Chapter 1
Advances in Nano Based Biosensors for Food and Agriculture

Kavita Arora

Abstract Nanotechnology is revolutionizing development in almost all technological sectors, with applications in building materials, electronics, cosmetics, pharmaceuticals, food processing, food quality control and medicine. In particular, nano-based sensors use nanomaterials either as sensing material directly or as associated materials to detect specific molecular interactions occurring at the nano scale. Nano biosensors are used for clinical diagnostics, environmental monitoring, food and quality control. Nano biosensors can achieve *on site, in situ* and *online* measurements.

This chapter reviews nanobiosensors and nanosensors, and their applications to food and agriculture. Nanosensors exhibit an unprecedented level of performance and the ability to 'nano-tune' various properties to achieve the desired levels of sensitivity and detection limit. Nanobiosensors are used for the monitoring of food additives, toxins and mycotoxins, microbial contamination, food allergens, nutritional constituents, pesticides, environmental parameters, plant diseases, and genetically modified organisms. Applications include: a nano-diagnostic briefcase kit for *in situ* crop investigation; a dip stick nanosensor kit '4-my-co-sensor' for multi-analyte detection; a barcode assay for genetically modified organisms (GMO) using Surface Enhanced Raman Spectroscopy (SERS); and a mobile barcode enzymatic assay.

Keywords Nanoparticles • Nanobiosensors • Nanosensors • Food • Agriculture • Environmental monitoring • GMOs

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1.1 Introduction

Nano-based biosensors and nanosensors are sensors designed to sense parameters of interest either by measuring chemical, physical, biological 'signals or interactions' at nano scale or by making use of nanomaterials for measuring desired parameters in specific application range. Applications of sensors and biosensors can be traced all around us, from our bathroom, kitchen, laundry through clinical diagnostics, environmental monitoring, safety alarms to industrial process etc. to almost every technology that involves measurement of some parameter. This becomes very important to understand basics of sensor and biosensor before understanding a nano based biosensors (Dasgupta et al. 2015, 2017; Shukla et al. 2017; Jain et al. 2016; Ranjan et al. 2014).

A typical sensor is a device, which detects or measures a physical property and then responds, records and indicates the measured phenomena into understandable form by observer or an instrument. It consists of three parts viz. sensor, transducer, detector and coupled to output display device as shown in Fig. 1.1. This device responds to electrical or optical or mechanical signal and converts that physical parameter with the help transducer to be detected into a signal output. Physical parameter can be temperature, blood pressure; humidity etc. Simplest example of sensor is thermometer that has mercury that expands when temperature increases, which is measured through visual movement of the mercury at a calibrated scale of 1 atmosphere pressure. In order to be a good sensor, it must have accuracy, specificity, ability to measure in the desired analyte range along with easy calibration, good resolution, reusability and low cost.

A Biosensor is a self-contained analytical device that incorporates a biologically active material in intimate contact with an appropriate transducer to qualitatively or quantitatively sense chemical or biochemical phenomena occurring at sensor surface. It converts a biological recognition response into an electrical signal (Arnold 1985) which is further processed to be represented as output display. The schematic arrangement of a typical biosensor is shown in Fig. 1.2. It consists of three primary components: bio-receptor, transducer and amplifier coupled to display output.

A biosensor may use biomolecule as a bio-receptor component such as tissue, microorganisms, organelles, cell receptors, enzymes, antibodies, nucleic acids, etc. interfaced to a desired transducer component (Chaubey and Malhotra 2002). Signals generated due to biomolecular interaction can be electrical, electrochemical,

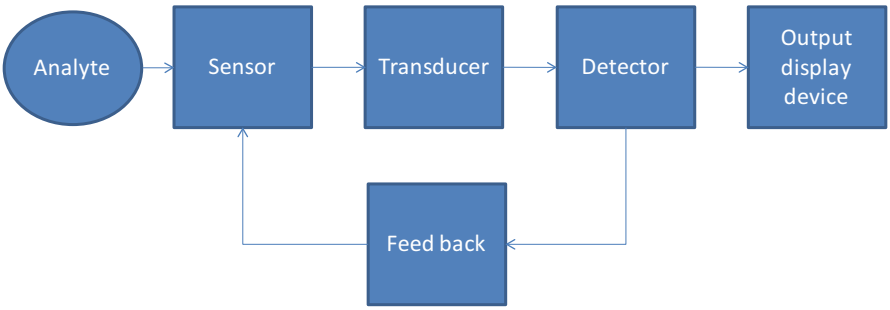


Fig. 1.1 A typical sensor consisting of sensor, transducer and detector connected to output display unit to collectively sense process and display change in parameter/analyte of interest

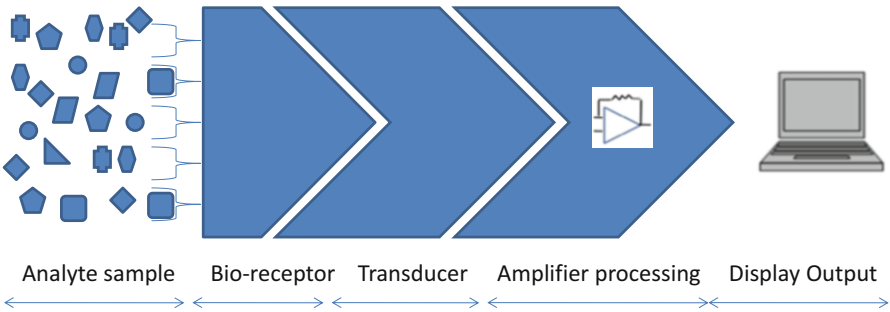


Fig. 1.2 A simple biosensor consisting of biomolecule coupled or linked to substrate/sensor surface in close contact with transducer-amplifier and display unit for signal to be expressed in user-desired scale/ units of measurements

physicochemical, optical, piezoelectric or thermal, which is converted into electrical signal *via* desired transducer that is easily measured, quantified, amplified and processed to associated electronics for display as output in user friendly form or desired units/scale of measurement (Gerard et al. 2002, Arora et al. 2006a, b). A variety of signals can be generated from the different types of biomolecular interactions which can be measured and processed using different types of transducers such as potentiometric, amperometric, voltammetric, surface conductivity, electrolyte conductivity, fluorescence, colorimetric measurements, absorption, reflection, surface plasmon resonance, resonance frequency of peizocrystals, heat of reaction, heat of absorption etc.

Nanosensors are basically chemical sensors, which help in detection of presence of chemical species or monitor various parameters through use of nanomaterials / nanostructures that may or may not lie at nano-scale. These may include electronic nose, miniaturized point of care devices, silicon computer chips, nano robots etc. that are urbanized to operate at nanoscale and give extraordinary sensation aptitude at cellular or molecular lever. Their vocation is by scheming and quantifying ups downs and adapts dislodgment, dislocations, concentration, volume, acceleration,

external forces pressure or temperature. Henceforth, nano based biosensors are set of sensing devices that make use chemical or physical or mechanical or biological phenomena to measure change in parameters (biological/nonbiological) of interest at nano-scale and may make use of nanostructures or materials as integral part through use of biological molecules as sensing (recognition) material.

Use of nanotechnology in the area of sensing technology has offered wider opportunities to construct sensors to provide high product competence that has influenced all areas including home, communication, transportation, medicine, agriculture, and industry. Nanomaterials are materials with structure at the nano scale that have unique optical, electronic, physical or mechanical properties that are absent in the bulk form and can be used for various applications. These unique and bracing features of nanomaterials facilitate opportunities to improvise and enhance the performance characteristics for various sensing applications too. Nano materials can exist in single, fused, aggregated or agglomerated forms with various shapes such as spherical, tubular, and irregular shapes. Depending on structure, composition and configuration nanomaterials can be made from carbon, metals or organic or inorganic materials. Common types of nanomaterials may include nanotubes, dendrimers, quantum dots, nanoparticles, nanowires and fullerenes. Diverse spectrum of anisotropic nanomaterials reported in the literature may include nanorods (Pérez-Juste et al. 2005), nanowires (Chen et al. 2007), nanotubes (Hu et al. 1999), triangles (Jin et al. 2001; Millstone et al. 2005), plates and sheets (Wang et al. 2005), ribbons (Swami et al. 2003), and so on.

As per US National Nanotechnology initiative, nanotechnology has moved from first generation- passive nanostructures (2000-dispersed nanostructured metals, polymers, ceramics, composites) to second generation-active nanostructures (2005- bioactive drugs, biodevices, amplifiers, actuators, transistors etc.) to third generation – systems of nanosystems (2010- guided assemblies, 2D networking, robotics, evolutionary structures etc.) to fourth generation- molecular nanosystems (2015 onwards- by designing molecular devices, emerging functions etc.) to molecular manufacturing. Nano based biosensors developed through nano molecular systems can play a far larger and vital role in healthcare and biomedical industry. Although, nano based implications impend future productivity of counting robotics, transportation, construction, energy storage, food management, environmental monitoring, security, surveillance and military (Touhami 2014). Production processes still holds it back for nanosensor development due to challenges imposed through high cost and technical limitations involved in fabrications to design physical nano based biosensors or nanosensors.

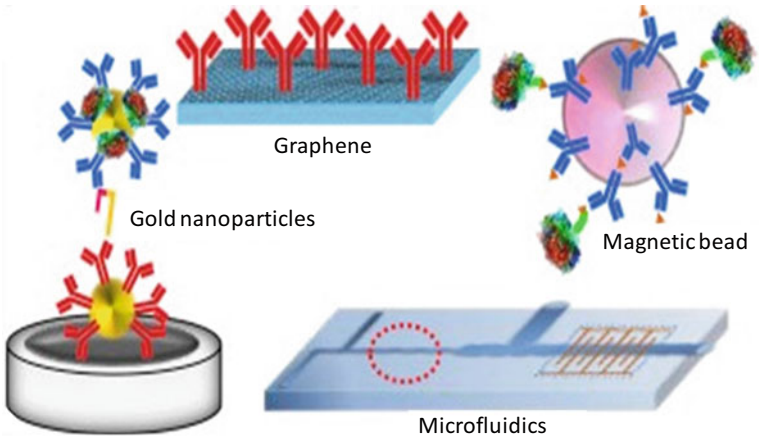
This chapter intends to bring in detailed review some important nano based biosensors and nanosensors while explaining role of nanomaterials towards enhancing various working principles and performance characteristics of the intended devices for various applications towards food and agriculture. Attempts have been made to include various arenas in food and agriculture for measurement of food additives, toxins and mycotoxins, microbial contamination, food allergens, nutritional constituents in food, pesticides, environmental parameters, in food and environment, plant diseases, genetically modified organisms/plants (GMOs), pH etc. reported in past 5 years.

1.2 Nano Based Biosensors and Nanosensors for Food and Agriculture

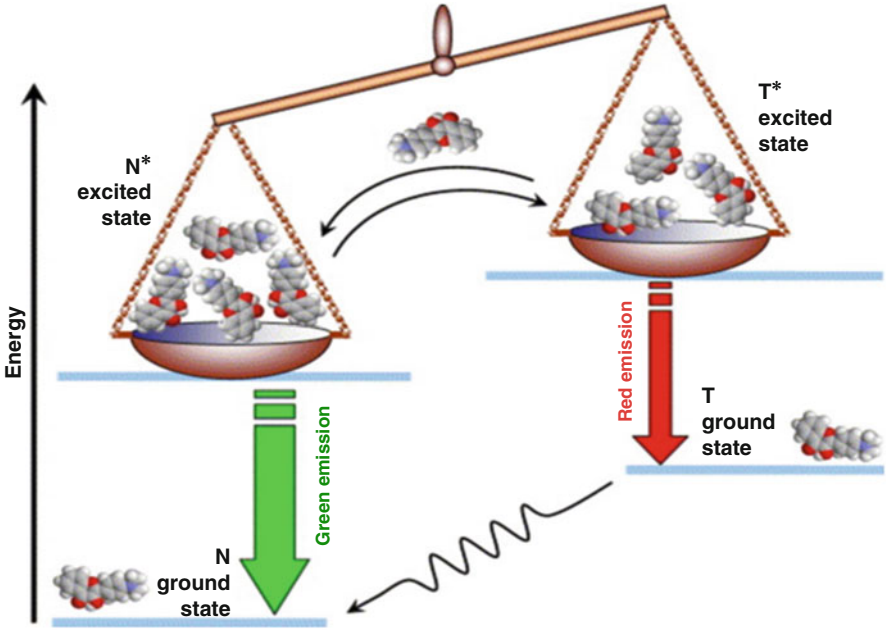
The requisite objective of any sensor especially a nano based biosensor or a nanosensor is to spot any chemical or biophysical or biochemical indication occurring at lone molecular or cellular levels. As explained earlier, use of nanomaterials offers miniaturization of a sensor dimension to achieve enormous resourcefulness for assimilation into multiplexed, mobile, convenient, wearable, *in situ* and even implantable medical devices. This also incorporates application areas to be limited not only to industrial production processes, environmental monitoring and molecular diagnostic purposes in health care but lot more including food and agriculture. Besides, the dominating biomedical applications and need to achieve point-of-care diagnostics, nano based biosensors and nanosensors appear to be the major step and the panorama impact of these nano-molecular systems for *onsite* or *online* testing remains unrivalled.

Nano based biosensors made from various carbon, metal based nanomaterials and screen printed electrodes generally utilize electrochemical mode of measurement and/or microfluidics based system to achieve simple and compact analytical devices for detection of toxins, various applications in food, agriculture and environmental monitoring (Fig. 1.3a, Reverté et al. 2016; Hughes et al. 2016). Although, several reports do exist on various electrochemical/ acoustics nano based biosensors, till date majority of them are based on optical methods due to feasibility of ease of visual detection. Demchenko 2006, had elaborated on advantages and application of fluorescence probes for probing and sensing for proteins, cells and bio membranes. He explained that two band maxima containing two different dyes can be simultaneously used to demonstrate two different phenomena occurring at nanostructure levels (Fig. 1.3b, Demchenko 2006). This phenomenon made use of the principle of coupling of wavelength shifts with two-band ratiometric response in fluorescence intensities. Different intermolecular interactions resulted in a strongly amplified fluorescence signal, where two fluorescence dyes at ground state are denoted as N and T and two excited species as N* and T* in dynamic equilibrium. For each fluorophore change of intermolecular interactions leads to change of energy separation between ground (N or T) and excited (N* or T*) states, expressed through shifts of their "green" and "red" fluorescence bands. These shifts are common and can be used in fluorescence sensing. Some examples of such dyes include 3-Hydroxychromone dyes, 3-hydroxyquinolones etc.

Food and agricultural analysis may involve: quality check for presence of toxins, microbial/fungal/viral contamination, rotting; food production quality control i.e., control of various parameters like, pH, temperature pKa, sugar/glucose content; or monitoring environmental parameters for qualitative/quantitative analysis of soil, water, fertilizers, pesticides/herbicide etc.to achieve desired level of food and agricultural production. Next sections are categorized to facilitate nano based biosensors reportedly available to achieve for aforesaid objectives.



(a)



(b)

Fig. 1.3 (**a**) Electrochemical nano based biosensors that measure biorecognition event through change in electrochemical properties at receptor/sensors surface (Reprinted from Reverté et al. 2016 with © permission from Elsevier Publishing company), (**b**) Optical nano based biosensors that use fluorescence response of two different fluorophores (N and T) giving two different fluorescence signals (N* to N, T* to T) with change in intermolecular interaction occurring at receptor/sensor surface (Reprinted from Demchenko 2006 with © permission from John Wiley and Sons Publishing Company)

1.2.1 Food Additives

Present day food industry is governed by changing customer interests that has drifted the attention of producers towards the attractive looks, colour, flavor and taste rather than the nutritional values. Intentional and unintentional additives in food have led to significant health problems which points towards the need for food analysis. Food additives may include artificial colours, flavours, texturants, antibiotics, pesticides etc.

Sivasankaran et al. reported a fluorometric nanosensor for detection of blue food colorant Brilliant blue FCF in food samples like sports drink and candies, demonstrating its potential in food analysis (Sivasankaran et al. 2016). They had developed a L-cysteine capped cadmium sulphide quantum dots based nanosensor in a fluorometric quenching assay (Fig. 1.4a) for discriminative detection and determination up to 3.50×10^{-7} M and a linear range of 4.00×10^{-5}–4.50×10^{-6} M Brilliant Blue FCF.

