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REVIEW PAPER

Diagnosis of hepatitis via nanomaterial-based electrochemical, optical or piezoelectrical biosensors: a review on recent advancements

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Abstract

This review (with 145 refs.) summarizes the progress made in the past years in the field of nanomaterial based rapid detection of hepatitis viruses. Following an introduction into the field (with subsection on the significance of hepatitis and on fundamentals of biosensors), conventional methods for detection of hepatitis are discussed, along with their limitationss. The next section covers electrochemical sensors, with subsections on voltammetric, amperometric, potentiometric, impedimetric and conductometric biosensors. A further large section covers optical methods, with subsections on methods based on fluorescence, photometry, surface plasmon resonance, surface-enhanced Raman scattering and chemiluminescence. A concluding section discusses current challenges and gives an outlook on potential future developments.

Keywords Hepatitis · Liver disease · Nanosensors · Nanoparticles · Signal amplification · Nanotechnology

Hepatitis

Hepatitis can be noninfectious or infectious. The category can be identified by a range of histological and clinical signs [1]. Enlargement of liver is one of the most prevalent symptoms of hepatitis on physical analysis which is pursued by jaundice [1]. Hepatitis viruses include six type of viruses from A to E and G, the target of each virus is liver and the major signs of hepatitis are very close [2]. Approximately 1.4 million cases of Hepatitis A virus (HAV) infection occur annually in the world [3]. Mortality rate of chronic Hepatitis B virus (HBV), liver and cirrhosis cancers due to infection with HBV has been reported to be about one million individuals by the World Health Organization (WHO) [4–8]. Every year, 3–4 million of the world population is infected with hepatitis C virus (HCV), approximately 3% [7, 9–13]. The severity of HEV (Hepatitis E virus) death is very high in pregnant women, and about 15 million people in the world are infected with Hepatitis D virus (HDV) [14]. Hepatitis viruses are varied in antigenic patterns, severity, type of genomic, chronicity and transmission mode, etc. [15].

Early diagnosis is the most powerful method to limit the spread of hepatitis viruses [16, 17]. Some noticeable attempts have been made in order to improve the different techniques for detection of targets derived from hepatitis viruses involving: IgG and IgM for hepatitis A virus, HBV DNA and all markers of serology (anti-HBe antibody, anti-HBc antibodies [IgG and IgM], HBsAg and HBeAg) for hepatitis B virus, HCV RNA and anti-HCV antibodies for hepatitis C virus, HDV antigen and anti-HDV antibodies for hepatitis D virus and HEV RNA and anti-HEV antibodies

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for hepatitis E virus [18, 19]. In general, a variety of laboratory diagnostic methods for viral diseases are based on cytology tests, electron microscopy, virus isolation and culture, identification of viral proteins through the use of enzymes and antibodies, identification of viral genomes, and serology [14]. The versatile and general methods of detecting pathogenic agents are related to immunoassay techniques. The most traditional ones are ELISA [20] and RIA which are applied for detection of hepatitis viruses [21]. The most improved immunoassay methods are lateral flow immunoassay and immunochemiluminescent assay. Currently, molecular techniques have been became inevitable implements for viral disease diagnosis with reliable and accurate results [22, 23]. Identification of hepatitis viruses via broadly used molecular techniques is based on amplification of nucleic acid. Formats of strategies based on amplification can be described in this way: signal, amplifications of probe and target [24]. The serological-based immunoassays that target the antibodies or antigens of virus were accurate and selective, however, these techniques have some technical limitations like not giving quantitative data and serological results [6]. Nowadays, novel detection methods of hepatitis are combined molecular and serological techniques with high-tech tools based on chemistry, nanotechnology and electronics sciences [25]. The technique which is newly used for biological tasks is named biosensor that has attractive features like being inexpensive, sensitive, reproducible, rapid and specific and also does not need any sample preparation in comparison with traditional strategies [26]. Hence, the purpose of this review is to bring up to date information and introduce the improved different types of biosensors applied for diagnosis of hepatitis viruses. In this article we have displayed a snapshot of the latest improvements in the bio and nano-sensors field and an overview of strategies for amplifying signals based on application of nanomaterials as well as describing a comparison about different hepatitis detection techniques and their limitations.

Conventional methods for viral hepatitis detection

A variety of different laboratory techniques including traditional and modern technologies are being employed for detection hepatitis viruses. Some of these methods that can be mentioned are immunoassay techniques, molecular methods as well as biosensors. Each detection method has its special benefits and limitations. The most prevalent techniques for hepatitis detection is blood testing which includes recombinant immunoblot assay, PCR (polymerase chain reaction), biomarker assay, enzyme immunoassay and hepatitis RNA quantification in the serum [27]. Immunoassay techniques were explained as versatile and common methods for determination of pathogenic agents. Antibodies and antigens, which are derived from hepatitis virus, are the chief components for all immunoassay methods [28]. As a detector element, antibodies serves vital role in immunoassay techniques various formats. The most significant and typical techniques for hepatitis virus detection involve; RIA (radio-immunoassay), EIA (enzyme immunoassay), immuno-chemiluminescence and ICA (immuno-chromatographic assay). Enzyme immunoassays are significant serological techniques applied for detection of hepatitis viruses. Procedures of EIAs are convenient and simple to set-up and sensitive to target's low levels, as well as requiring few reagents, potential for being automated and qualitative and quantitative testing are some plus points of enzyme immunoassays. Whereas, they are expensive and need prolonged time. Fast viral hepatitis detection, immediately after infection, is an urgent need of treatment prevention of infection transmission [20, 28].

After immunoassay methods, molecular techniques have been become unavoidable procedures for viral disease diagnosis, with reliable and accurate results. While serological methods are not definite, molecular methods are very beneficial for all infections of hepatitis viruses detection, specially HBV and HCV [23]. Broadly application of molecular strategies for hepatitis viruses' detection relies on amplification of nucleic acid [24]. Molecular techniques developed for genomic materials of virus diagnose, some of these methods including; PCR (polymerase chain reaction), NAT (nucleic acids tests) and real-time PCR, but real-time PCR are employed as reference and gold-standard setting. Some advantages and limitations of molecular techniques are having greater sensitivity and specificity with wide dynamic action range than serological techniques as well as need for special tool, lack of ability to show viability of pathogen, respectively [23]. New biosensors are accounted as intriguing, attractive and beneficial devices for hepatitis virus infections detection. These are novel label-free tools that can sense special targets via bio-molecular interactions like antibody–antigen or receptor–ligand complexes and substrate-enzyme reactions [26, 29]. Combination of immunological and molecular strategies coupled with mass-sensitive, electrochemical, electrical and optical sensing models are the basis of biosensors. The main plus points of biosensors are cost-efficient, rapid and reliable procedure, providing a quantitative test for determination with 100 copies of viral hepatitis, as well as throughput, manifold analysis and automation [29, 30] Table 1.

Among these, the metabolic biomarkers analysis is strong method for improving the hepatitis diagnosis, therapy and prevention. Infection of liver lead to measurable alterations in some metabolite levels such as phenylalanine, tryptophan, L-proline, histidine, ethanol, tyrosine, fumaric acid and lactic acid. Remarkably, the amino acids concentration is found changed in liver diseases. The high levels of lactate in blood

also has a significant role in liver dysfunction. Both chronic and acute hepatic diseases can lead to lactic acidosis and accumulation of lactate. Moreover, several research reported the association between hepatic enzymes (a predictor of hepatic injury) and blood alcohol concentration in these patients [27]. Various kinds of biosensing techniques have been developed for detection of metabolic biomarkers in order to rapid hepatitis diagnosis. They demonstrate perfect performances like good repeatability, great selectivity and enhanced sensitivity in comparison to non-enzymatic biosensors [27].

Biosensors

A growing number of various biosensors have been employed in clinical research such as biosensor for blood glucose [6]. Biosensor can be defined as an analytical tool with the ability to provide precise semi-quantitative or quantitative analytical data through connection of chemical, biochemical and biological recognition element (biochemical receptor) with a transducer element in which receptor interacts indirectly or directly with analyte leading to generation of signal [31, 32]. Bio-receptor, signal-transducer and amplifier are the components of a biosensor. The interaction which is occurred between bio-receptor and analyte changed into measurable signals. Whole cells, nucleic acids, tissues, antigens, enzymes and antibodies can be employed as bio-receptor [31]. Biosensors have a variety of different applications in broad ranges involving drug monitoring, medical filed, diagnosis, biodefence and security, food safety and environmental controlling [31, 33]. Based on the transduction or biological element they can be categorized into various types. Categorization based on the transducer element divided into four groups: I) optical (surface plasmon resonance, colorimetric, fluorescent, luminescent and interferometric), II) electrochemical (voltammetric, amperometric, potentiometric, condutometric and impedametric), III) calorimetric, IV) mass-based (magnetic or piezoelectric and acoustic-wave, e.g., quartz crystal microbalance), V) magnetic and VI) mechanical biosensors [32, 34–36]. Biosensors have the capability to detect targets in wide range from little molecules like pesticide and antibody to medical targets such as viral and bacterial pathogens [26, 37]. The biosensor performance is usually determined based on its selectivity, reproducibility or precision of the response, response to matrix interferences, sensitivity, linear range as well as limit of detection (LOD) [38–40]. Additionally, the latest improvement in nanotechnology and nanoscience pave the way for making very small scale electrodes that nanoscale biosensors caused to generation of new type of diagnostic biosensors termed Nano-biosensors [41]. Nanomaterials play roles in different fields, including targeting, imaging and sensing that not only they are powerful tools for enhancement of biosensing techniques but also they lead to advancement of available detection methods. Nanomaterials serve as prosperous candidate for construction of high sensitive biosensors. Outstanding features of nanomaterials, for instance high surface area, very unique electrochemical attributes, catalytic activities, high surface to volume ratio, unique size and shape and physical-chemical properties are precious for creation and amplification of signals and enhancing analytical activity [34]. Different nanomaterials such as metallic nanoparticles (NPs), quantum dots (QDs), silica (SiO_2) NPs, graphene and carbon nanotubes (CNTs) have been combined with biosensors and lead to fabrication of specifically sensitive biosensors [41–43]. Hence, application of nanomaterials in biosensors not only do not change the properties of biosensors but also lead to signal amplification, performance improvement, sensitivity of them, and fast analysis of multiple components due to their nano-metric dimensions and unique features [35, 41]. Fast viral detection technique has vital importance for healthcare. Conventional techniques of diagnosing specific viruses are expensive and prolonged for long time. Hence, viral biosensors are sensitive and accurate with rapid recognition system [26]. The primary focus of article is on

Table 1 Summary of diagnosis testing techniques of hepatitis

	Method	Advantages	Limitations	Ref.
Immunoassay	ELISA[a] RIA[b] CA[c] LFIA or LFA[d]	Easily settled, required few reagents, sensitive to target's low levels	Expensive, time-consuming	[28]
Molecular approaches	PCR[e] NASBA and TMA[f] Real-time PCR or qPCR[g] LAMP[h] bDNA[i]	Great sensitivity, specificity, broad dynamic action range	Requiring special tools, unable to show viability of pathogen agents	[23]
Biosensors	Electrochemical Optical Piezoelectric	Cost-low, higher sensitivity and selectivity, simple, accurate, reproducibility, rapid, low limit of detection up to femto (f) ranges	–	[26]

[a] Enzyme-linked immunosorbent assay. [b] Radioimmunoassay. [c] Immunochemiluminescent Assay. [d] Lateral flow immunoassay. [e] Polymerase Chain Reaction. [f] Nucleic Acid Sequence-Based Amplification and Transcription-Mediated Amplification. [g] Real-Time Polymerase Chain Reaction or quantitative PCR. [h] Loop mediated isothermal amplification. [i] Branched DNA

