among in other nano-carbons (Fig. 3) [43]. However, CNOs, composed of a hollow, spherical fullerene core surrounded by concentric and engraved graphene layers with increasing diameters, have higher thermal stability than fullerene (C_{60}) and a higher chemical reactivity than CNTs [44]. Moreover, the use of electroactive CNOs in biological/medical applications is promising as a result of cytotoxicity studies. Additionally, CNOs with a diameter of 5–6 nm (Fig. 4) have been reported to have unusual physicochemical properties and a high nano-porous structure [43, 45]. Despite all its outstanding features, the use of abrasive and toxic precursors with the difficulties in the scalability of CNOs production methods [43] suggests the need for the development of new production techniques for the use in biosensor applications.

Among the nano-carbons recommended for use as electrochemical transducers in biosensor applications, fullerene and CNTs are notable for their easy enzyme immobilization and reproducible electrochemical behavior [7, 8]. Since the discovery of the Fullerene (C_{60}) due to its extraordinary properties, it has attracted the attention of many researchers. It is known that Fullerene has great potential for use in biosensor applications due to its easy chemical modification, high conductivity, and electrochemical properties, unique and useful properties [7]. It can be claimed that these features distinguish

the fullerene from the other members of the nanocarbon family which offer many advantages. However, in Fig. 3, few studies have been conducted for the fullerene. This may be due to the difficulties involved in integrating the fullerenes into the biosensors and the difficulty in achieving high performance under different experimental conditions. Besides, the modification and bio-conjugations required for adaptation of fullerenes to biosensor applications require costly agents and precursors, resulting in increased cost [2]. However, if these problems are overcome, it is thought that fullerene-based biocompatible sensor components, which are equipped with high sensitivity, selectivity, and good repeatability characteristics, can be used successfully in real samples.

On the other hand, has the most percentage of publications in biosensor applications after graphene (Fig. 3), CNTs, are promising materials in sensor applications due to their various attractive features like fullerenes. However, CNTs are separated from graphene due to their chiral structure. This structure gains optical features to CNTs whereas graphene does not have different chiral forms, and thus external labeling is required for graphene in applications such as probing applications, living cell imaging [46]. Dimensions of CNTs are generally in ranging from 1 to 100 nm (Fig. 4), in this respect, it differs from CNFs, which has conductivity and stability properties similar to CNTs and has dimensions up to micron-scale according to the production technique [27, 47]. This size range gives the CNT a high surface area/volume ratio. Additionally, CNTs have an outstanding ability to mediate rapid electron transfer kinetics for a wide variety of electroactive species such as hydrogen peroxide. Furthermore, CNTs can easily be chemically modified and functionalized. This means that almost all kinds of the chemical can be bound to the CNT structure. Thus, biodegradability and biocompatibility of CNTs could be increased [5]. This size range gives some outstanding features such as large size diameter and aspect ratios which providing a high surface area/volume ratio to the CNTs.

Consequently, CNTs and fullerenes are promising materials in biosensor applications due to their unique properties. For this reason, in this review, we aimed to discuss the changes in functional properties of CNTs and fullerenes -based biosensors, and their contribution to biosensing applications. Firstly, we focused on investigating the structural, physical, and chemical properties of CNTs and fullerenes with historical background. Considering the three different biosensor application areas (glucose-sensing, urea-sensing, immuno-sensing) that have been extensively studied by researchers recently, we have compiled studies on synthesized and functionalized CNTs and fullerenes-based nanostructured electrodes and applications in the field of bio-sensing were investigated.

2 CNTs

Since its discovery by Iijima, CNTs have pioneered many interdisciplinary types of research with numerous features offered by the unique structural, electronic, opto-electronic, semiconductor, mechanical, chemical [48]. Lengths (up to a few microns) and small diameters (a few nanometers) result in a wide aspect ratio. They may be seen as a proximately 1-D form of the fullerenes. CNTs are a member of the fullerene family of carbon allotropes. These are cylindrical molecules that contain a hexagonal arrangement of sp^2 hybridized carbon atoms. They are also referred to as a hollow tubular material composed of carbon atoms with nanometer-scale diameters and lengths. CNTs can be classified as two types formed by rolling single-walled or multi-walled graphene sheets into continuous cylinders. Two forms of these cylindrical structures are called single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) [49].

Nowadays, CNTs has created a great variety of research and important applications based on its superior characteristics in the scientific world. CNTs have potential use in the chemical sensors [50, 51], field emission materials [52, 53], catalyst carriers [48], electronics [54, 55], in modern healthcare applications [56, 57], and energy storage areas [58]. Furthermore, publications related to biomedical applications of CNTs have been investigated in the Scopus database, from 2009 to 15th February 2019, using keywords such as cancer, photodynamic therapy, antiviral, anti-bacterial, HIV, DNA, toxicity, biosensor, antioxidant, imaging, drug delivery, stem cell, and Fig. 5 shows the distribution of these areas.

Recently, CNTs which become available in macroscopic amounts will give directions for future nanoscience and nanotechnology. This section aims to introduce biosensors based on different biological components

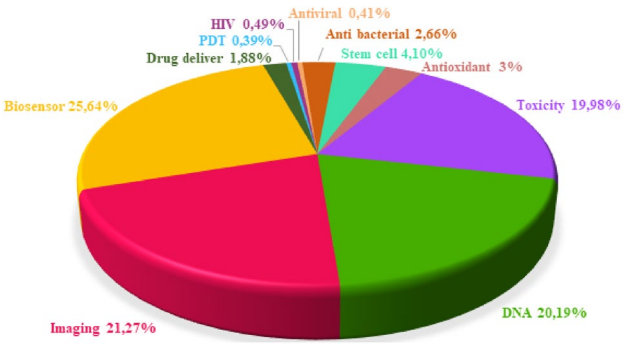


Fig. 5 Pie chart showing the distribution of CNTs in biomedical applications

with MWCNT and SWCNT and to present the recent developments and innovations.

2.1 History of CNTs

CNTs can be assumed to have a history of approximately 30 years as you can see in Table 1. However, carbon nanofilaments, probably first nanotubes, were first observed by Radushkevich and Lukyanovich [59]. Hillert and Lange [60], reported the dense bamboo structure of carbon filaments. Bollman and Spreadborough synthesized the graphite layer in 1960 in a cylindrical shape [61]. Oberlin et al. [62] reported the growth of carbon nanofibers (CNF) by a chemical vapor deposition technique with the disintegration of benzene. Iijima [63] reported double and MWCNTs and explained their crystal structure. This remarkable discovery by Iijima [63] has led scientific circles to focus on research in nanotubes. In 1993, SWCNTs with the aid of metal catalyst particles were synthesized by Iijima and Ichihashi [64].

2.2 Structure and features of CNTs

The properties of the CNTs depend on atomic regulation (the shape of rolling graphite layers), the diameter and length of the tubes, and the morphology or nanostructure. CNTs are found as single-walled or multi-walled structures, and MWCNTs are simply composed of concentric SWCNTs [65]. SWCNTs have extremely high material properties which are very close to their theoretical limits such as electrical and thermal conductivity, strength, hardness, and low density. The impressive mechanical properties of the SWCNTs are due to their geometrical structure and C–C bonds. The carbon–carbon bond in the base plane of graphite is one of the strongest bonds in nature. SWCNTs with small diameters have a high Young modulus and tensile strength. This means that SWCNTs are too hard and hard to bend. In fact, SWCNTs are very flexible. They can be bent like a pipette without breaking. They can return to their original structure without any damage. Most materials are broken during bending due to the presence of defects or dislocations. However, SWCNTs have very few defects in the side walls. Therefore, they have very high mechanical properties and flexibility [27, 66].

SWCNTs can exhibit metallic or semiconductor behavior depending on their diameters and the chiral angle between hexagons and the tube axis, whereas the MWCNTs have a current carrying capacity of up to 10^9 A cm^{-2}, are always metallic and have zero bandwidth. Additionally, the open end of the MWCNTs has a fast electron transfer rate similar to graphite electrodes, while the SWCNTs have a much slower electron transfer rate. The MWCNTs have a structural complexity and current carrying capacity like the metallic/semiconductor SWCNTs. However, unlike SWCNTs, there are also different parameters for each layer in MWCNTs. Moreover, when the mechanical properties of SWCNTs and MWCNTs were compared, the tensile strength of MWCNTs and SWCNTs shows values close to each other (11 to 63 GPa, 13 to 52 GPa, respectively); however, there is a significant difference between the bending strength values (14.2 ± 80 GPa, 28.5 GPa, respectively). Besides, MWCNTs offer superior opportunities than SWCNTs, as they are easier to produce due to lower product cost per unit, advanced thermal and chemical stability, and easier control of the growth process [67, 68].

All the extraordinary features of the CNTs, especially the superior electrical features such as electron mobility (100,000 cm^2/Vs), field effect mobility (79,000 cm^2/Vs) and electrical conductivity (10^4 S/cm) [68], have made CNTs the perfect candidate for improving bio-sensing tools.

2.3 Synthesis of CNTs

The prevalence of the biosensor applications of CNTs has led to an increased need for CNTs in the sector [1]. Therefore, several different methods have been proposed to synthesize CNTs in recent years. However, there are three main synthesis techniques (arc discharge, laser ablation and chemical vapor deposition (CVD) for CNTs production [69]. Compared to arc-discharge and laser ablation methods, CVD is a simple and economical method for the synthesis of CNTs at low temperature and ambient pressure. Additionally, it allows serial CNT production with higher efficiency and purity. Moreover, CVD is the most efficient technique for control of the structure or CNT architecture [69, 70]. In the CVD method, a catalyst material is heated to high temperatures in a tube furnace, while the precursor hydrocarbon gas flows through the tube for a while. In the process, the method is also versatile because the versatile hydrocarbons can be used in any state (solid, liquid or gas). Furthermore, since various substrates are used, it allows the production of a wide range of different structures [71, 72].

Table 1 Historical progressive of CNTs

Date	Event
1952	Carbon nanofilaments were observed
1958	Dense bamboo structure of carbon nanofilaments was reported
1960	The graphite layer was synthesized
1976	The production of carbon nanofibers (CNF) was carried out via chemical vapor deposition
1991	MWCNTs were reported and explained
1993	SWCNTs were synthesized

2.4 Functionalization of CNTs

Due to its stable structure and large absorption capacity of the inner tube, CNTs are not soluble in most solvents. To overcome this problem, which significantly restricts the use of CNTs in biosensor applications, CNT functionalization is required [73]. Since its discovery, numerous studies have been carried out to dissolve in solvents and functionalize. The pioneering works in the functionalization of CNTs have developed three main approaches. These are as follows;

1. Covalently linking chemical groups to the skeleton of CNTs,
2. Adsorption of various functional molecules to CNTs,
3. Endohedral filling of the internal cavity of CNTs [74].

In biomedical applications, surface modifications are applied to increase solubility, increase biocompatibility and reduce toxicity. The surface modification involves combining different functional groups on the surface and end caps of CNTs. The covalent and non-covalent immobilization of different chemical groups such as gold, silver, platinum, graphene, glass, and silica provide an opportunity for the CNTs to perform appropriate biosensors and to increase the electron transfer rate. Several studies on CNT-polymer composites focused on improving dispersion and load transfer efficiency by improving compatibility between CNTs and polymers. The final products, ends, and sidewalls include short length nanotubes equipped with a high density of various oxygen-containing groups (mainly carboxyl groups). Carboxylic functional groups can be replaced with more reactive groups such as –COCl or $–CORNH_2$. The addition of these functional groups on CNTs causes molecular repulsion between functional groups on the surface, and this overcomes the weak van der Waals between the CNTs. It is also vital to stabilizing the dispersion to prevent the re-agglomeration of CNTs. Thus, a wide range of surface functions can be created on CNTs [27, 73, 75].

The chemical modification of the surface of the CNTs has great effects on the creation of sensitive functional groups that prevent agglomeration, improve host compatibility and enhance solubility in different solvents [73]. Therefore, it is clear that CNTs can be suitable for biosensing applications by functionalization and chemical modifications.

