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RESEARCH ARTICLE

NANOMATERIAL SURFACES BASED SENSING PLATFORM FOR HIGHLY SENSITIVE IMPEDIMETRIC DNA DETECTION: A CRITICAL REVIEW

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ABSTRACT

Advancement innanoscience & nanotechnology hasled to parallel increase in fabrication of newer, improved nanomaterials. Recent trends in nanotechnology is emphasized on generating novel nanomaterials with attomolar efficiencyby employing combination of polymer and nanomaterial. The present review demonstrates the status quo of progress in fabrication of sensing materials and sensing efficiency of DNA sensors (genosensors) that utilizes electrochemical impedance spectroscopy as a transduction technique. This reviewis centered on the use of nanomaterials or developing and improvising the performance of these specific biosensors. It covers the different principles that are used in the measurements and detection of DNA sequence or in amplification of finally obtained signal. The use of nanomaterials for the above listed aspects, viz., use of carbon nanotubes or other nanoscopic elements in the construction of the electrodes and usage of metallic nanomaterials, polymeric nanoparticles and mesoporous materials for signal enhancement,are thoroughly summarized in this review.

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INTRODUCTION

Use of nanomaterials in electrochemical biosensing has been exponentiallyenhanced since last 10 years. A wide variety ofnanoscale materials of different sizes, shapes and compositions are now applicable for biosensing purposes(1). The huge interest of peoples in application of nanomaterials is driven due to itsexclusive properties;particularly, the ability to tailorthe size and structure in accordance to the desired novel sensing systems (2-3) and also for enhanced performance of bioanalytical assays. Designing of nanomaterial for a wide range of morphology is done by varying the physical conditions and the method of synthesis. Nanoscale materials are being frequently used as effective transducers in biosensing and bioelectronic devices due to their high contact surface area, nontoxicity, biocompatibility and charge-sensitive conductance (4-7). This is especially applicable with theBiomolecules (DNA) that are having same order of dimension asofnanocomponents. These nanostructured materials are integrated with electrochemical devices and results in high sensitivity, fast response time,exquisite selectivity and rapid recovery (reversibility). In addition, the nanomaterials based electrochemical sensing have potential for integration of arrays format on a massive scale, which sets it apart from other sensors technologies available today.

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The sensitivity of asensoris directly related tomorphological shapes (tube, wire, fiber and rod) and dimension of the nanomaterials involved. Nanomaterials actas effective mediators by facilitating the electron transfer between the active sites of probe DNA and surface of the electrodes. The use of nanomaterials via impedimetric genosensing involves two different approaches. First approach focuses on the construction of new sensing platforms that are based on nanoscale materials with the aim of improvising the impedimetric response (8-10)due to enhancement of the sensitivity and improved reproducibility. Second approach isbased on the use of DNA oligonucleotides in association with different types of nanoparticles for high signal amplification. Although the major obstacle in improvedimpedimetric response lies in the sterical hindrance (orientation) or electrostatic repulsion due to nanoparticles accumulation on electrode surface and much improvement still needs to done in this direction(11-12).

Nanomaterials in Impedimetric Genosensing

Metal and Metal Oxide Nanoparticles Based Sensors

Metal NP (Nanoparticle) Based sensor: Nanomaterials show unique optical and magnetic properties for sensor applications. Nanoparticles (NPs) are generally combined with organic, biocompatible, or biological target specific shells which shows minimum destructive effect on the intrinsic properties and shape.

High conductance and easy fabrication of metal nanoparticle has led to the increased use and its fabrication.Metals like gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) have been successfully utilized in the fabrication of sensors and bioanalytical devices. Metal nanoparticle cores with silica as outer shell have been utilized for encapsulating biological species (like DNA) and polymers(PEG, dextran,etc.,) (13-15).External functionalization of such metal NPs with target specific biomolecules and fluorescent/raman active dyes are applied to form sensors, viz.,thiol functionalized AuNPs detection methodology based oncolorimetric, scanometric, agglomeration, gel electrophoresis, polynucleotide and DNA detection assays (16-20). In 2009,, Boisselier discussed in his review about the basic concepts, up-to-date literature results regarding the prominent use of gold nanoparticles (AuNPs) for medicinal applications. It also includedAuNP synthesis, assembly and conjugation with biological and biocompatible ligands,plasmon-based labelling and imaging, optical and electrochemical sensing,diagnostics and therapy (drug vectorization and DNA/gene delivery) for various diseases (cancer, Alzheimer, HIV, hepatitis, tuberculosis, arthritis, diabetes) (21).

Electrochemical DNA sensor for CtrA (gene) responsible for meningitis detectionhad been fabricated by immobilizing thiolated single stranded oligonucleotide (ssDNA) probe onto gold coated glass electrode, using hybridization with complementary DNA (CtrA) in presence of methylene blue (MB). The DNA/Au electrode could detect the complementary DNA in the range of 7–42 ng/l in 5 min (hybridization) with response time 60 s. The electrode was stable for about 4 months when stored at 4˚C. The sensitivity of dsDNA/Au electrode was 115.81 A/ng with 0.917 regression coefficient (R).The current response of the sensor increased linearly with the concentration of target from 2.12×10^{-6} to 2.12×10^{-12}mol l^{-1} with a relative coefficient of 0.9938. The detection limit (3) was 3.25×10^{-13}mol l^{-1}. Its detection limit was in picomole as compared with Patel work since it has no overhangs thiolated/covalent bonding is not involved with DNA(22). In 2012, Erik reviewed the use of colloidal gold nanoparticles and its use in biomedicine. This critical review providedintensive description about the design, synthesis, functionalization and applications of these artificial molecules in biomedicine. He also discussed about detailed interactions with biological systems in the field of health industry (23). In his words, field of gold nanotechnology enabled biomedicine popularly known as 'gilding the (nanomedicinal) lily' which further gave rise to a new 'Golden Age' of biomedical nanotechnology. It also covers novel chemical and physical methods of functionalizing gold nanoparticles with compounds which promote efficient binding, clearance and biocompatibility with regard to their safety to biological systems and also check for long-term term effects on human health and reproduction. Quantitative study of detection mechanism of a label-free impedance biosensor using ultrananocrystalline diamond microelectrode array was also reviewed (24).Later combination of nanoparticles were used.A highly sensitive electrochemical impedance sensing method of PEP gene based on integrated Au–Pt alloy nanoparticles and polytyramine. for detection of DNA targetsequence from 1.0×10^{-12}M to 1.0×10^{-7}M and LOD was measured as 3.6×10^{-13}M.