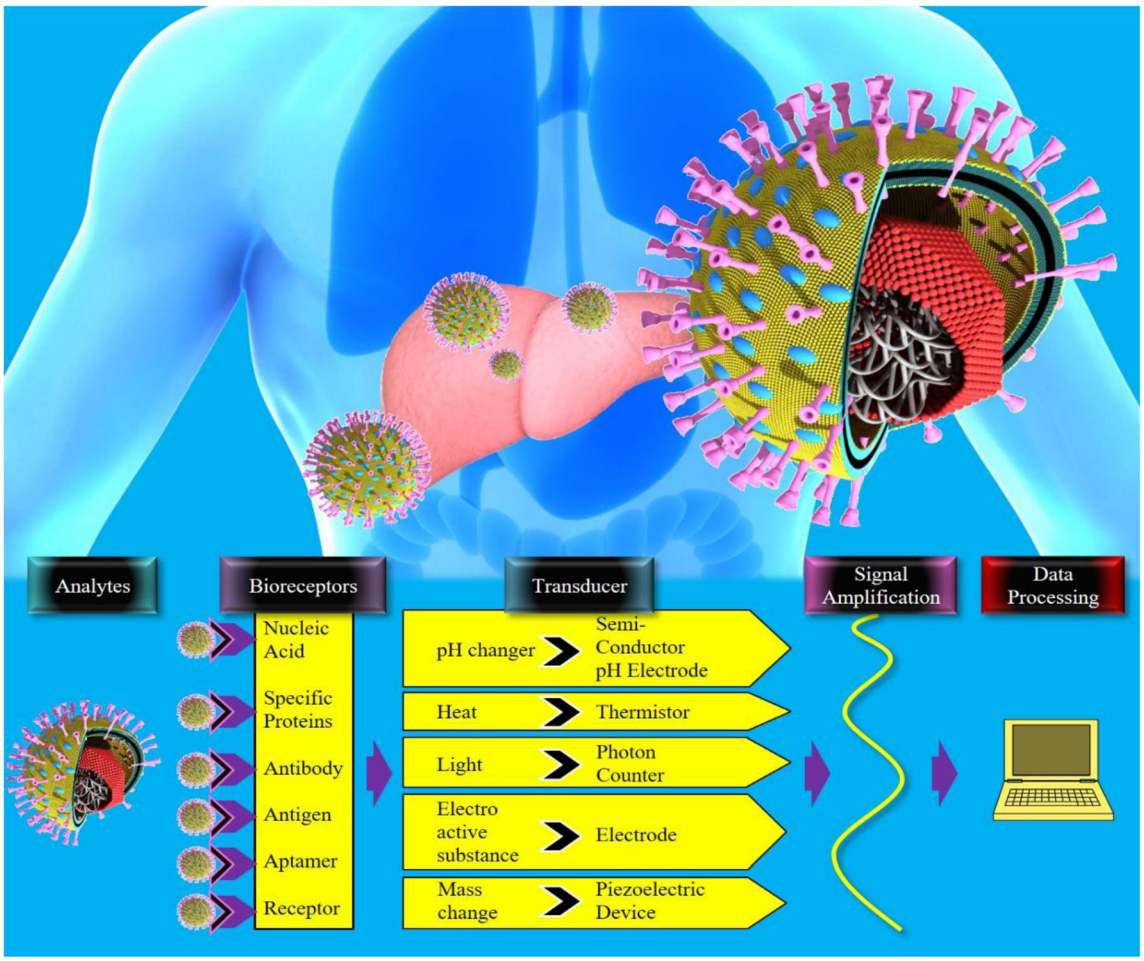
describing variety of biosensor with regard to specific, rapid and efficient detection of hepatitis virus. Scheme 1 illustrates components of a biosensor used for hepatitis virus detection. Biosensors can diagnose special target via interactions of biomolecules like substrate-enzyme reaction, antigen-antibody or ligand-receptor complexes. Viral hepatitis detection by biosensors can be done in a rapid, reliable and cheap procedure [29]. The following sections describe employed biosensors for hepatitis virus detection in detail depending on the transduction component such as electrochemical, optical and piezoelectric detection.

Electrochemical biosensors

Electrochemical biosensors have caught noticeable attention and supplied accurate, fast, sensitive, low-cost platform for a range of applications in medical diagnosis [44–48]. The compound formed from binding of biomolecule and bioreceptor at the surface of sensor leads to detectable alteration, changed into quantitative amperometric, impedimetric or potentiometric signal [26, 49, 50]. These biosensors are multifunctional tools obtaining electrochemical transducers (impedimetric, voltammetric, condutometric and amperometric) in order to recognize some biological incidents such as formation of antibody-antigen complex, hybridization of nucleic acids, enzymatic reactions and binding of ligand-receptor. Voltammetric and amperometric biosensors are broadly utilized for hepatitis virus detection [2]. Tables 2 and 3 gives an overview on various types of electrochemical biosensors developed for hepatitis viruses' detection.

Voltammetric biosensors

There are different types of voltammetric methods such as SWV (square-wave voltammetry), LSV (linear sweep



Scheme 1 Schematic presentation of biosensor components applied for detection of hepatitis viruses. Biosensors varies based on types of their transducers and bioreceptors. The interaction of analyte, hepatitis virus that leads to liver diseases, with various types of bioreceptor components such as aptamer, nucleic acid, antigen, and etc., in different biosensors converted to quantifiable signals through a transducer and then analyzed in a system. In order to amplification of generated signals different nanoparticles can be used, hence this type of biosensors termed nanosensors

Table 2 Overview on specifications of electrochemical biosensors for hepatitis B virus (HBV)

Target	Biosensor specifications	Method	Electrode	LOD	Assay time	Linear range	Ref
HBV[1]	DNA probes-biotin–streptavidin	EIS	Gold electrode	50 pmol	–	–	[70]
HBV DNA	poly(4-aminophenol)-poly(GA)-ss-DNA	DPV	graphite electrode	2.61 nmol L^{-1}	15 min	0.18×10^{-6}-1.8×10^{-6} mol L^{-1}	[53]
HBV DNA	–	ACV/ CV	Gold electrode	5 fM.	–	0.000001–1 nM	[52]
HBV DNA	probe/avidin/o-aminobenzoic acid	DPV	GCE	3.00×10^{-13} M	3 h	4.00×10^{-13}– 4.00×10^{-9} M	[71]
HBV DNA	STA-coated magnetic beads/biotin/ HBV probe	DPV	PGE [2]	74.8 fmole/mL	20 min	–	[72]
HBV DNA	dsDNA/ss-DNA-diaquabis[N-(2-pyridinylmethyl) benzamide-κ2N,O]-cadmium(II) dinitrate	DPV	GCE	7.19×10^{-9} mol L^{-1}	1 h	1.01×10^{-8}- 1.62×10^{-6} mol L^{-1}	[73]
HBV DNA	bovine IgG -DNA-CNT	SWV/CV	–	0.2 mL	–	035–0.242 mg/mL	[74]
HBV DNA	ss-DNA-$[CuL_2]^{2+}$	CV/ DPV	GCE	2.40×10^{-8} M	1 h	1.74×10^{-9} - 3.45×10^{-7} M	[75]
HBV DNA	chitosan /ss-DNA/methylene blue	DPV	CPE	3.0×10^{-10} mol l^{-1}	15 min	1.5×10^{-9}- 1.5×10^{-7} Mol l^{-1}	[76]
HBV DNA	ss-DNA-Thioglycolic acid	CV	gold electrode	–	30 min	–	[77]
HBV DNA	ss-DNA /$Cd(bzim)_2^{2+}$	DPV	GCE	8.4×10^{-8} M	15 min	1.49×10^{-7} M - 1.06×10^{-6} M	[78]
HBV DNA	ss-DNA/$[Co(dmp)(H2O)(NO_3)_2]$	DPV	GCE	1.94×10^{-8} M	–	3.96×10^{-7} M - 1.32×10^{-6} M	[79]
HBV DNA	ss-DNA/2-aminophenoxazine-3-one(AP)	DPV	GCE	1.00×10^{-7} M	45 min	3.53×10^{-7} - 1.08×10^{-6} M	[80]
HBV DNA	4,4'-DAAB (4,4′-diaminoazobenzene)/MWNT (multi-walled carbon nanotube)/ss-DNA	DPV	GCE	1.1×10^{-8} M	35 min		[81]
HBV DNA	ss-DNA/$[Cu(dmp)(H_2O)Cl_2]$ (dmp = 2,9-dimethyl -1,10-phenanthroline)	DPV	GCEs	7.0×10^{-8} M	1 h	8.82×10^{-8}- 8.82×10^{-7} M	[82]
HBV DNA	Ag/4-ABA (4-aminobenzoic acid)/MWCNTs / Luteolin C30H18CuO12(CuL2)	DPV	GCE	6.46×10^{-13} M	40 min	3.23×10^{-12} - 5.31×10^{-9} M	[83]
HBV DNA	Methylene blue–ss-DNA/ds-DNA	DPV/CV	CPE [3]	–	–	–	[84]
HBV DNA	Probe maker / oligo(dT) magnetic beads/ streptavidin-coated gold nanoparticles	Chrono Potentiometric (PSA)	Gold screen printed electrode	0.7 ng/ml	–	–	[63]
HBV DNA	an anodic aluminum oxide /GNPs (gold nanoparticles)/ ss-DNA	EIS	gold electrode	111 copies/mL	30 min	$10^2 \times 10^3$ and $10^3 \times 10^{5.1}$ copies/mL	[85]
HBV DNA	ss-DNA-MWCNT-nanocrys Zeo (Nanocrystals of zeolites)/FTO (Fluorine doped tin oxide glass electrode)/MB	EIS	–	50 copies/ml	5 min	150–106 copies/ml	[66]
HBV DNA	CPE/MNP (magnetic nanoparticles)/3-(trimethoxysilyl)-1-propanthiol /GNP/ss-DNA	EIS	CPE	3.1×10^{-13} M	30 min	8.3×10^{-13} - 6.4×10^{-7} M	[68]
HBV DNA	SWCNTs/gold/ss-DNA	EIS	–	1 × 10–18 M	2 h	1×10^{-18} M – 10^{-6}	[86]
HBV DNA	Gold nanorods (GNRs)- ss-DNA	CV	gold electrode	2.0×10^{-12} mol L^{-1}	–	1.0×10^{-12} 10.0×10^{-6} mol L − 1	[87]
HBV DNA (B-type)	BSA-dual-probe/biotin/avidin-HRP	Amperometry	gold electrode	1.12 pM	1 h	100–800 pM	[4]
HBV DNA (C-type)	BSA-dual-probe/biotin/avidin-HRP	Amperometry	gold electrode	1.64 pM	1 h	100–800 pM	[4]
HBV DNA PCR production	ferrocenium hexafluorophosphate /Thioglycolic acid/ss-DNA	DPV	gold electrode	1×10^4 copies	1 h	–	[88]

[1] Hepatitis B virus. [2] Pencil graphite electrode. [3] Carbon paste electrode

Table 3 Overview on specifications of electrochemical biosensors for other types of hepatitis virus

Target	Biosensor specifications	Method	Electrode	LOD	Assay time	Linear range	Ref.
Anti-HBc [1]	Glycine-HBc (hepatitis B core protein)-HA (hyaluronic acid)–CNT (carbon nanotubes)	SWV	GCE [5]	0.034 ngmL^{-1}	1 h	2.0 ng-5.0 mL	[54]
HBsAg [2]	MNP (m agnetic nanoparticles)- Ag/Ab/HRP (horseradish peroxidase)	CV	GCE	0.9 pg.ml^{-1}	30 min	0.001–0.015 ng/ml	[89]
HBsAg	HRP-gold NPs/Ag/Ab/N-succinimidyl ester /NPG(nanoporous gold)	DPV	GCE	2.3 pg/mL	90 min	0.01–0.1 ng/mL	[90]
HBsAg	Ab- Cu-GNP-MNP - Fe3O4 – APES(3-aminopropyltriethoxysilane)	ASV	GCE	87 pgmL^{-1}.	–	0.1–1500 ngmL^{-1}	[91]
HBsAg	CNT- poly (pyrrole propionic acid)/ Monoclonal anti-Ag,/polyclonal anti-Ag/ALP(alkaline phosphatase)	DPV	GCE	0.01 ng/mL	1 h	–	[92]
HBsAg	antibody/(nanogold/Co(bpy)$_3^{3+}$) $_n$ /Nafion	Amperometric	Platinum electrode	0.005 g/mL	12 min	0.05–4.5 g/mL	[93]
HBsAg	Antibody/(nanogold/Co(bpy)$_3^{3+}$ (Tris(2,2_-bipyridyl)cobalt(III)))$_n$ /Nafion	potentiometric	Platinum electrode	0.015 g/mL	12 min	0.05–4.5 g/mL	[93]
HBsAg	MB/α-HIgG (human IgG)/gold NPs	Chrono-amperometry	SPCEs [6]	3 mIU/mL	30 min	5–69.2 mIU/mL	[94]
HBsAg	PAA-Fc/gold NPs/HBsAb/BSA	Amperometric	GCE	40 pg mL^{-1}	–	0.1–150 ng mL^{-1}	[95]
HBsAg	HBsAb/nano-gold/Thionine/Nafion	Amperometry	Gold electrode	0.85 ng/ml.	5 min	2.56–563.2 ng/ml	[96]
HBsAg	Cyanogen bromidem/anti-HBs	potentiometric	SCE [7]	18.0 ng/ml	1 h	20.0–320 ng/ml	[97]
HBsAg	glutaraldehyde/goat-anti-rat IgG/anti-HBsAg /anti-HBeAg /HRP/3-amino-9-ethyl carbazole	EIS	Gold electrode	10 pg ml^{-1}	–	10 pg ml^{-1} - 1 ng ml^{-1}	[98]
HBsAg	Ab-gold- (3-mercaptopropyl) trimethoxysilane	Potentiometric	Gold electrode	1.9 ng·mL^{-1}	12 h	4–960 ng·mL^{-1}	[64]
HBsAg	HBsAb-gold- polyvinyl butyral	EIS	Platinum electrode	7.8 ng_ml^{-1}	10 min	20–160 ng_ml^{-1}	[99]
HBsAg	BSA/HBsAb/gold NPs/L-Cys-Nf	CV/EIS	GPE	0.1 ng mL^{-1}	–	0.5–800 ng mL^{-1}	[100]
HCV [3]	Ag(I)-coordinated hairpin DNA	SWASV	SPCE	0.36 nM	–	1.0 nM – 8.0 μM,	[101]
HCV DNA	ss-DNA/MB@SiNPs (methylene blue doped silica nanoparticles)/FTO	EIS	–	90 copies/mL	1 h	100–106 copies/mL	[67]
HCV RNA	siloxane–poly(propylene oxide) hybrids/streptavidin-biotin/probes	Amperometry- sol–gel method	Graphite electrode	–	–	–	[102]
HCV core antigen	vanadium oxide nanobelts film	CV/DPV	GCE	1.3 fg mL^{-1}		10 fg·mL^{-1} - 100 ng·mL^{-1}	[103]
HCV core antigen	celestin blue-antibody-Nafion@TiO2 composite nanoparticle labeled secondary antibody	DPV	SPCE	25 fg·mL^{-1}		0.1 to 250 pg·mL^{-1}	[104]
HCV core/E1 region	Peptide nucleic acid(PNA)/ double stranded plasmid(ds-Pl)-/MB	DPV	Gold electrode	9.5 pg/ml	3 h	10–300 pg/ml	[105]
HCV core antigen	polyclonal HCVcore antibody/ CMWNTs (carboxyl multi-wall carbon nanotubes)/ auxiliary probe / biotin-streptavidin / HRP/GMCs–MB / monoclonal HCV core antibody	SWV	Gold electrode	0.01pgmL^{-1}	30 min	0.25–300 pgmL^{-1}	[55]
HCV core antigen	Ab2/gold NPs/SiO2-Chits/HCV core antigen/BSA/Ab1/gold NPs/ZrO2-Chits	Amperometric	GCE	0.17 ng mL^{-1}	–	2–512 ng mL^{-1}	[106]
HCV core antigen	BSA/Ab/AgNPs/GQDs-SH (thiol graphene quantum dots)/ ribiflavin	DPV	GCE	3 fg mL^{-1}	–	0.05 pg mL^{-1} -60 ng mL^{-1}	[107]
(HCV3a) core/E1 region	peptide nucleic acid (PNA)/6-mercapto-1-hexanol /MB	DPV	Gold electrode	5.7 × 10^{-11} M	150 min	1–50 nM	[108]
HCV1a	poly(L-glutamic acid)/ Prob HCV1a	SWV	PGE	40.6 nM	30 min	50 nM – 1.0 μM	[10]
HCV1a	N-(3-dimethylamino) propyl)-N -ethylcarbodiimide hydrochloride/N-hydroxysulfosuccinimide /HCV1a	SWV	PGE	54.9 nM.	5 min	0.05–0.75 μ M	[11]
HCV3a	Peptide nucleic acid-SAM (PNA selfassembled monolayer (PNA-SAM))/ds-DNA/MB (methylene blue)	DPV	Gold electrode	1.8 × 10^{-12} M	20 h	10–100 pM	[109]
HAV [4] antigen	HRP-anti-IgG-anti-HAV-BSA-HAV	Chrono-amperometry	CNPE [8]	26.10^{-5} IU.mL-1	20 min	2.10^{-4} - 5.10^{-3} IU.mL-1	[59]
5-type hepatitis virus antigens	Nanogold/ protein A/HAV, HAV, HCV, HDV, and HEV monoclonal antibodies/protein A	potentiometric	Gold electrode	0.5, 0.3, 0.8, 0.5, and 1.0 ng/mL	5 min	–	[62]

