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# Nanomaterials for Foodborne Pathogen Detection and Isolation

**Wanwisa Poonlapdecha[1], Mohammadali Masigol[2], Larry E Erickson[2], Ryan R Hansen[2], Kooranee Tuitemwong[3*] and Pravate Tuitemwong[1,4*]**

[1]Department of Microbiology, King Mongkut's University of Technology Thonburi, Thailand

[2]Department of Chemical Engineering, Kansas State University, USA

[3]Department of Microbiology, Faculty of Science, Kasetsart University, Thailand

[4]Food Safety Center, King Mongkut's University of Technology Thonburi, Thailand

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**Corresponding author:**
Pravate Tuitemwong, and Kooranee Tuitemwong
Food Safety Center, Institute for Scientific and Technological Research and Services, King Mongkut's University of Technology Thonburi, Bangkok 10140, Thailand,
Email: ptt59@hotmail.com, fscikrt@ku.ac.th

## ABSTRACT

Nanomaterials have potential to improve the detection of foodborne pathogens. Research progress in the development of rapid methods to identify pathogen in several kinds of food is important for food safety and for clinics and hospitals where patients are tested for infection from food pathogens. The accuracy, time for analysis, limit of detection, cost of the assay, specificity of pathogen identification, simplicity of the method, equipment required, and qualifications of the laboratory workers are motivations for developing better methods. Nanomaterials have several features that have enabled new methods with beneficial advances to be reported. One of features is biosensor application for bacterial detection. Biosensors from nanomaterials were shown ability of these alternative methods especially, detection time and limit of detection that was improved when assay developing with nanomaterials. The specific focus of this review is on the physical and chemical aspects of nanoparticles for recognition, capture, and detection of this pathogen. Nanoparticle properties and features, bioconjugation techniques, and processes to concentrate foodborne are important in developing new detection technologies.

## INTRODUCTION

### The need for foodborne pathogens detection

Foodborne pathogens have a prevalent influence on public health. The six major foodborne pathogens are Escherichia coli O157:H7, non-O157 Shiga Toxin-Producing Escherichia Coli (STEC), Salmonella (non-typhoidal serotypes), Listeria monocytogenes, Staphylococcus aureus, and Campylobacter spp [1,2,3]. Food-borne pathogens have become an issue in the international food industry that is worth 578 billion US dollars. According to worldwide statistics reported by Centers for Disease Control (CDC), an estimated one-third of human fatalities are caused by infectious bacterial disease [4]. Among the identified foodborne pathogens, E. coli O157:H7 has gotten increasing attention. Its infective dose is 100 cells with the capability of producing toxin that damage the intestinal lining and causing anemia [5]. Transmission of E. coli O157:H7 to human body can occur through the consumption of contaminated food products such as under-cooked meet, polluted water, yogurt and cheese, and unpasteurized fresh-pressed apple cider [5]. Campylobacter infections are the second leading cause of