In 2013, Xian-Wen proposed electrochemical DNA sensor for determination of p53 tumor suppressor gene. Such novel electrochemical DNA (E-DNA) sensor was fabricated by incorporation of gold nanoparticles on a gold electrode. A modified gold nanoparticles (GNPs) for sensor was prepared by using GNPs by in situ potentiostatic deposition on the gold electrode surface(25). The reduction peak current of mediator MB shows linear relation to the concentration of p53 tumor suppresser gene for range 1.0 to1000 nM with a detection limit of 0.8 nM under optimal conditions. (S/N= 3) and relative standard deviation obtained was 3.8%. Glass carbon modified biocompatible PtNP nanoparticles were employed for the detection of *Listeria monocytogenes* with LOD 3.3 X 10-12M as shown in figure 1 (26)

Metal oxide based NP sensor: Metal oxide nanoparticles findmajor applications in catalysis, sensors, electronic materials and environmental remediation.These metallic nanoparticles are usually prepared by sol-gel method in a controlled manner. Demerits of metallic nanoparticles lie in its toxicity to human health (27). Fabrication and characterization of zinc oxide nanoparticles and their sensor applications for electrochemical monitoring of nucleic acid hybridization. Single-use graphite electrodes modified by ZnO nanoparticles enriched with poly (vinylferrocenium) (PVF+) were done for the electrochemical monitoring of nucleic acid hybridization related to the Hepatitis B Virus (HBV). Electrochemical behavior of these electrodes was also explored using both techniques differential pulse voltammetry (DPV) and electrochemical impedance spectroscopy (EIS)(28). NiO and Graphene oxide based platform was constructed for the immobilizing the Glucose oxidase for glucose detection. Excellent bioelectrocatalytic activity for immobilized glucose oxidase was shown as 2.7mM. Fast amperometric response with sensitivity 446.2nA/mM, detection limit of 24 microM and wide concentration range of 30 microM to 5mM(29). Ultrasensitive electrochemical detection of 27 mer DNA hybridization using Au/Fe3O4magnetic composites combined with silver enhancementwith detection limit around 100 aM, which is 8000 times lower than using gold nanoparticles as label in control experiments(30) Fabrication of a label-free genosensor for BRCA1 related sequence based on Polycarboxyindole on ITOwas used to give detection limit of 1 X10-17M with a linear range from 1X10-8Mto 1X10-18M using impedance Spectroscopy (31). Comparatively increased LOD was reported by Kjallmanwork (32).He made use of CdTe nanoparticle-modified hairpin probe for direct and sensitive electrochemical detection of DNA with LOD 4.7fM.This increase was contributed by the stem–loop structured probes and the blocking poly (ethylene glycol, PEG) molecules were self-assembling on the goldelectrode through S–Au bonding.The sensor showed reliable and sensitive detection of 4.7 fM of target DNA.

In the year ,Dong, proposed an electrochemical approach based on the HRP-functionalized Fe3O4 nanoparticles for the sensitive detection of sequence-specific DNA with LOD of 0.7 fmol with a range covering 4 orders in magnitude and shows excellent differentiation for two-base mismatched DNA and non-complementary DNA sequences under optimal conditions. This clearly shows that enzyme based modified nanoparticles can give enormously effective response (33).

Later the Bhuvana in 2013, fabricated sensor based on Gold surface supported spherical liposome–gold nano-particle nano-compositesingle stranded DNA (ssDNA) in the presence of (Fe (CN) 6)3/4. This sensor can discriminate the hybridized (complementary target hybridized), unhybridized (non-complementary target hybridized) and even single base mismatch target sequence hybridized to the surfaces with high sensitivity and selectivity.Lowest target DNA concentration for this sensor was detected as 0.1 X 10-12M(34). Labelled sensor based on nanoparticles showed lower response as shown by Noorbakhshin 2011.Hediscussed about fabrication of electrochemical DNA biosensor using ssDNA immobilized on the surface of nickel oxide nanoparticles modified glassy carbon electrode with novel (Ru(NH3)5Cl)PF6 complex and nickel oxide nanomaterials (NiOxnp) modified glassy carbon electrode was developed for detection of TNF factor. The linear dynamic range, sensitivity and detection limit of the proposed biosensor were 4×10−10M to1×10−8M, 34.32 nA nM−1and 6.8×10−11M, respectively (35).

Electrodeposited-AuNPs on ITO surface based DNA sensor for apolipoprotein E gene (ApoE) detection responsible for Alzheimer's disease was developed and detection is done via electrochemical impedance spectroscopy (36).Thisdual-detection platform was applied to detect DNA hybridization related to a specific point mutation in which was related to the progression of and its LOD was in range of few femtomole. Gold electrode modified with coated magnetic microspheres and titanium dioxide nanoparticles along with DNA dendrimer used for activity detection of the polynucleotide kinase activity with 0.003 U/ml. A low detection of 0.003 U mL-1and linear range of 0.01- 30 U/ml were achieved with this platform via electrochemical impedance. (37).This sensing platform clearly states how the structure of the nanoparticle can largely effect theLOD as compared with plain spherical nanoparticles. Generally the sensitivity increases by the order of 2. Fabrication ofa label-free electrochemistry biosensor based on flower-like 1 3-dimensional ZnO superstructures for detection of DNA. Novel label-free DNA hybridization biosensor was fabricated using flower-like 24 3-dimensional (3D) ZnO superstructures as enhanced sensing platform, employing 25 chitosan (CS) as film-forming material as shown in fig 2. Under optimum conditions, the peak currents of redox marker were found linear with the logarithm of the concentrations of complementary DNA from 1.0 × 10-14 to 1.0 × 10-10 M with a detection limit of 2.0 × 10-15 M (3σ/S)(38).