[1] Anti-hepatitis B core antibody. [2] hepatitis B surface antigen. [3] Hepaptitis C virus. [4] Hepatitis A virus. [5] Glassy carbon electrode. [6] Screen-printed carbon electrodes. [7] Saturated calomel electrode. [8] Carbon nanopowder paste electrode

voltammetry), DPV (differential pulse voltammetry), CV (cyclic voltammetry), hydrodynamic voltammetry, stripping voltammetry, ac voltammetry and polarography. These methods have a wide linear range with ability to measure low concentrations of target [38, 45, 51]. Li and co-workers have developed a "signal on" electrochemical bio-sensing method for specific detection of gene sequence of HBV (hepatitis B virus) based on the PDHB (protection- displacement-hybridization-based) signaling process. The designed biosensor consisted of three types of probes; i) CP (capturing probe), ii) AP (assistant probe) and iii) MB-modified SP (signaling probe modified with 3-methylene blue). Assistant probe is co-immobilized on the surface of gold electrode and the MB-modified SP presents freely in the solution of detection. Assistant probe and capturing probe are co-immobilized on the surface of gold electrode through Au-S binding with hybridization in order to generate a duplex with 14-base. Then, the free signaling probe in solution hybridizes with assistant probe to create a duplex with 10-base. Capturing probe is specifically bind to gene sequence of HBV. A duplex is generated between assistant probes and signaling probe with target, hybridized with capturing probe. Hence, the methylene blue labels of signaling probe can be got closer to the surface of electrode that resulted in efficient transferring of electron as well as production of greater signal of detection. In order to characterize the biosensor, two kinds of electrochemical testing methods including CV (cyclic voltammetry) and ACV (alternating current voltammetry) are utilized. Under optimum circumstances, the designed biosensor demonstrates a great sensitivity with LOD (limit of detection) of approximately 5 fM for gene sequence of HBV. In the utilization of biosensor for discernment of point mutation, it shows superior capability and its special great adjustability [52]. In a study in 2014, an electrochemical genosensor was developed to detect HBV special DNA sequence based on modification of graphite electrodes with poly(4-aminophenol) and incorporation of special oligonucleotide probe. Probe-contained modified electrode was assessed via DPV (differential pulse voltammetry) with/without complementary HBV special DNA sequence's incubation. Detection was completed through direct detection in which oxidizable DNA bases was monitored or via indirect detection in which ethidium bromide was used as indicator for hybridization procedure (Fig. 1). The biosensor's LOD for target was 2.61 nmol L^{-1}. Detecting indirectly through ethidium bromide was helpful for differentiating mismatches which is worthwhile feature for detecting point mutation-related diseases. Furthermore, it was probable to discover differences between non-hybridized and hybridized surface by AFM (atomic force microscopy) [53].

The earliest marker of HBV infection, which is persisted all life after connection with virus, is termed Anti-HBc. Anti-HBc is believed to be most significant marker for application in blood bank screening. Cabral and colleagues have designed label-free electrochemical immunoassay for anti-HBc detection (antibodies to HBV core protein). Amino CNTs (carbon nanotubes), which is modified by hyaluronic acid, utilized as a nano-hybrid surface on the surface of GCE (glassy carbon electrode) for anti-HBc detection (Fig. 2). The response of electrode was evaluated via direct interactions of anti-HBc antigen by SWV (square wave voltammetry). The linear range of electro-immunoassay for concentrations of anti-HBc was 6 ng mL^{-1} with 0.03 ng mL^{-1} LOD. The results indicated that

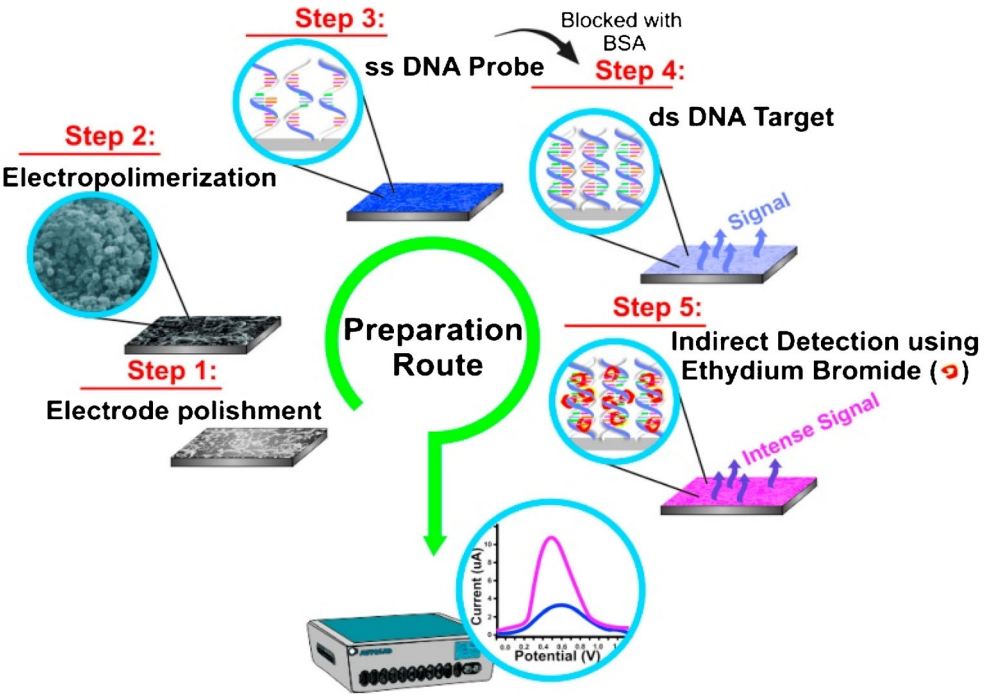


Fig. 1 Schema represents the detection of specific DNA sequence of the hepatitis B virus using a DNA biosensor preparation process. This figure is obtained with permission from Ref [53]

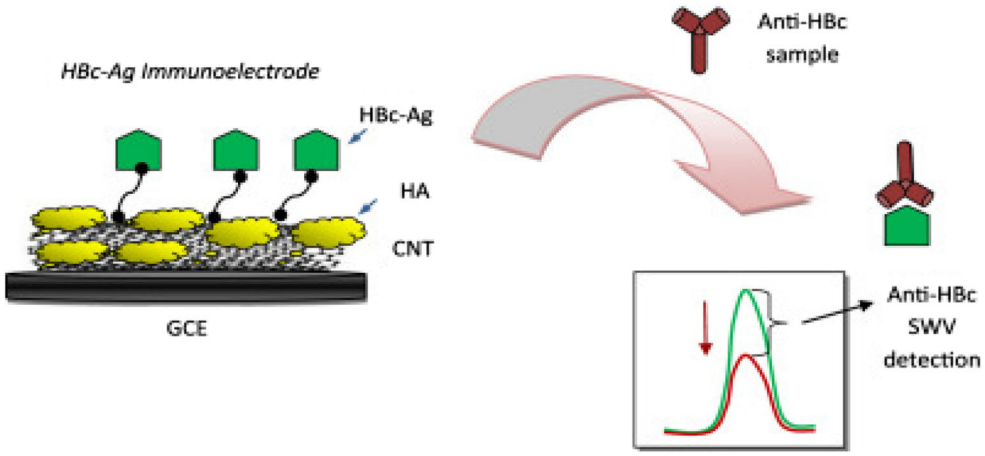


Fig. 2 A schema illustrating the electrochemical immunosensor based on use of HA–CNT and immobilization of the HBc antigen. This figure is obtained with permission from Ref [54]

the designed electro-immunoassay can be considered as a promising platform for usage as a bench mark for disposal of blood bag. The great performance of this immunoassay seems maybe because of HA-CNTs synergic effect that allowed immobilization of a great amount of antigens and enabled increment of electron transfer, which led to a great diagnostic sensitivity. CNTs were selected because of their good structure, mechanical and electrical properties, enhancing the electroactive area so increase the rate of immobilization to the surface of electrode [54].

In 2013, a selective and ultrasensitive immunosensor was designed for HCV core antigen (hepatitis C virus) detection. Components of immunosensor were GMCs–MB nanocomposite (graphitized mesoporous carbon– methylene blue) and HRP (horseradish peroxidase)-DNA-coated CMWNTs (carboxyl multi-wall carbon nanotubes) as a material for electrode modification and secondary layer of antibody, respectively. After modification with nanocomposite, the electrodeposition of gold nanoparticles was performed onto electrode for immobilization of captured antibodies. CMWNTs linked with secondary antibodies and bridging probe, and concatamers of DNA were got by hybridization of supporting probes and biotin-labeled signal. Eventually, streptavidin-HRP were tagged on the secondary layer of antibody through streptavidin-biotin system. The immunosensor demonstrated 0.25–300 pg mL^{-1} linear range and 0.01 pg mL^{-1} with great selectivity. Results exhibited acceptable reproducibility and stability, as well as desirable recovery in human serum for hepatitis C virus core antigen. The designed immunosensor had high potential for utilization clinically (Fig. 3) [55].

An electrochemical DNA biosensor which has sensitive, label-free, low-cost, simple and disposable characteristics was developed for HCV1a (HCV genotype 1a) detection. Immobilization of amino-bound inosine-substituted 20 mer probes onto disposable PGE (pencil graphite electrode) via covalent linkage leads to development of biosensor. The SWV results of designed DNA biosensor demonstrated detection limit of 54.9 nM with linear range of 0.05–0.75 μM [11].