2.5 CNTs in biosensors

The first enzyme electrode was introduced by Clark and Lyons. Since then, the electrochemical biosensors based on the utilizing of enzymes have attracted considerable interest due to the advantages of the biocatalytic activity of enzymes and the combination of superior sensitivity and versatility of electrochemical transduction. CNTs have been reported to be especially beneficial for electronic communication with redox enzymes. Due to their small dimensions, they can arrive at the redox-active zones easily. CNTs may function as molecular cables to provide effective electron transfer between the main electrodes and the redox centers of the enzymes, as shown in Fig. 6. On the other hand, they can contribute to the direct electron transfer reaction of proteins (Fig. 7) [69]. In addition, CNT modified electrodes can reduce the effects of contamination on the surface. These features make CNTs very attractive for a wide variety of electrochemical biosensors.

Additionally, CNTs have an outstanding talent to mediate rapid electron transfer kinetics for a wide variety of electroactive species such as hydrogen peroxide or NADH. Moreover, CNTs can easily be chemically modified and functionalized. This means that almost all kinds of chemicals allow the CNTs to be bound to its structure. Thus, the biodegradability and biocompatibility of CNTs can be increased. As a result, it is possible to produce composite electrodes containing well-distributed CNTs in a suitable matrix [5].

2.6 Modification of electrodes with CNTs

It is well known that CNTs-based electrodes have specific features that are equal to or better than most other conventional electrodes. Moreover, CNTs play a very significant role in the development of biosensors with higher sensitivity, lower detection limits and faster response times than conventional sensor designs with carbon electrodes. Because of its rapid electron transfer speeds, high conductivity, and other desirable chemical and physical properties, CNTs are frequently used as mediators between glassy carbon, platinum or gold electrodes, and enzyme components. Furthermore, the biofunctionalization of CNTs increases the sensitivity of

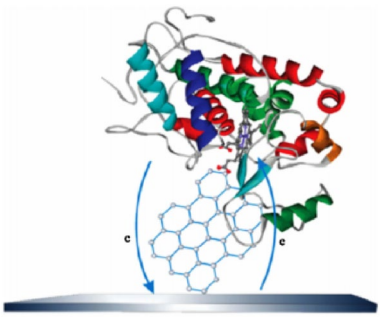


Fig. 6 Wiring of proteins by CNT for electrochemistry (CNT-supported hemeproteins at the surface of GCE) [69]

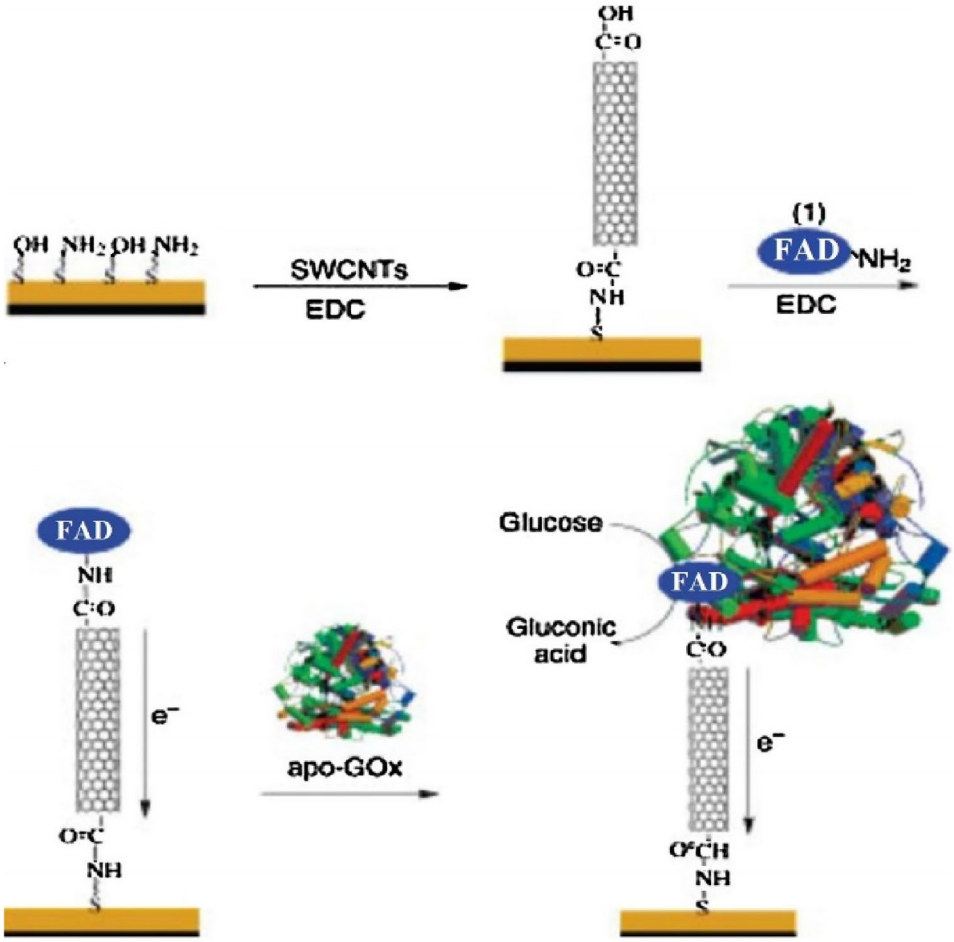


Fig.7 Assembly of the CNT electrically contacted glucose oxidase electrode [69]

the biosensor to be obtained. Additionally, large surface area CNTs allow large amounts of the enzyme to be doped. Thus, high-precision, selectivity, rapid response, and superior properties are provided in biosensors with superior, bio-functionalized CNTs-modified electrodes [76, 77]. CNTs may be used in the modification of surfaces of various electrodes in the oriented or non-oriented manner, the GCEs being the most widely used electrode. With CNTs as oriented, modifications of the electrode are made by depositing CNTs on the surface. The CNTs placed in this way serve as molecular cables that provide electrical transmission between the electrode surface and the redox enzyme [78].

Based on leading studies, the CNT-modified electrodes increase the electron transfer reactions at lower potentials and minimize the surface degradation of the sensors compared to the CNT- non-modified electrodes [5, 79]. Moreover, improved electrode sensitivity by CNTs results in improved detection performance in biosensors is possible. These advantages have increased interest in CNT-modified electrodes [80].

2.7 Biosensors based on functionalized CNTs

There is an increasing requirement for fast, low-cost, reusable, reliable and sensitive detection systems for the environment and human health. Numerous traditional methods need very special tools and are additionally slow, high cost, and limits in sensitivity and reproducibility. On the other hand, it has been reported in a large number of studies that the selectivity and sensitivity performance of detectors increased significantly with CNT modification. Thanks to the before-mentioned unique structures and properties, the CNT can be used as an active component of sensors for the detection of biomolecules. Furthermore, in the biosensing systems designed with CNTs, a wide variety of features, exist together, can be found that cannot be achieved with conventional biosensors designed with single, and multi-crystalline structures [81, 82]. Therefore, in this chapter, CNTs-based biosensor studies in the literature are classified and investigated according to enzymes.

2.7.1 Glucose biosensors based on functionalized CNTs

Since glucose is an important molecule in the diagnosis of diabetes and fermentation technology, the determination by enzyme-CNT electrodes is the most widely performed analyte [83]. Many strategies are used for the immobilization of enzymes for glucose determination. For instance, Gokoglan et al. [84] produced a new flexible glucose biosensor using vertically aligned CNTs and a conjugated polymer (CP) to determine the glucose content in various beverages. They reported that this new biosensor showed superior kinetic parameters such as high sensing capacity and high sensitivity. They also emphasized that the novel matrix with the new combination they synthesized offers excellent immobilization for biomolecular deposition [84].

In another study, new glucose oxidase (GO_x) based catalysts that can exactly calculate the concentration of glucose in the blood, increase the sensitivity of the glucose biosensor and make glucose measurements at the widest possible concentration range are developed. The CNTs reinforced hybrid composite material was synthesized in this catalyst. In the analyses performed, it has been shown that high-performance glucose biosensor can be developed with excellent properties such as high catalytic activity, and high chemical stability of CNTs-modified hybrid material. Additionally, it has been proven that biosensors can be used effectively for hypoglycemia and diabetes real patients [85].

Song et al. [86], the use of CNTs with mesoporous metal–organic frameworks proved to be effective in the development of more effective biosensors in the determination of glucose detection. In the new composite they developed, they combined the micropores of Tb @mesoMOFs with the ultra-high surface area, and excellent electrical conductivity of CNTs. Thus, the new hybrid material served as a support matrix for loading as a methylene green (MG) and electron mediators and glucose dehydrogenases (GDH) as an electrocatalyst on a GCE to form the electrochemical glucose biosensor (Fig. 8). As a result, they reported that CNT modified hybrid material developed a rapid electron transfer and could provide large surfaces for immobilization. They stated that CNT modification also causes high performance in glucose detection [86].

CNT modified biosensors can also be used in photoelectrochemical applications. For instance, Cakiroglu and Ozacar [87] developed a self-powered photoelectrochemical (PEC) glucose biosensor with CNT and CO_2O_4 modification. They also indicated that CNT was added to the system to improve the supercapacitor behavior of the photoelectrochemical sensor [87].

Nowadays, in glucose sensing applications, researchers have shown interest in electrode modification with the composites they form with CNTs. This is because of the multifunctional glucose sensing devices are obtained by hybrid structures formed by combining one or more of the structures of polymer [88, 89], nanoparticles [90], metallic nanosheets [91–93], alloys and bimetallic particles [94], and other carbon allotropes [95] with CNTs. Consequently, recent studies have shown that the superior electronic properties of CNTs that can be functionalized by various and different nano-sized materials or molecules play a

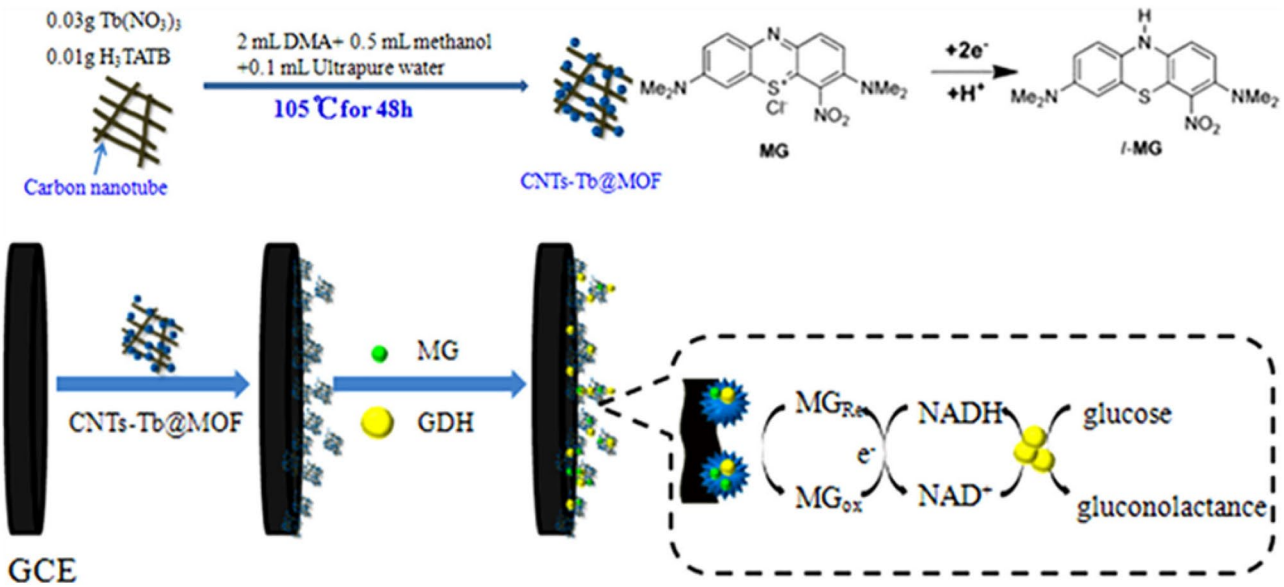


Fig. 8 Detection principle of CNT modified novel glucose biosensor [86]

crucial role in the development of novel hybrid materials that are promising to be used in the glucose biosensor.