Melamine is an additive, which is often added in dry milk powder, dried egg and protein powders as a food adulterant to increase protein content, which has been shown to have toxic effects for humans. Chondroitin sulfate-reduced gold nanoparticles (using green synthesis) based nanosensor was used to detect melamine by measuring absorbance (surface plasmon resonance band) ratio (A620/A530). This nano based biosensor was reported to have melamine linear range 0.1–10 μM and was used to quantify melamine spiked in real infant formula at concentrations as low as 12.6 ppb (Noh et al. 2013). Wu et al. 2015 have reported combination of upconversion nanoparticles and gold nanoparticles composite based nanosensor for detection of melamine (Fig. 1.4b). As it can be seen that up conversion nanoparticles were prepared from sodium Yttrium fluoride doped with rare earth metals lanthanides (Ytterbium-Yb and Erbium-Er) i.e., $NaYF_4:Yb^{3+},Er^{3+}$ (explained in Sect. 1.2.2.). $NaYF_4:Yb^{3+}$, Er^{3+} possess unique fluorescence properties, that get quenched by associate gold nanoparticles under normal conditions. When melamine is added, gold nanoparticles get released from the surface of up conversion nanoparticles since melamine could cause gold nanoparticles to aggregates by N-Au interaction, resulting fluorescence of up conversion nanoparticles. This easily operatable nanosensor showed linear response to 32.0–500 nM melamine with a detection limit of 18.0 nM at pH (7.0) with 12 min incubation time and sensitivity of 0.968 in raw milk samples.

Formalin/formaldehyde is constituent of many fruits and vegetables at low concentrations, which is known to cause cancer at high dose. This is a commonly used additive to various foods like fish, milk and fruits to facilitate and sustain their shelf life. Nano emraldene-polyaniline based nanosensor was described to detect low concentrations of formaldehyde ranging from 0.0003 to 0.9 ppm in a dose dependent manner (Omara et al. 2016).

Urea is one of the metabolic products of protein metabolism and has a strategic function in the marine nitrogen cycle as a source of excreted nitrogen by invertebrates and fish. Likewise, the bacterial decomposition of nitrogenous materials and terrestrial drainage are influenced by urea. That is why, estimation of urea is very crucial in clinical diagnostics, food science and environmental-monitoring

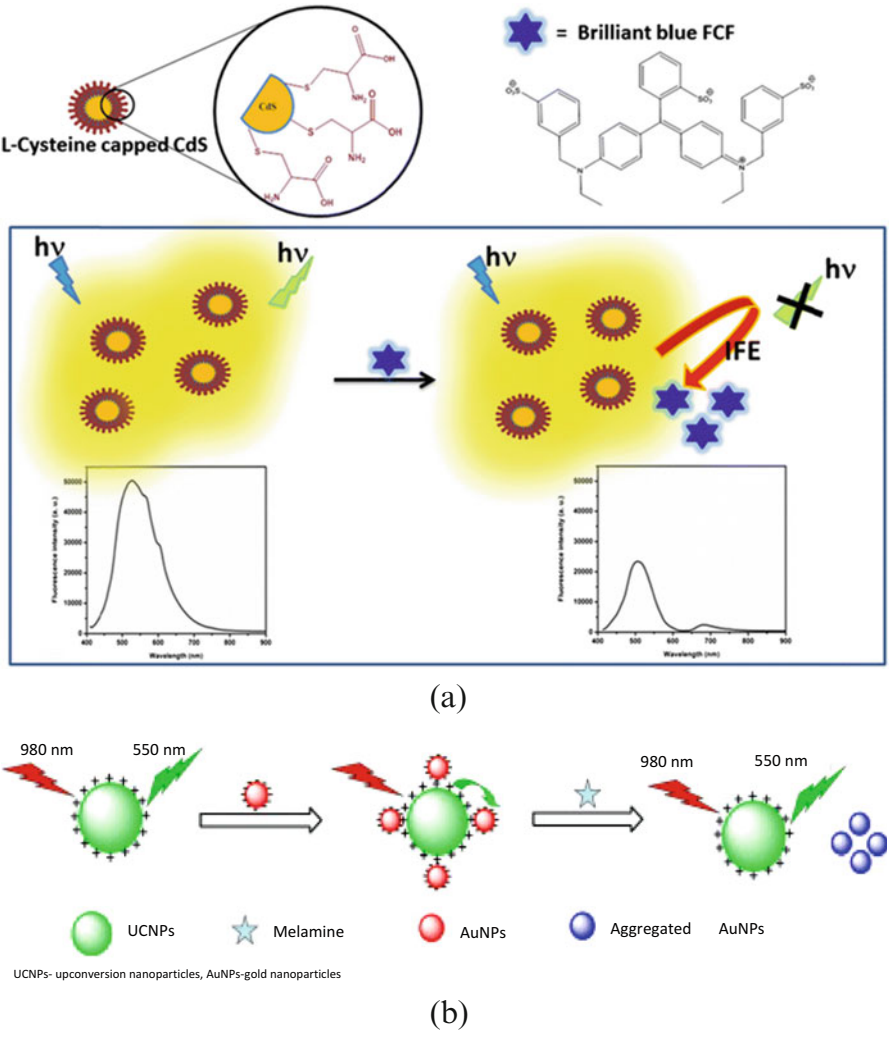


Fig. 1.4 Detection of (**a**) Brilliant Blue FCF using L-cysteine capped Cadmium sulfide (CdS) quantum dots based nanosensor that shows quenching in fluoresce signal upon addition of analyte (Reprinted from Sivasankaran et al. 2016 with © permission from Springer Publishing company) and (**b**) Melamine using up conversion nanoparticles (UCNPs) and gold nanoparticles (AuNPs) via fluorescence resonance energy transfer (FRET) phenomena based fluorescence 'turn on' assay (Reprinted from Wu et al. 2015 with © permission from Elsevier Publishing company)

(Saeedfar et al. 2013). Urea is used as fertilizer too and annual worldwide production of urea exceeds 100 million metric tons where overuse of nitrogen fertilizer application can lead to decrease in soil pH and pest problems (increasing birth rate, longevity, and overall fitness of certain pests etc.). Urease (from *Arthrobacter creatinolyticus*) immobilized membrane (PAN-[poly(acrylonitrile-methylmethacrylate-sodium vinylsulfonate)] membrane) was employed in analysis of urea spiked milk samples that showed detection range of urea concentration from

1 to 100 mM (Ramesh et al. 2015).The immobilized urease had good storage stability for a period of 70 days at 4 °C and could be effectively reused for 13 cycles.

Intentional addition of various antibiotics in food and its products is a usual practice to increase its shelf life throughout the world. Although, repercussions of excessive use of antibiotics has been realized and despite the fact that now there are known adverse affects to human health, very few countries could impose regulations of their uses. Tendency of these compounds to get accumulated, warrants need of easy *onsite*/*in situ* sensing devices for suspected antibiotics in various food matrices. Danofloxacin is one broad spectrum antibacterial fluoroquinolone compound used for treatment of respiratory diseases in human and veterinary diseases. At higher concentrations, i.e., after accumulation, this may have adverse reactions and can detrimentally affect muscle, central nerve system, peripheral nerve system, liver, and skin. Therefore, prescreening and determination of the level of danofloxacin in foods or food products becomes very important. An surface plasmon resonance based nanosensor was reported that used RNA (ribonucleic acid) aptamers for danofloxacin (Han et al. 2014). The selected specific RNA aptamer were shown to have potential for specific detection of danofloxacin that could be uploaded on sensor systems and was found to be useful as a rapid, selective, and sensitive monitoring/ diagnostic/ detection of ligand for danofloxacin in food animals. In a similar row, a chemiluminescence biosensor based on aptamer functionalized gold nanoparticles for detection of p53, a tumor suppressor protein up to 10 pg/ml and showed 10-fold improvement in p53 detection gold nanoparticles based colorimetric assay (Shwetha et al. 2013). Counting on similar kinds of reports mentioned in this chapter, the potential of aptamers as specific biorecognition elements could substantially enhance the performance of nanobiosensors.

Tetracyclin, is a widely overused antibiotic whose exact and rapid quantification in an aqueous buffer solutions and complex biological samples such as milk is of high importance. An ultra long zinc oxide (ZnO) nano walls based nanobiosensor was developed and demonstrated for real-time electrical measurement of dynamic molecular interactions via monitoring phenomena of binding of the tetracycline repressor (TetR) to its operator DNA (deoxyribonucleic acid) and its inducible release by the addition of tetracycline (Menzel et al. 2013). This exciting method allows ultra-sensitive measurements of tetracycline concentrations as shown in Fig. 1.5a. When tetracycline is added, the induced switching and release causes a down bending of the surface energy bands (E_V – valence band and E_C – conduction bands, E_F – Fermi energy level) due to the reduction of negatively charged molecules. The process is reversed when TetR molecules are attached to the surface again.

Tobramycin, a aminoglycoside is water soluble antibiotic which is utilized to treat the infections caused by aerobic Gram-negative and some Gram-positive microorganisms) and excessive use of this drug may result in ototoxicity and nephrotoxicity. Tobramycin imprinted poly(2-hydroxyethyl methacrylate–methacryloyl amidoglutamic acid) [p(HEMA–MAGA)] molecular imprinted

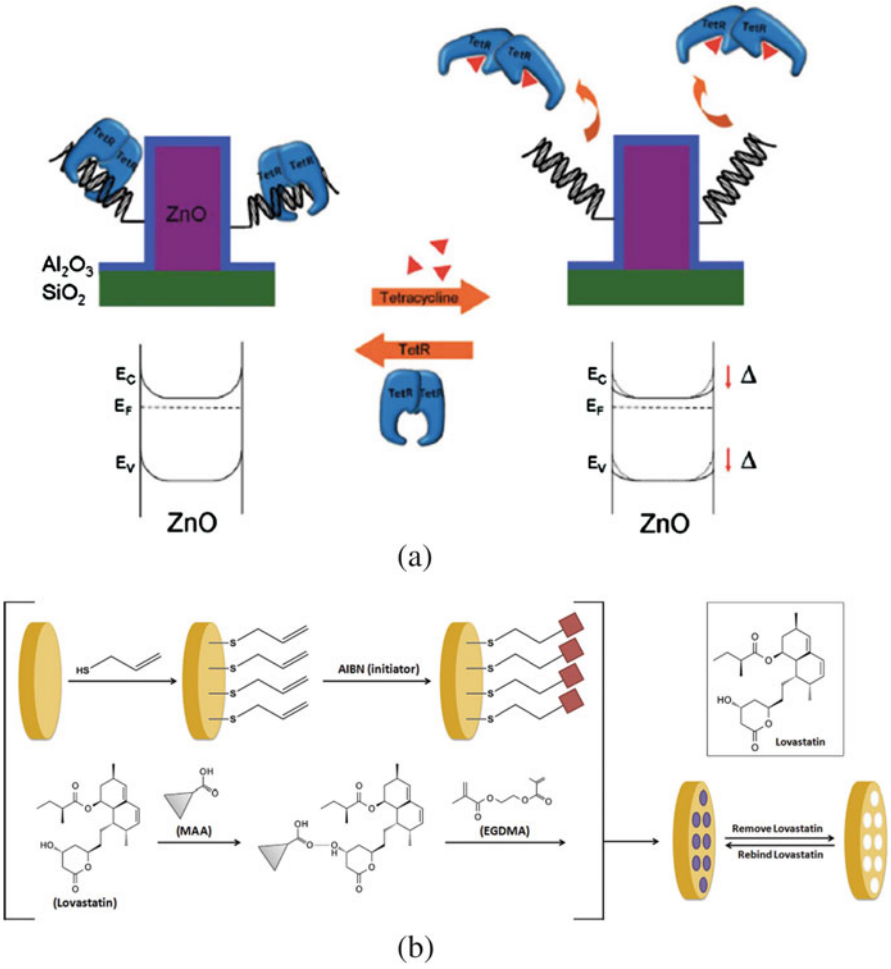


Fig. 1.5 Detection of (**a**) tetracyclin using zinc oxide/aluminum oxide (ZnO/Al_2O_3) nanowall nanobiosensor (cross section) that uses affinity of tetracyclin with its repressor /operator DNA where binding of tetracyclin results in down bending of surface energy bands (*where TetR-tetracyclin repressor, zinc oxide/aluminum oxide -ZnO/Al_2O_3, SiO_2 – silicon oxide, E_V – valence band and E_C – conduction bands, E_F – Fermi energy level))* (Reprinted from Menzel et al. 2013 with © 2013 permission from Royal Society of Chemistry); (**b**) lovastatin using molecular imprinted polymer (pMAA) – gold – quartz crystal based nanosensor where binding of analyte shall be indicated by directly proportional change in vibrational frequency of quartz crystal *(where EDGMA-ethylene glycol dimethacrylate, AIBN- N,N′-azobis-iso-butyro-nitrile, pMAA- poly2-hydroxy ethyl methacrylate–methacryloyl amido aspartic acid* (Reprinted from Eren et al. 2015 with © 2015 permission from Elsevier Publishing company) and (**c**) Small drug molecule using a plasmonic nanosensor in a sandwich structure through anchored capture antibodies onto substrate and gold nanocluster labeled antibodies where presence of analyte shall facilitate formation of sandwich structure and will favour formation of gold nanoparticles *(where gold nano clusters-AuNCs, gold nanoparticles- GNPs, $HAuCl_4$- auric chloride and H_2O_2- hydrogen peroxide*) (Reprinted from Zhao et al. 2016 with © 2016 permission from ACS publications)

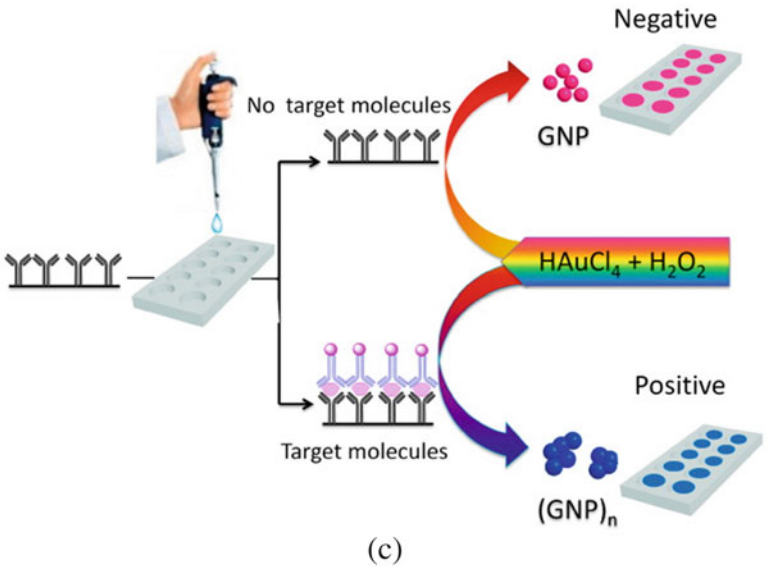


Fig. 1.5 (continued)

polymer film was generated on the gold surface to prepare a nanosensor for tobramycin (Yola et al. 2014). This nanosensor was described to give linearity range and detection limit of 1.7×10^{-11}–1.5×10^{-10} M and 5.7×10^{-12} M, respectively for pharmaceuticals, and food samples like chicken egg white and milk extract.

Lovastatin is a member of the class of statins, which are produced through fermentation process and are used to lower the cholesterol content in hypercholesterolemia. Red yeast rice is a dietary supplement in south Asia and this, being fermentation product grown on rice, contain lovastatin drug residue. Increased use of this food supplement is causing cardiovascular diseases and posing serious risk of the over release of lovastatin drug residue to the environment that may cause increased incidences of coronary artery disease, muscle and liver damage. Therefore, a simple, sensitive and quick molecular imprinted gold quartz crystal microbalance chip based nanosensor (Fig. 1.5b) was developed to detect lovastatin in natural samples (Eren et al. 2015). Lovastatin imprinted poly(2-hydroxyethyl methacrylate–methacryloyl amido aspartic acid) [p(HEMA–MAAsp)] nano film was attached on the mercapto propane based self assembled monolayer deposited gold surface of quartz crystal microbalance chip. The fabricated specific nanosensor gave linear performance for lovastatin at 0.10–1.25 nM and detection limit of 0.030 nM in red yeast rice.

A plasmonic nanosensor using gold nanoclusters was fabricated to enable visually quantitative determination of ultra-trace target molecules like synthetic small molecules or drugs. This method combines enzyme-mimetic gold

nanoclusters assisted visual color change exhibited by gold nanoparticles in visible range in presence of desired analyte (Fig. 1.5c) (Zhao et al. 2016). In this sensor, a target analyte can be captured by its antibody anchored on a solid surface and further covered by a layer of same antibody tagged with enzyme mimetic gold nano-clusters. Now, the formation of sandwich structure shall favor the formation of gold nanoparticles when immersed in into a solution of $HAuCl_4$ and H_2O_2, thereby leading to visual colour change. This system was demonstrated for protein avidin, cancer antigen 15-3 (a breast cancer biomarker shortened as CA15-3), 3,5,3′ -L –tri-iodo thyronine thyroid hormone (T3), and even synthetic small molecular drug such as methamphetamine. This systme possess potential to be utilized for its applications in analytical requirements of food and agriculture.