Another label-free DNA biosensor for detection of HCV1a was developed through modification of PGE (pencil graphite electrode) with PGA (poly(L-glutamic acid)). The surface of PGA modified PGE immobilized with inosine-substituted 20 mer probes via creation of amide bonds in covalent linkage. Through square wave voltammetry an oxidation peak was observed in +1.05 V that showed guanine oxidation signal in hybridization. Linear rang of 50 nM-1.0 μM and LOD of 40.6 nM were obtained by proposed biosensor for HCV1a detection. Consequently, PGA-modified DNA biosensor is disposable, low-cost as well as owning higher electrocatalytic impact on guanine oxidation [10]. In a report an electrochemical technique utilized for detection of ss-DNA oligonucleotide which has a sequence derived from HBV genome, in which CSD (circular strand displacement) and RCA (rolling circle amplification) methods mediated by MB (molecular beacon) was used. The ss-DNA hybridized with immobilized MB loop portion on the gold electrode surface, while the rest of MB partial DNA sequence hybridized with primer DNA. This provoked the MB-mediated circular strand displacement. The rolling circle amplification then begin to create a long strand DNA which lead to important increase of DPV response of the electrochemical methylene blue probe. Under optimum conditions, limit of detection was 2.6 aM with ultrahigh sensitivity and great selectivity. Also, the linear range was 10–700 aM concentration of DNA [56].

Amperometric biosensors

Amperometric biosensors might be a subclass of voltammetric type biosensors with electroactive species that endure the redox reaction at electrode surface [57]. In amperometric biosensors, the existing linear relationship between current intensity and analyte concentration is measured [58]. Chen et al., have demonstrated a biosensor based on BSA (bovine serum albumin)-dual probe for detection of HBV B/C genotype in which there has been a relationship between temperature of melting and length of probe. With the specifically developed

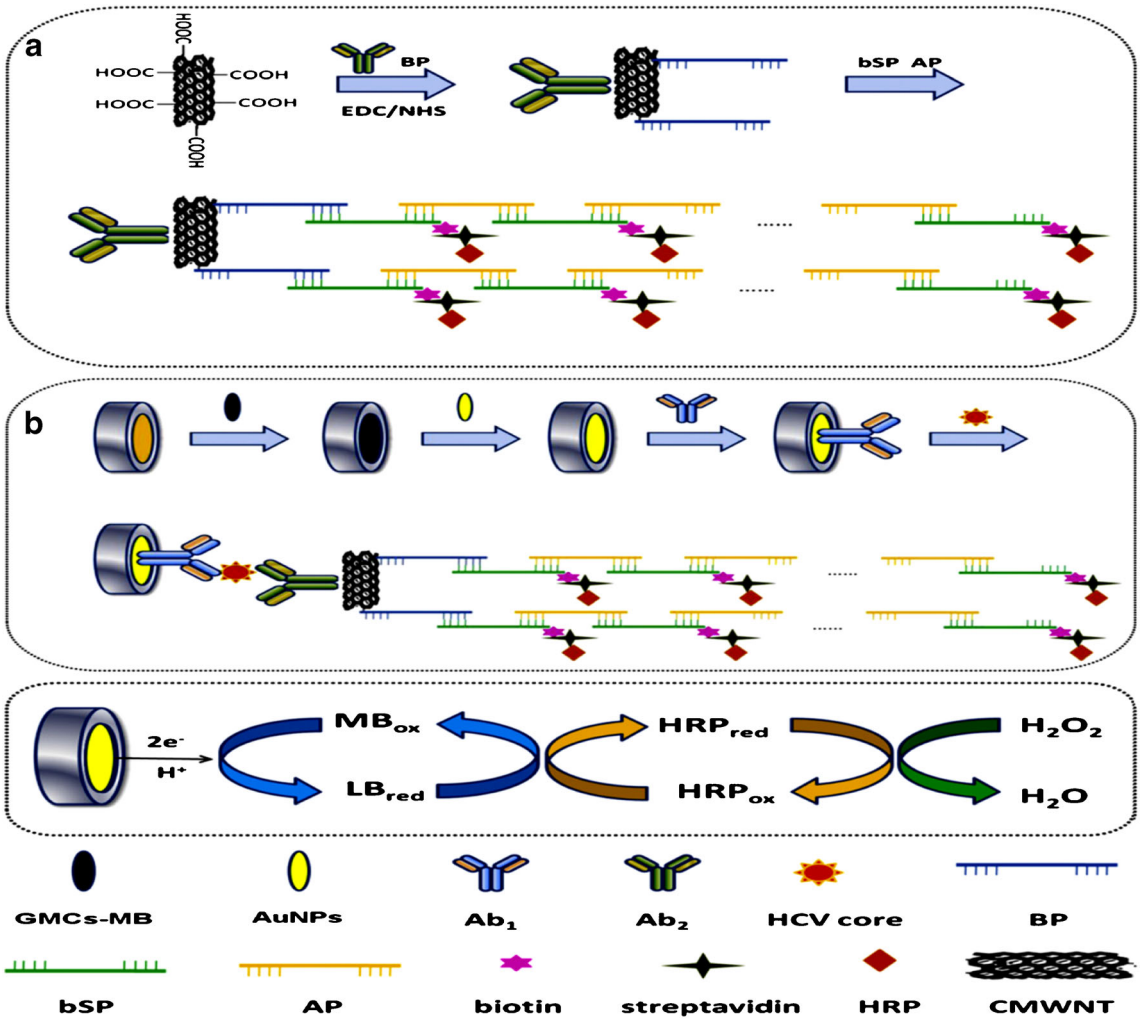


Fig. 3 Preparation of a HCV core inmunosensor: **a** preparation of the multi HRP-DNA-CMWNTs-Ab2 bio-conjugate; **b** fabrication of the HCV immunosensor. This figure is obtained with permission from Ref [55]

B/C genotype probes from hepatitis B virus, this suggested bovine serum albumin-dual probe sensing platform is incubated at two temperatures in the same specimen solution. The HBV genotype can be successfully identified due to the relationship of two signals of amperometry. Furthermore, B and C genotypes had the limit of detection of 1.12 pM and 1.64 pM, respectively. This biosensor was a novel technique for B/C genotypes of hepatitis B virus with plus points of being simple, reproducibility, rapidness and accuracy as well as opening novel window for genotyping based on DNA bio-molecular features [4]. Mandli and co-workers have designed an immunosensor for detection of HAV antigen through immobilization of hepatitis A virus on the carbon nano-powder paste electrode surface. Peroxidase utilized for labeling secondary antibody in order to monitor the target antigen. Adding hydroquinone and hydrogen peroxide as a mediator of redox resulted in analytical signal correspondence with amperometric current. A plot of amperometric signal versus hepatitis A virus antigen concentration resulted in the calibration plot shown in Fig. 4. With taking the results into consideration, LOD for hepatitis A virus antigen was 26×10^{-5} IU mL^{-1} with a wide linear range of 2×10^{-4} to 5×10^{-3} IU mL^{-1}. In addition, average RSD (relative standard deviation) of designed immunosensor was <3% and 7% on same days and different days of measurement, respectively. Therefore, the immunosensor showed high selectivity and stability for detection of hepatitis A virus antigen and was successfully utilized for HAV determination in water specimens [59].

Potentiometric biosensors

Potentiometric biosensors measure the charge potential accumulation in the working electrode in comparison with reference electrode in an electrochemical cell, where there are insignificant current flows between the electrodes [58, 60, 61]. Tang et al., have developed an integrated array of automatic immunosensor to detect five different antigens of hepatitis virus, including hepatitis A, B, C, D and E. Firstly, the

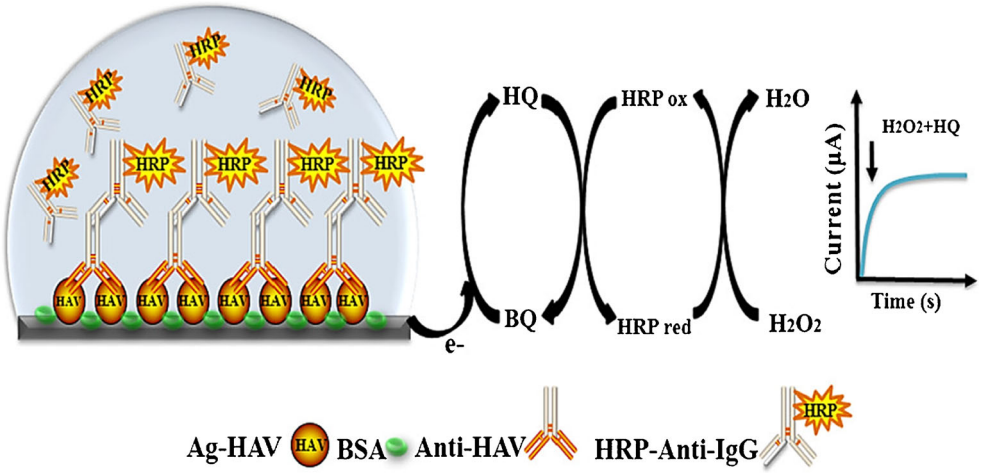


Fig. 4 A schema for the preparation of the electrochemical HAV competitive antibody immunosensor. This figure is obtained with permission from Ref [59]

immobilization of five type of antibodies of hepatitis virus onto array was done via utilization of nano-gold proteins and particles to capture related antigens with a one-step capture format. The determination was based on potential alteration before and after antibody-antigen reaction by utilizing a system of two-electrode. The designed immunosensor array leads to detection of hepatitis virus 5-kind antigens in five minute. The LOD for array was ≤1.0 ng/mL for most of the analytes. This immunoassay provides simple, label-free, low-cost and rapid detection of multi-analyte [62]. An electrochemical method based on gold nanoparticle was suggested by Hanaee et al., in 2007 for detection of DNA sequences of HBV. In this method, amplified DNA strands of HBV hybridized with probes which are spread out on paramagnetic beads. After non-complementary sequences' separation, gold-followed by Ag (silver) increment modified with streptavidin was used for treatment of magnetic beads which were hybridized. High sensitivity and selectivity were achieved applying electrochemical stripping determination of Ag ions deposited on gold nanoparticles. It is worth noting that the detection limit was 0.7 ng ml^{-1} [63].

A novel immunosensor developed for surface antigen of HBV detection through gold nanoparticles self-assembly with thiol-involved sol-gel network. The 3D sol-gel network and colloidal gold nanoparticles were utilized as new amplification method and enhancing the sensitivity of immunosensor. Hydrolyzed (3-mercaptopropyl) trimethoxysilane sol–gel solution was used to immersing gold-electrode into it in order to gathering of 3D-silica gel. Following that, gold NPs were immobilized onto the thiol of the sol-gel network. Hence, the surface antibody of HBV was gathered onto gold nanoparticles surface. The procedure was evaluated via electrochemical impedance spectroscopy and CV. The created alterations in potentiometric results before and after the antibody-antigen reaction was used for detection. Results demonstrated that long-time stability, great reproducibility and extreme sensitivity with linear range of 4–960 ng mL^{-1} and 1.9 ng mL^{-1} LOD as well as one-month lifetime [64].

Impedimetric biosensors

These type of biosensors have low usage of energy so that they are cheap and can miniaturized with ease. As a transducer, impedametric biosensors are mostly utilized antibodies [31]. There are two basic types of methods for impedance measurement depending on employing EIS (impedance spectroscopy) or electrochemical impedance immunosensors in which mSAM (mixed self-assembled monolayer) base layer utilized for its construction [31]. Compared to potentiometry and amperometry, one of the advantages of EIS is lack of need for labels, which simplifies the production of sensor [65]. Narang and co-workers have developed a genosensor by using Zeolite nanocrystals (Nanocrys Zeo) and MWCNT (multi-walled carbon nanotubes) for detection of HBV DNA in patients' blood. CV, DPV and EIS was performed for characterizing electrode modified with ss-DNA-nanocomposite. The hybridization between target ss-DNA and probe ss-DNA was determined by reduction in current, created by interaction of MB (methylene blue) with 3'G (free guanine) of ss-DNA. Zeolite nanocrystals were deposited on the FTO glass electrode (fluorine doped tin oxide) in order to great ss-DNA immobilization when MWCNTs are integrated into assembly of zeolite for enhancing genosensor's electro-conductivity. The detection limit of geneosensor was 50 copies mL^{-1}. Therefore, the EIS method applied for HBV detection is convenient without prolonged time for analysis [66]. Singhal et al. Have reported an impedimetric genosensor for HCV1 (hepatitis C virus genotype 1) detection in serum, based on complementary cDNA target hybridization with probe. For this purpose, the probe DNA was immobilized on the MB@SiNPs/FTO (methylene blue doped silica NPs modified fluorine doped tin oxide) electrode surface. ss-DNA/ MB@SiNPs/

FTO modified electrode showed two features for detecting DNA of HCV in serum sample of patient, including; being a platform for signal amplification due to presence of SiNPs and also being electrochemical indicator because of methylene blue. The LOD and linear range of genosensor were 90 copies mL^{-1} and 100–10^6 copies mL^{-1}, respectively. Furthermore, this genosensor had 4 weeks of half-life [67]. Mashhadizadeh and colleagues have prepared a CPE (carbon paste electrode) modified with gold and magnetic nanoparticles for immobilizing thiol modified probe DNA of HBV in order to detect trace amount of hepatitis B virus DNA target. The usage of GNPs (gold nanoparticles) and MNPs (magnetic nanoparticles) led to enhancement of DNA biosensor electrochemical signal and sensitivity increment of biosensor towards detection of HBV DNA. Utilization of TMSPT (3- (trimethoxysilyl)-1-propanthiol) for passivation of MNPs can enhance the reproducibility and stability of the modified electrode. Although, TMSPT free S-H groups in the functionalized MNPs provide an improved loading interface for GNPs and probe hepatitis B virus ss-DNA. This DNA-biosensor demonstrated pleasing reproducibility, great sensitivity and selectivity for determination of HBV DNA. These superior characteristics can be associated with unique synergism between gold and magnetic nanoparticles in the immobilization of ss-DNA. The detection limit of this genosensor was 3.1 (±0.1) × 10^{-13} M, and successfully applied for label-free and sensitive impedimetric detection of hepatitis B virus DNA in the blood plasma and urine samples (Fig. 5) [68].