2.7.2 Urea Biosensors based on functionalized CNTs

Urea is the most important end product of protein degradation and is essential for the proper balance of blood in general. The optimum concentration of urine in the blood is an indicator of correct kidney function and therefore the determination of the amount of urea in the blood is also important [96]. On the other hand, as previously mentioned, the structural modifications of the CNTs have led to their use in combination with a wide range of hybrid materials in biosensor applications. Because of its suitability for cell immobilization, and high electrical properties, CNTs have been promising material in urea-sensor applications. In this chapter, there are some of the pioneering works done for this purpose.

Ahuja et al. [96] produced a new urea biosensor with urease immobilized MWCNTs embedded in the silica matrix deposited on the surface of the indium tin oxide (ITO) coated glass plate. They stated that MWCNTs with high electrocatalytic activity also offer high urease enzyme immobilization. They reported that the CNT-based biosensor compared with classical urea biosensors showed high urea detection and rapid response time [96]. A similar study was carried out by Tak et al. [97]. They synthesized a matrix containing a hybrid nanocomposite of zinc oxide (ZnO) and MWCNTs on indium tin oxide coated glass sheets for the development of an effective urea biosensor. They stated that the presence of MWCNT, which offers a large surface area and high electronic conductivity for enzyme immobilization, has a significant contribution to the determination of urea [97].

Nguyen and Yoon [98] prepared an enzymatic electrode by the sequential coating of CNTs, urease (Urs) and polyion complex on an ITO glass. They reported that the addition of CNTs in this new electrode for the urea biosensor caused a significant increase in urea sensitivity of the electrode [98]. In 2016, the same authors developed a non-enzymatic highly sensitive urea biosensor with a new CNTs-based hybrid composite material. They deposited nickel oxide in a cellulose/CNTs composite and modified this material to electrodes. They reported that modified electrodes showed high feasibility for urea analysis in urine samples [99].

In their study, Dervisevic et al. [100] modified the CNTs to the Au electrode and designed the new urea biosensor based on the immobilization of the urease enzyme. They investigated the performance parameters such as the potential applied with optimum pH, temperature and reproducibility. Additionally, they demonstrated that the electrode has an excellent performance in the detection of urea in undiluted human blood plasma [100].

Similar to glucose detection, today, intense interest in mixed hybrid materials with CNTs is noteworthy in the urea sensing applications [101–104]. For instance, Hassan et al. [105] synthesized CNT hybrid materials with conductive polymer for direct detection of urea in blood samples. Hassan et al., stated that the highest electrochemical signal was obtained by poly-o-toluidine (PoT)/CNT and emphasized that no electrochemical signal was obtained from the polymer when used alone (Fig. 9). As a result, they reported that the sensor platforms obtained with CNT/PoT/screen-printed electrodes offer superior properties such as high redox reactions, surface modification, structural control, and large-scale production [105].

2.7.3 Immunosensors based on functionalized CNTs

Immuno-sensing is based on standard bioavailability analysis of hybrid materials with enzyme, fluorophore

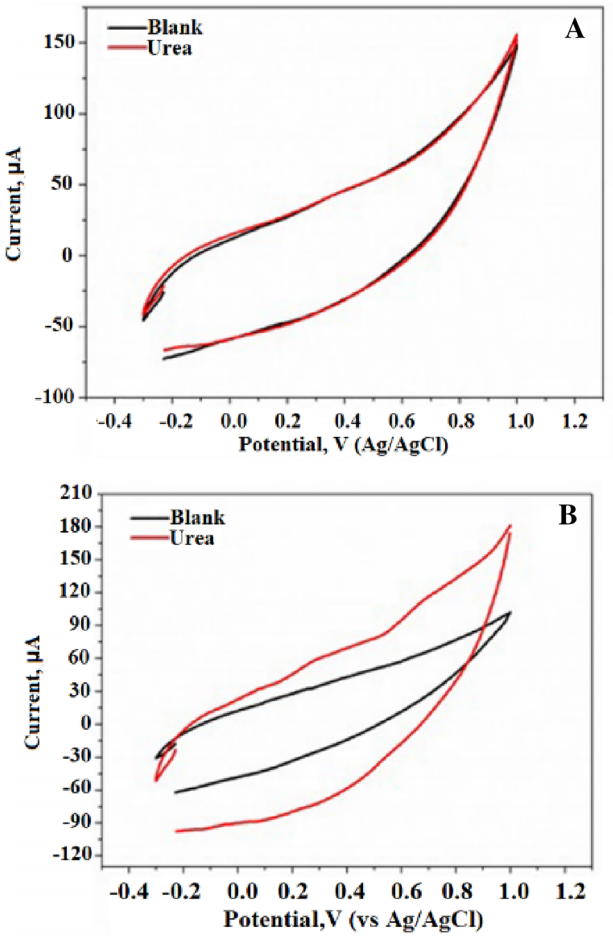


Fig. 9 CV profiles for the direct electrochemical responses of immobilized urease; PoT (alone) (**a**), PoT/CNT (**b**) [105]

or nanoparticle labels to detect disease-related proteins and chemical toxins. As with most biosensors, responding directly to the analyte and getting an immediate response are the features that should be in immunosensors. CNTs are widely used in the development of these features due to their high electronic properties. In this section, studies on immunosensors developed by CNT are summarized.

Yun et al. [106] synthesized highly oriented MWCNTs on a $Fe/Al_2O_3/SiO_2/Si$ substrate via a CVD method. By electrochemically activating the CNT modified electrode they obtained, they exposed the COOH groups on the surface and immobilized anti-mouse IgG to these ends. They proved that the CNTs-modified electrode has a fast electron transfer with cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) analyses. They also reported that CNTs for the immunosensor applications can easily be produced on the electrode and that the sensor they obtain has high sensitivity [106].

In another study, Lin et al. [107] immobilized the antigen, gold nanoparticles, and CNT-doped chitosan film on the GCE to produce a high-sensitivity immunosensor. They stated that the sensor they developed to detect α-fetoprotein (AFP) in human serum could be applied to other antigens or other bioactive molecules. Additionally, they reported a high detection limit for AFP and high surface area for cell immobilization with CNT additive. They also demonstrated that the biosensor has good bioactivity and high storage stability [107].

In their study Singh et al. [108] used graphene oxide and CNT to develop a reusable, low cost and effective immunosensor for lung cancer. They stated that the immunosensor they developed by CNT-based nanocomposites had superior properties such as the highest current, high stability, reproducibility. In addition to this, they reported that the rapid response to the analyte with CNT additive [108].

Moreover, it can be seen different hybrid materials which contain CNTs in immuno-sensing applications, as in the before-mentioned glucose and urea sensing applications [109–111]. For instance, Rezaei et al. [112] have developed a highly sensitive immunosensor for use in the diagnosis of cardiovascular diseases. They stated that CNTs offer a high surface area for immobilization by embedding into nanofibers (WNF), which they used as transducer platforms. For the detection of Cardiac Troponin I (cTnI), the integration of the immunocomplex (anti-cTnI/cTnI/HRP-anti-cTnI) into the CNTs and the production of the immunosensor is shown in Fig. 10. As a result, they developed an immunosensor that exhibits good selectivity, reproducibility, wide detection range properties [112].

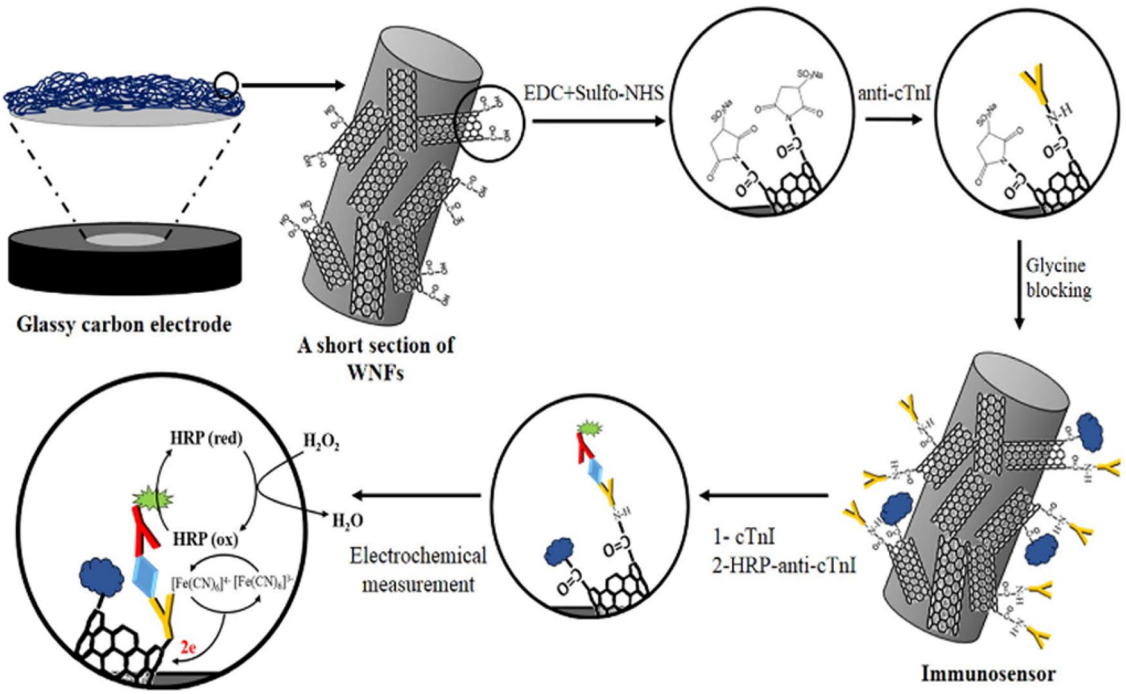


Fig. 10 The stepwise production of the immunosensor [112]

3 Fullerenes

With the discovery and production of fullerenes, a very promising member of the carbon nano-structure family, and a field of research involving organic transformations of other carbon-based hollow nanomaterials have come into question. The C_{60}, which is the most comprehensive member of the fullerenes, has attracted great attention in recent years due to the opportunities offered by its nearly global structure with its closed cage system. The C_{60} may be electronically defined as having a closed shell configuration containing 30 bonding molecule orbital with 60 p electrons. On the other hand, the C_{60} offers high advantages such as having a high symmetry, being relatively inexpensive, being relatively inert (in mild conditions), easily producible, and relatively non-toxic. In addition, fullerenes have unusual properties such as multiple redox states, stability in many redox forms, signaling, light source switching, and easy functionalization. As a result of these outstanding features, the C_{60} structure has been used in many different applications such as superconductors, sensors, biosensors, catalysts, the development of optical and electronic devices [7, 113]. Furthermore, publications related to biomedical applications of fullerene have been investigated in the Scopus database, from 2009 to 15th February 2019, using keywords such as cancer, photodynamic therapy, antiviral, anti-bacterial, HIV, DNA, toxicity, biosensor, antioxidant, imaging, drug delivery, stem cell, and Fig. 11 shows the distribution of these areas. The aim of this section is to introduce the biosensors based on the fullerene-C_{60} and different biological components and to present recent developments and innovations.

3.1 History of fullerenes (C_{60})

Fullerene consists of curved pentagons and hexagons that form a fused structure. The smallest, most synthesized, and most stable fullerene acquired by the customary production technique is the Ih-symmetric buckminsterfullerene C_{60}. The breakthrough of Buckminsterfullerene (C_{60}) was made in 1985 by R. Smalley, R. Curl, and H. Kroto who received the 1996 Nobel Prize in Chemistry. The stable structure after C_{60} is C_{70}. Additionally, C_{74}, C_{76}, C_{78}, C_{80}, C_{82}, C_{84},etc. fullerene structures are also available.