Toxic metal content in food, pharmaceutical industry and clinical diagnostics is one of the area of concern, therefore, monitoring trace levels is desired for various applications (Maddinedi et al. 2015, 2017; Tammina et al. 2017; Siripireddy et al. 2017; Sannapaneni et al. 2016). Cu^{2+} ions are among frequently monitored species, especially where strict purity guidelines are implemented e.g., medical industry, pharmaceutical applications, dialysis water, microelectronics and manufacturing of integrated circuit semiconductor chips etc. Kacmaz et al. 2015 reported a nanosensor based on fluoroionophore DMK7 or 2-{[(2-aminophenyl)imino]methyl}-4,6-di-tert-butylphenol doped nano-fibrous (polymeric ethyl cellulose) films to detect ultra-low concentrations of Cu ions giving detection limit of 3.3×10^{-13} M and detection range of 5.0×10^{-12}–5.0×10^{-5} M (Fig. 1.6a). Additionally, this extremely specific nanosensor exhibited high selectivity over convenient cations like Na^+, K^+, Ca^{2+}, Mg^{2+}, NH_4^+ and Ag^+, Al^{3+}, Ba^{2+}, Co^{2+}, Cr^{3+}, Fe^{3+}, Fe^{2+}, Hg^{2+}, Li^+, Mn^{2+}, Ni^{2+}, Pb^{2+},Sn^{2+} and Zn^{2+}.

Selenium is known as an essential nutrient responsible for immunity and antioxidant activity. Its deficiency and excess intake causes both have been reported to be unsafe for human health, therefore, the accurate detection of trace amounts of Se has great significance on environmental, medical and nutritional sciences. A ratiometric fluorescent nanosensor for accurate and *on-site* sensing of SeO_3^{2-} by linking the recognition molecule 3,3′-diaminobenzidine onto the surface of carboxyl group modified cadmium telluride embedded silica nanospheres or quantum dots that were was explained to have single fluorescence peak at 655 nm (Chen et al. 2016a, b). Addition of SeO_3^{2-}onto nanosensor results in two emissions peaks (530 and 655 nm) of Se-diaminobenzidine and Se-cadmium telluride embedded silica nanosphere quantum dots under a single excitation wavelength as shown in Fig. 1.6b. This nanosensor presented detection range 0–2.5 μM and detection limit of 6.68 nM (0.53 ppb) of selenium ions. No interference to the performance of nanosensor was observed for other common anion ions and some amino acids, such as NO^{2-}, CO_3^{2-}, SO_3^{2-}, SO_4^{2-}, S^{2-}, HS^-, HSO_3^-, ClO^-,HPO_4^{2-}, $H_2PO_4^-$ Br^-, NO_3^-, H_2O_2, GHS and Cys under the same experimental conditions. Nano sensor was tested on real water samples spiked with different amounts of Se(IV) and in food samples like rice, lettuce and radish.

Mercury is the most toxic water soluble elements known in ecosystems which is non-biodegradable and can only get absorbed through plants and water resources to

be subsequently accumulated in food chain. Monitoring Hg^{2+} level in environmental, food and biological samples is an important issue to understand its distribution and potential pollution. A dual emission fluorescent probe nanosensor for Hg^{2+} detection was developed by Tan et al. 2015, that used lanthanide combination of green emitting terbium (Tb^{3+}) embedded and red emitting europium (Eu^{3+}) covalently tagged SiO_2 nanoparticles. In dual-emission fluorescent probe, one fluorophore functions as reference unit and another as response moiety to ensure naked eye distinction and accuracy in quantification. As shown in Fig. 1.6c, two lanthanide (Tb^{3+} and Eu^{3+}) chelates were synthesized by the chemical coordination dipicolinic acid (2.6-pyridinedicarboxylic acid) denoted as Tb- dipicolinic acid chelate and Eu- dipicolinic acid chelate) and the surface of SiO_2 nanoparticle doped with Tb- dipicolinic acid chelate was functionalized by diethylene tri-amine penta acetic acid to immobilize Eu- dipicolinic acid chelate at periphery. Diethylene tri-amine penta acetic acid as functional ligand offers its carboxyl groups to coordinate with Eu- dipicolinic acid chelate to form 'Diethylene tri-amine penta acetic acid-Eu-dipicolinic acid' ternary complex on surface of the SiO_2 nanoparticle and also assist dipicolinic acid to offer selective response to Hg^{2+}. Since Hg^{2+} has higher binding constant ($K = 10^{26.4}$) compared to Eu^{3+} ($K = 10^{22.39}$) the binding of Hg^{2+} is favored to enhance its detection. Upon addition of Hg^{2+} onto nanosensor, the fluorescence of Eu^{3+} chelates gets selectively quenched, while the fluorescence of Tb^{3+} chelates remained unchanged (Fig. 1.6c) and this nanosensor gave excellent selectivity and high sensitivity up to 7.07 nM detection limit in drinking water and milk samples.

Bisphenol analogs or popularly known as BPAs are compounds, which are ubiquitously involved in our daily commodities and for this reason this has become a part of our food ingredients due to unintentional leaching from all around. BPA is known as ubiquitous endocrine disrupter and considering its serious adverse human health risks; its use has been banned in many countries. Since, tyrosinase being ortho-hydroxylation oxidase can oxidize BPA to corresponding o -diphenols and o -quinones (Ragavan et al. 2013), it has been used to fabricate metal − organic frameworks and chitosan based tyrosinase nanosensor (Lu et al. 2016). This nanosensor consists of Cu- metal organic frame works i.e., metal nodes connected/linked to organic chains or network to lead to a nano-porous materials. In this work, two organic ligands, chitosan and tyrosinase were used to sense bisphenol analogs (BPAs). The Cu- metal organic frame works based nanobiosensor showed a wide linear range for BPE from 5.0×10^{-8} to 3.0×10^{-6} mol L^{-1} with sensitivity as 5.51 A M^{-1} cm^{-2}, and the limit of detection as 15 nmol L^{-1} ($S/N = 3$). This nanosensor showed sensitive response to bisphenol A, bisphenol F, bisphenol E, bisphenol B, and bisphenol Z in order of sensitivity as BPE > BPF > BPA > BPB > BPZ ranging from 5.51 to 1.13 A M^{-1} cm^{-2} and anti-interference ability to anti-interference ability to heavy metals like Hg^{2+}, Pd^{2+}, Cu^{2+}, Fe^{2+}, Co^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, and Ni^{2+}. Authors also illustrated the advantage of using Cu metal organic frame works, as BPA tends to preconcentrate on the

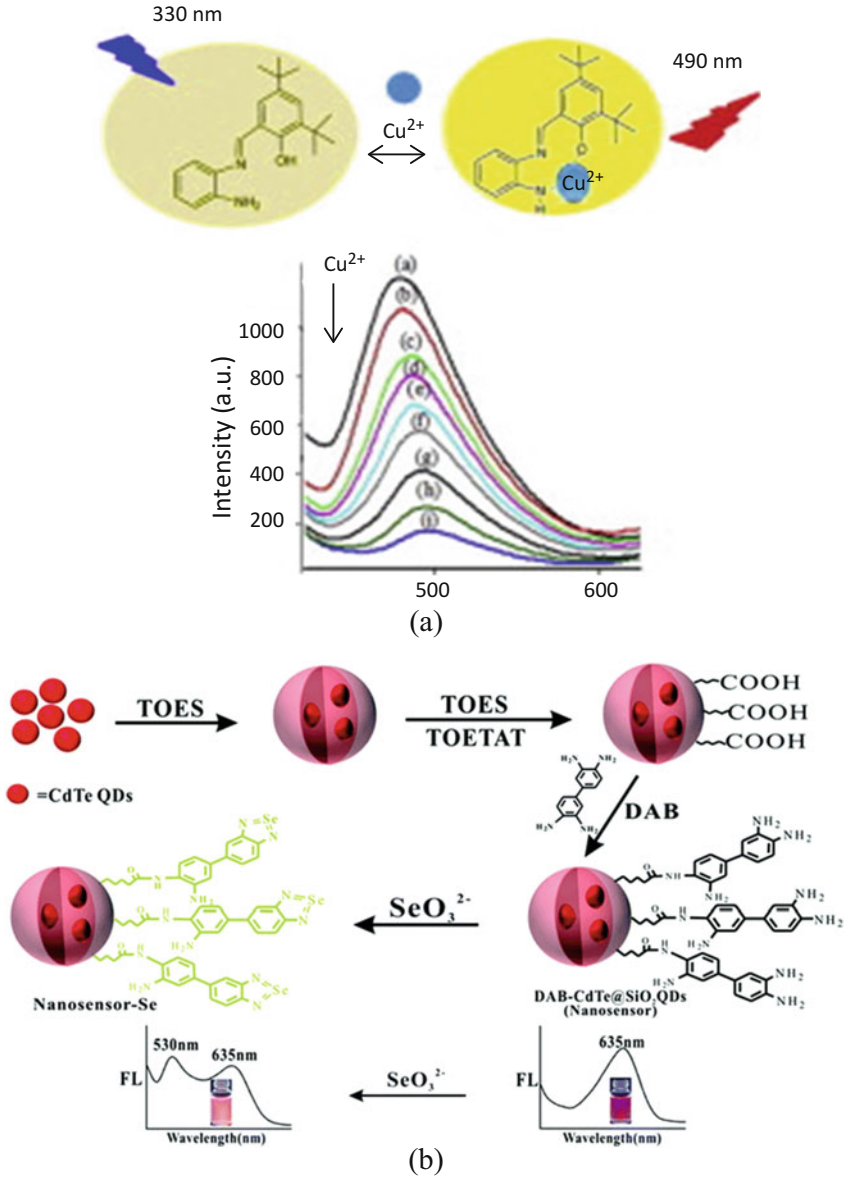


Fig. 1.6 Detection of (**a**) Copper ions (Cu^{2+}) using nano-scale fluorescent chemo-nanosensor where selective binding of analyte resulted in fluorescence quenching (Reprinted from Kacmaz et al. 2015 with © 2015 permission from Elsevier Publishing company); (**b**) Selenium ions (SeO_3^{2-}) using diamino benzidine (DAB) – cadmium telluride coated silicon oxide (CdTe@SiO_2) quantum dot (QuD) nanosensor where presence of analyte causes an additional emission peak at 530 nm (TOETAT-N-((trimethyloxy)silylpropyl) ethylene diamine triacetic acid trisodium salt, TEOS- tetra ethyl orthosilicate) (Reprinted from Chen et al. 2016b with © permission from Royal Society of Chemistry) and (**c**) mercury ions (Hg^{2+}) using dual-emission fluorescent probe Tb-DPA@SiO_2-Eu-DPA nanosensor where presence of analyte favors quenching of fluorescent surface via selective replacement of Eu^{3+} ions from nanosensor surface (*where Tb- terbium and Eu- europium and dopants to DPA-dipicolinic acid; DTPA- diethylene tri-amine penta acetic acid; SiO_2- silicon oxide*) (Reprinted from Tan et al. 2015 with © 2015 permission from Elsevier Publishing company)

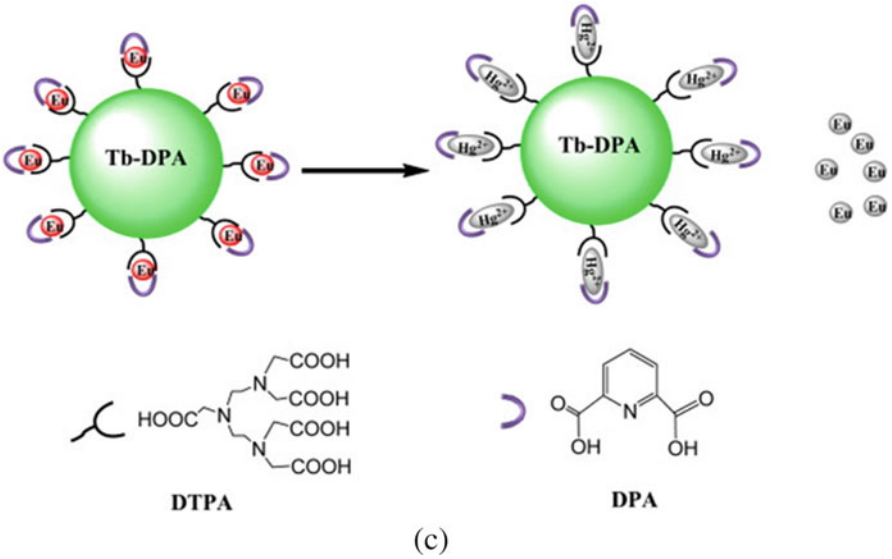


Fig. 1.6 (continued)

biosensor surface through a $\pi - \pi$ stacking interaction between the aromatic rings of BPA and the organic ligands of metal organic frame works coupled with favorable immobilization of tyrosinase in a biologically stable environment.

A super paramagnetic nanoparticle and tannic acid hybrid nanosensor was shown to detect polyphenol (dihydroxybenzene derivatives and their polymers) content in blueberries by using square wave voltammetry (Magro et al. 2016). This unique core–shell hybrid nanomaterial was formulated due to ability of metal organic frame works for stable colloidal suspensions without organic or inorganic coating i.e., no aggregations and at the same time to be able to bind to specific to organic molecules to form composites and associating properties of tannic acid (P-penta-O-galloyl-d-glucose) to form easy complexes with Fe^{3+} ions imparting low solubility in water and corrosion inhibition (Iglesias et al. 2001). This nanosensor exhibited square wave voltammetric based studies to sense tannic acid in linear range of 25–500 μM with sensitivity 312.81 nCμ M^{-1} cm^{-2} and detection limit of 8.57 μM.

1.2.2 Toxins and Mycotoxins

Mycotoxins are secondary metabolites that are produced by fungal/microbial contamination of crops and foods. These are highly resistive in nature and cause severe toxic effects leading to teratogenic, carcinogenic, and nephrotoxic situations in humans. Conventionally mycotoxins are detected by diode arrays, multi-

chromatographic and enzyme linked immunosorbent assay (popularly known as ELISA) based immunological techniques that require sample pretreatment, laborious synthetic procedures and expensive instrumentations.

A nanostructured cerium oxide film-based immunosensor was also developed for the detection of food-borne mycotoxins ochratoxin-A (Kaushik et al. 2009). Then, a nanobiosensor using aflatoxin B1 antibodies linked cysteamine capped gold nanoparticles attached onto a 4-mercaptobenzoic acid self assembled monolayer coated gold electrode was used to detect aflatoxin B1 in the range of 10–100 ng L^{-1} (Sharma et al. 2010). Subsequently, a sol–gel derived nano-zinc oxide based immunosensor was developed for ochratoxin A (Ansari et al. 2010). This group and many other groups made attempts to develop and review nano based biosensors for mycotoxins (Maragos 2016; Ruscito et al. 2016; Lin and Guo 2016; Chauhan et al. 2016; Turner et al. 2015; McPartlin et al. 2016) for detection mycotoxins such as aflatoxins, ochratoxin B, citrinin, patulin, ergot alkaloids, fumonisins, trichothecenes, zearalenone etc. and multi-mycotoxin detection nanobiosensor (Mak et al. 2010). Around the same time, a new signal transduction by ion nano-gating sensors for the ultrasensitive detection of mycotoxins was described, with a detection limit up to 100 fg mL^{-1} (Actis et al. 2010; Lattanzio et al. 2012).

A nanodiagnostic kit was developed as 'lab in a box' system having sophisticated measuring devices, reagents, power supply and other features packed in a briefcase like box that can be implemented to field for *in situ* crop investigations to prevent disease epidemics (Goluch et al. 2006; Pimentel 2009). Recently, a dip stick multi parameter detecting nanosensor kit '4-my-co-sensor' based on competitive antibody assay for the real-time detection of mycotoxins such as zearalenone, trichothecene (T-2/HT-2), deoxynivalenol and fumonisin (B1/B2) for corn, wheat, oat and barley samples was reported (Lattanzio et al. 2012). This proposed immunoassay protocol was fast, cheap, easy-to-use and suitable for the purpose of quick screening of mycotoxins in cereals.