Conductometric biosensors

Application of polymers like polypyrrole, polyaniline, polythiophene and polyacetylene draws great attention towards development of electrochemical immunoassay based biosensors. The conductive polymers play an important role as an electrochemical transducer causing alteration of signals into electrical signals to be used in sensing [40]. Liu and coworkers have designed a conductometric immunoassay for detection of HBsAg (hepatitis B surface antigen) in which double-codified nano-gold particles utilized as label for micro-comb-type electrode. Covering an interdigitated transducer with *anti*-HBs/protein A/nano-gold leads to fabrication of the micro-comb-type electrode. Conjugation of HRP (horseradish peroxidase) with *anti*-HBs antibodies labeled with nano-gold-labeled employed for preparation of the double-codified nano-gold particles. Immune-complex formation caused to alter the direct electrical transmission between electrode and carried- horseradish peroxidase and hence variations of local conductivity can be evaluated based on bio-electro-catalytic reaction of carried-horseradish peroxidase. By application of *anti*-HBs conjugated with HRP, as secondary antibodies, the linear range was 1.5–450 ng/mL HBsAg, whereas by employing double-codified nano-gold particles sensitivity sensor enhanced to 0.01 ng/mL with 0.1–600 ng/mL HBsAg linear range. The designed immunosensor demonstrated great sensitivity, acceptable reproducibility and stability [69].

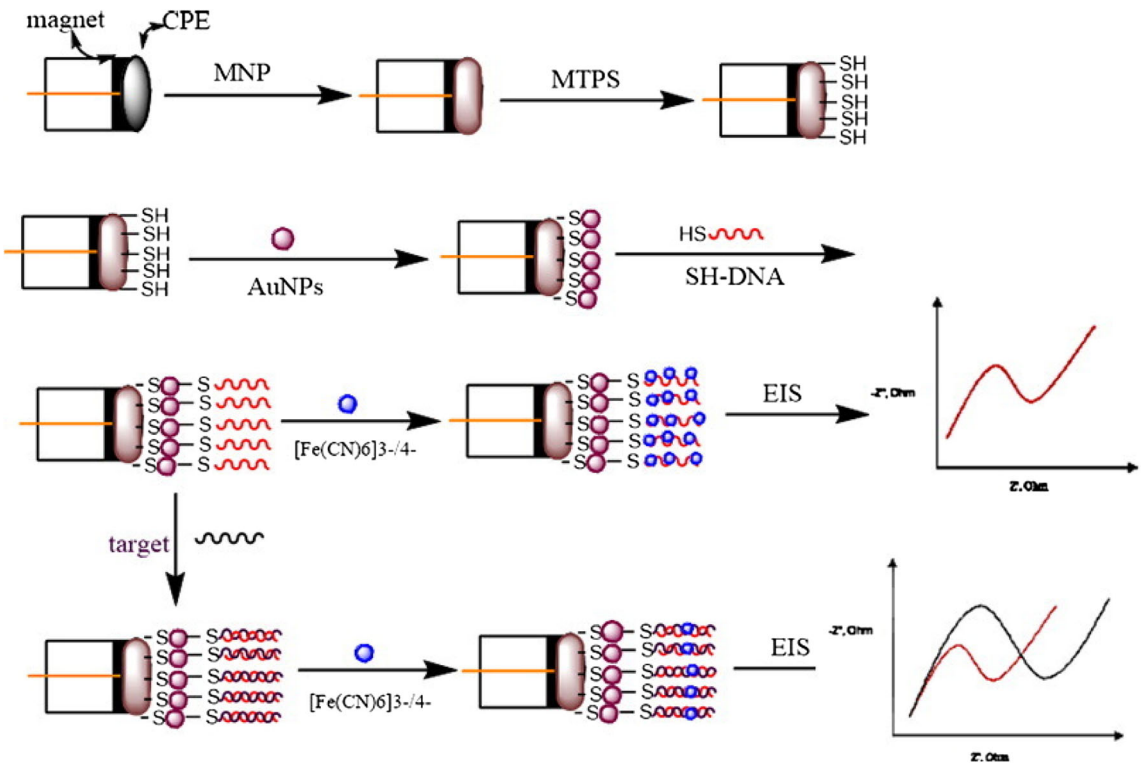


Fig. 5 Schematic representing the construction steps of the electrochemical DNA biosensor. This figure is obtained with permission from Ref [68]

Optical biosensors

Considerable improvements have been achieved in optical biosensors that makes it as a valuable and significant component of novel activities in drug screening and biosensing field. Hence, optical biosensors become one of the most applicable kinds of biosensor [31]. Having a broad range of spectroscopies (e.g., fluorescence, Raman, refraction, absorption, SERS, phosphorescence and dispersion spectroscopy) has enabled this method to be used in several biosensor classes [110–112]. Table 4 is enlisted various optical biosensors developed for diagnosis of hepatitis virus.

Fluorometric biosensors

Label-based fluorescence optical methods utilize labels such as fluorescence proteins, dyes and QDs (quantum dots). Fluorescence based biosensors can be classified in two groups of in vivo and in vitro. The metabolic activity of microorganism in the in vitro measurements leads to changes in emission of light because of presence of exogenous fluorescent constituent, whereas in the in vivo measurements some microorganisms have the capability to generate fluorescence without addition of exogenous constituent, such as GFP (green fluorescent protein) [31]. Transfer of energy in a donor-acceptor pair of fluorophore is the basis of fluorescence resonance energy transfer (FRET) biosensors [65]. Zhu et al., have reported a FRET (fluorescent resonant energy transfer) biosensor for detection HBV DNA. The biosensor was built using gold NPs as acceptor and PEI (poly(ethylenimine)) modified NH2-UCNPs (up conversion nanoparticles) as energy donor. Two strand of ss-DNA were respectively conjugated with NH2-UCNPs and gold nanoparticles. After mixing the conjugated DNA strands together, hybridization between UCNPs and gold NPs-conjugated complementary DNA lead to up conversion luminescence quenching due to the fluorescent resonant energy transfer process. Addition of target DNA leads to release of gold NPs from UCNPs surface and restoration of the up conversion luminescence due to the formation of stable ds-DNA on UCNPs. The designed biosensor demonstrated great selectivity and sensitivity with potential for use in clinical analysis of hepatitis B virus and others [113]. Yue and colleagues have reported a fluorescence biosensor for detection of DNA based on usage of CuS particles. Biotin-modified capture DNA was then modified on Streptavidin MagneSphere PMPs (Paramagnetic Particles) and hybridized with HBV target DNA. This process was followed by hybridization of the bound target DNA with particles of DNA-CuS, creating a sandwich-like structure. Acid can cause the destruction of CuS particles on the sandwich structures leading to formation of Cu(II). Furthermore, sodium ascorbate can be applied to reduction of Cu(II) to Cu(I), which successively resulted in the catalyze of the reaction between propargyl alcohol and a weak-fluorescent 3-azido-7-hydroxycoumarin in order to create a compound of fluorescent 1,2,3-triazole. The detection limit and linear range of this biosensor was 0.04 nM and 0.1–100 nM, respectively, with great sensitivity and reproducibility [114]. Lu et al., have reported a FRET system including FAM (fluorescein) and AuNRs (gold nanorods) for HBV DNA sequences detection. Gold NRs surface was coated with CTAB (cetyltrimethylammonium bromide) thin layer in order to make them positively charged. In the time of FAM-ss-DNA (FAM-tagged ss-DNA) addition into suspension of gold NRs, adsorption of it onto gold NRs surface led to generation of ternary complex of FAM-ss-DNA–CTAB-gold NRs. The formed structure caused FRET (fluorescence resonance energy transfer) from FAM to gold nanorodes and quenching of FAM fluorescence intensity. Addition of complementary target DNA to complex solution of FAM-ss-DNA–CTAB–gold NRs caused further reduction in fluorescence intensity due to enhanced fluorescence resonance energy transfer efficiency. The linear range and LOD were 0.045–6.0 nmol L^{-1} and 15 pmol L^{-1} [115]. For determination of the single mismatch in HBV gene and target DNA, Wang and co-workers have reported a QDs-DNA (quantum dots-DNA) nano-sensor based on FRET technique. In the present research, TOPO (trioctylphosphine oxide) on the QDs surfaces was replaced with MPA (3-mercaptopropionic acid) in order to prepare the water-soluble CdSe/ZnS quantum dots. Following that, oligonucleotides were immobilized on the QDs surface in order to create the quantum dots -DNA conjugates. Then, by adding of signal DNA modified with Cy5 and DNA targets into the quantum dots-DNA conjugates the sandwiched hybrids were generated. The final assembly shortens the distance between the QDs (the donor) and Cy5 fluorophore (the acceptor), which results in the emission of fluorescence by the acceptor employing FRET on the donor's illumination. In order for effectively identify HBV gene single-base mutants, ligation method was applied. If there was a single-base mismatch, which can be determined by ligase, the probe was not ligated and due to lack of fluorescence resonance energy transfer (FRET), Cy5 emission was not generated. With regard to results, the LOD was 4.0 nM for synthetic 30-mer oligonucleotide targets derived from the HBV (Fig. 6) [116].

Colorimetric biosensors

Colorimetric biosensors are rapid and portable which allow immediate pathogenic microorganisms observation with bare eyes so that provided low-cost diagnosis instruments. The components which used in colorimetric biosensors are flat substrate (glass and paper) and small amount of specimen [31]. A new type of gold NPs biosensor, which is both colorimetric and quantitative, has introduced by Shawky et al., in order to directly identify the unamplified HCV RNA in clinical models and transcripts of DNA restoration from cell lines.

Table 4 Specifications of some optical biosensors for diagnosis of hepatitis viruses

Target	Method	Biosensor specifications	LOD	Assay time	Linear range	Ref
HBsAg	Chemiluminescence	Anti-HBsAg-Ag /GNPs / Luminol	14 pg/mL	30 min	0.12 to 30 ng/mL	[125]
HBsAg	Chemiluminescence	Anti-HBs-Ag/STR/biotin-GNP/luminol	0.358 pg mL^{-1}	30 min	1.7 to 1920 pg mL^{-1}	[124]
HBsAg	LSPR	GNRs was modified with monoclonal hepatitis B surface antibody	0.01 IU/mL	–	0.01 IU/mL to 1 IU/mL	[128]
HBsAg	SPR	plasma-treated parylene-N film	less than 10 pg/ml	30 min	10 pg/ml to 1 μg/ml	[129]
HBsAg	SPR	self-assembled monolayer	0.1 ng mL^{-1}	15 min	–	[130]
HBsAg	SERS	anti-HBsAg/gold NFs-Ramanr eporter	0.01 IU/mL	–	0.0 to 60.0 IU/ml	[122]
anti-HBsAg	SPR/ LSPR	gold-binding polypeptide- fused single chain antibody/GBP-HBsAg	1 $pgmL^{-1}$	1 h	$pgmL^{-1}$ to 10μgmL^{-1}	[131]
Anti-HBs	SPR	poly[(N-(2-hydro-xypropyl) methacrylamide)-co-(carboxybetaine methacrylamide)]/ HBsAg	0.3 $ngcm^{-2}$	10 min	–	[120]
anti-HBs	SPR	avidin-biotynylated antibodies and peroxidase–anti-peroxidase complex	0.64 nM	2 h	–	[132]
HBsAb	SPR	poly(hydroxyethyl methacrylate-N-methacryloyl-L-tyrosine methyl ester) / allyl mercaptane	208.2 mIU/mL	2 h	0–120 mIU/mL	[133]
HBV DNA	FRET	CdSe/ZnS-QDs-TOPO-MPA-Cy5-signal DNA	4.0 nM	0.5 h	–	[116]
HBV DNA	FRET	FAM-ss-DNA–CTAB–gold NRs	15 pmol L1	50 min	0.045 to 6.0 nmol L1	[115]
HBV DNA	FRET	PEI-NH2-UCNPs-gold NPs	250 pM	1 h	0 to 50 nM	[113]
HBV DNA	Fluorometry	Biotin-Streptavidin-PMPs- CuS	0.04 nM	2 h	0.1 to 100 nM,	[114]
HBV DNA	Fluorometry	AgNC/MoS2 hybrids	10.7 nM	–	5 to 30 nM	[134]
HBV DNA	Colorimetric PCR-based biosensor	DNAzyme-containing probe-ss-DNA-hemin- ABTS-H2O2	10 copies	30 min	10 to 107 copies	[118]
HBV DNA	Colorimetric	CuNCs-ss-DNA-ABTS-H2O2	12 × 109 molecules	2 h	12×10^{9} to 12×10^{13} molecules	[117]
HBV DNA	SPR LAMP sensing cartridge	–	2 fg/ml	–	–	[135]
HBV DNA	SERS	Ag nanorice@ Raman label@ SiO2	50 nM	0.5 h	0.5 to 100 fM	[121]
HCV RNA	Colorimetric	Gold NPs-cysteamine-CTAB	4.57 IU/μl	–	–	[12]