In 1966, the Daedalus had thought of the possibility of creating the large hollow carbon cage (giant fullerene). In the following years, there was an ongoing adventure with the latest discovery of C_{60} ions in space as seen in the nano-system and nanotechnology field. Pioneering studies (Table 2) on fullerene discovery were carried out between 1983–1990 [27, 114].

3.2 Structure and features of fullerenes (C_{60})

Fullerene offers a high symmetrical lattice in different sizes (C_{60}, C_{76} and so on) with its unusual structure containing sp^2 carbons. The most abundant types of fullerene in the synthesized are C_{60} and C_{70}. Each fullerene with $2n+20$ carbon atoms consisting of n hexagon. The C_{60} contains 60 carbon atoms, and in terms of shape, the fullerene C_{60} is as a soccer ball, it comprises 12 of pentagons with 60 vertices and a polygonal with 32 faces and 20 of them are hexagons. Regarding the crystallographic features of the fullerene molecule, the existence of symmetrical elements containing 30 two-ply axes, 20 three-ply axes, and 12 five-ply axes made fullerene the most symmetric molecule controlled by the Gold Mean rule.

Different spectroscopic methods such as Raman spectroscopy, UV–Vis, NMR and FTIR can be used in the

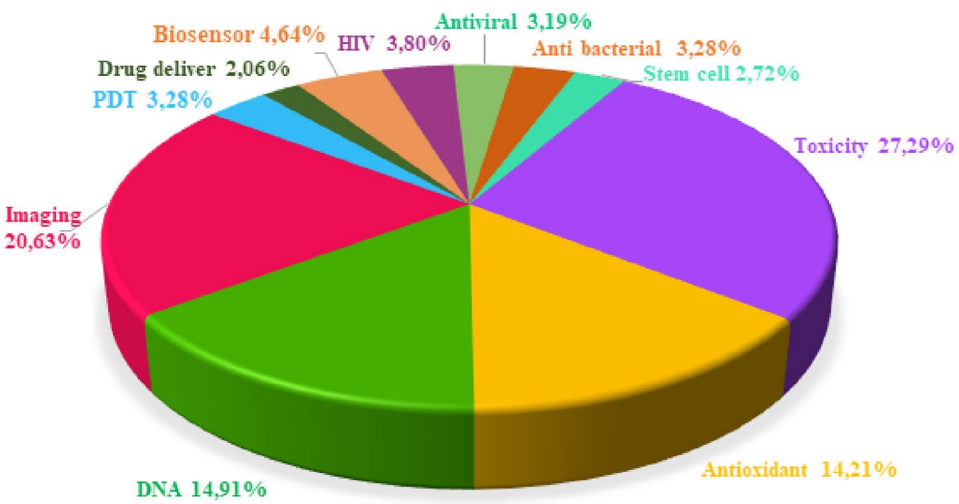


Fig. 11 Pie chart showing the distribution of fullerene in biomedical applications

Table 2 Historical progressive of fullerene

Date	Event
1966	D.E.H Jones thought of the structure of a giant fullerene
1970	Osawa proposed the spherical Ih-symmetric soccer ball structure for the first C_{60} molecule
1984	It was observed that large carbon clusters (Cn) could be obtained via laser evaporation of graphite
1985	Kroto and Smalley proved the existence of C_{60} and C_{70}, which can be produced under specific clustering conditions
1990	Kratschmer and Huffman identified the C_{60}'s absorption line in laboratory analogs of interstellar powders
2010	Fullerenes (C_{60}) were discovered in a cloud of cosmic dust at 6500 light-years away

characterization of this symmetric molecule. On the other hand, fullerene is a nanomaterial compatible with biomolecules. The C_{60} is capable of producing oxygen species when exposed to visible light and makes it an appropriate candidate for photodynamic therapy. Moreover, the C_{60} has thermal stability in the solid phase with medium-phase cubic lattices (FCC).

Fullerene has an interesting behavior of solutions and its solubility has been investigated by controversial experiments. However, the solubility of the fullerenes is unclear, and a reliable theory has not yet been suggested to clarify the behavior of the fullerenes in the various solvents. Fullerene is readily soluble in organic (especially aromatic) solvents such as toluene, chloroform, and benzene due to its hydrophobic structure, whereas the solubility is very low in polar solvents, and this is important for biological and medical applications. Several techniques have been developed to increase the solubility of fullerene in the water, such as the preparation of biphasic colloidal solutions, the synthesis of fullerene derivatives. The hydrophobicity of the fullerene ensures some degree of compatibility in a biological environment. However, the hydrophilicity of the materials in biological media is of greater significance compared to hydrophobicity [27, 115, 116]. To provide the integration of fullerene into biological environments, the addition of various polar functional groups or molecules into the fullerene core overcomes the almost complete insolubility of the C_{60} and at the same time retains the unique natural fullerene properties and achieves reasonable bioavailability [117].

As mentioned previously, each carbon in a fullerene-C_{60} atom is bound to the others and the sp2 is hybridized. The C_{60} molecule has two bond lengths, 6: 6 ring bonds are acceptable as double bonds and are shorter than 6: 5 bonds. C_{60} is not super aromatic and results in weak electron delocalization. For this reason, the spherical C_{60} acts as an electrically insufficient alkene and reacts handily with electron-rich species. The C_{60} has a good electron affinity (EA) (2.7 eV) and a good ionization potential (IP) (7.8 eV). These values show that it can readily promote the electron transfer reaction and has a superior electrochemical behavior that makes them suitable candidates for biosensing applications [7, 117].

3.3 Synthesis of fullerenes

Fullerene can be produced by a laser beam on the graphite in the helium atmosphere. However, the total yield is insufficient considering the potential application areas and industrial areas. Therefore, various methods are developed for the synthesis of an effective and efficient fullerene [7]. The second method proposed in the synthesis of fullerene is the laser ablation of graphite. This method permits the production of macroscopic amounts of fullerene from the graphite under high-temperature conditions. In this method, materials are removed from the solid surface using a laser beam. When the graphite is exposed to the laser beam, the materials removed from the solid surface evaporate, and to become plasma. By cooling the gas, the vaporized and combined atoms form the fullerene [7, 118]. Another alternative method proposed in the synthesis of fullerene is the arc-discharge process. The arc discharge of graphite is one of the most common techniques used in the production of novel fullerenes. In this method, the graphite evaporates with the electric arc formed between the two electrodes. However, the temperature conditions of the carbon arc prevent an existing device for detecting the types that occur during the production. On the other hand, there are also non-equilibrium plasma methods where the fullerene is produced without a high temperature [7, 119].

3.4 Functionalization of fullerenes

Fullerenes have great potential for use in materials science and biological applications as previously mentioned. However, fullerenes cannot be used in full yield due to the limited solubility in the polar solvent, the hydrophobicity of the carbon cage, and the tendency to agglomeration. To overcome these problems, fullerenes can be chemically modified. They can be organically derivatized by various reactions. The hydrophobic surfaces of the fullerenes can be functionalized and converted to hydrophilic for

therapeutic purposes. With functionalization, different and useful extensions can be added to the nearly spherical structure of the fullerenes, so that they can be gained novel features. The functionalization process changes the solubility and electrochemical properties of the fullerenes. Therefore, the application areas and diversity of the fullerenes also increase [27, 120, 121].

In view of the closed cage system of the C_{60}, the added substances can be added to the central surface of the C_{60} and the most reaction occurs at the hexagonal-hexagonal edges. Some of these reactions are the Bingel reaction, called as nucleophilic cyclopropanation of the C_{60}, [4 + 2] cycloaddition (Diels Alder reaction), [3 + 2] cycloaddition (Prato reaction), and [2 + 2] cycloaddition [27, 122].

3.5 Fullerenes in biosensors

At present, we see a wide range of biosensors based on different physicochemical detectors used for recognition and classification, remote sensing of bacteria in the air, detection of pathogens, and other human and environmental healthcare applications. Since its discovery, biosensors have attracted a great deal of interest by researchers. However, in the development of biosensors, the discovery of the fullerene (C_{60}) has made a breakthrough. The reason for this is due to the nature of the fullerene unique properties. These features include wide light absorption in the UV–Vis region, a combination of nucleophilic and electrophilic dual properties, structural angle tension, singlet oxygen production, the ability to be doped with multiple electrons and endohedral metal atoms, photo-thermal effect, long life triple state, the ability to act as an electron acceptor [2]. Due to these unique functions, fullerene has the advantage of offering high sensitivity to various biological and biomedical analysts, improved sensitivity, high selectivity, real-time responsiveness, and rapid signal transmission. Moreover, fullerenes that are not dangerous to biological systems and materials are sufficiently small so that they can detect close distance in the active areas of the biomolecules. They can also easily exchange electrons to species surrounding the biomolecules. Furthermore, they serve as an ideal substrate to receive and release electrons to a transducer. Consequently, it possesses a high potential for biosensor applications [7, 123].

In the part of the identification of a biosensor, biological constituents such as antibodies, cells, microorganisms, organelles, enzymes, and tissues are utilized. Fullerenes are used as a mediator between the identification part and the electrode of a biosensor to increase the speed of electron transfer generated by reason of the biocatalytic or biochemical reaction of the analyte in contact with the biological element at the identification field (Fig. 12) [2].

3.6 Modification of electrodes with fullerenes

Electrodes modified chemically with fullerene (C_{60}) were first presented in Compton et al [124]. They performed immobilization by dropping C_{60} films onto the surface of the electrodes. They then covered the electrodes with a protective film. In their analysis, they reported that obtained a better signal [124]. After this pioneering work, the electrochemical behaviors of C_{60} modified electrodes in aqueous solutions were meticulously investigated. Nowadays, chemically modified electrodes with C_{60} can be produced via different methods such as physical vapor deposition [125], dropping [7], electrochemical deposition [126], electro-polymerization [127].

3.7 Biosensors based on functionalized fullerene

New hybrid materials with unique properties are created by combining two or more different materials. Bio-macro molecules and nano-sized carbon materials are utilized in the establishment of various hybrid materials. Superior hybrid materials are produced by combining biomolecules and carbon-based nanomaterials, and research is being carried out for use in biosensor applications [7]. Fullerene has been a leading nano-sized carbon allotrope in the formation of hybrid materials with bio-molecules due to the before mentioned superior properties. Therefore, it is one of the most remarkable carbon-based nanomaterials in nano-biosensor design and development. In this section, fullerene-based biosensor studies are classified and investigated according to enzymes.

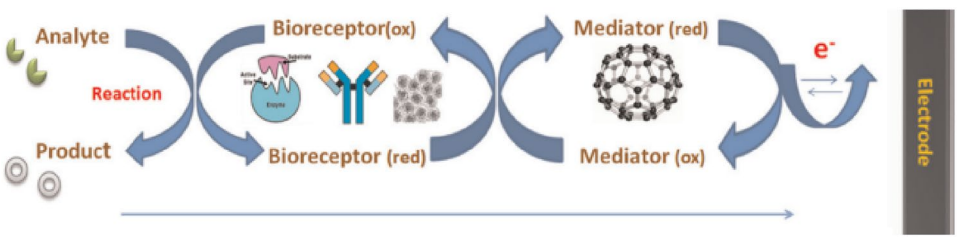


Fig. 12 Biochemical signal to electric signal: Role of fullerene [2]

3.7.1 Glucose biosensors based on functionalized fullerene

Diabetes mellitus, a chronic disease caused by insufficient insulin secretion, leads to increased mortality rates worldwide. Hence, the determination of blood glucose levels is of vital importance to reduce the complications associated with diabetes. Among the various analytical methods available, the traditional electrochemical glucose sensor is commonly preferred because of its features previously mentioned [128]. However, in the detection of glucose in the blood, other biological molecules in the blood (galactose, tyrosine, uric acid, cysteine, etc.) prevents the determination of glucose.[129, 130]. In order to overcome this obstacle, the use of the fullerene in biosensors is recommended. In the production of various biosensors such as piezoelectric and amperometric sensors, glucose detection using fullerene was first performed by Gavalas and Chaniotakis. Gavalas and Chaniotakis [131] developed an amperometric biosensor for the detection of glucose oxidase (GO_x) enzyme using different amounts of fullerene in their study. They reported that the sensitivity of the biosensor they obtained increased with the rise in the quantity of fullerene [131]. In another study conducted on the same dates, novel glucose bio-sensor was designed by plating fullerene-cryptand-22 with piezoelectric (PZ) quartz crystal on silver metal electrodes, and the results suggested that the fullerene-based biosensor exhibits superior sensitivity to molecules of glucose.[129]. Later, Zhilei et al. [132] produced fullerene-modified glucose biosensor by utilizing ferrocene (Fc), chitosan (CS) and ionic fluid (IL). Thus, GO_x served as a catalyst in the oxidation of glucose determined by the electrodes. Zhilei et al., emphasized the need for a biocompatible media to provide electron exchange between GO_x and electrodes, and enzyme immobilization. In their study, Fc, CS, and IL with the use of fullerene ensured this necessity. Figure 13 shows the cyclic voltammogram of the modified glassy carbon electrode (GCE) sample in the absence of glucose and at different glucose concentrations [132].