A typical example of self-assembled monolayer (increasesthe surface area) for fabrication of the DNA sensor (39).He described development of a genosensor for the electrochemical detection of genomic DNA from*Mycobacterium tuberculosis*. Such biosensor preparation was based on self-assembled monolayers of mercaptobenzoic acid (MBA) and magnetite nanoparticles (Fe3O4NPs) on bare gold electrode for immobilization of DNA probe (6 ng/μl).

Polymeric and metal-polymer composite: Polymeric nanomaterials based sensors are one of the most important classes of materials that have been widely used for the fabrication of sensors. A very nice review in this area has been written by Hatchett and Josowicz (40). He has emphasized on conducting polymers with nanoscale structures, such as, polyphenylacetylene (PPA) nanospheres, and its use as sensing.Furthermore, many polymers with intrinsic conducting properties and porous structures can be immobilized with metallic ions and finds applications in sensing. As mentioned previously, many metal nanoparticles have intrinsic electronic, optical and electrochemical properties that can play crucial role in chemical and biochemical sensing. However, many metal nanoparticles are not stable enough to be used directly as a sensor and need to be stabilized by a polymeric matrix or membrane. On one hand, the polymer can prevent the aggregation of nanoparticles and also enhance the sensitivity of nanoparticles to their surroundings and on the other side, the presence of nanoparticles within the polymer enhances the conductivity of the latter or its composite structure.

Consequently, polymers in conjunction with nanoparticles or nanowires have shown to be very effective in chemical and biochemical sensing of many types of analytes. In addition, the flexibility in manipulating the morphology of polymer providesan additional advantage of processibility to the nanocompositein fabrication of chemosensors and biosensors. For instance, encapsulation of Pt, Pd, Au, metal oxide nanoparticles and carbon nanotubes within polymeric matrices are useful for many types of sensitive sensors including gas sensors for detection of various gaseous substances (41-43). The most commonly used method to make metal-polymer nanocomposite materials and sensors begins with the reduction of metal ions within polymeric supports to produce metal nanoclusters embedded within the polymer matrix. The resulting composite material can then be coated on the surface of an electrode for fabrication of an electrochemical sensor. Using this method, many metal nanoparticle immobilized polymer sensors have been fabricated.

Similarly, metal nanoparticles immobilized in organometallic polymers have been synthesized and used for chemical sensing. Sensitive detection of lip genes by electrochemical DNA sensor based on monolayer of thiolated capture probe was developed (44). Sensing probe was formed on a gold electrode through self-assembling for *Phanerochaetechrysosporium.* Sandwich hybridization strategy was used for the recognition of target sequences of lignin peroxidase (lip) genes immobilized on the gold electrode. After hybridization with target DNA and biotinylated detection, streptavidin –horse radish peroxidase (HRP) conjugate was placed on electrode. Current response of such HRP catalyzed reaction shows linear relation tothe natural logarithm of the target nucleic acid concentration for range from 0.6 to 30nM with correlation coefficient of 0.9722. An enhanced strategy for rapid detection of DNA oxidative damage induced by hollow TiO2 nanocubes, using membrane comprising of hollow TiO2 nanocubes and poly (m-aminobenzene sulfonic acid, PABSA) nanofibres modified glassy carbon electrode (GCE) (45). The TiO2/PABSA membrane was effectively used for efficient dsDNA immobilization, dsDNA oxidation through photogenerated hydroxyl radicals. The resulting oxidative damage of dsDNA was detected by monitoring the CV response of an intercalated electroactive probe, namely CoðphenÞ3þ3.

Table 1. List of Patents given in Nanomaterials based Sensing

S No	Patent number	Description	Referee
1.	WO 2012098758	A detection apparatus for a biosensor with an optical prism incident surface and a detection plate adhesion surface that are set at a specific angle; useful in, e.g., the medical field.	National Institute of Advanced Industrial Science and Technology (Tokyo) Akiyama S, Fujimaki M, Nagata K
2.	MX 2010012079	A regenerable biosensor for determining the enzyme activity of protease. The biosensor is provided with a resonator that is provided with a quartz microbalance unit, where the quartz microbalance unit is provided with a coercive power of 10,000–40,000 units, ensuring a simple and efficient biosensor.	Autonomous University of Baja California (Mexicali, Mexico) Salas BV, Stoytcheva MS, Zlatev RK
3.	WO 2012096162	A sensor chip for measuring properties of substances, e.g. cells, comprising a diaphragm provided with two different surfaces and through-hole(s) formed between surfaces, where a portion of the surfaces and through-hole is covered with a silicon layer.	Panasonic (Osaka, Japan) Hashimotodani K, Nakano Y, Nakatani M, Oka T, Ushio H, Yamada Y, Yamamoto T
4.	US 20120178178	A biosensor cartridge, e.g., mass-based sensor, optical sensor, electrical sensor, quartz crystal microbalance, cantilever sensor and surface acoustic wave sensor, for automating biosensor processes to detect biological material from a biological sample, e.g., blood.	Samsung Electronics (Suwon, S. Korea) Choi YS, Do Jae P, Han KY, Kim SK, Lee HJ, Lee JH, Lee JN, Lee SS, Lee YH
5.	US 20120168306	A biosensor system for performing affinity-based detection to detect an analyte in a biological sample. Uses include but are not limited to toxin, hormone, DNA strand, protein and bacteria.	University of Texas System (Austin, TX, USA) Hassibi A, Jang B, Manickam A, 2011
6.	JP 2012122744	A method for manufacturing a biosensor involving adhering an electrode layer and a cover layer on the surface of a spacer layer by hot melt adhesive.	Murata Manufacturing Co. (Kyoto, Japan) Tanigawa M, 2011
7.	KR 2012057808	A biosensor useful for detecting gonyautoxin (GTX) from phytoplankton, comprising anti-GTX antiserum separated from a combination of protein and GTX from immunized mouse.	Korea Ocean R&D Institute (Ansan, S. Korea) Jae HL, Lee TK, Man C, 2011
8.	KR 2012057596	A sensibility diagnostic system comprising a sensibility diagnostic chip equipped with a biosensor, where the sensibility diagnostic unit converts emotions into an emotional quotient based on the received signals from the subject. The system is useful for diagnosis of sensibility, e.g., stress.	Yonsei University Industrial-Academic Co-operative Foundation (Seoul) Hyo IJ, Jung HL, 2011
9.	KR 2012055009	A biosensor useful for multiplexed diagnostics, comprising a plane light source, specific antibody, detection area, color charge-coupled device camera and long-pass filter.	Electronics and Telecommunications Research Institute (Daejon, S. Korea) Bong PH, Moon YJ, Park JW, 2011
10.	CN 102477416	A high-salt lipase useful in the printing, petrochemical and environmental industries, single-cell protein production, cosmetic production, biological material, biosensor and biomedical fields. The high-salt lipase is cost effective and has strong selectivity and specificity with improved enzyme activity, stability and practicability	
11.	PB nol20140206562	Glass and PDMS, microfluidic deviceDetection synthesis and lysis of DNA, RNA, cDNA	John Edward Maccormac 2014
12.	9605302	Semiconductor based nanomaterial for detecting nucleotide sequence DNA/RNA and its LOD is in fM	2014
13.	Pub no20110294685	Methods for nucleic acid detection	Sensitive detection,single molecular level fM or less Jonathan James O'Halloran
14.	US 6165335 A	Gravimetric/Spr , An Optical Sensor, for sensitive detection of DNA based on ligand receptor model.	
15..	5,485,277 and 5,492,840	SPR based sensor	
16.	US 8947656 B2	Biomolecular assay	