Immunoglobulin (anti-mycotoxin viz. anti-aflatoxin B1 and anti-deoxynivalenol) coupled rare earth-doped up conversion nanoparticles i.e., trivalent ions (ytterbium-Yb^{3+}, holmium-Ho^{3+}/thulium-Tm^{3+} and gadolinium-Gd^{3+}) doped sodium-yttrium-fluoride ($NaYF_4$) nanoparticles were used to simultaneously detect mycotoxins (aflatoxin B1 and deoxynivalenol) linked to SiO_2 magnetic nanoparticles having sensing range of 0.001–0.1 ng ml^{-1} with the limit of detection of 0.001 ng ml^{-1} in adulterated peanut oil (Chen et al. 2016a, b). Antigen-modified magnetic nanoparticles were employed as biosensing probes and antibody-functionalized improved up conversion nanoparticles were used as signal probes. As shown in Fig. 1.7, this method involved magnet-assisted separation of antigen-antibody complex and subsequent discriminative (aflatoxin B1 and deoxynivalenol) fluorescence bioassay facilitated by Ho^{3+} and Tm^{3+} doped up conversion nanoparticles coupled to anti-AFB1 and anti-DON, respectively. Discriminative fluorescence/ luminescence properties were introduced via doping rare earth metals (Ho^{3+}/Tm^{3+}) to $NaYF_4$ nanoparticles that can efficiently convert a long wavelength radiation (e.g. near-infrared light) into a sharp and short wavelength luminescence emission (e.g. visible light) in narrow bandwidth giving large anti-Stokes shifts and

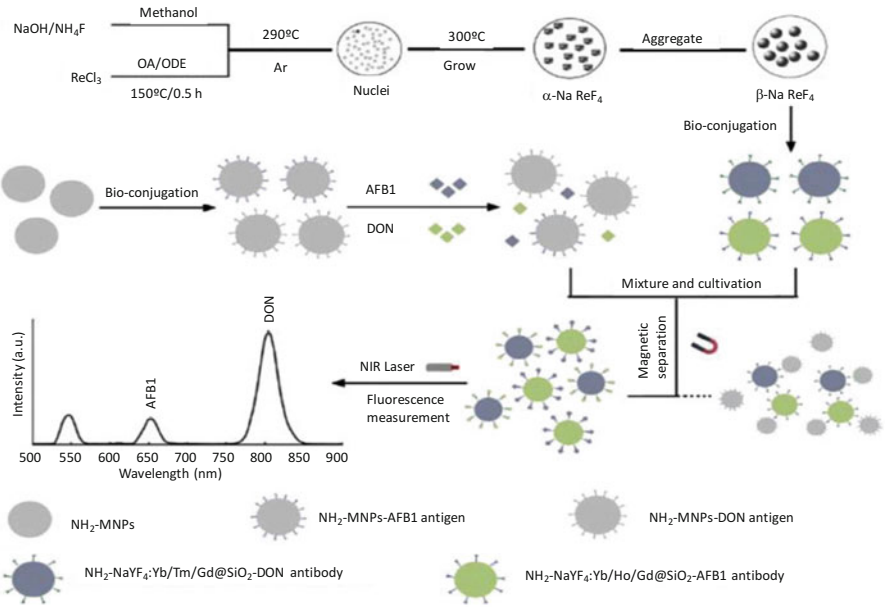


Fig. 1.7 A photo-luminescence nanobiosensor for simultaneous detection of mycotoxins: aflatoxin B1 (AFB1) and deoxynivalenol (DON) is shown to be made of antigen (AFB1 or DON)-modified magnetic nanoparticles (MNPs) and antibody-functionalized upconversion nanoparticles (UCNPs) signal probes. Selective detection of both mycotoxins: AFB1 and DON in single reaction is facilitated by selective/ separate doping of rare earth metals Ho^{3+} and Tm^{3+}, respectively (where $NaReF_4$: Sodium-Rare earth Fluoride with Re = ytterbium-Yb^{3+}, holmium-Ho^{3+}/thulium-Tm^{3+} and gadolinium-Gd^{3+}, SiO_2 silicon oxide nanoparticles) (Reprinted from Chen et al. 2016a, b with © 2016 permission from Elsevier Publishing company)

improved signal to noise ratio. Flexible chemical features and low toxicities for *in vitro* and *in vivo* systems also make them suitable for biological applications.

Detection of aflatoxin B1 was achieved via aptamer-gold nanoparticles based nanosensor in a colourimetric (red to purple) analysis showing linear range aflatoxin B1 concentrations from 80 to 270 nM and the detection limit of 7 nM (Hosseini et al. 2015).

Phylotoxins are some potent marine toxins found in temperate waters. These are known worldwide for their extreme toxicity and ability to contaminate seafood thereby causing intoxications and/or fatalities. Zamolo et al. 2012 developed a chemiluminescence based nanobiosensor that was able to produce a concentration-dependent light signal, allowing phylotoxins quantification in mussels, with a limit of quantification (LOQ = 2.2 μg kg^{-1} of mussel) more than 2 orders of magnitude more sensitive than that of the commonly used detection techniques, such as liquid chromatography-mass spectrometry/mass spectrometry (popularly known as LC-MS/MS). This method used anti-PITX linked to multiwalled carbon nanotubes bound on polysuccinimidyl acrylate-indium tin oxide substrate and Ruthenium

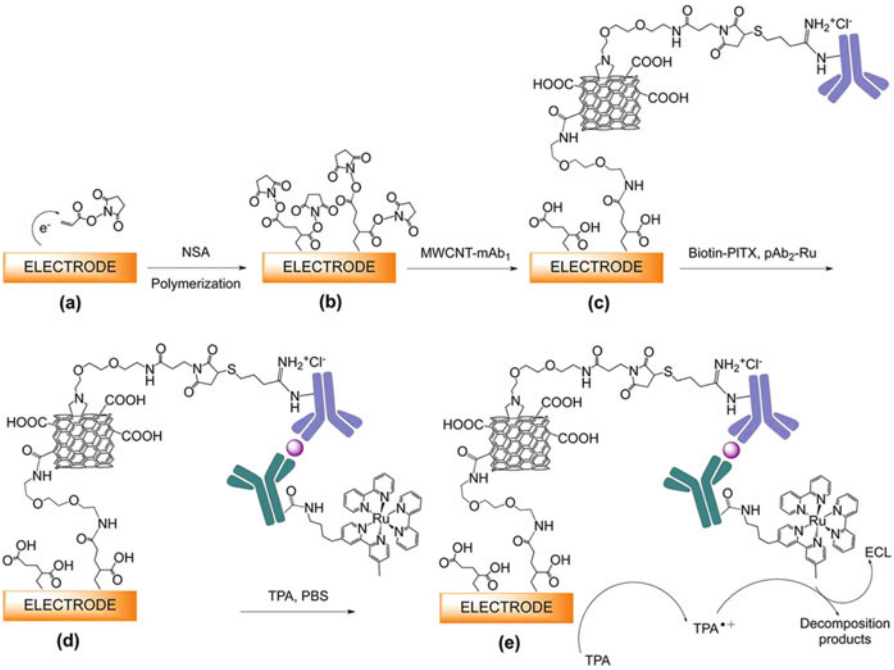


Fig. 1.8 A nanobiosensor for phylotoxin (purple sphere, Biotin-PITX) showing (**a**) Electrografting of indium tin oxide (ITO) with N-succinimidyl acrylate (NSA), (**b**) Functionalization of multiwalled carbon nanotube with antibodies against PITX (MWCNT-mAb1); (**c**) Addition of biotin-PlTX (purple sphere) followed by addition of Ruthenium complex labelled antibodies (pAb2 –Ru) to PITX and (**d**) Addition of the tripropyl amine (TPA) co-reactant for electrochemiluminescence (ECL) generation and (**e**) ECL measurement which resulted in concentration dependent light generation (Reprinted from Zamolo et al. 2012 with © 2012 permission from ACS publications)

complex linked anti-phylotoxins with tripropyl amine co-reactant for detection of phylotoxin as shown in Fig. 1.8.

1.2.3 Microbial Contamination

Microbial contamination in food and water is known to cause major food borne outbreaks that has major impact on human health. *E. coli (O157:H7), Salmonella, Campylobacter, Staphylococcus, Shigella, Clostridium, L. monocytogenes*, *Bacillus cereus* are most common microbes known to cause food borne outbreaks (Arora et al. 2006a, b). Most food pathogens are easily transmitted through untreated water supply, undercooked or raw meat, milk, fruits, vegetables, food. Use of common facilities make easy contamination and provide higher probabilities of causing

outbreaks. This is important to know that sometimes presence of 1 cfu *E.coli* O157: H7 in 25 g of food is considered at its dangerous level!

A simple approach was developed for rapid determination of *Escherichia coli* using a flow-injection system where microbial metabolism induced $K_3Fe(CN)_6$, reduction was electrochemically measured, and used as direct evidence of microbial metabolism (Hashimoto et al. 2008). This method allowed the quantitative determination of bacteria / fungi in 20 min. This new biosensor system gave opportunity for rapid diagnosis of soil-borne diseases which consisted of two biosensors made up of equal quantities of two different microbes, each individually immobilized on an electrode (Hashimoto et al. 2008).

Raman spectroscopy has been a routine practice for label free analysis chemical and biological components of a sample at micrometer scale. Surface Enhanced Raman Scattering (popularly named as SERS) is one of the available technique that is increasingly being used to detect changes occurring at the surface through antigen-antibody based specific binding (Chae et al. 2013). This convenient and reliable nanobiosensing technique was demonstrated for detection of bacteria *E. coli* using antibody (against *E. coli*) bound to gold nanoparticles deposited Indium Tin Oxide substrate chip via studying concentration dependent SERS peak intensity Raman shift in raw milk sample. Likewise, use of nanoparticles have potential to enhance Raman signal in the order of 10^4–10^6 using surface enhanced Raman spectroscopy via surface plasmon resonance (SPR) phenomena giving extended applications in detection, imaging and bacterial discrimination. Due to higher negative charge availability onto to surface of gram positive bacteria compared to gram negative bacteria, significantly distinguishable SERS spectra can be obtained through use of nanoparticles over wide range of wavelengths. A magnetic–plasmonic Fe_3O_4–Au core–shell nanoparticle synthesis was used to concentrate, detect and identify different bacterial cells by applying an external point magnetic field through SERS (Zhang et al. 2012). A silver nanoparticle coating was used to design a nanobiosensor for the detection of live bacteria in drinking water (Zhou et al. 2014) as well as anthrax spores on nanosphere substrates (Zhang et al. 2005) through simple mixing process. This enabled external spectra of the bacterial cells which are very much similar for two categories of bacterial (Gram positive and Gram negative). In this is row, an interesting label-free near infrared SERS based nanosensor using silver nanoparticles was reported. This method discriminated wide range bacteria in water by analysing inner side of the cell wall through synthesis of silver nanoparticles within bacterial culture (*E. coli, P. aeruginosa, Listeria monocytogenes, L. innocua* and Methicillin-resistant *Staphylococcus aureus*) in presence of cell membrane disruption agent (Triton X 100) in less than 5 min. This could enable to achieve distinguishable SERS spectra of inner side of bacterial walls avoiding an additional sample preparation step (i.e., isolating bacterial plasma) (Chen et al. 2015).

A label-free ultrasensitive nanosensor based on Surface Enhanced Raman Scattering (SERS) for detection of bacteria is recently reported via one step assembly

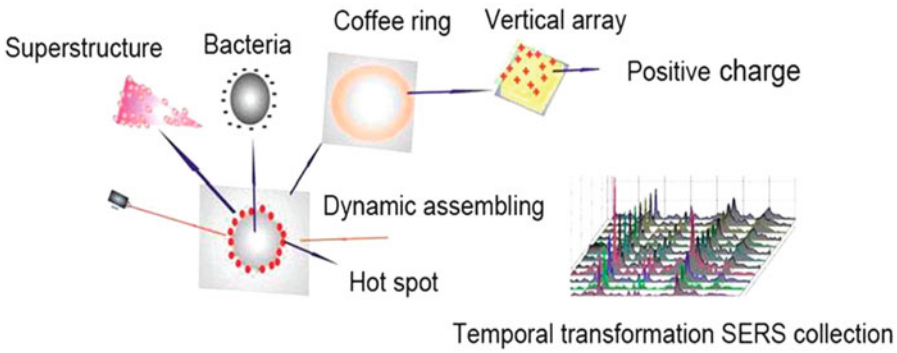


Fig. 1.9 One-step assembling and Surface Enhanced Raman Spectrometry (SERS) based detection of bacteria by adding plasmonic superstructure on bacteria – Au@Ag nanorod columnar array resulting in formation of coffee ring (distinguishable SERS spectra) (Reprinted from Qiu et al. 2016 with © 2016 permission from ACS Publications)

phenomena guided by electrostatic attraction of negatively charged bacteria with positively charged plasmonic nanoparticles (silver @ gold core shell (Ag@Au) nanorods) and two-dimensional bifacial nanoparticle liquid crystalline superstructure (SH-polyethylene glycol-NH_2 coated triangular gold nanoplates – gold nanospheres based bifacial plasmonic assembly) (Qiu et al. 2016). In this method, a 'bifacial superstructure-bacteria-columnar array' assembles when nanoparticle liquid crystalline superstructure is added onto bacterial sample placed onto a 'columnar array of Au@Ag nanorods' as shown in Fig. 1.9. Presence of food borne Gram positive bacteria resulted in formation of dynamic optical hotspots leading to a hybridized nano-assembly under wet – dry critical state, thereby amplifying efficiently the weak vibrational modes. A SERS spectrum was measured at 730 cm^{-1} for detection of bacteria on a nanorod columnar array using bifacial triangular gold nanoplates – gold nanospheres superstructure. This method represents an attractive detection approach that can detect presence of bacteria in various samples/matrices. Moreover, in this report this method limits its application to be not able to distinguish likewise bacteria detected (*S. xylosus, L. monocytogenes, and E. faecium*).

An *E. coli* (O157:H7) specific 22mer oligonucleotide functionalized SiO_2 nanostructure (70 nm sized) coated shear horizontal surface acoustic wave YX $LiNbO_3$ substrate was fabricated to detect high performance nanobiosensor for detection of *E. coli* showing sensitivity of 0.6439 nM/0.1 kHz and detection limit of 1.8 femtomolar (1.8×10^{-15} M) (Ten et al. 2016).

Recently, a co-polymer brushes based functional coating was used to exhibit high fouling resistance and biorecognition capabilities for variety of food matrices (like milk, spinach, cucumber, hamburger, and lettuce) for detection of bacterial contamination using a surface plasmon resonance shift as function of binding with specific antibodies against bacteria like *E.coliO157:H7, E.coliO145:H2*, and

Salmonella. Detection parameters were found to be within concentrations ranging from 1.5×10^{-2} to 1.5×10^{-7} CFU mL^{-1} (colony forming unit per millilitre), 1.5×10^{-2} to 1.5×10^{-7} CFU mL^{-1}, and 2.5×10^{-2} to 2.5×10^{-7} CFU mL^{-1}, respectively (Lísalová et al. 2016). *Bacillus cereus* spore-forming, gram-positive bacilli (found in diverse environmental conditions, including soil and food such as dairy products, rice and vegetables) was electrochemically detected using electrochemical gold nanoparticles and DNA (single stranded DNA of nheA gene) based nanobiosensor in milk. The nano based biosensor showed up to 10 colony forming units per milliliter (CFU mL^{-1}) with a detection limit of 9.4×10^{-12} mol L^{-1}. The infected milk sample was pre-treated and extracted for the specific target DNA prior to detection using nanobiosensor (Izadi et al. 2016).

Some of recent reviews describe variety of available nanobiosensors for detection of waterborne bacteria (Deshmukh et al. 2016); use of nanotechnology for microbial biosensors (Lim et al. 2015) and detection of pathogenic microbes (Yoo and Lee 2016) to demonstrate the potential of nanobiosensors and nanosensors for detection of microbes in wide range of matrices.

1.2.4 Food Allergens

Food borne allergies share a major food safety and public health concern globally and impose huge cost to patients and sometimes death. Since there exist no cure for any kind of allergies, the only significant way is to avoid intake of allergen containing food (Alves et al. 2016).Till date food allergens are being tested by immunological and DNA based methods that involves use of ELISA based kits and use of polymerase chain reaction (known as PCR) based methods (such as PCR-ELISA, real-time PCR, PCR-peptide nucleic acid-high performance liquid chromatography, duplex PCR and multiplex real-time PCR etc.). Recently, Alves et al., have reported available biosensors both immunosensors and DNA biosensors for detection of allergens in various food matrices along with sample preparation methods (Table 1.1).This review contains few nano based biosensors that make use of optical and electrochemical modes of signal transduction mechanisms explained as follows.

Beta-lactoglobulin, a milk based allergen was detected via sensitive label-free graphene modified screen printed based voltammetric immunosensor (Eissa et al. 2012). Cyclic and differential pulse voltammetry (DPV) based measurement were taken to study the response of fabricated nano based biosensor as a function of b–lactoglobulin concentration at pg mL^{-1} level (Table 1.1) in different samples from cake, cheese snacks and biscuits.