Lin and Shih [133] developed an electrochemical glucose sensor based on the cobalt (II) hexacyanoferrate and fullerene C_{60}-enzyme. In their study, glucose in aqueous solution was oxidized with C_{60}-oxidase (O_x) on GCE. Oxidation of the reduced C_{60}-GO_x (dark) with oxygen (O_2) was then realized in solution and H_2O_2 was generated. H_2O_2 is capable of oxidizing the cobalt (II) hexacyanoferrate ($Co_3[Fe(CN)_6]_2$) on the GCE. The oxidized cobalt (II) hexacyanoferrate is reduced by an electrode voltage applied at 0.0 mV (according to the Ag/AgCl reference electrode). Thus, the reduced current can be quantitatively measured for the analysis of glucose. Additionally, Lin and Shih reported that this new electrochemical glucose sensor had an effective electrocatalytic activity, high reproducibility,

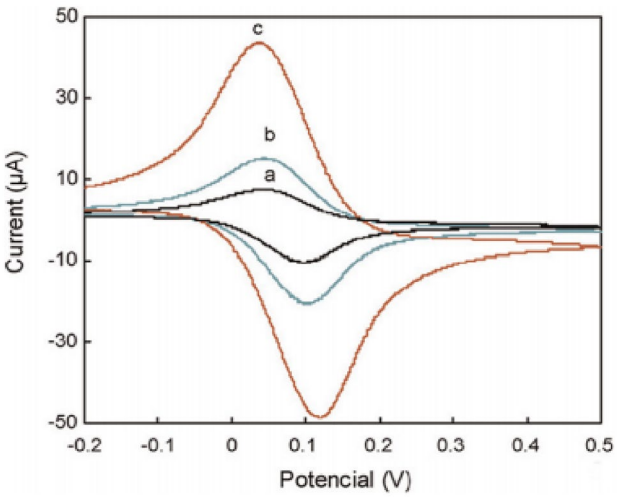


Fig. 13 Cyclic voltammogram of fullerene modified electrode at pH 7.0 PBS and at 100 mV/s; **a** in the absence of glucose, **b** presence of 1.0 M glucose, **c** 5.0 M glucose [132]

and high selectivity [133]. In another study, Thirumalraj et al. [134] designed a glucose biosensor with GCEs modified with reduced graphene oxide (RGO) and fullerene (C_{60}) composite. They stated that the biosensor they produced had a good ability to detect glucose in human blood serum samples. Furthermore, the biosensor prepared by simple electrochemical reduction of the GO-C_{60} (Fig. 14a), showed a wider response interval than other electrodes, a rapid response time of 3 s, and high sensitivity. Additionally, amperometric responses (Fig. 14b) from the biosensor they developed proved to have good potential for real-time detection of glucose in blood serum samples [134]. The study, in which the ultra-sensitive glucose biosensor was produced by the modification of another GCE with fullerene, was carried out by Ye et al. [135]. They deposited tetraoctylammonium bromide-functionalized fullerene on the surface of GCE and reported that the sensor they designed was highly sensitive to detect the glucose in the saliva [135].

The studies showed that fullerene contributes to a large extent to develop advanced products and designs for glucose biosensors. Sutradhar and Patnaik [136] using the 3-amino-5-mercapto-1,2,4-triazole as the ligand, produced a new generation fullerene C_{60}-thiol-coated gold nanoparticle-based nano-composite. They reported that the GCEs they modified with their composite showed high sensitivity in the detection of glucose, and additionally had high selectivity, repeatability, long-term stability, anti-interference ability and resistance to chloride poisoning [136]. In another study, Piotrowski et al. [137] developed a new hybrid system based on a glucose dehydrogenase immobilized on C_{70} fullerene coated

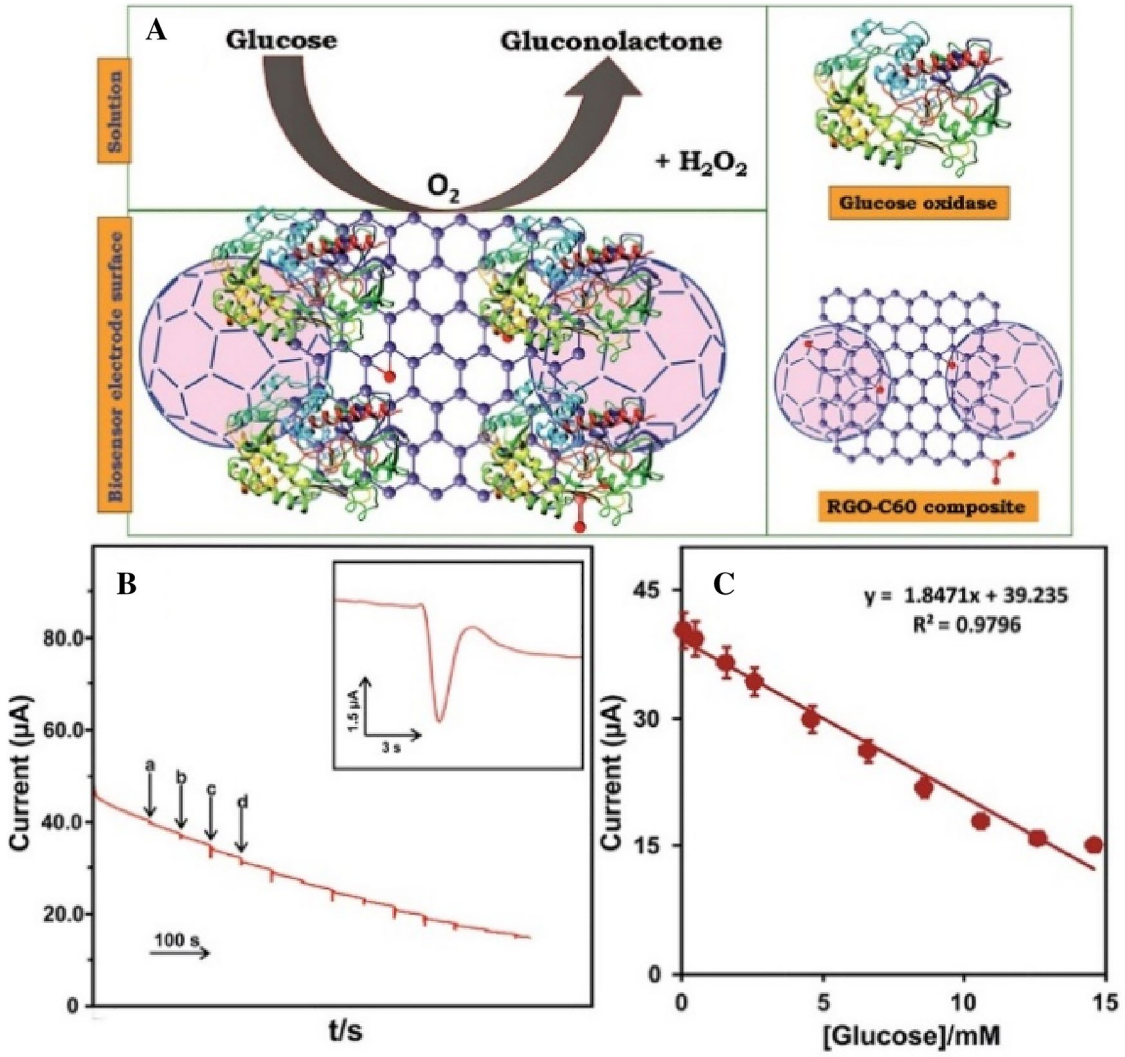


Fig. 14 **A** Schematic presentation for the sensing of glucose at RGO–C60/GOx biosensor. **B** Amperometric i–t response from glucose sensor for the addition of (*a*) 0.1 mM, (*b*) 0.5 mM, (*c*) 1 mM of glucose, (*d*) up to 14.6 mM glucose into the constantly stirred oxygen saturated PBS; working potential is −0.42 V. Inset shows the enlarged view of amperometric response of the biosensor for addition of 1 mM glucose into the solution, and **C** The calibration plot [134]

gold nanoparticles (AuNP) for the efficient biosensor and quantitative detection of glucose. According to the amperometric measurements, the hybrid biosensor they designed showed high sensitivity, wide linear range and fast characteristic response (3 s). They emphasized that the new hybrid nanocomposite prepared with these unique properties has a strong potential as a biosensor which can be used for the fast and quantitative determination of glucose [137].

Therefore, pioneering studies have shown that fullerenes that can be functionalized with various and different nano-sized materials or molecules are promising materials in biosensor applications for the detection and diagnosis of glucose.

3.7.2 Urea biosensors based on functionalized fullerene

Urea, the final product of protein metabolism, is generally used as a nitrogenous fertilizer for plants. In addition to medical diagnosis, it is significant to determine the urea in the food industry, agriculture, and biochemistry [138]. Similar to the previously mentioned study on the determination of glucose in the blood [131], Wei and Shih [139], in their study, they developed a piezoelectric-fullerene biosensor for urea detection in urine. Similar to the glucose biosensor of Gavalas and Chaniotakis [131], they covered the surface of PZ quartz crystal using fullerene- cryptand -22 and proved that urea can be detected in urine with the new fullerene-based biosensor [139]. Likewise Chou et al.

[140] developed an immobilized urease-based Fullerene C_{60}-cryptand-22 coated piezoelectric quartz crystal urea sensor. The experimental setup they prepared (Fig. 15) contains the C_{60}-urease enzyme membrane immobilized for the piezoelectric quartz crystal urea detection system. They stated that the piezoelectric urea sensor they developed showed high sensitivity, repeatability and relatively good selectivity for urea [140].

Saeedfar et al. [141] developed a fullerene-modified bio-conjugate sensor on an acrylic-based hydrogen ion-sensitive membrane to detect the quantity of urea in the urine sample. They functionalized the fullerene by sonication, heat, and ultraviolet (UV) radiation and then realized the immobilization process. They have proven that the functionalized fullerene-based biosensor they designed has 2 min for each determination and that the responses show good sensitivity and response time [141].

Yao et al. [138] developed a deep yellow fullerene (C_{60}) colloid under the ultrasound conditions to determine the amount of urea in food products. In their study, they used fullerene as a donor. The reason for this is that the fullerene had two strong RRS (resonance Rayleigh scattering) peaks at 385 and 530 nm. Following an increase in urea concentration, they emphasized that the intensity of RRS decreased at 530 nm due to the increase in RRS-ET, thus they explained the urea determination mechanism of the fullerene (Fig. 16) [138].

3.7.3 Immunosensors based on functionalized fullerene

There are numerous studies on the development of C_{60}-based immunosensors in the medical diagnosis of various disorders that occur because of any deterioration in our body's metabolism [2]. Recently, some studies have been carried out with real samples, and the capability of C_{60}-modified immunosensors has been demonstrated in the determination of microorganisms [142–144]. Additionally, the use of fullerene in immunosensors has been reported to facilitate the electron transfer between the redox proteins and the electrode [145].