PABSA synergistic effect with the hollow TiO2 can do the detection of DNA damage and such sensor is also capable of quick assessment of gene toxicity of chemicals. Electrochemical determination of calf thymus DNA by Zr(IV) immobilized gold–mercaptopropionic acid self-assembled monolayer (Au–MPA–Zr SAM)(45). Determination of ct-DNA were performed by cyclic voltammetry (CV), Osteryoung square wave voltammetry (OSWV) and electrochemical impedance spectroscopy (EIS) in the presence of suitable redox reaction probe. A linear range calibration curve from 1.0×10^{-4} to 5.0×10^{-7} gmL^{-1}ct-DNA with a detection limit of 9.5×10^{-8} gmL^{-1}and mean of relative standard deviations (R.S.D) of 2.5% for n=4 at each point was observed in the best conditions by EIS. Regeneration of the surface was successfully carried out by 5 min sonication in 0.1 M KOH solution followed by 1 min incubation in 1.0×10^{-3}M Zr(IV) with a good reproducibility, R.S.D =1.5% for n=4 as detected by EIS. Storage stability (long term) of the electrode was also studied. Development of electrochemical nucleic acid sensor using the PANI. As compared with Au NP and carbon nanotube based sensors, PANI based nanotube sensor shows similar sensitivity without doing any signal enhancement, purification. PANI based sensor showed signal enhancement for target DNA concentration as low as 1 fM (approx. 300 zmol of target molecules) (45).

Table 2. Given shows the various nanomaterial and their LOD with applications

Nanomaterial used	LOD	Analyte	References
1) Au coated Glass electrode	7-42 ng/ml	arbitrary sequence	Patel et al.,2009
2) Au dendrimer	1.4 X 10-11 to 2.7 X 10-4 mol/l 1.4 X 10-14 mA/L	arbitrary sequence	Li et al.,2009
3) Conjugate modified Au electrode	0.6 to 30 nM 0 .03 nM	arbitrary sequence	Tang et al.,2009
4)PSS/PDOA/Au/Fe3o4		100 aM	Bai et al.,2010
5)Au/MPA/Zr(IV)	1 X 10-4 to 1 X10-7M 9.5 X 10-8 M	-	-
6) CdTe hair pin	4.7 fM		Kjallmen et al.,
7) MWCNT/Au napthalenediamine Modified GCE	1 X 10-15 to 1 X 10-10 M		Liu et al.,2011
8) Graphene/Au composite	200 pM to 500 nM		Lin et al.,2015
9)MWCNT/GNP/CS modified CPE electrode	1 nM		Zhang et al.,
10)amine terminated PAMAM	317 nm (with DNR)	Daunorubicin	Erdem et al.,2014
12)Graphene/PANI nanowire	2.12 X 10-6 to 2.12 X 10-12 M 3.25 X 10-13 M		Bo et al.,2011
13)AuNP modified gold electrode	7 X 10-12 to 2 X 10-7 M	Chronic lymphocytic leukemia	Ensafi et al.,2011
14)Au /Psi(mesoporous)	10-14 M		Feng et al.,2011
15)Nioxnp	4 X 10-10to 1 X 10-8 M		Noorbaksh et al.,2014
16) Thionine /Graphene	1 X 10-12 M to 1 X 10-7 M 1.26 X 10-13 M		Zhu et al.,2012
17)GSGH Graphene mesoporous silica hybrid	6.6 pM		Du et al.,2011
18) Au/PtNP modified Pty film	1 X 10-12 to 1X 10-7 M 3.6 X 10-15 M		Yang et al.,2013
19) ERGNO/PANI	1 X 10-15 to 1 X 10-8 M	PAT gene	Yang et al.2013
20) SWCNT /Au platform	1 0 zM 100 aM	(10 bp arbitrary sequence) (one base mismatch)	Li et al.,2012
21)Aptamer(label free)	1 X 10 -8 to 1 X 10-11 M 2 X 10-11M	B estradiol	Lin et al.2012
22) amino thiophenolAuNP	1.4 X 10-11 to 2 X 10-9 M 9.5 X 10-11 M	tolazoline	Zhang et al.,2010
23) Nanostructured superhydrophobic electrode	10-18 M		Ebrahimi et al.,2013
24)Dithriotiol tagged AuNP	5 fM to 500 pM		Wang et al.,2013
25) DOPE liposome/AuNP	1 X 10-12 M		Bhuvana et al.,2013
26) GNP anchored to DNA via thiol group	1 to 103 nM		Wen et al., 2013
27)AuNPelectropolymerised onto SWNT array platform	0.1 pM		Wang et al.,2013
28)AuNP/ZnO-CS	1 X 10-14 to 1 X 10-10 M		Feng et al.,201
29)HRP/DNAzymenanocomposite	50 nM		Wang et al.,2014
30)Polypyrrole- Au nanocomposite	2 X 10-13 to 2 X 10-6 M 8.4 X 10-13 M		Nowicka et al.,
31)PPyNW	10 pM		Tran et al.,2014
32)CS/MWCNT composite	0.01 X 10-12 M		
34) MBA /Fe304	6 ng/ml	Tuberculosis	Costa et al.,2014
35) MWCNT/Au	1 X 10-17 M	TP 53 gene	
36)Nanoporous membrane Ag/AuNP	50 pM		Ye et al., 2014
37)ERGO			Gong et al 2015
38)Hemin/G-quadruplexDNAzyme	10 pM to 10 nM;0.5 pM	HBV DNA	