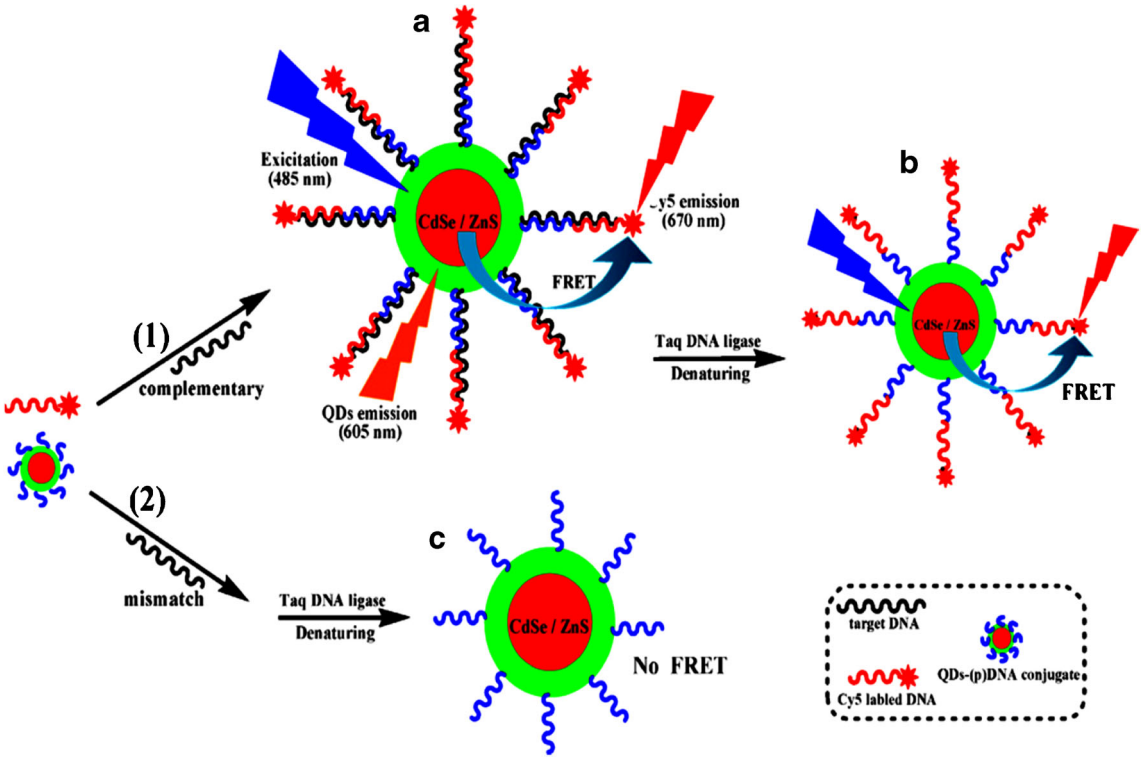


Fig. 6 Detection technique of DNA SNP based on FRET, in which the QDs-(p) DNA nanoassembly was applied. (**a** and **b**) excitation of QDs at 485 nm and induction of realse of PL from Cy5 via FRET between Cy5 acceptors and QDs donor in the nanoassembly are observed. (**c**) lack of presence of the most efficiently matched target DNA resulted in ligation failure. Therefore, no FRET was found in this respect. This figure is obtained with permission from Ref [116]

The method was based on inducing accumulation of citrate-gold NPs modified with specific probe. Two kinds of gold nanoparticles, CTAB and cysteamine were compared to obtain maximum method performance. The method was rapid, low-cost and simple with great specificity, 93.3% sensitivity as well as 4.57 IU μL^{-1} detection limit (Fig.7) [12]. In a study, a colorimetric detection technique of ss-DNA based on DNA-templated copper nanoclusters was reported by Mao and co-workers. The reported technique was able to easily detect three-base-pair mismatches of target DNA and the limit of detection was 12×10^9 molecules for HBV DNA. [117]. A novel technique was presented by Yang et al., to identify the quantitation of HBV viral load according to colorimetric polymerase chain reaction (PCR) using DNAzyme-based probe. The specific DNAzyme showed activity like peroxidase in the existence of hemin for reporting colorimetric signal. This technique have demonstrated wide linear range, great sensitivity and builds significant basis for obtaining accurate detection limit of HBV DNA [118].

Ding, Lu and co-workers have utilized atom transfer radical polymerization technique for synthesis of β-cyclodextrin-cored poly(acrylic acid) (PAA) with controllable and uniform molecular weight. After loading on the surface of silica nanoparticles functionalized with adamantane through interaction of host-guest, then probe ss-DNA and glucose oxidase were immobilized on the prepared nanoparticles. Also, capture single strand DNA was functionalized on magnetic beads which modified with amino. In the existence of ss-DNA sequence of HBV containing totally matched sequence of both capture and probe ss-DNA, a bio-conjugate was created (Fig.8). By controlling the absorption intensity alteration of gold nanoparticles at 530 nm, this biosensor with possessing novel signal amplificatory probes can be applied for highly selective and sensitive detection of DNA sequence of hepatitis B virus in both serum and buffer samples. The designed method has opened new windows for construction of gold NPs covered with PAA brushes in the area of clinical diagnosis and different life sciences [119].

Surface plasmon resonance

The advantages of SPR (Surface plasmon resonance) biosensors are: i) The possibility of online monitoring of affinity interactions, and ii) Direct detection, without any additional labeling [6]. Some of the major disadvantages of this potent method include completed mechanism, need for largely expensive equipment, and enormous size of presently obtainable instruments. However, some portable SPR kits, such as Texas Instruments' Spreeta system, are commercially accessible [65]. Localized SPR (LSPR) is based on metallic

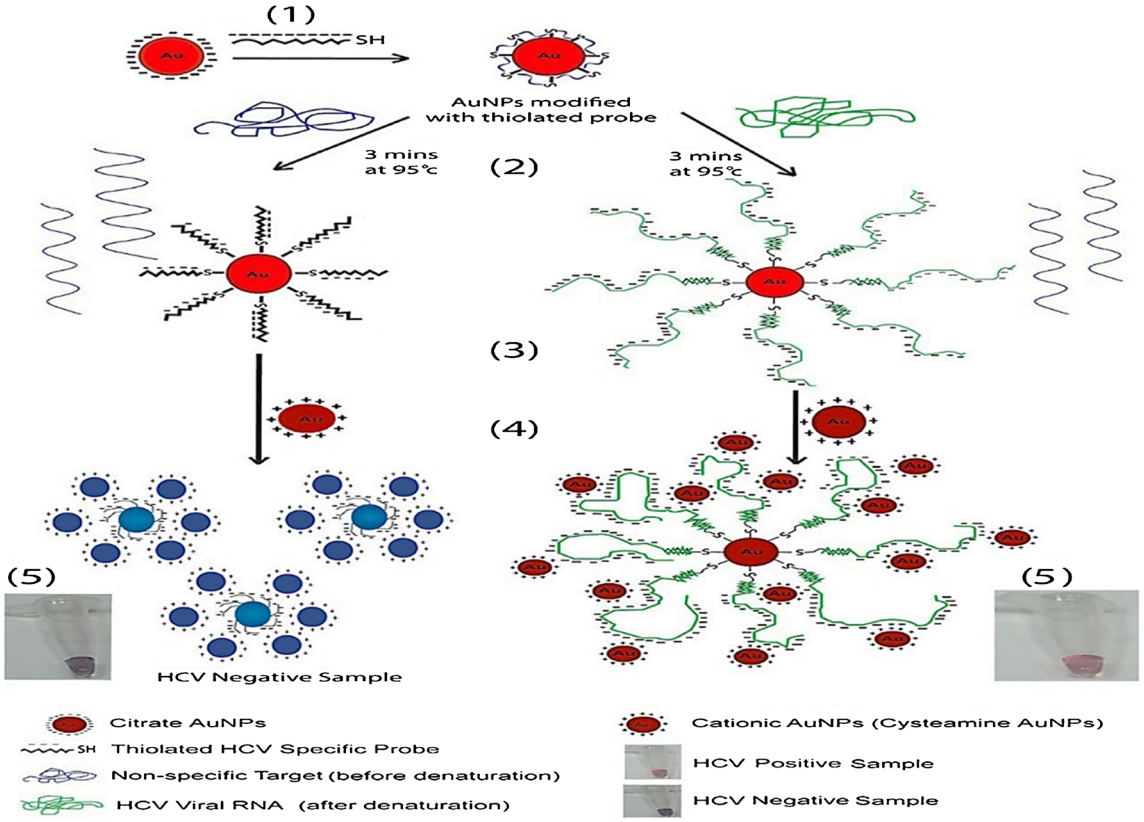


Fig. 7 Direct identification of unamplified HCV RNA colorimetric biosensor in clinical examples: 1) Functionalization of citrate capped gold NPs with thiolated HCV specific probe, which leads to the formation of nanoprobes, 2) Mixing of the nanoprobe with the RNA sample, followed by three minutes of being heated at 95 °C, 3) Right panel: hybridization of the HCV viral RNA to the HCV specific nanoprobe using sequence complimentarily. Left panel: lack of presence of HCV RNA (non-particular RNA target), thereby lack of occurring of hybridization. The next stage included the incubation of the mixture at room temperature, 4) Adding of the cationic gold NPs, 5) Right panel: remained color of red of the mixture solution in the company of HCV RNA, which reflected the gold NPs' dispersion onto the folded HCV RNA, resulting in the protection of the nanoprobes from being aggregated through cationic gold NPs. Left panel: binding of gold NPs to the probe phosphate backbone electrostatically in the lack of a complementary target, leading to the reduction of the inter-particle distance between the cationic gold NPs and nanoprobes and accumulation and change of color from red to blue. (The reader is referred to the web version of this work for explanation of the references to color in this figure legend). This figure is obtained with permission from Ref [12]

nanostructures (MNPs (gold, silver, etc.) having unique optical properties, which are not observed in large metal structures [110]. A particularly striking example of such phenomenon is the red color of aqueous dispersions of colloidal gold particles, which is a manifestation of LSPR. Interaction of incident light with MNPs, induction of collective electron charge oscillations, which are confined in MNPs, by electromagnetic light field, and succeeding light absorbance in the ultraviolet-visible (UV-VIS) band lead to the optical phenomenon of LSPR. In this regard, SPR and LSPR methods vary in terms of local induction of plasmon oscillate on the nanostructure instead of along the metal/dielectric interface [110]. Riedel et al., have reported a plasmonic biosensor for detecting protein biomarkers. Bioreceptor-functionalized poly[(N-(2-hydro-xypropyl) methacrylamide)-co(carboxybetainemethacrylamide)] brushes based- new bio-interface structure was employed for analysis of clinical serum specimens (Fig. 9). Outstanding resistance to fouling was provided via this bio-interface even after functionalization and for the first time permitted direct determination of anti-HBs (antibodies against HBsAg (HBV surface antigen)) in clinical serum specimens utilizing SPR. This surface plasmon resonance biosensor permitted recognition of positive and negative anti-HBs clinical specimens within 10 min. The results exhibited that regeneration of biosensor can be done though treatment with glycine buffer [120].

Surface-enhanced Raman scattering

In surface-enhanced Raman scattering (SERS) biosensing technique, the intensity of the vibration spectra of a molecule enhanced by several orders of magnitude when it is in close proximity to nano-roughened metallic surfaces or nanoparticles composed of either gold or silver [110]. Two mechanisms are involved in the amplification of SERS intensity in Ramen labels, including electromagnetic (EM) and chemical (CE)

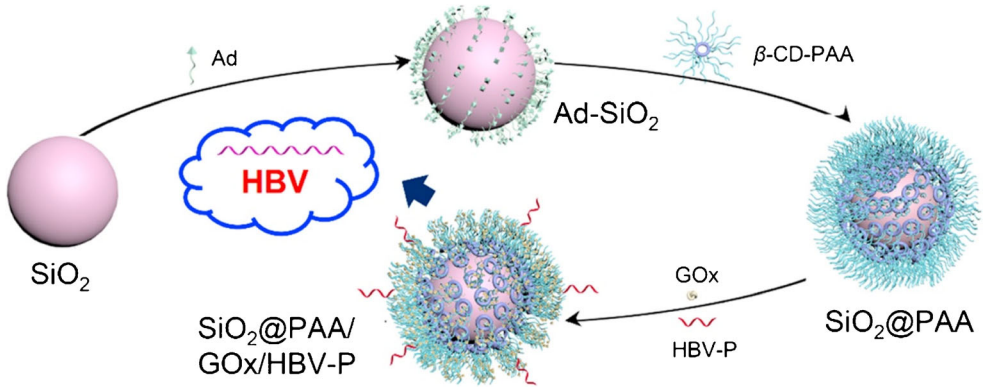


Fig. 8 A schema representing the formation of the probe based on SiO2@PAA/GOx/HBV-P NPs. This figure is obtained with permission from Ref [119]

improvements. The origin of EM improvement is the localized surface plasmon resonance (LSPR), which centralizes the incident light and generates locally intense fields of EM. Given the fact that the fourth power of the EM field and SERS signal has the same volume, enhancement of the form, size and conformation of plasmon nanostructures leads to significant improvement in SERS sensor detection [121]. Li et al., have fabricated SERS sensor to detect HBV DNA based on Ag nanorice@Raman label@SiO_2 sandwich nanoparticles. It is expected to be associated with spatial improvement of EM field in the quasi-periodic array, which eventually results in ultrasensitive SERS identification. Malachite green isothiocyanate (MGITC) molecules are selected as Raman labels lodge between the SiO_2 shell and Ag nanorice core of the sandwich nanoparticles, which centers the Ramen labels and inhibits the leaching of the labels throughout the process of sensing. The results indicated that the detection limit was 50 aM and had discrimination ability toward DNA single-base mutant [121]. A greatly sensitive SERS immunoassay was introduced by Kamińska and co-workers so that Hepatitis B virus antigen (HBsAg) can be detected in human blood in a microfluidic system. A sandwich structure created by the fuchsine-labeled immuno-gold nanoflowers with antibody and antigen immobilized on surface-enhanced raman scattering-active substrate based on gold-Ag covered GaN. Surface-enhanced raman scattering-active substrate with great reproducibility and stability serves pivotal role in enhancing the efficacy of surface-enhanced raman scattering immunoassay. The limit of detection for HBsAg was 0.01 IU mL^{-1}, this immunoassay showed high specificity for HBsAg detection [122].