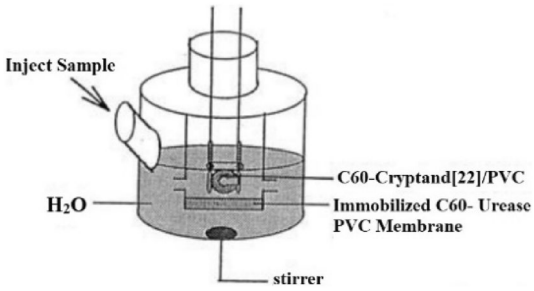


Fig. 15 The sample mechanism of urea piezoelectric crystal sensor with immobilized C_{60}-urease membrane [140]

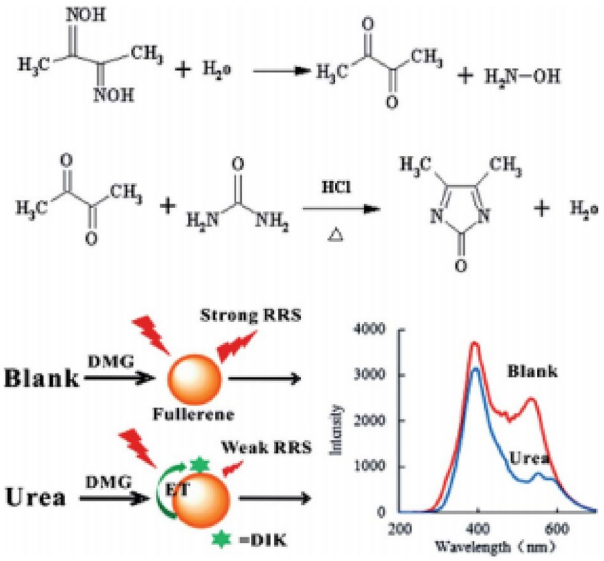


Fig. 16 Mechanism of the RRS-ET method for the detection of urea [138]

Pan and Shih [146], in their study, have used the antibody immobilized fullerene to detect immunoglobulin G (IgG) and hemoglobin (Hb) which have a very critical role in the human immune system. For this purpose, they prepared C_{60}-fullerene-antibody-coated quartz crystals and firstly added the C_{60} to metal electrodes coated with silver (Ag). Following this process, they carried out the adsorption of antibodies such as anti-human IgG and anti-hemoglobin with an aqueous solution (Fig. 17) [146]. A similar study was performed in 2013 by the production of C_{60}-myoglobin (C_{60}-Mb), C_{60}-Hb and C_{60}-gliadin coated piezoelectric (PZ) quartz crystal immunosensors by Liao and Shih [147].

Mazloum-Ardakani et al. [148] has developed nanocomposites containing fullerene-functionalized CNT and ionic fluid for use in the non-enzyme detection of tumor necrosis factor α antigen (TNF-a). They stated that the new and sensitive electrochemical immunosensor they designed to exhibit high electrocatalytic behavior [148].

In their study Demirbakan and Sezginturk [149] designed an immunosensor with a GCE modified with C_{60} to determine the heat shock protein 70 (HSP70) in

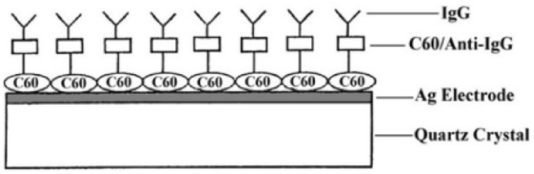


Fig. 17 C60-based quartz crystal electrode [146]

human blood serum samples. They reported that the biosensor they obtained showed high reproducibility [149].

The widespread use of *Enrofloxacin* (Enro), a type of antibiotic used against bacterial infections in livestock raising, causes permanent residues in the environment and adverse ecological effects. Chen et al. [150] have carried out the production of fullerene mats chemically modified by Au nanoparticles for use in the detection of Enro. Consequently, they obtained fullerene-based high-quality Enro-immonusensor with high-sensitive [150].

In summary, studies have shown that fullerene which is immobilized with various biomolecules can be an important component in immunosensors used to detect other biomolecules produced due to metabolism.

4 Conclusion and future prospective

In this review, various biosensor applications, features, and structures of CNTs and fullerenes are summarized. The use of CNTs and fullerenes as a biosensor component has led to breakthrough discoveries. The surprising chemical, optical, electrical and mechanical properties of CNTs and fullerenes play an important role in providing vital features in biosensor applications. Various biochemical particles can be integrated into CNT and fullerene structures through covalent/non-covalent methods. Thus, the immobilization can be achieved. Moreover, CNTs and fullerenes have a high surface area/volume ratio, therefore, they offer a large immobilization area for the molecule to be detected in biosensor applications. CNTs and fullerenes are easily accessible due to their small size in the detection of small particles that are not accessible by conventional biosensors. Thus, these nano carbon materials can be used as a tool in different biosensor platforms to prevent environmental threats, deadly diseases, and infectious diseases. However, there are still difficulties in terms of practical applicability in the use of these carbon nanomaterials in biosensor applications. The current stage of research on these nano-carbon needs the synthesis methods, the improvement of these methods, standardizations to achieve consistent characterizations, and experimental results, toxicity assessment, and the development of these nano-carbon in industrial application. Future works require an interdisciplinary study of fields such as materials science, biology, and electrical engineering. In the near future, it is thought that the development of hybrid nanostructures with CNTs and fullerene-based electrodes will result in the production of fast, efficient, reliable, low-cost biosensors in areas such as food, packaging, quality, homeland security, diagnosis of diseases, agriculture.

Acknowledgements The authors appreciate to Dokuz Eylul University, Center for Production and Applications of Electronic Materials (EMUM) that inspiration of this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Yang N, Chen X, Ren T, Zhang P, Yang D (2015) Carbon nanotube based biosensors. Sens Actuators B Chem 207:690–715
2. Afreen S, Muthoosamy K, Manickam S, Hashim U (2015) Functionalized fullerene (C60) as a potential nanomediator in the fabrication of highly sensitive biosensors. Biosens Bioelectron 63:354–364
3. Minot ED, Janssens AM, Heller I, Heering HA, Dekker C, Lemay SG (2007) Carbon nanotube biosensors: the critical role of the reference electrode. Appl Phys Lett 91(9):093507
4. Solanki PR, Kaushik A, Agrawal VV, Malhotra BD (2011) Nanostructured metal oxide-based biosensors. NPG Asia Mater 3:17
5. Balasubramanian K, Burghard M (2006) Biosensors based on carbon nanotubes. Anal Bioanal Chem 385(3):452–468
6. Farka Z, Juřík T, Kovář Trnková Skládal DLP (2017) Nanoparticle-based immunochemical biosensors and assays: recent advances and challenges. Chem Rev 117:9973–10042
7. Pilehvar S, De Wael K (2015) Recent advances in electrochemical biosensors based on fullerene-C60 nano-structured platforms. Biosensors 5:712–735
8. Sotiropoulou S, Gavalas V, Vamvakaki V, Chaniotakis NA (2003) Novel carbon materials in biosensor systems. Biosens Bioelectron 18:211–215
9. Beitollahi H, Movahedifar F, Tajik S, Jahani S (2018) A review on the effects of introducing CNTs in the modification process of electrochemical sensors. Electroanalysis 31(7):1195–1203
10. Sireesha M, Jagadeesh Babu V, Kranthi Kiran AS, Ramakrishna S (2018) A review on carbon nanotubes in biosensor devices and their applications in medicine. Nanocomposites 4:36–57
11. Erol O, Uyan I, Hatip M, Yilmaz C, Tekinay AB, Guler MO (2018) Recent advances in bioactive 1D and 2D carbon nanomaterials for biomedical applications. Nanomed Nanotechnol Biol Med 14:2433–2454
12. Kumar R, Singh R, Hui D, Feo L, Fraternali F (2018) Graphene as biomedical sensing element: state of art review and potential engineering applications. Compos B Eng 134:193–206
13. Suvarnaphaet P, Pechprasarn S (2017) Graphene-based materials for biosensors: a review. Sensors 17:2161
14. Yáñez-Sedeño P, Campuzano S, Pingarrón J (2017) Fullerenes in electrochemical catalytic and affinity biosensing: a review. C J Carbon Res 3:21
15. Prasad BB, Singh R, Kumar A (2017) Synthesis of fullerene (C60-monoadduct)-based water-compatible imprinted micelles for electrochemical determination of chlorambucil. Biosens Bioelectron 94:115–123
16. Tuerhong M, Yang XU, Xue-Bo YIN (2017) Review on carbon dots and their applications. Chin J Anal Chem 45:139–150
17. García-Mendiola T, Bravo I, López-Moreno JM, Pariente F, Wannemacher R, Weber K, Popp J, Lorenzo E (2018) Carbon nanodots based biosensors for gene mutation detection. Sens Actuators B Chem 256:226–233