Screen printed electrodes modified with AuNP and PANI acts as working electrode. Furthermore such modified electrode with bioreceptoravidi and HRP was used for sensigh DNA at LOD 0.01 fM and linear range 1000 to 0.001pM(46). Preparation of nanotexturedsuperhydrophobic electrode for detection of attomolar-scale DNA concentration within a droplet by non-faradaic impedance spectroscopy Continuous monitoring of the impedance of individual droplets as a function of evaporation time was exploited to dramatically improve the sensitivity and robustness of detection. (47).Construction of impedimetric sensor for toxigenic *Penicilliumsclerotigenum* detection in yam based on magnetite-poly (allylamine hydrochloride) composite usedfor the DNA hybridization interaction detection. Electrical impedance spectroscopy (EIS) was used to evaluate and quantify the hybridization degree. The Fe3O4–PAH composite was a good platform for the immobilization of biomolecules.Gradual increase inΔRe values were observed for range 50 to 200 pg/μL(48). In 2012, Wang developed a strategy signal-on impedimetric electrochemical DNA sensor using dithiothreitol modified gold nanoparticle tag for detection of DNA lower than 1 attomole complimentary hepatitis B single-stranded DNA (ssDNA), which corresponded to have 600 ssDNA molecules in a 1.0 mL sample.

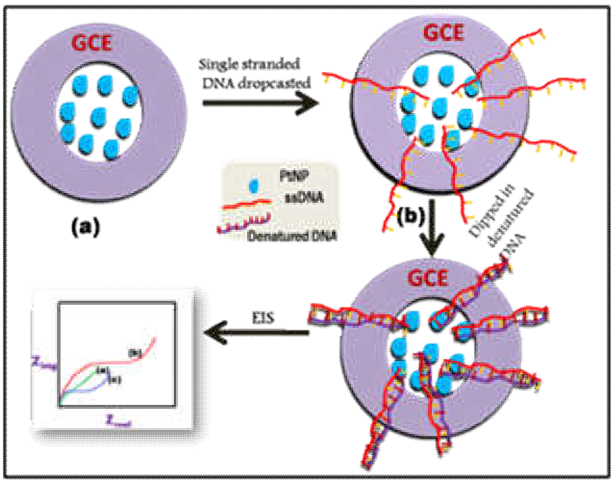

Fig. 1. Fabrication of gene sensor (a) ssDNA is dropcasted on PtNp modified glassy carbon (b) whole electrode is dipped in denatured DNA solution and EIS shown in inset

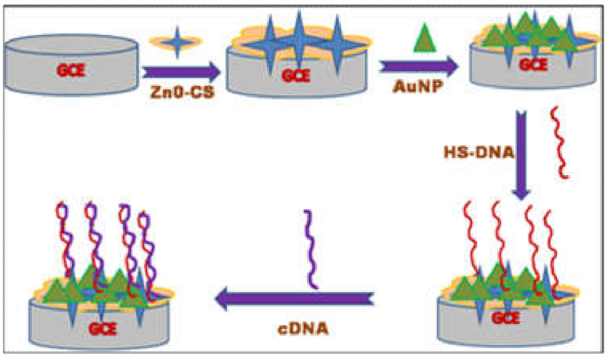

Fig 2. Fabrication of ZnO-CS/AuNP modified GCE electrode for C-DNA sensing

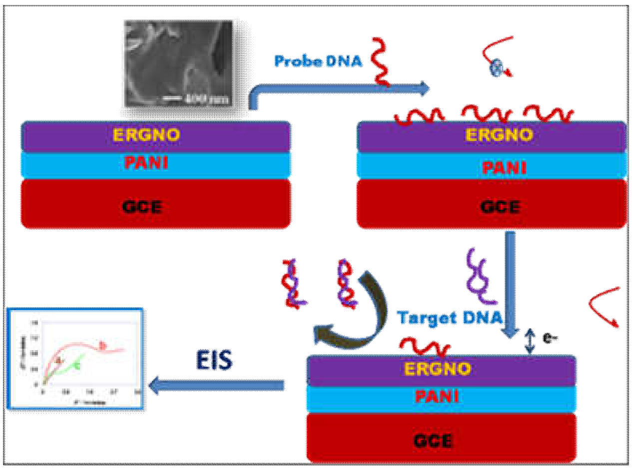

Fig.3. Schematic representation of the immobilization and hybridization of DNA on the ERGNO/PANI/GCE

For a 1-base mismatched hepatitis B ssDNA, the experimental detection limit was 0.1 pmol(49). Lin et al. fabricated novel aptamer-based biosensor for 17b-estradiol (50). The aptamers were firstly immobilized on the gold electrode through Au–S interaction; the aptamer probe was then bound with the addition of 17b-estradiol to form the estradiol/aptamer complex on the electrode surface and is detected by EIS. The change in the resistance had a linear relationship with 17β-estradiol concentration in the range of 1.0 × 10-8 to 1.0 × 10-11mol L-1, with a detection limit of 2.0 × 10-12mol L-1.