Mascini and group reported large number of publications on food allergens/contaminants. Hazelnut allergens were reportedly detected by voltammetric genosensor made up of screen printed eight sample-DNA-array for PCR amplified samples from various food items at nanomolar range. This method provided favorable poor non-specific signal and high sensor stability (Bettazzi et al. 2008;

Table 1.1 Biosensors for detection of food allergens

	Biosensors		Matrix	Allergen	Limit of Detection	References
	Colorimetric	Genosensor	Cereal bar	Lectin, Ara h 3, Ana o 3, mitochondrion DNA (beef, chicken), 16S rRNA (fish, shrimp)	Absolute: 0.5 pg of cashew DNA Practical:0.001% (w/w)	Wang et al. (2011)
			Chocolate			
			Biscuit			
			Fried mud ...			
Optical	Surface Plasmon resonance (Spr)	Immunosensor	Chocolate	Peanut allergens	0.7 µg/mL of extract; 7 ppm peanut sample	Mohammed et al. (2001)
			Olive oil	Hazelnut protein	0.08 µg/g of hazelnut proteins in olive oil	Bremer et al. (2009)
			Chocolate pasta	Ovomucoid, ovotransfemin, β-lactoglobulin, tropomyosin, proteins from hazelnut, peanut, and sesame	<1–12.5 µg/g in samples	Yman et al. (2006)
			Bread			
			Surimi			
			...			
			Processed sea food products	Parvalbumin	3.55 µg/L	Lu et al. (2004)
			Chocolate bars	Ara h 1	0.09 µg/mL	Pollet et al. (2011)
		Aptasensor	–	Ara h1	–	Tran et al. (2013)
	Localized Spr	Immunosensor	Milk	Casein	10 ng/mL	Hiep et al. (2007)
	Imaging Spr	Immunosensor	Cookies and dark chocolate products	Peanut, hazelnut, milk, soy, lupine, egg, pine nut, and tree nuts allergens	Cookies: 0.2–3.2 mg/kg	Raz et al. (2010)
					Dark chocolates: 0.4–5 mg/kg	
	Resonance Enhanced Absorption	Immunosensor	Egg-containing food products	Ovalbumin	1 ng/mL	Maier et al. (2008)
				Ovomucoid		
			Processed milk matrices	β-lactoglobulin	–	Hohensinner et al. (2007)

Electrochemical	Voltammetry	Genosensor	Chocolates	Hazelnut allergens (Cor a 1.03 and Cor a 1.04)	Cor a 1.03: 0.3 mol/L Cor a 1.04: 0.1 mol/L	Bettazzi et al. (2008)
			Snacks			
			Biscuits			
			Soy milk, peanut			
	Voltammetry	Immunosensor	Cake, cheese snacks, biscuit	β-lactoglobulin	0.85 pg/mL	Eissa et al. (2012)
	Impedance	Immunosensor	–	Ara h 1	0.04 μg/mL	Singh et al. (2010a, b)
			–	Ara h 1	<0.3 nM	Huang et al. (2008)
Piezoelectric/ electrochemical		Immunosensor	Shrimp	Pen a 1	0.333 μg/mL	Xiulan et al. (2010)

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Farabullini et al. 2007) and allows simultaneous analysis of eight samples. This makes use of PCR derived biotinylated hybrids binding to streptavidin–alkaline phosphatase conjugate in naphthyl phosphate solution (that acts as electro-active indicator) giving current proportional to the target analyte.

To detect ovalbumin or ovomucoid allergens, a resonance enhanced absorption based colorimetric solid-phase immunoassay on a planar chip using biofunctionalized gold nanoparticles as signal transducers in a highly sensitive distance-dependent interferometric setup (Maier et al. 2008). Resonance enhanced absorption involves use of labeled detection reagents and when noble metal nanoclusters are deposited at nanometric distances from the highly reflective mirror of an interferometric setup in optical near field and change in absorption is measured as a function of binding. Binding of gold nanoparticles – conjugated IgGs (immunoglobulin-G, i.e., polyclonal rabbit antisera against ovalbumin and ovomucoid) was successfully demonstrated for food allergens or antigen (ovalbumin or ovomucoid) immobilized on the surface of the optically transparent distance layer (poly(styrene-methyl methacrylate)copolymer) of a Aluminium foil chip. In a similar type of setup, a sandwich assay was described for the detection of lactoglobulin (milk allergen) in processed milk matrices using antibody (purified polyclonal rabbit anti-bovine-lactoglobulin, IgG) pre-coated matrix to capture the antigen (Hohensinner et al. 2007). And, detection of antigen was accomplished by second gold nanoparticles-labeled readout antibody, which within a certain resonance distance generated a visually detectable colorimetric signal (strong blue color) on the chip that could be photometrically read for a semi-quantitative measurement.

A peanut protein ‘Ara h1’, known to be responsible for peanut allergy was detected using gold-coated nanoporous polycarbonate based impedance immunosensor by measuring the change in the pore conductivity (Singh et al. 2010a, b). These authors reported to study binding of Ara h 1 to antibody bound within nanopore as a function of the membrane pore diameter (15, 30 and 50 nm) and the protein concentration. Interestingly, highest sensitivity was achieved with the smallest pore diameter membrane with improved limit of detection of 0.04 m g/mL compared to SPR based immune assay for Ara h1 detection (0.09 m g/mL, as mentioned in Table 1.1).

Recently, aptamer/quantum dots-functionalized grapheme oxide biosensor is reported for food allergen (peanut, Arah1) detection on a microfluidic platform. It utilizes fluorescence quenching and recovering properties of graphene oxide through the adsorption and desorption of Quantum Dots conjugated aptamers (Weng and Neethirajan 2016). This microfluidic platform introduced features like decreased sample/reagent consumption and rapid fluorescent signal detection on a miniature size optical detection while avoiding probe immobilization procedures as shown in Fig. 1.10. This microfluidic system is governed by powerless sampling that can be generated by hexagons capillary pump, which introduce capillary force, and favours liquid sucking into the microfluidic channel. Capillary-driven retarding inlet valve (Mohammed and Desmulliez 2013) help avoiding air capture in

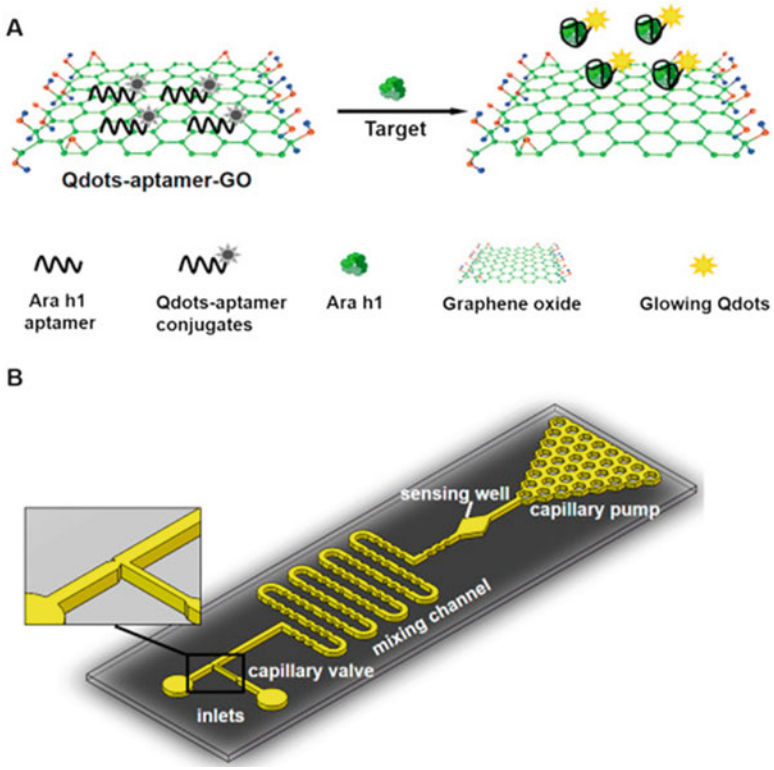


Fig. 1.10 Schematic showing (**a**) sensing mechanism of Quantum dots (Qdots)-aptamer-Graphene oxide (GO) quenching system. (**b**) microfluidic chip driven capillary forces consisting of two inlets for loading the Quantum dots-aptamer-Graphene oxide probe mixture and the Ara h 1 sample, mixing/incubation channel (zig zag), diamond shaped sensing well aligned to sensing Si photodiode window and a capillary pump at the end (Reprinted from Weng and Neethirajan 2016 with © 2016 permission from Elsevier Publishing company)

the microchannel while dispensing the Qdots-aptamer-GO probe mixture and the Ara h 1 sample into the inlets. Ara h1 was demonstrated to be detected in linear response region between 200 ng mL^{-1} and 2000 ng mL^{-1} with detection limits of 56 ng mL^{-1} within 5 min of quenching and fluorescence recovery time (Weng and Neethirajan 2016). These interesting findings warrants realization of integration of existing nano- and bio- sensor technology with microfluidics. This shall facilitate achieving enhanced features of performance through throughput processing, desired transport for controlling the flow conditions, increase the mixing rate of different reagents, smaller sample / reagents volume (down to nanoliter) leading to increased sensitivity of detection, and utilize the same platform for both sample preparation and detection (Luka et al. 2015).

There are various reports available that show selection of various specific aptamers that are being isolated and have been isolated for potential harmful

bacteria (Lee et al. 2012; Han and Lee 2013), suggests that aptamer based nanosensors possess immense potential for monitoring bacterial contamination in various food and agricultural matrices.

1.2.5 Nutritional Constituents in Food

Vitamins are important constituents of living things, which are not only measured and monitored, as important ingredients of food items but are also equally important for health care diagnostics. Vitamins are complex group of compounds that are known to play important role in various biochemical pathways and have been found to have chemical structures that give rise to electrochemical properties. Vitamins like vitamin C (L-ascorbic acid), compounds in the B vitamin group: vitamin B_2 (riboflavin); vitamin B_6 (pyridoxine); vitamin B_7 (biotin); vitamin B_9 (folic acid); and vitamin B_{12} (cyan) are either naturally electroactive or electroactive under modified conditions (Ho et al. 2010). Hence, their properties continue to be exploited using electrochemical techniques. Nanobiosensors for vitamin C (linear range 50.00–400.00 μM), polyphenols, vanilla flavours, and isoflavones were reported by Crevillén et al. 2007, 2008 using a multi-walled carbon nanotube screen printed carbon electrode coupled with a capillary electrophoresis micro-chip device through amperometric detection. A gold nanoparticle enhanced biotin (vit B_7) detection was carried out in a competitive electrochemical immunosensor assay by Ho et al. 2010.

Choline is an essential food ingredient (mainly milk) that has nutritional value for all age groups as it is required for essential roles in brain development, metabolic functions, signalling in central nervous system, memory functions etc. Although, it is synthesized in body, its dietary intake is also required to sustain appropriate development especially in kids/infants. Any disbalance in choline metabolism has been found to lead to Alzheimer's, Parkinson's and prostate cancer (Richman et al. 2012; Zeisel and Blusztajn 1994). Recommended levels of choline intake ranges from 125 mg day^{-1} in infants to 550 mg day^{-1} in males over age 14 years and in breast-feeding women (Zeisel and Blusztajn 1994). An chemiluminescence bi-enzyme (choline oxidase and horseradish peroxidase) linked Zinc oxide nanorods film based nanobiosensor was developed for detection of choline in range of 0.0005–2 mM as shown in Fig. 1.11 (Pal et al. 2014). In this chemiluminescence assay enzymatic action on analyte choline resulted in production of hydrogen peroxide which was used for quantification through HRP enzyme in presence of chemiluminescence indicator luminal to generated photons directly proportional to the analyte. This nanobiosensor presented a promising example a stable assembly that retained 78% enzyme activity till 28 days.

Glucose is an important food ingredient and an central parameter which needs to be monitored due to various clinical and food production reasons. Magnetite (Fe_2O_3) – Prussian blue nano-composites were described to sense glucose exhibiting fast response time 3–4 s, lower detection limit of 0.5 μM, wide linear

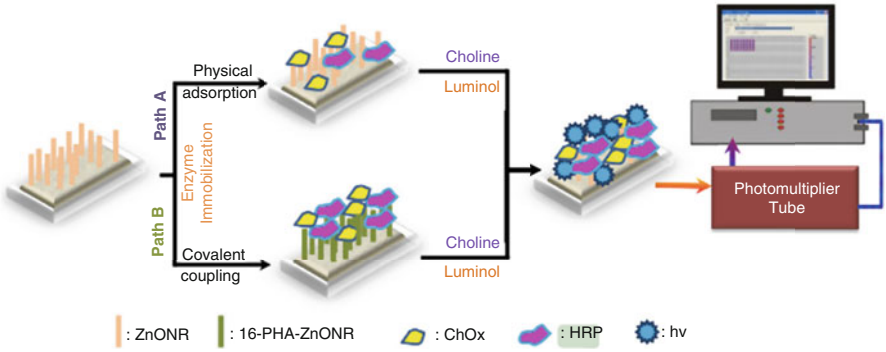


Fig. 1.11 Zinc oxide (ZnO) nanorods (NR) based choline nanobiosensor using bi-enzyme-cholesterol oxidase/horseradish peroxidase (ChOx/HRP) through physical adsorption (Path A) and covalent coupling (Path B), showing detection of choline using chemiluminescence assay where production of hydrogen peroxide by ChOx is quantified by second enzyme HRP in presence of luminol which intern generates photon directly proportional to analyte choline (Reprinted from Pal et al. 2014 with © 2014 permission from Elsevier Publishing company)

range from 5 μM to 1.2 mM, sensitivity of 32 μA mM^{-1} cm^{-2} and good long-term stability (Jomma and Ding 2016).

Lactate is another important analyte for clinical analysis, sports medicine and food industry. Besides, its clinical importance, lactate in food is an import analyte that is monitored in food industry. It can indicate microbial contamination leading to lactate fermentation (Gyawali and Ibrahim 2012; Muyanja et al. 2012). An amperometric lactate nano-biosensor based on lactate dehydrogenase functionalized graphene was reported to have sensitively from 0.08 mM to 20 mM, with a fast steady- state measuring time of 2 s y measuring formation of hydrogen peroxide as a result of enzymatic reaction (Labroo and Cui 2013).

Amino acid phenylalanine and proteins like lysozyme (Lys) and bovine serum albumin was detected through a gold nanorods based nanobiosensor via use Surface Enhanced Raman Spectra (SERS) based detection mechanism (Fazio et al. 2016). In this novel approach radiation pressure was utilized to locally push gold nanorods and induce their aggregation in buffered solutions of biomolecules, achieving biomolecular SERS detection at almost neutral pH reaching detection limits in the μg mL^{-1} range and achieve single molecule sensitivity. The addition of nanoparticles aggregates to protein solutions paved the way to quantitative estimation. SERS exploits electromagnetic enhancement of localized surface plasmon resonance of metal nanoparticles to tailor molecular sensitivity, by creating SERS-active clusters i.e., nanoparticle embedded molecules leading to 'hotspots' that enhance Raman Scattering for magnified detection. In a similar way, SERS based detection of uric acid in human serum was achieved with limits of detection (LOD) ~240 μ M (equivalent to 40 μ g mL^{-1}) (Zakel et al. 2011).

Polyphenolics are a broad class of compounds present in many fruits, vegetables, and their products, including grapes and wines. Wines, particularly red wines are

known contain biologically active poly-phenols which provide antioxidant properties and contribute substantially to the quality by color, flavor, stability, and aging behavior. Tyrosinase-immobilized nanobiosensors based on poly(acrylic acid)-grafted multi-wall carbon nanotube and poly(maleic anhydride)-grafted multi-wall carbon nanotube as substrate materials were fabricated (Kim et al. 2010). This amperometric nanobiosensor could show sensing range of 0.2–0.9 mM and 0.1–0.5 mM for phenol in phosphate buffer solution, respectively for both nanobiosensors. Laccase (p-diphenol oxidase containing copper ions) was co-immobilized with Tyrosinase in a sol–gel matrix of diglycery silane) to detect wide range of phenolic compounds present in wine (Montereali et al. 2010). Yang et al. 2009 used a tyrosinase nanobiosensor based on polyglucosyl 4-vinyl phenyl boronate-multiwall carbon nanotube using cyclic voltammetry and suggested that the amounts of phenolic compounds in commercial red wines range between 68.50 and 655.0 mg L^{-1} for Lindemans wine to Duchessa Lia wine. About ten times higher content of these phenolic compounds is responsible for typical bitter taste of the Duchessa red wine.

Heterocyclic amines are constituents of cooked food, which are formed as a result of incomplete combustion process of proteins at high temperature. As per International Agency for Research on Cancer (IARC 1993) some of the heterocyclic aromatic amines as possible human carcinogens e.g., Class 2B: (2-amino-3,4-dimethyl-imidazo [4,5-f]-quinoline, 2-amino-3,8-dimethyl-imidazo [4,5-f] quinoxaline and 2-amino-3,4,8- trimethylimidazo [4,5-f]-quinoxaline, 2-amino-3,7,8-trimethyl-imi-dazo [4,5-f]-quinoxaline and Class 2A: 2-amino-3-methylimidazo [4,5-f]-quinoline (Puangsombat et al. 2012, John and Beedanagari 2014, IARC 1993). A carbon dots based nanosensor was prepared from lactose using microwave process and was used as such without any further functionalization for detection of four different heterocyclic aromatic amines. Specific binding of heterocyclic aromatic amines, reportedly quenched the fluorescence of carbon dots at 455 nM and facilitated detection of heterocyclic aromatic amines in exponential manner in concentration range of 0.35–0.45 mg L^{-1} (Lopez et al. 2015).