18. Silva TA, Moraes FC, Janegitz BC, Fatibello-Filho O (2017) Electrochemical biosensors based on nanostructured carbon black: a review. J Nanomater 2017:1–14
19. Rifai A, Pirogova E, Fox K (2019). Diamond, carbon nanotubes and graphene for biomedical applications. Encyclop Biomed Eng 97–107
20. Martel-Estrada S-A (2018) Recent progress in biomedical applications of nanodiamonds. Nanosci Nanotechnol 8(1):11–24
21. Song Y, Luo Y, Zhu C, Li H, Du D, Lin Y (2016) Recent advances in electrochemical biosensors based on graphene two-dimensional nanomaterials. Biosens Bioelectron 76:195–212
22. Bollella P, Fusco G, Tortolini C, Sanzò G, Favero G, Gorton L, Antiochia R (2017) Beyond graphene: electrochemical sensors and biosensors for biomarkers detection. Biosens Bioelectron 89:152–166
23. Reina G, González-Domínguez JM, Criado A, Vázquez E, Bianco A, Prato M (2017) Promises, facts and challenges for graphene in biomedical applications. Chem Soc Rev 46:4400–4416
24. Orecchioni M, Ménard-Moyon C, Delogu LG, Bianco A (2016) Graphene and the immune system: challenges and potentiality. Adv Drug Deliv Rev 105:163–175
25. Wang J, Qiu J (2016) A review of carbon dots in biological applications. J Mater Sci 51:4728–4738
26. Mishra V, Patil A, Thakur S, Kesharwani P (2018) Carbon dots: emerging theranostic nanoarchitectures. Drug Discov Today 23:1219–1232
27. Mathur RB, Singh BP, Pande S (2016) Carbon nanomaterials: synthesis, structure, properties and applications. Taylor & Francis, Milton Park
28. Yan Q-L, Gozin M, Zhao F-Q, Cohen A, Pang S-P (2016) Highly energetic compositions based on functionalized carbon nanomaterials. Nanoscale 8:4799–4851
29. Schrand AM, Hens SAC, Shenderova OA (2009) Nanodiamond particles: properties and perspectives for bioapplications. Crit Rev Solid State Mater Sci 34:18–74
30. Luszczyn J, Plonska-Brzezinska ME, Palkar A, Dubis AT, Simionescu A, Simionescu DT, Kalska-Szostko B, Winkler K, Echegoyen L (2010) Small noncytotoxic carbon nano-onions: first covalent functionalization with biomolecules. Chem A Eur J 16(16):4870–4880
31. Kempel F, Schlarb AK (2008) Strain sensing with nanoscale carbon fiber–epoxy composites. Appl Mech Mater 13:239–245
32. Song X, Gunawan P, Jiang R, Leong SSJ, Wang K, Xu R (2011) Surface activated carbon nanospheres for fast adsorption of silver ions from aqueous solutions. J Hazard Mater 194:162–168
33. Lin Y, Sun X, Su DS, Centi G, Perathoner S (2018) Catalysis by hybrid sp2/sp3 nanodiamonds and their role in the design of advanced nanocarbon materials. Chem Soc Rev 47:8438–8473
34. Mochalin VN, Shenderova O, Ho D, Gogotsi Y (2012) The properties and applications of nanodiamonds. Nat Nanotechnol 7:11
35. Aversa R, Petrescu RV, Apicella A, Petrescu FI (2016) Nano-diamond hybrid materials for structural biomedical application. Am J Biochem Biotechnol 13:34–41
36. Yang N, Foord JS, Jiang X (2016) Diamond electrochemistry at the nanoscale: a review. Carbon N Y 99:90–110
37. Lounasvuori MM, Kelly D, Foord JS (2018) Carbon black as low-cost alternative for electrochemical sensing of phenolic compounds. Carbon N Y 129:252–257
38. Marinho B, Ghislandi M, Tkalya E, Koning CE, de With G (2012) Electrical conductivity of compacts of graphene, multi-wall carbon nanotubes, carbon black, and graphite powder. Powder Technol 221:351–358
39. Bokobza L, Bruneel J-L, Couzi M (2015) Raman spectra of carbon-based materials (from graphite to carbon black) and of some silicone composites. C J Carbon Res 1(1):77–94
40. Nieto-Márquez A, Romero R, Romero A, Valverde JL (2011) Carbon nanospheres: synthesis, physicochemical properties and applications. J Mater Chem 21:1664–1672
41. Miao J-Y, Hwang DW, Narasimhulu KV, Lin P-I, Chen Y-T, Lin S-H, Hwang L-P (2004) Synthesis and properties of carbon nanospheres grown by CVD using Kaolin supported transition metal catalysts. Carbon N Y 42:813–822
42. Zhang P, Qiao Z-A, Dai S (2015) Recent advances in carbon nanospheres: synthetic routes and applications. Chem Commun 51:9246–9256
43. Mohapatra J, Ananthoju B, Nair V, Mitra A, Bahadur D, Medhekar NV, Aslam M (2018) Enzymatic and non-enzymatic electrochemical glucose sensor based on carbon nano-onions. Appl Surf Sci 442:332–341
44. Sek S, Breczko J, Plonska-Brzezinska ME, Wilczewska AZ, Echegoyen L (2013) STM-based molecular junction of carbon nano-onion. ChemPhysChem 14:96–100
45. Mykhailiv O, Zubyk H, Plonska-Brzezinska ME (2017) Carbon nano-onions: unique carbon nanostructures with fascinating properties and their potential applications. Inorg Chim Acta 468:49–66
46. Zhu Z (2017) An overview of carbon nanotubes and graphene for biosensing applications. Nano-micro Lett 9:25
47. Huang J, Liu Y, You T (2010) Carbon nanofiber based electrochemical biosensors: a review. Anal Methods 2:202–211
48. Rao GP, Lu C, Su F (2007) Sorption of divalent metal ions from aqueous solution by carbon nanotubes: a review. Sep Purif Technol 58:224–231
49. Yellampalli S (2011) Carbon nanotubes-synthesis, characterization, applications. InTech, Rijeka, pp 191–217
50. Meyyappan M (2016) Carbon nanotube-based chemical sensors. Small 12:2118–2129
51. Schroeder V, Savagatrup S, He M, Lin S, Swager TM (2018) Carbon nanotube chemical sensors. Chem Rev 119:599–663
52. Giubileo F, Di Bartolomeo A, Iemmo L, Luongo G, Urban F (2018) Field emission from carbon nanostructures. Appl Sci 8:526
53. Gu Q, Chen J (2018) Carbon-nanotube-based nano-emitters: a review. J Lumin 200:181–188
54. Xiang L, Zhang H, Hu Y, Peng L-M (2018) Carbon nanotube-based flexible electronics. J Mater Chem C 6:7714–7727
55. Karnetzky C, Holleitner AW (2018) Towards femtosecond electronics based on single-walled carbon nanotubes. In: Betz M, Elezzabi AY (eds) Ultrafast phenomena and nanophotonics XXII Proc. SPIE 10530
56. Alshehri R, Ilyas AM, Hasan A, Arnaout A, Ahmed F, Memic A (2016) Carbon nanotubes in biomedical applications: factors, mechanisms, and remedies of toxicity: miniperspective. J Med Chem 59:8149–8167
57. Kumar S, Rani R, Dilbaghi N, Tankeshwar K, Kim K-H (2017) Carbon nanotubes: a novel material for multifaceted applications in human healthcare. Chem Soc Rev 46:158–196
58. Wen L, Li F, Cheng H (2016) Carbon nanotubes and graphene for flexible electrochemical energy storage: from materials to devices. Adv Mater 28:4306–4337
59. Radushkevich LV, Lukyanovich VM (1952) About the structure of carbon formed by thermal decomposition of carbon monoxide on iron substrate. Russ J Phys Chem 26:88–95
60. Hillert M, Lange N (1959) The structure of graphite filaments. Zeitschrift für Krist Mater 111:24–34
61. Bollmann W, Spreadborough J (1960) Action of graphite as a lubricant. Nature 186:29
62. Oberlin A, Endo M, Koyama T (1976) Filamentous growth of carbon through benzene decomposition. J Cryst Growth 32:335–349

63. Iijima S (1991) Helical microtubules of graphitic carbon. Nature 354:56
64. Iijima S, Ichihashi T (1993) Single-shell carbon nanotubes of 1-nm diameter. Nature 363:603
65. Thostenson ET, Ren Z, Chou T-W (2001) Advances in the science and technology of carbon nanotubes and their composites: a review. Compos Sci Technol 61:1899–1912
66. Li Q, Zhang J, Yan H, He M, Liu Z (2004) Thionine-mediated chemistry of carbon nanotubes. Carbon N Y 42:287–291
67. Mallakpour S, Khadem E (2016) Carbon nanotube–metal oxide nanocomposites: fabrication, properties and applications. Chem Eng J 302:344–367
68. Rana MM, Ibrahim DS, Mohd Asyraf MR, Jarin S, Tomal A (2017) A review on recent advances of CNTs as gas sensors. Sens Rev 37:127–136
69. Lawal AT (2016) Synthesis and utilization of carbon nanotubes for fabrication of electrochemical biosensors. Mater Res Bull 73:308–350
70. Manawi Y, Samara A, Al-Ansari T, Atieh M (2018) A review of carbon nanomaterials' synthesis via the chemical vapor deposition (CVD) method. Materials (Basel) 11:822
71. Kumar M, Ando Y (2010) Chemical vapor deposition of carbon nanotubes: a review on growth mechanism and mass production. J Nanosci Nanotechnol 10:3739–3758
72. Tran T-T, Mulchandani A (2016) Carbon nanotubes and graphene nano field-effect transistor-based biosensors. TrAC Trends Anal Chem 79:222–232
73. Same S, Samee G (2018) Carbon nanotube biosensor for diabetes disease. Crescent J Med Biol Sci 5:1–6
74. Wu H-C, Chang X, Liu L, Zhao F, Zhao Y (2010) Chemistry of carbon nanotubes in biomedical applications. J Mater Chem 20:1036–1052
75. Cardenas-Benitez B, Djordjevic I, Hosseini S, Madou MJ, Martinez-Chapa SO (2018) Covalent functionalization of carbon nanomaterials for biosensor applications: an update. J Electrochem Soc 165:B103–B117
76. Gooding JJ (2005) Nanostructuring electrodes with carbon nanotubes: a review on electrochemistry and applications for sensing. Electrochim Acta 50:3049–3060
77. Putzbach W, Ronkainen N (2013) Immobilization techniques in the fabrication of nanomaterial-based electrochemical biosensors: a review. Sensors 13:4811–4840
78. Deo RP, Wang J (2004) Electrochemical detection of carbohydrates at carbon-nanotube modified glassy-carbon electrodes. Electrochem Commun 6:284–287
79. Merkoçi A, Pumera M, Llopis X, Pérez B, del Valle M, Alegret S (2005) New materials for electrochemical sensing VI: carbon nanotubes. TrAC Trends Anal Chem 24:826–838
80. Baig N, Sajid M, Saleh TA (2018) Recent trends in nanomaterial-modified electrodes for electroanalytical applications. TrAC Trends Anal Chem 111:47–61
81. Zaporotskova IV, Boroznina NP, Parkhomenko YN, Kozhitov LV (2016) Carbon nanotubes: sensor properties. A review. Mod Electron Mater 2:95–105
82. Gupta S, Murthy CN, Prabha CR (2018) Recent advances in carbon nanotube based electrochemical biosensors. Int J Biol Macromol 108:687–703
83. Wang J, Musameh M, Lin Y (2003) Solubilization of carbon nanotubes by Nafion toward the preparation of amperometric biosensors. J Am Chem Soc 125:2408–2409
84. Gokoglan TC, Soylemez S, Kesik M, Dogru IB, Turel O, Yuksel R, Unalan HE, Toppare L (2017) A novel approach for the fabrication of a flexible glucose biosensor: the combination of vertically aligned CNTs and a conjugated polymer. Food Chem 220:299–305
85. Christwardana M, Ji J, Chung Y, Kwon Y (2017) Highly sensitive glucose biosensor using new glucose oxidase based biocatalyst. Korean J Chem Eng 34:2916–2921
86. Song Y, Shen Y, Gong C, Chen J, Xu M, Wang L, Wang L (2017) A novel glucose biosensor based on Tb@ mesoporous metal-organic frameworks/carbon nanotube nanocomposites. ChemElectroChem 4:1457–1462
87. Cakiroglu B, Ozacar M (2018) A self-powered photoelectrochemical glucose biosensor based on supercapacitor Co_3O_4–CNT hybrid on TiO_2. Biosens Bioelectron 119:34–41
88. Gopal N, Shukla P, Sahney R (2018) Development of CNT–polymer film-based electrode for the detection of glucose. In: Gupta B, Ghosh A, Suzuki A, Rattan S (eds) Advances in polymer sciences and technology. Materials horizons: from nature to nanomaterials. Springer, Singapore, pp 177–186
89. Choi Y-B, Kim H-S, Jeon W-Y, Lee B-H, Shin US, Kim H-H (2018) The electrochemical glucose sensing based on the chitosan-carbon nanotube hybrid. Biochem Eng J 144:227–234
90. Christwardana M, Chung Y, Tannia DC, Kwon Y (2018) Effects of the gold nanoparticles including different thiol functional groups on the performances of glucose-oxidase-based glucose sensing devices. Korean J Chem Eng 35:2421–2429
91. Movlaee K, Raza H, Pinna N, Leonardi SG, Neri G (2018) Ultrasensitive non-enzymatic electrochemical glucose sensor based on NiO/CNT composite. In: Ando B et al (eds) Sensors. Springer, Cham, pp 135–140
92. Zhang X, Xu Y, Ye B (2018) An efficient electrochemical glucose sensor based on porous nickel-based metal organic framework/carbon nanotubes composite (Ni-MOF/CNTs). J Alloys Compd 767:651–656
93. Qian Q, Hu Q, Li L, Shi P, Zhou J, Kong J, Zhang X, Sun G, Huang W (2018) Sensitive fiber microelectrode made of nickel hydroxide nanosheets embedded in highly-aligned carbon nanotube scaffold for nonenzymatic glucose determination. Sens Actuators B Chem 257:23–28
94. Dhara K, Mahapatra DR (2018) Electrochemical nonenzymatic sensing of glucose using advanced nanomaterials. Microchim Acta 185:49
95. Jeong H, Nguyen DM, Lee MS, Kim HG, Ko SC, Kwac LK (2018) N-doped graphene-carbon nanotube hybrid networks attaching with gold nanoparticles for glucose non-enzymatic sensor. Mater Sci Eng C 90:38–45
96. Ahuja T, Kumar D, Singh N, Biradar AM (2011) Potentiometric urea biosensor based on multi-walled carbon nanotubes (MWCNTs)/silica composite material. Mater Sci Eng C 31:90–94
97. Tak M, Gupta V, Tomar M (2013) Zinc oxide–multiwalled carbon nanotubes hybrid nanocomposite based urea biosensor. J Mater Chem B 1:6392–6401
98. Nguyen LTM, Yoon HH (2015) Potentiometric urea biosensor based on carbon nanotubes and polyion complex film. J Nanosci Nanotechnol 15:1150–1153
99. Nguyen NS, Yoon HH (2016) Nickel oxide-deposited cellulose/CNT composite electrode for non-enzymatic urea detection. Sens Actuators B Chem 236:304–310
100. Dervisevic M, Dervisevic E, Şenel M (2018) Design of amperometric urea biosensor based on self-assembled monolayer of cystamine/PAMAM-grafted MWCNT/Urease. Sens Actuators B Chem 254:93–101
101. Pundir CS, Jakhar S, Narwal V (2018) Determination of urea with special emphasis on biosensors: a review. Biosens Bioelectron 123:36–50
102. Durairaj S, Sidhureddy B, Cirone J, Chen A (2018) Nanomaterials-based electrochemical sensors for in vitro and in vivo analyses of neurotransmitters. Appl Sci 8:1504
103. Yarahmadi S, Azadbakht A, Derikvand RM (2019) Hybrid synthetic receptor composed of molecularly imprinted