Use of freely switchable impedimetric for detection of target gene sequence based on synergistic effect of ERGNO/PANI nanocomposite modified glassy carbon electrode (GCE)as shown in fig 4. After hybridization with the complementary DNA, the formation of helix induced dsDNA to release from the surface of conjugated nanocomposite which was accompanied with the curtailment of the impedimetric value. The fabricated biosensor exhibited excellent performance for the detection of specific DNA sequence with a wide linear range (1.0X10–15M) (51). In 2014, Costa developed a sensor for the electrochemical detection of genomic DNA from *Mycobacterium tuberculosis* based on self-assembled monolayers of mercaptobenzoic acid (MBA) and magnetite nanoparticles (Fe3O4Nps)on bare gold electrode for immobilizing the DNA probe. Charge transfer resistance was observed for the different genomic concentrations. Detection limit for such platform was observed as 6ng/µl(52).

Chitosan–ionic liquid modified single-use sensor for electrochemical controlling of Chitosan-(CHIT) and ionic liquid- (1-butyl-3-methylimidazolium hexafluorophosphate, IL) customized single-use graphite electrodes (PGEs) were developed for the first time as sequence-selective Hepatitis B virus (HBV) DNA hybridization detection tool was developed. CHIT–IL modified PGEs were preferable due to DNA hybridization which imparted it superior selectivity, sensitivity and also suitable even when the target/mismatch mixtures is in ratio 1:1. (53). Electrically conductive polymer based nanowire (ECPNW) sensors for detecting nucleic acid sequences, proteins and pathogens was fabricated. As formed DNA sensor could detect target DNA concentration as low as 0.01 × 10−12M, with sensitivity as 52.57 k/fM. The reusability and shelf life of the DNA sensor were also investigated and it was found that the electron-transfer resistance decreased to approximately 35% after 8 weeks and approximately 80% after 12 weeks of storage. (54) Polypyrrole-Au nanoparticles composite based platform for DNA sensor using electrochemical impedance spectroscopy was developed. It showed higher efficiency by two orders of magnitude as compared with thiol sensing layers response in terms of Rct. The obtained detection limit of target DNA was circa 8.4 X 10−13M. This limit corresponded to the detection of circa 3.5 X 10-6copies of DNA in a 7- 11 droplet or circa 5X10-11DNA copies in 1 1 sample(55).

In 2015, Wehbefabricated switchable SwAps, controlled-affinity aptamersaptamers for biosensing and bioseparation of viruses.They offered switchable aptamers (SwAps) to purify vesicular stomatitis virus (VSV) as a model case. However, this technique could be extended to all biologically significant molecules (56). Gelatin was used as a mold for electrochemically synthesizing the polypyrrolenanowires (PPy NWs) onto the surface of working electrode for the immobilization of the DNA. The initial results showed that the sensor can detect to 10 pM of DNA sequence in the solution (57).

Mesoporous materials based sensors: Mesoporousmaterials are desirable for open pore structure and high surface area that it provides to receptor interface to the mesoporous materials for desirable sensing uses. Pores anchorsor encapsulates active DNA probes molecules, helps in growth of catalytic nanoparticles and also acts as accumulation centres for the target and proteins. Such structure also facilitates the rapid diffusion of analytes over large surface areas, and analytes can be easily discriminated on the basis of size and solubility. Major applications lies in inorganic sensing, anion detection, calorimetric and fluorimetric chemical sensing biosensing (58-59). Recently in mesoporous biosensors, there have been numerous studies dedicated toward the immobilization of biological species. The immobilization of enzymes, such as, glucose oxidase (GOD)Horseradish peroxidase (HRP), cytochrome c (Cyt c), b-nicotinamideadenine dinucleotide (NADH), and choline oxidase (ChOx), etc. Materials such as SBA-15, MCM-41 and titanium with MCM-41 (Ti-MCM-41), and silica spheres, have beenanalysed extensively by means of cyclic voltammetry (CV) with regard to the development of amperometric electrochemical biosensors. These sensors have been employed to measure the concentration of analyte mixtures by taking advantage of electrochemical enzymatic reactions, such as, the oxidation of glucose with GOD immobilized mesoporous silica indirectly. Speciallymesoporous silica has been widely used for the GOx(60-61)

Graphene based mesoporous silica gold NP hybrids (GSGHs) used for enhancing the sensing selectivity drastically as it relies on strand-displacement DNA polymerization and parallel-motif DNA triplex system that actedas dual amplifications. This present sensing strategy based on GSGHs was able to detect target DNA with a fairly high detection sensitivity of 10 fM through the hybridization of duplex DNA to the acceptor DNA .The detection limit for target DNA was about two orders of magnitude lower than that of graphene-based DNA electrochemical impedance spectroscopy (EIS) sensor (6.6 pM) (62)