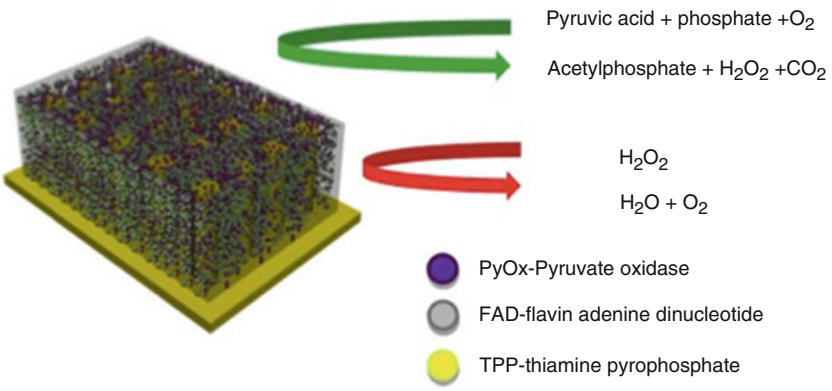
1.2.6 Monitoring Environmental Parameters for Food and Agricultural Applications

Phosphate levels in aquatic environments are very important tool in understanding the quality of water to facilitate production of fishes and aquatic plants as well as to sustain balance in ecosystem for various purposes. Phosphorus is usually present in the natural water as phosphates (orthophosphates, polyphosphates, and organically-bound phosphates) (Nollet and Gelder 2013; Spellman 2013) at a very low concentration of 0.025–0.1 mg L^{-1} (Fadiran et al. 2008a, b). Use of excessive fertilizers, industrial effluents, laundry, human and animal waste has caused increase in

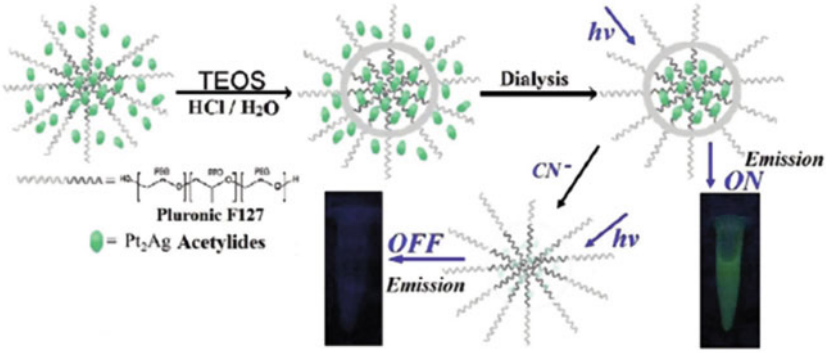
phosphate level of water bodies. This over-fertilized situation of aquatic plants results in "eutrophication" (Smith et al. 1999) i.e., explosive growth of the plants and algae due to oversupply of the nutrients. Thereby, causing hypoxia condition in water for fishes due to consumption of all O_2 (Upadhyay and Verma 2015). Therefore, a stable amperometric phosphate nanobiosensor was developed to quntitate phosphate levels in water samples using pyruvate oxidase and its cofactors, thiamine pyrophosphate and flavin adenine dinucleotide closely integrated with a highly ordered gold nanowires array (Fig. 1.12a). This nanobiosensor gave detection limit of 0.1 mM, a linear concentration range of 12.5–1000 μM, and a sensitivity of 140.3 μA mM^{-1} cm^2 (Ogabiela et al. 2015).

Cyanide is acutely toxic to mammals by all routes of administration. These are produced by plants biologically and also by anthropogenic activities which can be used a potential bio war agent. Therefore, detection of cyanide contamination in food and water is extremely important. A nanosensor for cyanide detection was developed using a pair of two luminescent hetero-trinuclear complexes $[Pt_2Ag(\mu\text{-dpppy})_2(CuCC_6H_4R\text{-}4)_4](ClO_4)$(R = H, 1; R = CH_3, 2) as self-assembling building blocks of $[Pt(CuCC_6H_4R\text{-}4)_4]^{2-}$ and $[Ag_2(\mu\text{-dpppy})_3]^{2+}$ to achieve Pt_2Ag (platinum silver) acetylides. These were further associated with mono dispersed silica nanoparticles to form new kind of luminescent nanoparticles called '$Pt_2Ag@SiO_2$ nanoparticles' (Lin et al. 2014a, b). This interesting 'platinum-silver @ silicon oxide' nano assembly had specific fluorescence quenching response phenomena for cyanide anions and had improved water solubility, stability and luminescence signal enhancement that could be observed through naked eye (Fig. 1.12b). Nanosensor was reported to have ratio of the luminescence intensity (I_0/I) vary in a linear relationship with concentration of cyanide anions in the range of 0.1–10.0 μM ($R^2 = 0.9984$) having detection limit of 0.08 μM at S/N = 3. This nanosensor could sense in the range of acceptable cyanide ion limits (<1.9 μM) prescribed for drinking water by World Health Organization (WHO). A new two-photo excitation nanosensor using graphene quantum dots @gold nanoparticle conjugate for sensing and imaging endogenous biological CN^-ions was reported (Wang et al. 2015). This nanosensor could detect CN^- up to 0.52 μ M and at deeper penetration depth (about 400 μ m) in sample matrices, to realize *in situ* sensing and imaging of CN^- ions in different types of plant tissues and food samples using fluorescent sensing and imaging (Wang et al. 2015). In this unique hybrid nanosensor a peptide-mediated graphene quantum dots /gold nanoparticles hybrid assembly was achieved through $\pi - \pi$ stacking of graphene quantum dots and peptide to form the nanosensor. The nanosensor underwent disassembly upon addition of CN^-, gold nanoparticles were etched to lead to fluorescence of graphene quantum dots to be released to be able to sense and image presence of CN^- ions. Whereas in the absence of CN^-, the fluorescence of graphene quantum dots would remain quenched by gold nanoparticles through the fluorescence resonance energy transfer (commonly known as FRET) (Fig. 1.12c).

Green fluorescent protein (commonly known as GFP)-tagged sensor proteins, ArsR-GFP and CadC-GFP, were used as nano-biosensors for simple and low-cost quantification of As(III) or Cd(II) in drinking water (Siddiki et al. 2012). The sensor



(a)



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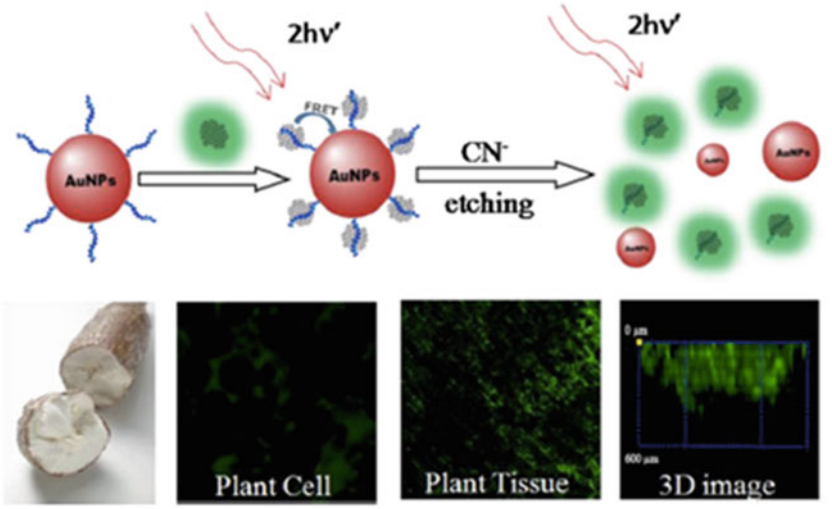


(c)

Fig. 1.12 Detection of (**a**) phosphate ions using gold nanowires array–thiamine pyrophosphate (TPP)–pyruvate oxidase (PyOx) nanobiosensor that amperometrically measures enzymatic degradation of analyte (Reprinted from Ogabiela et al. 2015 with © 2015 permission from Elsevier

protein-promoter DNA complexes bound to surfaces of magnetic particles of different sizes so that they can be separated by magnets, and can release different amounts of GFP-tagged protein, as per metal concentrations within 5 min leading to increases in fluorescence. A detection limit of 1 μg/L for As(III) and Cd(II) in purified water was obtained only with the nanoparticles exhibiting enough magnetization after heat treatment for 1 min.

1.2.7 Pesticides in Food and Environment

Use of pesticides is an indispensable component of modern crop management practices as they are believed to improve the nutritional value of food and minimize the loss in agricultural productivity caused by insects and pests. Pesticides like methyl parathion, organophosphorus compounds, ethyl parathion, malathion, 2,4-dichlorophenoxyacetic acid (2,4-D), atrazine, dichlorodiphenyltrichloroethane (DDT) and hexachlorocyclohexane (HCH) are some examples of chemicals that had been used in agriculture for controlling weeds, insects and rodents to increase productivity. On the contrary, use of pesticides, herbicides and chemical fertilizers have resulted in various harmful effects to environment and disbalance in ecosystem besides bringing in revolution in the production quantity. Hazardous health effects and toxicological interventions due to use of pesticides has led to wide range of diseases throughout the world, that monitoring pesticide levels in various matrices like water, food, soil, ground water, and food at extremely low concentration i.e., pg levels has become need of hour to comply with environmental, product specification and government regulatory norms.

As per Nature Asia 2008, A nucleic acid and intrinsically conducting polymer based biosensor was reported, that could detect minute amounts of toxic organophosphate insecticides at nanomolar levels for screening of environmental samples such as drinking water, waste water and industrial effluents (Nature Asia, doi: https://doi.org/10.1038/nindia.2008.213 Published online 29 May 2008). The sensor could track chlorpyrifos (0.5–200 ppb) and malathion (0.005–10 ppm) a conducting polymer (polyaniline-polyvinyl sulfonate) and nucleic acid as a biorecognition element within 30 s exposure time having stability of about 6 months (Prabhakar et al. 2008). In a similar series of studies, double stranded calf thymus

Fig. 1.12 (continued) Publishing company); (**b**) cyanide anions using 'platinum-silver @ silicon oxide' ($Pt_2Ag@SiO_2$) nano-assembly based nanosensor where fluorescence quenching occurs in presence of analyte, which is shown to have affinity for especially designed nano-assembly (TEOS-tetraethyl orthosilicate) (Reprinted from Lin et al. 2014a, b with © 2014 permission from Royal Society of Chemistry) and (**c**) CN^- ions using gold nanoparticle (AuNP)-Peptide @ graphene quantum dot (GQD) nanosensor assembly where presence of analyte would dissociate the nano assembly to stop fluorescence resonance energy transfer (FRET) between AuNP and GQD facilitating *in situ* sensing and imaging in plant tissues (Reprinted from Wang et al. 2015 with © 2015 permission from ACS publications)

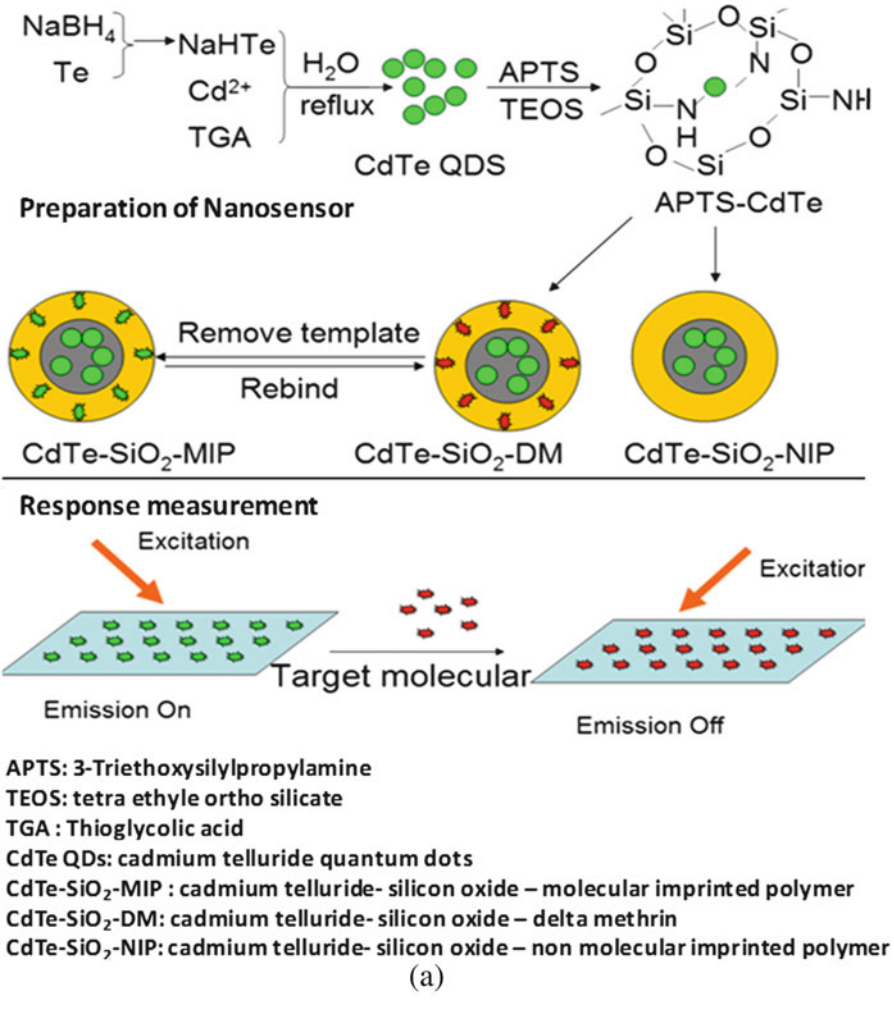
deoxyribonucleic acid entrapped polypyrrole-polyvinyl sulphonate films fabricated onto indium-tin-oxide coated glass plates were used to detect organophosphates such as chlorpyrifos (0.0016–0.025 ppm), malathion (0.17–5.0 ppm), 2-aminoantharcene (0.01–20 ppm) and o-chlorophenol (0.1–30 ppm) (Prabhakar et al. 2007, Arora et al. 2006a, b).

A nanosensor based silver nanoparticles was shown to be sensitive to herbicide in a solution that induced variation in colour of the nanoparticles from yellow to orange red and finally to purple in concentration depended manner (Dubertret et al. 2001). This method represents and interesting useful approach for detection contaminants, such as organic pollutants and microbial pathogens in water bodies and in the environment. In a similar way intrinsically conducting polymers like polyaniline, polythiophene and polypyrrole are being used to fabricate fast nanosensors that can detect molecular signals with very low intensity of chemicals/toxins spoilage and food-borne pathogens (Sekhon 2010).

Deltamethrin (a replacement of organochlorines and organophosphorus insecticides) was detected using cadmium telluride embedded molecularly imprinted polymers of fluorescent silica (SiO_2) quantum dots or nano spheres in concentration range of 0.5–35.0 g mL^{-1}, and corresponding detection limit of 0.16 g mL^{-1} in fruit and vegetable samples using fluorescence measurements (Ge et al. 2011, Fig. 1.13a). This nanosensor was reported to be highly specific to deltamethrin due to existence of a quenching mechanism (that facilitates electron transfer from the cadmium telluride-silica quantum dots to the deltamethrin species through the strong binding to the template molecule) and was shown to give no signal for trichlorfon, carbofuran, lambda-cyhalothrin, cypermethrin, permethrin and various ions (NH_4^+,NO_3^-, Na^+, Cl^+, CO_3^{2-}, Fe^{3+}).

Cartap, (a nereistoxin derivative and a pesticides used in agriculture) was detected using a novel up conversion nanoparticles [$NaYF_4$:Yb,Ho/Au nanocomposite or lanthanide (ytterbium-Yb and holmium-Ho) doped sodium yttrium fluoride-$NaYH_4$ nanocomposite on gold nanoparticles] through chemo-nano-sensor up to 10 ppb via luminescence resonance energy transfer (LRET) (Wang et al. 2013). LRET is reported to occur between upconversion nanocrystals and the gold nanoparticles and upon specific hydrogen binding of cartap to mercaptopropionic acid bound on gold nanoparticles that lie in close association with upconversion nanoparticles ($NaYF_4$:Yb,Ho nanocrystal) LRET is facilitated as shown in Fig. 1.13b.