foodborne pathogen infection according to Hsieh et al. (2018) [6]. Campylobacter are microorganisms that are known to exist in viable but non-culturable state under some conditions. Culturing methods will not detect Campylobacter in this stage. Oral exposure to approximately 500 cells of Campylobacter can cause illness within 2-5 days that can damage the intestinal epithelium of humans [7,8]. Campylobacter can be found to colonize in the intestine of poultry, humans, and monkeys [9]. It can take 3-7 days to confirm the presence of a foodborne pathogen through a process which includes isolation, biochemical testing with colonies and DNA, and serological confirmation. A conventional method for bacterial detection is the plate count method which requires biochemical confirmation, large sample volume, long incubation time, and significant technician labor [4]. Many researchers have investigated and developed alternative methods to provide results within minutes or hours and to improve assay sensitivity [10]. In addition, assays are designed to have simple procedures with reduced analysis time such that the operating personnel do not need microbiological expertise [11]. Well-known, molecular methods such as Polymerase Chain Reaction (PCR), Enzyme-Linked Immunosorbent Assay (ELISA), and Loop Mediated Isothermal Amplification (LAMP) are examples that decrease the analysis time. Some can identify genus and species. However, the chemical reagents and instruments can be expensive, and contamination can occur due to the complicated preparation. Some reagents have a short shelf life and must be kept below 0 °C [4]. These factors may limit the utility of these methods in developing countries and resource-limited environments. Another critical challenge is detection of bacteria in food samples that normally include complex food matrix with variety of components. Inorganic particles, biochemical compounds such as carbohydrates and proteins, vitamins, indigenous microflora, and non-pathogenic cells are example constituents in the food matrix [12,13]. Fats can interfere in the detection methods based on antibody-binding interactions, while carbohydrates are able to interfere with nucleic acid amplification methods [14,15]. Sodium chloride, sucrose, and lysine existing in food matrices make bonds to the nucleic acids and interfere with DNA polymerase functionality, which inhibits the accuracy of PCR and reduces its sensitivity [16]. It was shown that interference of lipids and proteins in broiler meat could decrease the SPR sensing and detection of Campylobacter jejuni [17]. Sharma et al reported that sugars and fats in milk decreased the sensor resonance frequency of piezoelectric cantilever sensors designed to detect the L. monocytogenes [18]. Considering all these limitations, inexpensive, sensitive, and rapid procedure to precisely detect the whole pathogenic bacteria cells present in food samples needless of trained personnel and performing pre-treatment experiments are necessary [15,19]. Many new innovations of rapid methods for microbe detection in food matrices use nanomaterials. Nanomaterials have offered significant improvements in detection sensitivity, selectivity, and practicality compared to traditional detection assays.

## CONVENTIONAL METHODS FOR FOODBORNE PATHOGEN DETECTION

Conventional or “gold standard” methods for the biosensing and detection of foodborne bacterial pathogens depend on culture–based methods with basic steps including pre-enrichment, selective enrichment, plating, culturing, standard biochemical detection/counting of bacteria, and serological confirmation [20]. Culture-based procedures provide both quantitative and information in a cost-effective and simple process. Unfortunately, these are insensitive, labor intensive, and time-consuming. Culturing takes a couple of days for initial results and up to 7–10 days to confirm the presence of these pathogens [21,22]. Hirvonen et al 2012, reported application of culture-based techniques for E. coli O157:H7 detection and demonstrated that E. coli O157:H7 culture on Sorbitol MacConkey agar (SMAC) provides an accurate and inexpensive detection method but emerging serotypes of sorbitol fermenting non-O157 and O157 Shiga toxin-producing E. coli (STEC) [23] could result in negative false data. Lee et al reported that chromogenic and fluorogenic growth media applied for detection of Salmonella resulted in a more convenient, specific, and selective detection method compared to SMAC agar. However, the major drawback is that the process for obtaining results by using these selective media is not quick enough to be used in applications such as bioterrorism events, Salmonella outbreak, or product recall [24].Over the past two decades, various rapid detection methods with high reliability, sensitivity and clinical or field feasibility have been introduced to address the limitations of culture-based detection

and isolation of foodborne pathogens [25,26,27,28]. These rapid methods should be able to detect the existence of bacterial pathogens both in processed and raw foods with certain level of accuracy and reliability. The sensitivity should reach to an efficient point that makes sensors able to detect microbes even in low concentrations. Fast detection techniques are classified into nucleic acid-based methods, immunological-based methods, and biosensor-based methods, all with their own limitations and advantages [26,29]. This section introduces recent detection approaches and their applications in foodborne pathogen detection along with their pros and cons, and highlights the need for synthetic materials and interfaces to improve the way bacteria are isolated and detected.