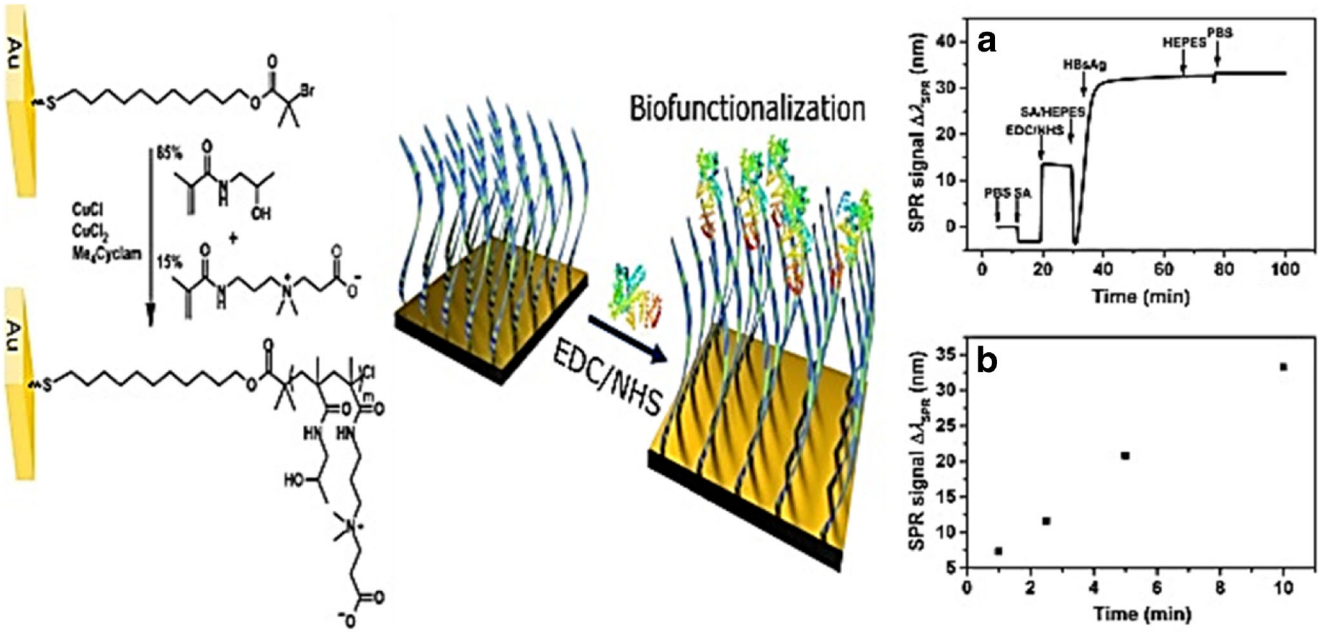


Fig. 9 Chemical structure and synthesis of gold surface with tethered brush modified wit protein ligand (right) and poly (HPMA-co-CBMAA) polymer brush (left). **a** SPR-based assessment of immobilization of HBsAg to poly (HPMA-coCBMAA) brush, **b** immobilization of HBsAg onto poly (HPMA-co-CBMAA) brush based on time. This figure is obtained with permission from Ref [120]

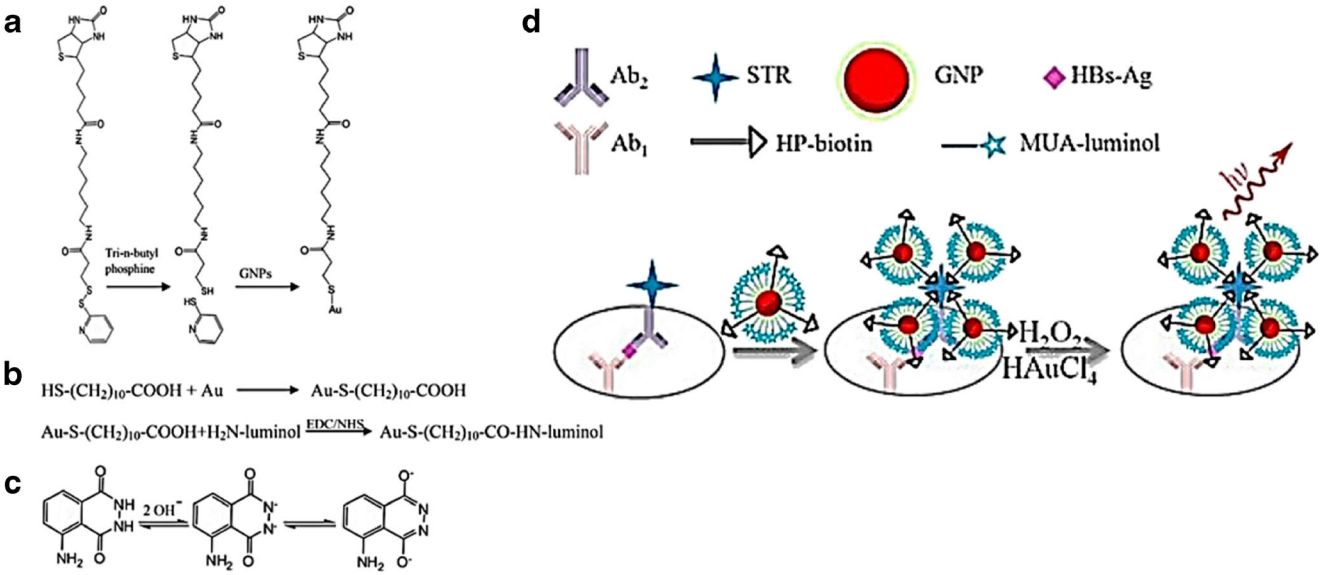


Fig. 10 **a-b** Illustration of modification processes of gold nanoparticles by biotin-HP and luminol, respectively. **c** Luminol dianion formation at pH 8. **d** The formation sandwich immunosensor for HBsAg detection. This figure is obtained with permission from Ref [124]

Other optical biosensors

Chemiluminescence (CL) draws noticeable attention nowadays due to its technological and scientific importance rapid reaction, great sensitivity, cost-efficient, broad linear range and simplicity in bio-analysis and clinical-analysis [40, 123]. Shourian and colleagues have designed a sandwich immunosensor for surface antigen of HBV detection, which demonstrates special affinity toward biotin-streptavidin interaction. In this technique, multi-functionalized gold nanoparticle, which bears luminol molecules and biotin, specifically coupled with secondary antibody-modified streptavidin. Application of gold nanoparticles as biolabeling in fabrication of immunosensor is because of their biocompatibility, chemical stability, easiness in surface modification and also these nanoparticles lead to signal amplification. In the existence of HAuCl4 and hydrogen peroxide as catalyst and oxidant respectively, the production of chemiluminescent signal is done through gold nanoparticles. The immunosensor indicated 0.358 pg mL^{-1} detection limit and 1.7 to 1920 pg mL^{-1} linear range (Fig. 10) [124].

Sabouri and co-workers have developed an immunosensor for detection of HBsAg in which co-immobilization of luminol and secondary antibody on gold nanoparticles was used to preparation of chemiluminescence label. Hepatitis B surface antigen and secondary antibody were targeted via immobilized primary antibody in polystyrene wells and co-immobilized on luminol-gold NPs, respectively. Recording of luminescence intensity of designed sandwich immunosensor was done in the presence of Au^{3+} and hydrogen peroxide as catalyst and oxidant, respectively. The linear range and detection limit for HBsAg determination were 0.12–30 ng mL^{-1} and 14 pg mL^{-1}. This method can successfully utilized for HBsAg determination in real serums of patients [125].

The RLS (resonance light scattering) was developed by Pasternack in 1993. Formerly, molecules and biomacromolecules with small sizes (e.g., proteins and DNA) were effectively identified by the RLS technique. Nevertheless, there is lack of possibility of using large entities (e.g., viruses) as analytes for RLS direct identification due to various features of these entities, including fragile self-assembled architecture, complex space structure, enormous volume and protein components, which are denatured with ease [126]. A new RLS sensor for special determination of trace quantities of HAV has presented by Yang et al., in which polydopamine (PDA)-covered totivirus-imprinted polymer was made known to the SiO_2 nanoparticle surfaces (Virus-imprinted SiO_2@PDA NPs) with the application of an effective one-stage method of synthesis. RSL intensity was elevated via the particular capturing of the target virus by the imprinted polymer films. With regard to the results, the LOD was 8.6 pmol L^{-1} [126]. Wang et al., have constructed homogeneous, washing-free, one-step nano-sensor based on gold NPs light scattering property via a sandwich model for detection of HBsAg. The two monoclonal and polyclonal HBsAb (hepatitis B surface antibody) conjugated onto gold NPs were nanoprobes of study. The detection limit was 0.005 IU/ml which exhibited great diagnostic ability [127].

Piezoelectric biosensors

Piezoelectric biosensors are considered as mass-sensitive systems which are able to detect the additional mass attached to the sensor and causes a detectable change in the resonance frequency of the crystal [5, 6, 65]. Crystals are employed in piezoelectric biosensors in order to detect alterations of mass in the sensing field. An enhancement in mass on the surface of

crystal such as antibody immobilization or antigen capturing led to reduction in resonant frequency. Piezoelectric biosensors are completely sensitive, cost-efficient, label-free as well as having capability to provide low levels of determination [31]. Some examples of various piezoelectric biosensors for detection of hepatitis viruses are summarized in Table 5.

For having the possibility of a real time and label-free determination of HBV DNA, Haung et al., have designed a completely combined system of DNA determination on a chip (SoC). After the standard construction of CMOS circuit, the DNA identification tool was obtained by post process according to a piezoresistive microcantilever. RIE (reactive ion etching) and biocompatibility of the post process are improved by gold deposition so that the micro-cantilever can be liberated. Moreover, the 19-mer nucleotide DNA probe of conserved sequences in HBV was changed by thiol group to join its polymer chains with the gold layer in order to assess the detection tool. On the other hand, the self-calibrated readout circuit, which is based on oscillator, was created and executed to improve the function of the combined SoC. The results indicated the detection limit 1 pM [136]. In a study by Cha et al., a silica nanoparticle-improved dynamic microcantilever biosensor was developed to detect HBV DNA. For target DNA, a 243-mer nucleotide of hepatitis B virus precore-core region was used. The detection probe and capture probe were conjugated with silica NPs and surface of microcantilever, respectively. The 243-mer target HBV DNA was determined up to pM level without nanoparticle and up to fM level through utilizing nanoparticle-based signal amplification procedure. There was a linear correlation between the frequency changes of resonant and HBV DNA concentration, which was initiated from elevated mass resulting from the attaching of the DNA probe to the HBV PCR product and in the middle of SiNPs and HBV PCR product to improve the signal (Fig. 11). The detection limit of this biosensor was 2.3 fM [137].