Same group of researchers worked on detection of organophosphorus pesticides and reported a novel nanosensor based on FRET between upconversion nanoparticles ($NaYF_4$:Yb,Er nanocomposite or lanthanide (Ytterbium-Yb and Erbium-Er) doped sodium yttrium fluoride-$NaYH_4$ nanocomposite) and gold nanoparticles as shown in Fig. 1.13c (Long et al. 2015). The detection mechanism is based on the fact that gold nanoparticles quench the fluorescence of upconversion nanoparticles and organophosphorus pesticides inhibit the activity of acetylcholinesterase which catalyzes the hydrolysis of acetylthiocholine into thiocholine. Acetylthiocholine is an analog of acetylcholine, a substrate of acetylcholinesterase, and it can be easily hydrolyzed to generate thiocholine. The electrostatic



(a)

Fig. 1.13 Detection of: (**a**) deltamethrin using cadmium telluride embedded molecularly imprinted polymers of SiO_2 based nanosensor where binding of target analyte results in quenching of fluorescence (Reprinted from Ge et al. 2011 with © 2011 permission from Elsevier Publishing company); (**b**) cartap using up conversion nanoparticles (UCNPs) and gold nano particles based LRET nano sensor, where a- Hydrogen-bonding between cartap and MPA, b-LRET between UCNPs and GNPs is favoured in presence of analyte (Reprinted from Wang et al. 2013 with © 2013 permission from Elsevier Publishing company); (**c**) organophosphate (OPs) pesticide using upconversion nanoparticles-gold nanoparticles (UCNPs-AuNPs) based nanosensor where presence of analyte deactivates acetylcholinesterase enzyme (AChE) and formation of thiocholine (ATC) goes down thereby leading to disintegration of nanosensor assembly to stop FRET between UCNPs and gold nanoparticles or no/less response signal and vice versa (Reprinted from Long et al. 2015 with © 2015 permission from Elsevier Publishing company); (**d**) Acetamiprid using aptamer-upconversion nanoparticles (UCNPs)–gold nanoparticles (GNPs) based nanosensor where presence of analyte leads to fluorescence signal due to no FRET between UCNPs and GNPs (Reprinted from Hu et al. 2016 with © 2016 permission from Elsevier Publishing company) and (**e**) organophosphorus (OPs) and carbamate Pesticides using colorimetric Sensor Array where presence of analyte results in decrease in colourimetric signal due to inhibition of Acetylcholinesterase (AchE) activity (ChOx-choline oxidase, S-ACh- acetyl thiol choline, ACh-acetyl choline) (Reprinted from Qian and Lin 2015 with © 2015 permission from ACS publications)

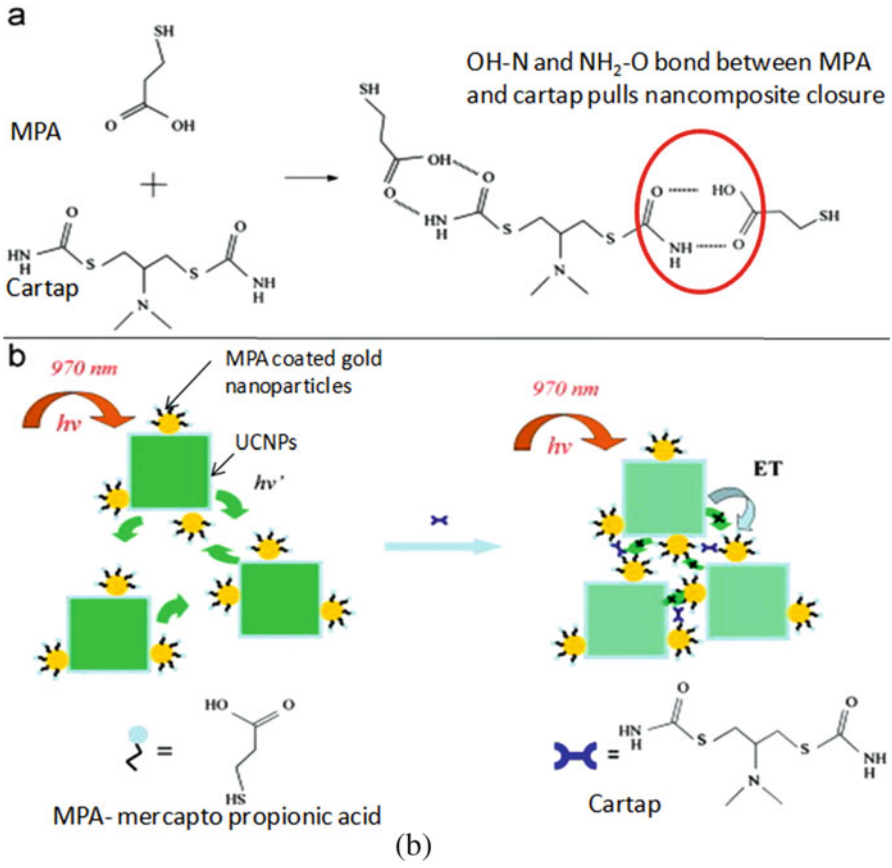
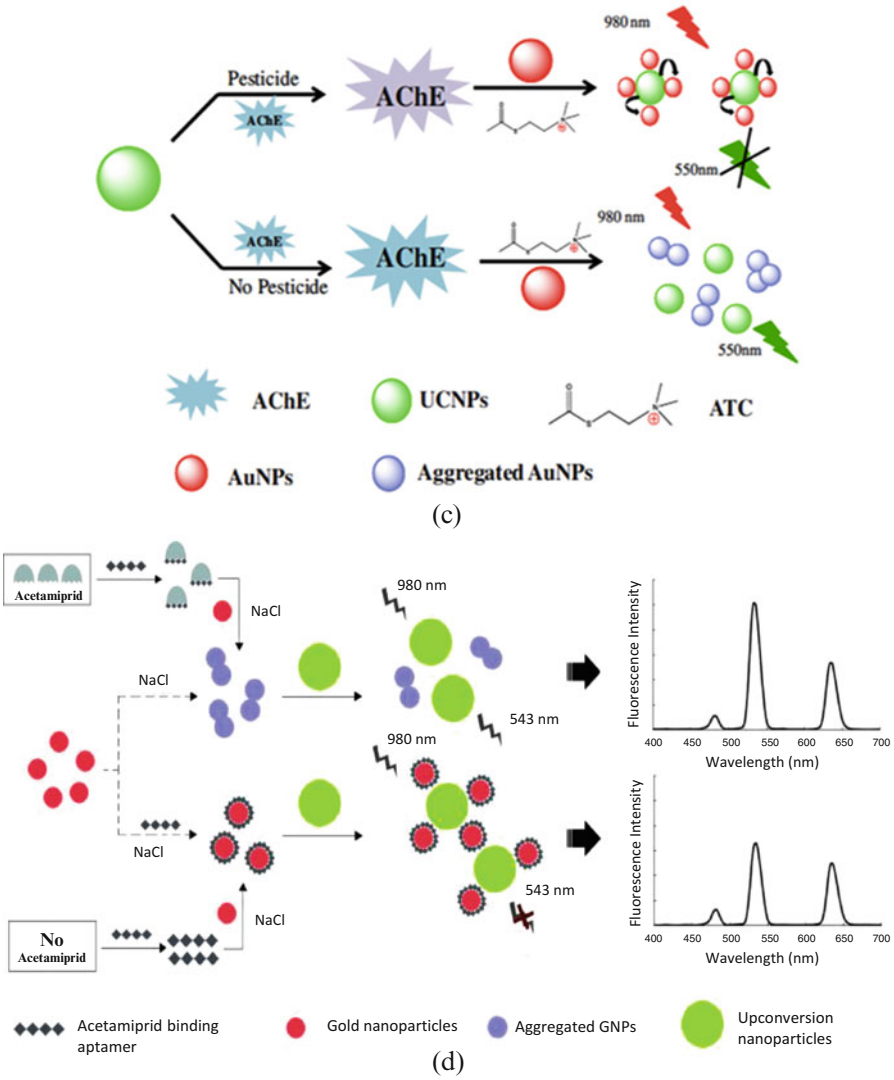


Fig. 1.13 (continued)



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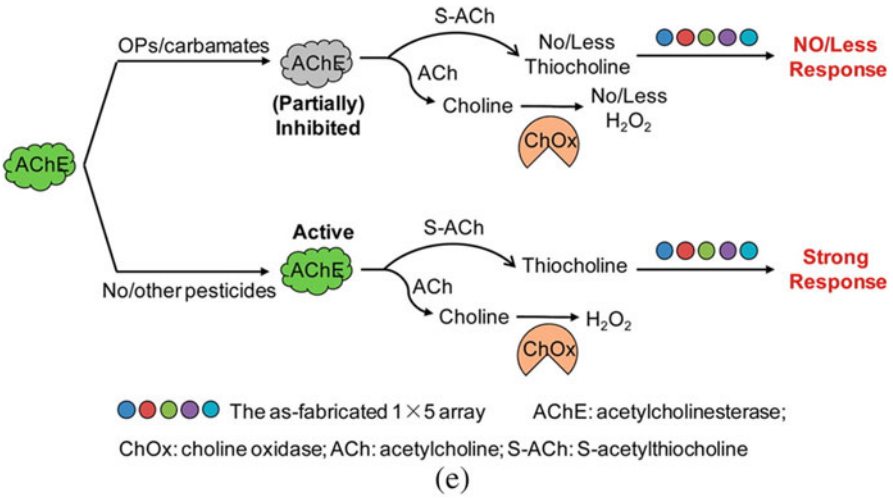

Fig. 1.13 (continued)

interactions and gold–thiols interaction between thiocholine and gold nanoparticles resulted the disintegration of the gold nano particles/upconversion nanoparticles assembly and the aggregation of gold nanoparticles. In presence of pesticides, activity of acetylcholinesterase is inhibited by pesticides that prevented the generation of thiocholine and facilitated the FRET system resulting in quenching of fluorescence of upconversion nanoparticles. The logarithm of the pesticides concentration was proportional to the inhibition efficiency offering detection limits of parathion-methyl, monocrotophos and dimethoate reached to be 0.67,23, and 67 ng L^{-1}.

In a similar strategy, a upconversion nanoparticles and gold nanoparticles based nanosensor was developed via use of specific aptamer for detection of acetamiprid as shown in Fig. 1.13d (Hu et al. 2016). Acetamiprid is a chloropyridinyl neonicotinoid, is widely used in agriculture and garden markets for its low toxicity and high insecticidal activity. As it is mentioned earlier, for most of the pesticides uncontrolled use of acetamiprid can also lead to dangerous levels of residues in food and its exposure of non-target organisms leading to various harmful effects. Hu et al. 2016 reported of linear detection range of acetamiprid to be from 50 nM to 1000 nM and detection limit of 3.2 nM in adulterated tea sample.

A colorimetric sensor array comprising five inexpensive and commercially available thiocholine and H_2O_2 sensitive indicators for the simultaneous detection and identification of organophosphates and carbamates was reported (Qian and Lin 2015) as shown in Fig. 1.13e. This system makes use of irreversible inhibition acetylcholinesterase activity in presence of organophosphates and carbamates thereby, preventing production of thiocholine and H_2O_2 from S-acetylthiocholine and acetylcholine, resulting in decreased or no color reactions by indicator arrays.

Anti-atrazine based immunosensor for detection of atrazine was reported using directly deposited gold nanostructures onto ITO glass slides for environmental monitoring (Singh et al. 2013a). Fabricated nanobiosensor could sense atrazine through Square Wave Voltammetry and was found to have dynamic linear range from 50 aM to 1 nM (10.78 fg mL^{-1}–215 pg mL^{-1}) in 60 s antigen exposure time. This nanobiosensors was also shown to retain substantial stability till 12 weeks upon storage at 4 °C in desiccated condition and showed no binding with non-specific antigens like malathion, parathion, 2-amino anthracene, albendazole etc.

Graphene oxide-magnetic (Fe_3O_4) nanocomposites based 'on-chip' enzymatic microreactor was developed for ultrasensitive organophosphorus pesticide, dimethoate. This novel on-chip enzymatic (acetylcholine esterase) microreactor exhibited a linear relationship between the inhibition rates of acetylcholine esterase as a function of dimethoate concentration from 1 to 20 μg L^{-1} with a detection limit of 0.18 μg L^{-1} (S/N = 3) (Liang et al. 2013).

Methyl parathion an organophosphorus pesticide which is toxic to both vertebrates and invertebrates (that act by inhibiting acetylcholinesterase enzyme in nerve tissue), is needed to be detected in wide range of matrices due to its extensive use in agriculture and fishes. In the reported smartphone-readable barcode assay, yellow color barcode formation is inhibited due to absence of the activity of acetylcholinesterase (enzyme) (Fig. 1.14).AchE hydrolyses acetyl-thiocholine iodide (substrate) to intermediate (thiocholine), which reacts with DTNB(dithio-bis-nitrobenzoate, a chromogenic reagent) to generate TNB (thionitrobenzoate), giving strong absorbance peak centered at 412 nm with a high extinction coefficient (14,150 M^{-1} cm^{-1}) in dilute buffer solutions (Guo et al. 2015). It can be seen that presence of pesticides(+) leads to enzyme inactivation and hence absence of yellow barcode. While, absence of pesticides(−) results in yellow bar code which is indicated as error code 39 in mobile application.

1.2.8 Plant Diseases

Increased food production is requirement throughout the globe to cope up with the increasing demands of exponentially rising population. Crop infections occurring due to pathogens like bacteria, viruses and fungi are major cause of agricultural losses past many centuries. As per projections an additional 70% of food production is required by 2050 throughout the world (Godfrey et al. 2010) to cope up with the daily nutritional needs especially for lower economies and developing countries. Although, decrease in agricultural productivity can be attributed to a variety of reasons, damage caused by pests and pathogens plays a significant role in crop losses throughout the world. This becomes highly important to ensure agricultural sustainability through addressing specific reasons of the losses and taking preventive measures. Identifying plant pathogens via conventional techniques may take several days and therefore researchers need rapid detection tools that can provide

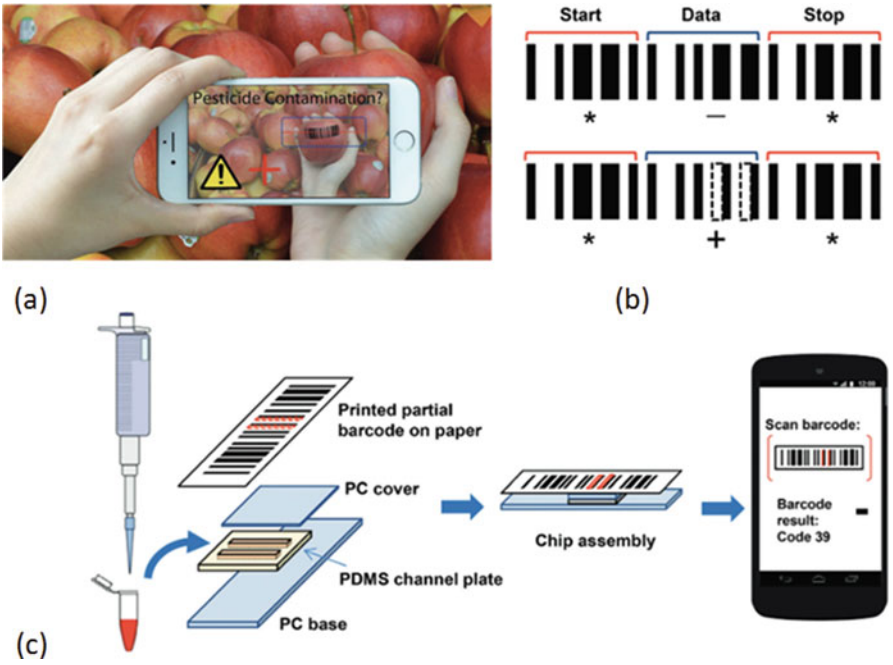

Fig. 1.14 (**a**, **b** and **c**) A smartphone-readable barcode assay for detection. Yellow bar code is formed due to active acetylcholinesterase. In presence of analyte yellow barcodes is not formed and quantitation of pesticide residues colorimetrically read as yellow bar code 39 in absence of pesticide (−) and absence of barcode 39 indicates presence of pesticide (+) (Reprinted from Guo et al. 2015 with © 2015 permission from Royal society of Chemistry)

results within a few hours. Conventionally, direct methods like, PCR: polymerase chain reaction; FISH: fluorescence *in-situ* hybridization; ELISA: enzyme-linked immunosorbent assay; IF: immunofluorescence; FCM: flow cytometry etc.(with detection up to 10^3–10^6 CFU (colony forming unit) mL^{-1}) (Fang and Ramasamy 2015) and indirect methods like, thermography, fluorescence imaging, hyperspectral techniques, gas chromatography are used for detection of various plant diseases. Potential nanotechnology applications in plant pathology can not only facilitate in detection of plant pathogens but also in plant disease control (Khiyami et al. 2014).