Carbon based platform: carbon nanotubes and nanostructured diamond: Nanodiamonds and carbon nanotubes showsvaried electronic properties according to their size and morphology.Carbon nanotubes are one of the most commonly used building blocks of nanotechnology.CNTfinds major applications in analytical applicationslike chromatography, sensors and biosensors, and nanoprobes, etc.In this review, we have focused on their use as sensors and biosensors application only. Multi-walled carbon nanotubes (MWCNTs) withpolypyrrole composite electrodesperformed impedance detection of hybridized DNA in the presence of a redox marker.. The complementary oligonucleotide was detected by the associated change in *Rct*, both with and withoutsubsequent metallization. In the former case, a*Rct* reduction was observed whilst in the latter the value of *Rct*increased as hybridization occurred. In both cases, CNTs were integrated within the sensing interface for imparting high conductivity and increased active surface area. For increasing the sensitivity(63). Polylysine/single-walled carbon nanotubes modified electrode for the detection of transgenic plants gene fragmentimpedimetrically and this platform offered an enhanced conductivity with an estimated detection limit around 0.1 pM(64). In the year 2011, Bonnani, adopted miniaturized platform which employed screen-printed electrodes, modified with carboxyl functionalized multi-walled carbon nanotubes as sensing candidates,for detection of oligonucleotide sequences specific for transgenic Bt maize (insect resistant) impedimetrically. Amino-modified DNA probe was covalently immobilized by EDC/NHS chemistry (65). The same platform was employed for the very sensitive detection of H1N1 influenza 60)gene correlated sequence and its LOD also lies in the pM range (66). Another platformconsisting of carboxylic acid functionalized single-walled carbon nanotubes modified graphite sensors was employed for electrochemical monitoring of direct DNA hybridization related to specific sequence of Hepatitis B virus (67). The obtained electrochemical signal showedincrement (in many orders) in the presence of carbon nanotubes compared to bare graphite.Novel biosensing platform of controlled geometry based on nano diamond were used as transducers for DNA detection.Electro-chemical and bio-chemical sensor properties were investigated by cyclic and differential pulse voltammetry as well as impedance spectroscopy with Fe(CN)63−/4−as redox markers, which provided sensitivities of 2 pM on 3 mm sensor areas and superior DNA bonding stability over 30 hybridization/denaturation cycles.

Moreover, various literature review has been published in this reference, which clearly mentions its applicability as electrochemical transduction materials such as silicon alternatives diamond. Nano diamond can effectively act as the bioreceptor molecules to provide the efficient interface for biosensing purposes (68-70). A novel biosensing platform using CNT-ECIS (electrochemical Cell Impedance sensor) for the very first time was prepared. It shows the sensitivity for cancer cells as low as 4000 cells cm-2 and sensitivity 1.7 X 10-3 Ωcm-2.Surface immobilization of biomolecules is done usingCNT.It also serves as efficient materials for the transduction of signals, recognition of analytes, disease markers and metabolites.

Carbon and Polymer composites: Carbon based polymer hybrid CNT shows wide applications in biosensing of DNA enzymes proteins antigens, metabolites) CNT acts as the suitable candidate because of its enormous surface area, and very efficient electrocatalytic behaviour and high electrical conductivity properties. Incorporation of polymers onto the carbon surface not only gives efficient and suffice dispersion but also imparts them the characteristics of redox behavior and biocompatibility and photoelectric and increased swelling capacity. They are employed in wide area such as gas pressure optical mass position stress strain and biological sensors.Mechanical properties are very remarkable for excellent sensibility and rapid and cost effective detection of(molecules) quenching behavior. It finds major applications in biofunctionalization for sensing purposes.Among the Polymer–carbon nanotube composites popular are singlewalled CNTs (SWCNTs), and multi-walled CNTs (MWCNTs). Carbon nanotubes enhances conducting of polymers without compromising other properties. Chemical sensors based on polymer composites with carbon nanotubes (CNTs) and graphene (G) shows application in diverse fields such as biosensing (DNA, enzymes, proteins, antigens and metabolites), using electrochemical and optical detection methods. In 2009,Guo reviewed graphene and its derivative based sensing materials for analytical devices.Itsscope included the future challenges and prospects of graphene along with its derivative for analytical devices (73).Nucleic acid-based electrochemical biosensor based ongold nanoparticle-adsorbed disposable graphite electrode and Meldola's blue as an intercalator.for the detection of influenza

B virus from PCR samples. Detection limit of this genosensor is 54 picomoles for the synthetic target and 3.3 × 107 molecules for the real samples (PCR) in 30 µl sample volume. Further to enhance sensitivity organic compounds, azo dye are also used (74). In the year 2011, Zengemployed gold nanoparticles (GNPs)/multiwalled carbon nanotubes (MWCNTs)/poly (1,5-naphthalenediamine) films modified glassy carbon electrode (GCE) for highly sensitive detection of cellobiose dehydrogenase gene (75).The effectiveness of the sensor was confirmed by sensitive detection of cellobiose dehydrogenase (CDH)gene thatwas extracted from *Phanerochaetechrysosporium* using polymerase chain reaction. The monomer of 1,5-naphthalenediamine was electropolymerized on the GCE surface with abundant free amino groups. Congo red (CR)-functionalized MWCNTs is well knownfor its excellent conductivity as well as high solubility in water.Horse radish peroxidase –streptavidin conjugates were labelled with biotinylated probes (biotin–streptavidin bond) for forming composite films to modify GCE. The amperometric current response to HRP-catalyzed reaction was linearly related to the common logarithm of the target nucleic acid concentration in the range of 1.0×10−15–1.0×10−10M with the detection limit of 1.2×10−16M.

Electrochemical detection of hepatitis B and papilloma virus DNAs using gold nanoparticles coated SWCNT array by electrochemical impedance spectroscopy technique was performed. The as-prepared electrochemical sensor could detect lower than 1 attomole complimentary hepatitis single-stranded DNA (ssDNA). This study illustrated that combining Au nanoparticles with the in situ fabricated SWCNTs array was a promising platform for ultrasensitive biosensing(76). In the year 2011, Lin fabricated electrochemical DNA sensor by the assembly of graphene and DNA-conjugated gold nanoparticles with silver enhancement strategy for detection of ssDNA bases. Onto the AuNPs catalyzed silver deposited surface oligonucleotide probe labelled AuNPwere hybridized in sandwich format.The resulting biosensor exhibited a good detection performance with a wide detection linear range from 200 pM to 500 nM, and a low detection limit of 72 pM (77). Additionally, the biosensor was proved able to discriminate the complementary sequence from the single-base mismatch sequence.