A successful Love-wave mode SAW (surface acoustic wave) sensing platform was developed by Lee et al., for detection of HBsAb in whole blood samples of various concentrations without any pretreatment. In order to protect the electrods and entraping acoustic energy, SiO_2 guiding layer was deposited on 36°YX $LiTaO_3$ piezoelectric single crystal substrate. Immobilization of HBsAg was done on the sensing area. Monitoring the shift of resonance frequency was done for detection of special connecting of hepatitis B surface antibody to immobilized hepatitis B surface antigen. For eliminating the other physical factors effect except mass alteration, the frequency of resonance was contrasted with that of a reference surface acoustic wave (SAW) tool covered with BSA (bovine serum albumin) for blocking linking of hepatitis B surface antibody. The immunosensor exhibited linking specificity to hepatitis B surface antibody and a linear association between antibody concentration and shift of frequency with 0.74 Hz/

Table 5 Comparative table of the analytical characteristics of piezoelectric biosensors reported in the literature for detection of hepatitis viruses

Target	Biosensor specifications	Method	Piezoelectric platform	LOD	Assay time	Linear range	Ref
HBcAg	anti-HBc/poly(acrylic acid) (PAAc)/	Hydrogel based biosensor	AT-cut 5-MHz quartz crystals -SiO2-Ti	0.6 μg/mL	1 h	2–2000 μg/mL	[140]
HBsAb	HBsAg/ antiglutamic acid decarboxylase	SAW	200-MHz-SiO2 guiding layer on 36°YXLiTaO3/ IDT electrode	10 pg/μl	30 min	–	[138]
HBV	monoclonal antibodies /protein A	–	16-MHz AT-cut-gold electrodes	3×10^4 virions/ml	30 min	1×10^5 to 1×10^{10} viruses in solution	[141]
HBV DNA	HBV nucleic acid probe/ PEI-Glu	QCM	9 MHz AT cut-gold electrodes	0.02 μg/ml	1 h	0.01–0.20 μg/ml	[142]
HBV DNA	RecA protein/ss-DNA/ biotin-avidin	QCM	10 MHz AT cut gold electrodes	8.6 pg/L	1 h	–	[143]
HBV DNA	19-mer nucleotide DNA probe	–	Microcantilever	1 pM	15 min	1 pmol to 10 nmol	[136]
HBV DNA	dDNA-SiNPs- cDNA	–	PZT (piezoelectric actuating layer)-microcantilever	2.3 fM	1 h		[137]
anti- HBV/anti- AFP	HBsAg, HBcAg / AFP	–	–	0.1 ng/ml	less than 2 h	0.1–10,000 ng/ml	[144]
HCV DNA	DNA probes/ biotin-avidin	QCM	10 MHz AT cuts- gold electrodes	–	?	–	[145]
HAV/HCV		MEMS biosensor		0.1 ng/ml (1.66 pM)			[139]
HAV	monoclonal antibodies /protein A	–	16-MHz AT-cut-gold electrodes	2.5×10^4 virions/ml	30 min	1×10^5 to 1×10^{10} viruses in solution	[141]

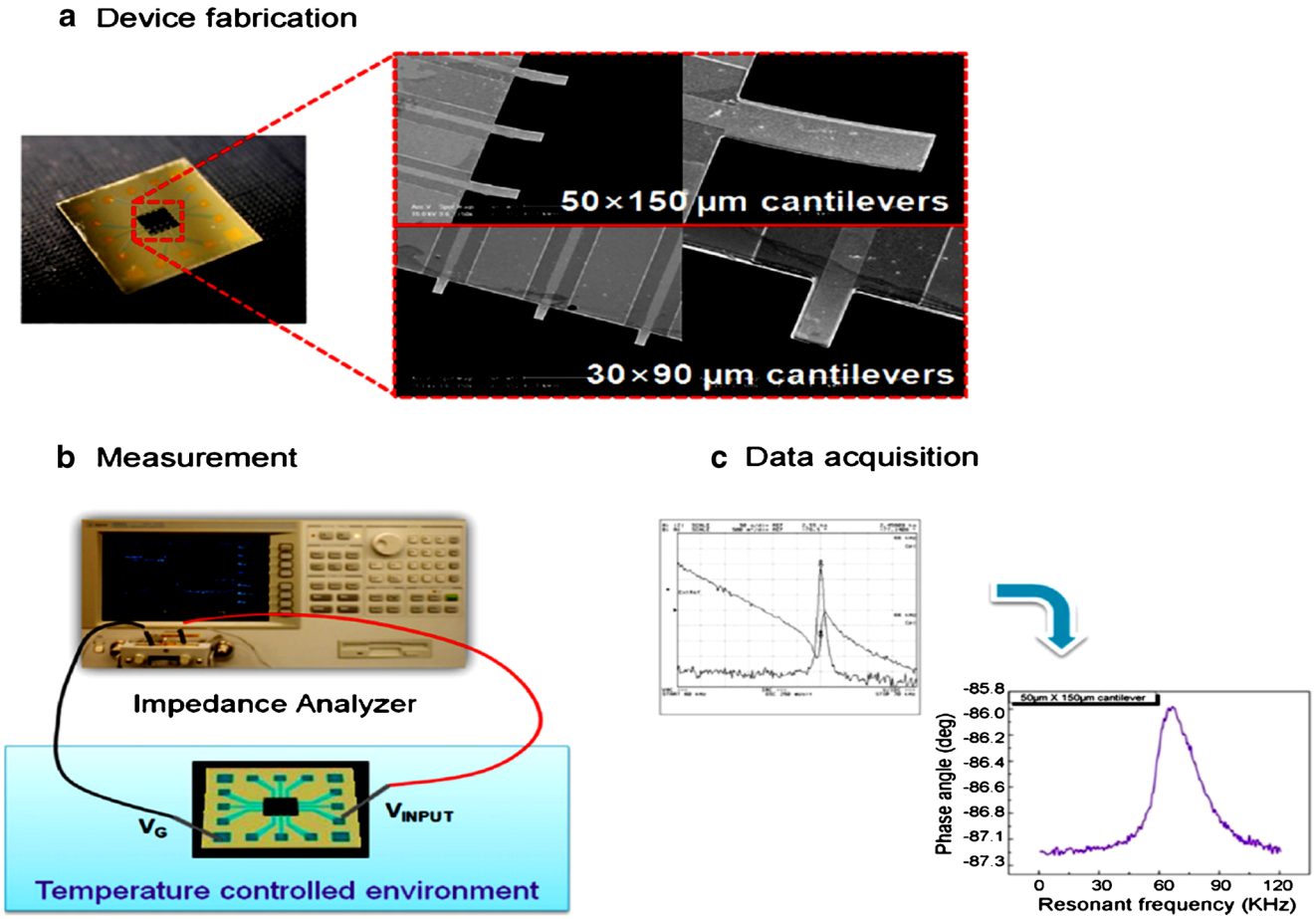


Fig. 11 Measurement of the resonant frequency by the process of data acquisition and dynamic microcantilevers: **a** one device with 12 microcantilevers and SEM images of 2 kinds of microcantilevers, **b** diagram of equipment applied for estimation of the frequency of resonant from the dynamic microcantilevers, for which an impedance analyzer is exploited, and **c** data on frequency of resonant, which is received from the impedance signal. This figure is obtained with permission from Ref [137]

(pg/μl) sensitivity and limit of detection less than 10 pg/μl (Fig. 12) [138]. MEMS cantilever sensors provided rapid measurement times and good performance. Timurdogan and colleagues employed dynamic mode microcantilevers without any labels or pre-amplification methods to detect HAV and HCV. The cantilevers of MEMS composed of Hepatitis antibody functionalized-electroplated nickel. Various concentrations of HAV and HCV antigens are added into undiluted bovine serum. Given the remote performing of detection and actuation, there is no electrical connection in the MEMS cantilevers, which leads to the formation of sensor chips that can be simply disposed. While interferometric optical detection was obtained via illumination of laser and attachment of deflection gratings at the end point of the cantilevers, actuation is accomplished by the application of an electromagnet. A frequency counter and a closed-loop control circuit with the self-sustaining ability is applied to monitor the frequency of resonant in the cantilevers of active motion. For both of Hepatitis A and C the determinable concentration limit was 0.1 ng/ml (1.66 pM) [139].

Conclusion

Hepatitis virus is believed as a global perilous health problem. With increment of chronic and acute diseases, reliable and sensitive diagnostic instruments will enhance treatment consequences. Diagnosis and therapy play a pivotal role in inhibition of hepatitis viruses spread. In order to accurate diagnosis and efficient treatment of hepatitis, it is necessary to have a relatively wide knowledge about infections of viral hepatitis. However, the traditional diagnostic tools employed for such purposes are powerful but most of them are restricted by cost and time consuming procedures and need high volume of test specimen. In this article we have displayed a snapshot of the latest advancements in the field of bio and nano-sensors and an overview of strategies for amplifying signals based on application of nanomaterials. Not only nanomaterials are efficient for signal amplification but also they act as ideal carriers for immobilization of different bio-receptors. The combination of unique characteristics of nanomaterials and high specificity and affinity of bio-receptors provides hopeful

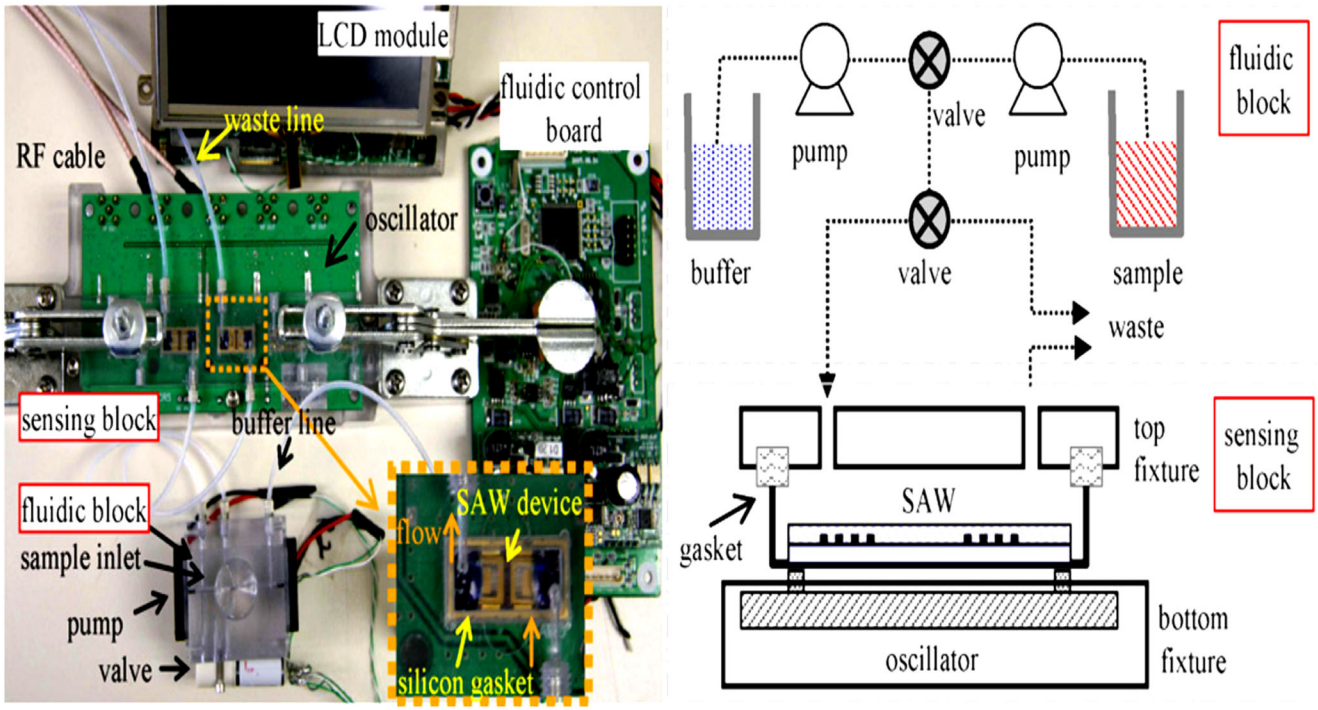


Fig. 12 Right: block diagram of the sensing and fluidic blocks; left: photograph of the SAW immunosensor containing the fluidic control board, the oscillator, the flow chamber, and the SAW device. This figure is obtained with permission from Ref [138]

opportunities for different biosensing applications. So, bio and nano-sensors are considered as a promising candidates for early diagnosis of viral hepatitis with low detection limits, fast response as well as being cost-efficient. For obtaining low detection limits, antigens and genomes are the preferred targets in viral hepatitis diagnosis. The majority of biosensors are developed based on combining existing immunological and molecular methods coupled with electrochemical, optical, electrical and mass-sensitive sensing models. High sensitivity is obtained with the use of several strategies applied to amplify the signal. Nanosystems, nanoprobes and nano-sensors provide rapid in-vivo analysis due to having submicron sizes. Novel nanomaterials with optical and electrical properties will lead to enhancement of biosensors performance. Characteristics of biosensors significantly influenced by current improvement in material science and nanotechnology for rapid determination of hepatitis viruses. They also enable custom engineering of the biorecognition component which itself will lead to more advancement in the reliability and usefulness of biosensors. With integration of microelectronics, microfluidics, microcantilever and improved biorecognition molecules, the technology of biosensors will continue to improve for viral hepatitis detection in the near future. Further researches are compulsory to make these detections techniques totally uniform in order to settle them as global recommendations for viral hepatitis detection. The construction of multiplexed nano-scale biosensors for coincident determination of various analytes has remained a main challenge at the frontier of nanotechnology. Biosensors development permit the coincident determination of numerous metabolic biomarkers of diseases which can get higher sensitivity of detection while lessening false positives. Consequently, it is believed that the nanomaterials will possess a good practical substructure in the design of new biosensors for POC (point-of-care) clinical diagnosis. Taking into consideration the unceasing progress in the advancement of unique nanomaterials, the use of novel sensing platforms based on multifunctional nanomaterials is believed to be widely improved in the future.

Compliance with ethical standards The author(s) declare that they have no competing interests.

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