Wide range of nanomaterials based biosensors and sensors have been reported for detecting plant diseases by utilizing DNA, antibody and enzymes as biorecognition element making use of variety of measurable signals/changes occurring onto infection containing plants, besides various other parameters that possess potential to be used for food and agricultural applications. As per a recent review from Fang and Ramasamy 2015, some examples of optical nanobiosensors include, antibody assisted fluorescent silica nanoparticles based nanobiosensor for *Xanthomonas axonopodis* that causes bacterial spot disease in *Solanaceae* plant (Yao et al. 2009a, b); gold nanoparticle-based optical immunosensors for karnal

bunt disease in wheat using surface plasmon resonance (SPR) (Singh et al. 2010a, b); DNA hybridization fluorescent oligo probes based single probe sensors/ nanochips based microarrays using for bacteria and viruses (Lopez et al. 2009); quantum dot-fluorescence resonance energy transfer based nanosensor for witches' broom disease of lime caused by *Candidatus* Phytoplasma aurantifolia (*Ca. P. aurantifolia*) using immunosensing at a detection limit of 5 *ca.* P. aurantifolia/ μL (Rad et al. 2012); fluorescent silica nanoparticles based immunosensor for *Xanthomonas axonopodis* pv. *vesicatoria* for bacterial spot disease in tomatoes and peppers (Yao et al. 2009a, b); Rhizomania (a most destructive disease) in sugar beet caused by *beet necrotic yellow vein virus* (BNYVV) carried by vector *Polymyxa betae* (Keskin) (Safarpour et al. 2012); copper oxide (CuO) nanoparticles and nanostructural layer immunosensors for detecting the *A. niger* fungi (Etefagh et al. 2013) and metal oxide nanoparticles (such as Au, SnO_2 and TiO_2) based nanobiosensor for *p*-ethylguaiacol (a volatile organic compounds (VOC)known to be released in various plant diseases) by infected strawberry (Fang et al. 2014a, b) at nanomolar concentration etc.

A recent report suggests detection of viral infection using novel combination of quantum dot incorporated Bacillus spore as nanosensor (Zhang et al. 2015). A spore-based mono disperse microparticles were used to form nanocomposites of spore-based mono disperse microparticles loaded with Cadmium telluride quantum dots. As shown in Fig. 1.15a cadmium telluride quantum dots were multicolor-coded microspheres that have quantum dots of different emission spectra and the capture antigen porcine parvovirus. This was coated on the microparticles loaded cadmium telluride quantum dots surface. The surface reactivity of the microparticles loaded cadmium telluride quantum dots was tested for immunoassay of porcine parvovirus antibody in swine sera using microparticles loaded cadmium telluride quantum dots as suspension beads in a heterogeneous assay system and reporter (labeled with Alexa fluor 647) secondary antibody by monitoring luminescence color by fluorescence spectroscopy, flow cytometry and isothermal titration microcalorimetry.(Fig. 1.15b). This method possesses excellent potential to be implemented for viral infections in the field of food and agriculture.

Amperometric immunosensors for plant pathogens viz. bacteria, viruses and fungi include *Cowpea mosaic virus*, *Tobacco mosaic virus*, *Lettuce mosaic virus*, *Fusarium culmorum*, *Puccinia striiformis*, *Phytophthora infestans*, orchid viruses, chlorotic mottle virus and *Aspergillus niger* (Fang and Ramasamy 2015). Some examples of nano-immunosensors include gold nanorods functionalized antibodies for *Cymbidium mosaic virus* (CymMV) or *Odontoglossum ringspot virus* (ORSV) infections with limits of detection 48 and 42 pg mL^{-1}, respectively, using surface plasmon resonance, 1 ng using quartz crystal microbalance technique in leaf saps (Lin et al. 2014a, b) and polypyrrole nanoribbon modified chemiresistive sensors for *Cucumber mosaic virus* (CMV) up to 10 ng mL^{-1} using amperometric technique (James 2013).

Nucleic acid based nanobiosensors use unique complementary nucleic acid sequences specific to bacterial/viral/fungal pathogens through DNA-DNA, DNA-RNA hybridization as biorecognition event (Arora et al. 2008, Singh et al.

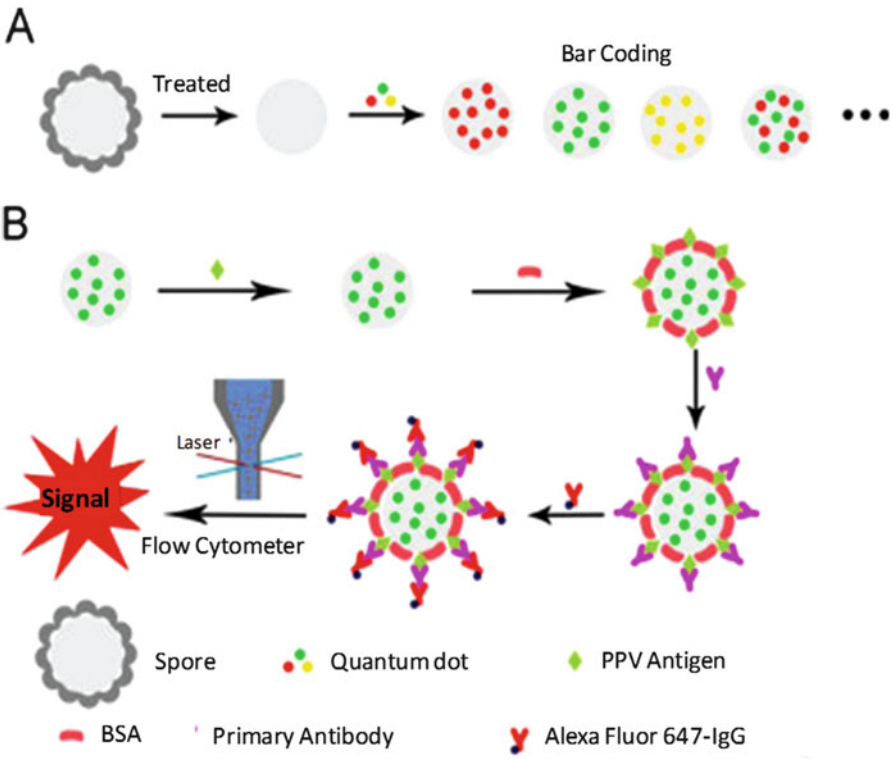

Fig. 1.15 Quantum dot-encoded Bacillus spores (**a**) and microparticles loaded cadmium telluride quantum dots for immunoassay (**b**) where PPV- porcine parvovirus, BSA- bovine serum albumin. Presence of analyte virus is captured by immune labeled microparticles loaded cadmium telluride quantum dots, which is further detected via fluorescent labeled secondary antibody (Reprinted from Zhang et al. 2015 with © 2015 permission from Elsevier Publishing company)

2013b, 2015a, b). Examples of DNA nanobiosensors include use of molecular beacons and quantum dots for two orchid viruses—*Cymbidium mosaic virus* (CymMV) and *Odontoglossum ringspot virus* (ORSV) to detect viral RNA of both orchid viruses up to 0.5 ng of viral RNA in 100 mg orchid leaves using fluorescent probe (Eun and Wong 2000) and presence of target RNA up to 1 ng and 10 ng in the crude sap using quartz crystal microbalance based detection (Eun et al. 2002a, b). A 5′ end fluorescent and 3′ end – gold nanoparticle labelled DNA oligonucleotide was used as a nano transducer to diagnose flavescence dorée phytoplasma of grapevine. Fluorescent signal was measured consequent to hybridization event occurring with complementary target (Firrao et al. 2005).

Enzymatic biosensors for plant pathogen detection usually utilize detection of volatile organic compound which are released in the infected plants only. Studies have shown that various redox enzymes catabolize several of phytohormones and these plant chemicals can be detected using enzyme-based nanobiosensors. Some

examples for detection of plant infection are: methyl salicylate with a bi-enzymatic system where analyte determination involves conversion of methyl salicylate to methanol and salicylic acid and then oxidation of methanol (Fang et al., 2014), alcohols and aldehydes such as *cis*-3-hexen-1-ol and *trans*-2-hexanal by alcohol dehydrogenase enzymes (Jansen et al. 2009), common phytohormones such as auxin, cytokinins and gibberellins by oxidases (e.g., Gibberellin by GA-2-oxidases for plant disease prediction)(Thomas et al. 1999; Kulagina et al. 1999).

Advancements in plant science research to analyse plant genomics, gene function, crop improvement and pathogen detection have taken edge with the help of nanotechnological tools and techniques. A recent example of such application suggests use of nanopore technology (Oxford Nanopore Technologies) and "DNA transistor" technology (companies like IBM and Roche are working on this) that can be used for DNA sequencing in minutes instead of hours and days (Niedringhaus et al. 2011, Ozsolak 2012, Zhang et al. 2011). Portable genome sequencer (MinION) is already available to sequence 10 kb of a single sense and anti-sense DNA strand to enable next-generation sequencing (NGS). A protein nanopore and enzyme were designed to control a single strand of DNA, and as the DNA goes through the nanopore a direct electronic analysis is conducted (Clark et al. 2009). The protein nanopore is inserted in a polymer bilayer membrane across the top of a microwell. Each microwell has a sensor chip that measures the ionic current as the single molecule passes through the nanopore. However, the speed at which the DNA strand travels through the nanopore is too fast for accurate identification.

Present day analytical nanosensors associated with biomolecular recognitions coupled with latest tools-technologies, possess capacity to detect and quantify minute amounts of contaminants such as viruses bacteria, fungi, toxins and other bio-hazardous substances in the agriculture and food systems. These nano-sensors can be linked to a global positioning system (GPS) for real-time monitoring of disease and distributed throughout the field to monitor soil conditions, water quality/quantity, ecological changes and crop health. In fact, Khiyami et al. had suggested that, 'nanosensors will allow us to identify plant diseases before visible symptoms appear and thus will facilitate their control and also that recision farming will allow improved agriculture production by providing precise data, helping growers to make better decisions' (Khiyami et al. 2014).

1.2.9 Genetically Modified Organisms (GMOs)

GMOs such as rice (e.g., stress/saline resistant or golden rice to added to its nutritional value), mustard, resistant cotton, tomatoes, fruits and many more had been the need of hour to bring in green revolution in agricultural production while avoiding food spoilage/losses and facilitating nutritional food available to poorest people throughout the world. Lot of GM crops/foods are available throughout the world nowadays, however, there is ongoing debate over use of GMOs and various

government based regulations have been applied to put a control on use of GMO crops. European continent has put complete ban over use of GMOs based food materials, however, US continent has been less stringent and liberal enough to allow declaration of use GMO on product packaging. Lot of GM crops and food products are in markets of US, Canada and Asian subcontinents. Presently, there are lot of methods available in the market which are based on polymerase chain reaction (PCR, multiplex PCR, qPCR etc.), microarrays, southern blotting, ELISA, western blots, strip tests including biosensors etc. are available for detection of GM crops or organisms (Singh et al. 2011).

Surface Enhanced Raman Spectroscopy (SERS)-barcoded nanosensor was reported that sensed *Bacillus thuringiensis* (Bt) gene transformed rice, expressing insecticidal proteins. This method used specific oligonucleotide conjugated silica encapsulated gold nanoparticles as 'SERS-barcoded nanoparticles spectroscopic tags' (Chen et al. 2012). The Bt genes usually used in rice are cry1Ab, cry1Ac, therefore, transition between the cry1A(b) and cry1A(c) fusion gene sequence was used to construct a specific SERS-based detection method and sucrose phosphate synthase (a rice gene) was used as interior reference gene of rice that gave detection limit of 0.1 pg mL^{-1} as shown in Fig. 1.16. The SERS-barcode nanosensor had sensitivity and accuracy comparable with real-time PCR. The SERS-barcoded analytical method provided precise detection of transgenic rice varieties but also informative supplement to avoid false positive outcomes.

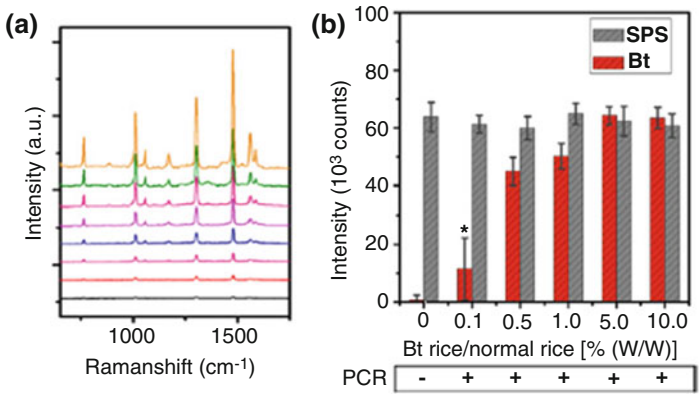

Fig. 1.16 (**a**) SERS spectra of the nanosensor for Bt (from bottom to top: 0.0 pg mL^{-1}, 0.05 pg mL^{-1}, 0.1 pg mL^{-1}, 1.0 pg mL^{-1}, 10 pg mL^{-1}, 100 pg mL^{-1}, 1.0 ng mL^{-1}, 10 ng mL^{-1}, black line: blank control by using sucrose phosphate synthase). (**b**) Normalized Raman intensity and real-time PCR results in the presence of different amount of Bt rice relative to normal rice. Error bars were calculated based on the standard deviation of eight measurements. *Comparison of obtained result with real-time PCR)Reprinted from Chen et al. 2012 with © 2012 permission from Elsevier Publishing company)

1.2.10 Measurement of pH

Food production requires large scale fermentation and bioreactors to achieve desired food product. In this context measurement of pH is one of important parameter not only at industrial scale but also at intra and inter cellular levels for various food and agricultural applications. Various pH control devices have been reported for such applications that involve use of nano based biosensors and/or nanosensors.

A triple fluorescent pH sensor was reported as a new tool for pH measurement that can measure pH 3.9–7.3 by simultaneously incorporating two complemental pH-sensitive fluorophores in a same nanoparticle in a cellular compartment by making use of octaarginine which mimics human immunodeficiency virus-1, Tat protein (a cell penetrating moiety) (Ke et al. 2016). Ratiometric pH nanosensors with tunable pK(a) were prepared by entrapping combinations of two pH-sensitive fluorophores (fluorescein isothiocyanate dextran and Oregon Green(®) dextran) and a reference fluorophore (5-(and-6)-carboxytetramethylrhodamine dextran), in a biocompatible polymer matrix (Chauhan et al. 2011). Dual-fluorophore pH nanosensors permit the measurement of an extended dynamic range, from pH 4.0 to 7.5. A polyacrylamide-based nanosensor with two pH-sensitive fluorophores, fluorescein and Oregon Green was reported to sense (pH 3.1–7.0) having pH-insensitive fluorophore rhodamine as a reference fluorophore. These nanosensors are spontaneously taken up via endocytosis and directed to the lysosomes where dynamic changes in pH can be measured with live-cell confocal microscopy (Sondergaard et al. 2014). Henceforth, it can be stated that nanosensors are available as exciting tools for determining *on line* / *in situ* pH in the micro and nano environments of living cells as well as in food production bioreactors, thereby allowing measurements of absolute values of pH at places that have so far been restricted by the limited sensitivity range of nanosensors, calibration challenges and the complexity of image analysis.

1.3 Future Prospects of Nano Based Biosensors

Nano based biosensors and nanosensors have demonstrated exceptional amount of developments and has combated various challenges of contemporary as well as competitive methods of detection of various parameters/analytes of interest to achieve unprecedented levels performance i.e. to sense ultra trace amounts with unsurpassed sensitivity. Having been through with entire set of available research in the literature, potential of existing various tools and technologies has been realized. Various techniques like molecular imprinted polymers, microfluidics, plasmonic nanosensors, Surface Enhanced Raman Scattering (SERS)/ fluorescence/chemiluminescence/ quartz crystal microbalance /advanced electrochemical measurements coupled with additional features i.e., ability to ‘nano-tune’ various properties of

fabricated 'nano-bio-molecular assembly systems' as per custom requirements offers limitless possibilities. Merging of chemical and biological components into a single platform can allow new opportunities for future nano sensing/ nano based biosensing applications with additional features of portability, disposability, real-time detection, unprecedented accuracies, and allowing simultaneous analysis of different analytes in a single device. However, it needs lot more to integrate and enable current methodologies to reach to desired level of performance characteristics and open doors to reach to realize *on site, in-situ, on-line* measurements. Moreover, this is also true that, there exists lot of unexplored potential in nano based biosensors, which have not been utilized for various food and agricultural applications till date. Achievements made so far suggest that nano based biosensors are the pioneers for the future diagnostic devices that offer unlimited opportunities to be tapped.

1.4 Conclusions

Nano based biosensors and nanosensors have witnessed successful demonstration of their potential to provide unsurpassed levels of detection limits and sensitivity utilizing various unique properties, features and affinities of biological as well as nanomaterials for various food and agricultural applications. Most of these available reports demonstrate their applications for measurement of food additives, toxins and mycotoxins, microbial contamination, food allergens, nutritional constituents in food, pesticides, environmental parameters, in food quality control, environment, plant diseases, genetically modified organisms/plants/crops (GMOs) etc. However, it can be established that most of these works continue to develop at their primitive stages and exists only till laboratory or researcher level. There had been very few techniques that are successfully translated to real world applications and lot more attention/efforts are needed to smoothen up and remove the barriers to bring these new developments to the market and serve masses throughout the world.

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