Muti *et al*.(78) reported electrochemical behaviour of carbon paste electrodes enriched with tin oxide nanoparticles using voltammetry and electrochemical impedance spectroscopy.SnO(2) nanoparticles were impregnated onto the carbon paste electrodes for the electrochemical behaviour voltammetric cyclic voltammetry (CV), differential pulse voltammetry (DPV) and electrochemical impedance spectroscopy (EIS) techniques has possible use of this material in biosensor development. Such modified (SNP) modified electrodes were tested for the electrochemical sensing of DNA purine base adenine for getting biosensor applications. Advancement in surface properties and the morphology of mesoporous silica and its biocompatibility is widely discussed in literature. Use of nanoscale porous materials in sesnsors for the selective detection of neurotransmitters and biological molecules (79). Furthermore, electrochemical sensors has been developed for the sensing of BPA (Bis Phenol A) and DNA damage as discussed convincingly in the literature (80).Sensing platformfor detecting propranolol enantiomers (chirality) based on size-controlled gold nanocomposite was developed. The size-controlled gold nanoparticle–methylene blue–multiwalled carbon nanotubes nanocomposite (nanoAu–MB–MWNTs) was successfully synthesized as electrochemical redox-probe indicator and immobilization matrix, onto which calf thymus double-stranded DNA (ctDNA) could be adsorbed for chiral sensing propranolol (PRO) enantiomers(81). The proposed sensor was applied to determine the enantiomeric ratios of R-PRO in mixture solutions, and high-performance liquid chromatography (HPLC) was used to validate the results by calculating F-test and t-test values. The DNA-immobilized sensing platform (ctDNA/nanoAu–MB–MWNTs/GCE) showed a larger electrochemical response for S-PRO than R-PRO, in which the association constant was calculated to be 1.154 × 10-4L mol−1for S-PRO and 4.638 × 10-3L mol−1 for R-PRO(82). Redox targeting of DNA anchored to MWCNTs and TiO2nanoparticles dispersed in poly dialyldimethylammonium chloride and chitosan. In this study, nanostructured films were deposited at the surface of a pencil graphite electrode (PGE) that was used as a working electrode. Two positively charged polyelectrolyte namely, poly dialyldimethylammoniumchloride (PDDA) and chitosan, were initially compared for DNA immobilization at the surface of MWCNTsand TiO2nanoparticles (TiO2NPs). The stability of the immobilized DNA (within several days)was found much higher in case of MWCNTs than TiO2NPs (83). Nanoporous alumina based mesoporous material are used in impedance sensing with AU NP tags and used for detection of DNA with LOD 50 pM. Miodek in the year 2015, MWCNT –Ppy and redox dendrimer based sensor for the electrochemical DNA detection of rpob gene of mycobacterium tuberculosis in real PCR sample. Developed Biosensor was suitable for the detection of sequences with a single nucleotide polymorphism SNP with detection limit 0.3pM(84). In the year 2018, Jiang designed CNT and polydimethylsiloxane composite modified electrode for DNA sensing via EIS. Such electrode was reusable, measurement time less than 30 min and 5 pM (85). List of patents given in field of nanomaterials used for sensing purposes is briefly given below in Table 1.

Conclusion

Among the nanomaterials carbon based nano materials occupies the highest and dominant position for sensing purposes. Due to the presence of qualities of chemical inertness and low toxicity to environment as well as human beings, carbon materials are very popular. However, it is not very efficient in sensing application due to its low level of sensitivity and poor response time. This can be overcome by employing the metal based nanomaterial that shows high sensitivity and conductivity. CNPs have been widely used in high-performance electrode materials in batteries, super capacitors and excellent photo luminescent materials. Efficiency of the sensors is greatly enhanced when noble metal nanoparticles are used. Metal nanoparticles successor is metal oxide nanoparticles (PtO, CuO, IdO) and finds applications in various sectors viz., electronics, solar cells, piezoelectric devices, fuel cells, coatings for the passivation of surfaces against corrosion, as catalysts,sensing and drug loading of medicines. Metal oxides,like Al2O3, MgO, ZrO2, CeO2, TiO2, ZnO, Fe2O3 and SnO, show both redox and acid/base properties for Absorption and Catalysispuposes.

Metal oxide shows high stability but nanomaterials imparts it low surface energy for mechanical or structural stability. Presence of oxygen moiety imparts it the conductivity and scavenging properties(antioxidant).Ease of functionalization, size dependent optical properties and greater sensitivity photostabilitymakes metal nanoparticles a suitable candidate for probe in detection and imaging of biomolecule with high LOD (10-12 M).However, high toxicity limits its frequent use. Compositing with polymers/ biopolymers significantly reduces its toxicity as well as enhances the surface area as a matrix for sensing. Nanodiamond displays the structures without dangling bonds at the interface, which find application innanoelectronicsfor diode and solar cell fabrication, and contacts in diode and transistor fabrication.

Advancement in this regard led to the development of Carbon polymer composite. Use of polymer provide it sufficient surface area as well as acts as stabilizing agent, which prevent leaching and thus increasing the scope of tailoring of materials in this aspect. Bio compatible molecules as partners in its composite preparation are quite popular these days due to their minimal toxicity. Further, Carbon nanomaterials have been successfully tailored with electroactive materials like biomecule NAD+ or with some intercalator dyes. Still some needs are not met in terms of stability, so people made coordination compound (organomettalllic) to overcome this demerit. But use of organometallics is not so popular because all of themdon not show electro activity. Further advancement led to the production of both carbon and metal based mesoporous materials. The pore size play very crucial role. Mesoporousmaterials are popular where ligand receptor is present. Carbon based nanomaterials can be easily functionalized with wide variety of nanomaterials without compromising the individualistic properties of the components. Higherdetection limit of carbon based mesoporous materials (attomol) was achieved as compared to metal based mesoporous nanomaterials (femto molar). Till now, a few works has been done in this field. Hence, it is still in its infancy. With popularity in portability and real time onsite uses, Miniaturization became a necessity. Miniaturization of sensing probe based on metal based nanoparticle has been enormously successful and finds use in environmental testing, glucose testing, point-of-care diagnostics, prediction of infection, etc.,. It is popularly known by the name of SPCE / lab on chip (LOC) platforms made of whatmann paper onto which nanomaterial is photo lithographically grafted (86).

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