polydopamine and aptamers for impedimetric biosensing of urea. Microchim Acta 186:71
104. Liu Y-L, Liu R, Qin Y, Qiu Q-F, Chen Z, Cheng S-B, Huang W-H (2018) Flexible electrochemical urea sensor based on surface molecularly imprinted nanotubes for detection of human sweat. Anal Chem 90:13081–13087
105. Hassan RYA, Kamel AM, Hashem MS, Hassan HNA, El-Ghaffar MAA (2018) A new disposable biosensor platform: carbon nanotube/poly (o-toluidine) nanocomposite for direct biosensing of urea. J Solid State Electrochem 22(6):1817–1823
106. Yun Y, Bange A, Heineman WR, Halsall HB, Shanov VN, Dong Z, Pixley S, Behbehani M, Jazieh A, Tu Y (2007) A nanotube array immunosensor for direct electrochemical detection of antigen–antibody binding. Sens Actuators B Chem 123:177–182
107. Lin J, He C, Zhang L, Zhang S (2009) Sensitive amperometric immunosensor for α-fetoprotein based on carbon nanotube/gold nanoparticle doped chitosan film. Anal Biochem 384:130–135
108. Singh A, Choudhary M, Kaur S, Singh SP, Arora K (2016) Molecular functionalization of carbon nanomaterials for immunodiagnosis of cancer. Mater Today Proc 3:157–161
109. Simão EP, Frías IAM, Andrade CAS, Oliveira MDL (2018) Nanostructured electrochemical immunosensor for detection of serological alkaline phosphatase. Coll Surf B Biointerfaces 171:413–418
110. Goud KY, Kalisa SK, Kumar V, Tsang YF, Lee S, Gobi KV, Kim K-H (2018) Progress on nanostructured electrochemical sensors and their recognition elements for detection of mycotoxins: a review. Biosens Bioelectron 121:205–222
111. Gao K, Sun Z, Pan BG, Qiao X, Hong C (2018) Electrochemical immunosensor for alpha-fetoprotein based on prussian blue-carbon nanotube@polydopamine. Micro Nano Lett 13:58–62
112. Rezaei B, Shoushtari AM, Rabiee M, Uzun L, Mak WC, Turner APF (2018) An electrochemical immunosensor for cardiac Troponin I using electrospun carboxylated multi-walled carbon nanotube-whiskered nanofibres. Talanta 182:178–186
113. Mateo-Alonso A, Tagmatarchis N, Prato M (2006) Fullerenes and their derivatives. In: Gogotsi Y (ed) Carbon nanomaterials. Taylor & Francis, London, pp 1–39
114. Penkova AV, Acquah SFA, Piotrovskiy LB, Markelov DA, Semisalova AS, Kroto HW (2017) Fullerene derivatives as nano-additives in polymer composites. Russ Chem Rev 86:530
115. Sinha A, Jain R, Zhao H, Karolia P, Jadon N (2018) Voltammetric sensing based on the use of advanced carbonaceous nanomaterials: a review. Microchim Acta 185:89
116. Goodarzi S, Da Ros T, Conde J, Sefat F, Mozafari M (2017) Fullerene: biomedical engineers get to revisit an old friend. Mater Today 20:460–480
117. Djordjevic A, Srdjenovic B, Seke M, Petrovic D, Injac R, Mrdjanovic J (2015) Review of synthesis and antioxidant potential of fullerenol nanoparticles. J Nanomater 16:280
118. Endo H, Taguchi Y, Matsumoto J, Achiba Y, Kodama T, Shiromaru H, Wakabayashi T (2015) Anticorrelated formation of fullerenes and polyynes upon laser ablation of graphite under various concentrations of hydrogen sources. Chem Phys Lett 642:35–38
119. Gao C, Abella L, Tian H-R, Zhang X, Zhong Y-Y, Tan Y-Z, Wu X-Z, Rodríguez-Fortea A, Poblet JM, Xie S-Y (2018) Double functionalization of a fullerene in drastic arc-discharge conditions: synthesis and formation mechanism of C2v (2)-C78Cl6 (C5Cl6). Carbon N Y 129:286–292
120. Yin R, Wang M, Huang Y-Y, Landi G, Vecchio D, Chiang LY, Hamblin MR (2015) Antimicrobial photodynamic inactivation with decacationic functionalized fullerenes: oxygen-independent photokilling in presence of azide and new mechanistic insights. Free Radic Biol Med 79:14–27
121. Hazrati MK, Hadipour NL (2016) A DFT study on the functionalization of C60 fullerene with 1, 2-benzoquinone. Comput Theor Chem 1098:63–69
122. Peyghan AA, Yourdkhani S (2014) Exohedral functionalization of C 60 by [4+ 2] cycloaddition of multiple anthracenes. Struct Chem 25:785–791
123. Maduraiveeran G, Sasidharan M, Ganesan V (2018) Electrochemical sensor and biosensor platforms based on advanced nanomaterials for biological and biomedical applications. Biosens Bioelectron 103:113–129
124. Compton RG, Spackman RA, Wellington RG, Green MLH, Turner J (1992) A C60 modified electrode: electrochemical formation of tetra-butylammonium salts of C60 anions. J Electroanal Chem 327:337–341
125. Lokesh SV, Sherigara BS, Jayadev AT, Mahesh HM, Mascarenhas RJ (2008) Electrochemical reactivity of C (60) modified carbon paste electrode by physical vapor deposition method. Int J Electrochem Sci 3:578–587
126. Zhang X, Ma L-X, Zhang Y-C (2015) Electrodeposition of platinum nanosheets on C60 decorated glassy carbon electrode as a stable electrochemical biosensor for simultaneous detection of ascorbic acid, dopamine and uric acid. Electrochim Acta 177:118–127
127. Schon TB, Dicarmine PM, Seferos DS (2014) Polyfullerene electrodes for high power supercapacitors. Adv Energy Mater 4(7):1301509
128. Jothi L, Jayakumar N, Jaganathan SK, Nageswaran G (2018) Ultrasensitive and selective non-enzymatic electrochemical glucose sensor based on hybrid material of graphene nanosheets/graphene nanoribbons/nickel nanoparticle. Mater Res Bull 98:300–307
129. Chuang C-W, Shih J-S (2001) Preparation and application of immobilized C60-glucose oxidase enzyme in fullerene C60-coated piezoelectric quartz crystal glucose sensor. Sens Actuators B Chem 81:1–8
130. Biju V (2014) Chemical modifications and bioconjugate reactions of nanomaterials for sensing, imaging, drug delivery and therapy. Chem Soc Rev 43:744–764
131. Gavalas VG, Chaniotakis NA (2000) [60] Fullerene-mediated amperometric biosensors. Anal Chim Acta 409:131–135
132. Zhilei W, Zaijun L, Xiulan S, Yinjun F, Junkang L (2010) Synergistic contributions of fullerene, ferrocene, chitosan and ionic liquid towards improved performance for a glucose sensor. Biosens Bioelectron 25:1434–1438
133. Lin L, Shih J (2011) Immobilized fullerene C60-enzyme-based electrochemical glucose sensor. J Chin Chem Soc 58:228–235
134. Thirumalraj B, Palanisamy S, Chen S-M, Yang C-Y, Periakaruppan P, Lou B-S (2015) Direct electrochemistry of glucose oxidase and sensing of glucose at a glassy carbon electrode modified with a reduced graphene oxide/fullerene-C60 composite. RSC Adv 5:77651–77657
135. Ye C, Zhong X, Chai Y, Yuan R (2015) Sensing glucose based on its affinity for concanavalin A on a glassy carbon electrode modified with a C 60 fullerene nanocomposite. Microchim Acta 182:2215–2221
136. Sutradhar S, Patnaik A (2017) A new fullerene-C60–Nanogold composite for non-enzymatic glucose sensing. Sens Actuators B Chem 241:681–689
137. Piotrowski P, Jakubow K, Kowalewska B, Kaim A (2017) Dioxygen insensitive C 70/AuNPs hybrid system for rapid and quantitative glucose biosensing. RSC Adv 7:45634–45640
138. Yao D, He Z, Wen G, Liang A, Jiang Z (2018) A facile and highly sensitive resonance Rayleigh scattering-energy transfer method for urea using a fullerene probe. RSC Adv 8:29008–29012

139. Wei L-F, Shih J-S (2001) Fullerene-cryptand coated piezoelectric crystal urea sensor based on urease. Anal Chim Acta 437:77–85
140. Chou F-F, Chang H-W, Li T-L, Shih J-S (2008) Piezoelectric crystal/surface acoustic wave biosensors based on fullerene C60 and enzymes/antibodies/proteins. J Iran Chem Soc 5:1–15
141. Saeedfar K, Heng L, Ling T, Rezayi M (2013) Potentiometric urea biosensor based on an immobilised fullerene-urease bio-conjugate. Sensors 13:16851–16866
142. Uygun ZO, Şahin Ç, Yılmaz M, Akçay Y, Akdemir A, Sağın F (2018) Fullerene-PAMAM (G5) composite modified impedimetric biosensor to detect Fetuin-A in real blood samples. Anal Biochem 542:11–15
143. Pandey A, Sharma S, Jain R (2019) Voltammetric sensor for the monitoring of hazardous herbicide triclopyr (TCP). J Hazard Mater 367:246–255
144. Wang H, Bai L, Chai Y, Yuan R (2014) Synthesis of multi-fullerenes encapsulated palladium nanocage, and its application in electrochemiluminescence immunosensors for the detection of streptococcus suis Serotype 2. Small 10:1857–1865
145. Zhang H, Fan L, Yang S (2006) Significantly accelerated direct electron-transfer kinetics of hemoglobin in a C60-MWCNT nanocomposite film. Chem Eur J 12:7161–7166
146. Pan N-Y, Shih J-S (2004) Piezoelectric crystal immunosensors based on immobilized fullerene C60-antibodies. Sens Actuators B Chem 98:180–187
147. Liao Y, Shih J (2013) Piezoelectric quartz crystal anti-protein immunosensors based on immobilized fullerene C60-proteins. J Chin Chem Soc 60:1387–1395
148. Mazloum-Ardakani M, Hosseinzadeh L, Khoshroo A (2015) Label-free electrochemical immunosensor for detection of tumor necrosis factor α based on fullerene-functionalized carbon nanotubes/ionic liquid. J Electroanal Chem 757:58–64
149. Demirbakan B, Sezgintürk MK (2016) A novel immunosensor based on fullerene C60 for electrochemical analysis of heat shock protein 70. J Electroanal Chem 783:201–207
150. Chen W, Zhou R, Yao X, Zhao K, Deng A, Li J (2018) Sensitive detection of enrofloxacin using an electrochemiluminescence immunosensor based on gold-functionalized C 60 and Au@BSA nanoflowers. New J Chem 42:14142–14148