**Molecular based methods**

Compared to the conventional techniques, molecular-based methods for foodborne pathogen detection are more sensitive, fast, and less laborious. Nucleic-acid methods, using synthetic oligonucleotide complementary to the target sequence to detect the specific DNA or RNA sequences of the microbe, is used to obtain accurate and precise results [30,31]. As the platform for biosensors, nucleic acid based methods are able to identify the genetic makeup of the pathogen [32]. There are several reports in the literature using different nucleic acid based methods for detection of foodborne microbes. For example simple Polymerase Chain Reaction (PCR) has been applied to identify C.jejuni in chickens [33]. Multiplex polymerase chain reaction (mPCR) has been employed to simultaneous detection of Salmonella, Escherichia coli O157:H7, S. aureus and in milk [34] and duck hatcheries [35]. Quantitative polymerase chain reaction (qPCR) was also applied for enumeration and simultaneous detection of Salmonella and C. jejuni in broiler breast meat [36]. Single PCR and multiplex PCR use one or more primers to detect pathogens in food. PCR provides high detection sensitivities down to one cell in different mediums. This method plays a crucial role in the identification and detection of foodborne microbial strains that exist in food samples. Real time PCR can detect pathogens by determining the fluorescent signal as a continuous condition and is considered as the most common technique due to its high sensitivity and specificity [22]. Liu et al reported in 2019 TaqMan real-time PCR assay for the simultaneous detection of 12 usual foodborne microbes. Limit of Detection (LOD) of the assay for cultured bacteria were 296, 495, 500, and 875 CFU/mL (E. coli O157:H7, C. jejuni, S. aureus, and L. monocytogenes) [22].

The detection limit for the assay in meat samples was $10^4$ CFU/g for 11 strains, while it was reported as $10^3$ CFU/g for V. parahaemolyticus. Authors showed that TaqMan real-time PCR assay could be considered as a fast and efficient alternative option for the high-throughput screening of multiple microbes simultaneously [22]. PCR also has been shown to be used for recognition and detection of bacteria strains that are viable but not culturable [37]. There are some limitations associated with each PCR technique. PCR might not be able to distinguish the viable and dead bacterial pathogens without using some expensive chemical reagents and protocols. Besides, isolates cannot be further characterized. This sometimes results in not-accurate interpretation of the cells viability [38,39,40]. In multiplex PCR, the interference of primers could occur resulting in some bacteria not be detected [41].

**Immunological assays**

In immunological based methods, a specific antibody interacts with a targeted antigen. Sensitivity and specificity of the method are directly affected by the strength of this specific binding. Polyclonal and monoclonal antibodies are particularly generated to detect microbe-specific epitopes to be used in immunological based techniques. Most widely applied immunological assays for the screening of foodborne microbes are enzyme linked immunosorbent assays (ELISA) [42,43], flow cytometry [44,45], and quantitative immunofluorescence [46]. ELISA identifies the protein, peptides, polysaccharide, and bacterial pathogens in a precise and sensitive way [47]. Zhu et al 2016, introduced a double-antibody sandwich ELISA designed for the sensitive and fast detection of Bacillus cereus in meat. Rabbit antiserum and mouse ascites were used to create the required polyclonal (pAb) and monoclonal antibodies (mAb) match to B. cereus. The detection range of this assay was in the range of $1.0\times10^4$–$2.8\times10^6$ cells/mL with the estimated LOD of $0.9\times10^3$ cells/mL in phosphate buffer saline. The assay provides selective detection and 94.9-98.4% recovery of B. cereus in a meat sample possessing similar pathogens such as B. thuringiensis, B. subtilis, B. licheniformis and B. perfringens [48]. Pang et al 2018, presented a paper-based enzyme-linked immunosorbent assay (p-ELISA) for

detection of E. coli O157:H7 from Chinese cabbage, providing an operation time of 3 hrs and detection sensitivity in the order of $10^4$ CFU/mL [49]. ELISA in conjunction with nanomaterials, has been used to improve the detection sensitivity. "Functional nanoparticle-enhanced enzyme-linked immunosorbent assay (FNP-ELISA)" for screening of E. coli (EHEC) O157:H7 was presented by Shen et al 2014 [50]. Monoclonal anti-O157:H7 antibodies were immobilized on immunomagnetic nanoparticles (IMMPs) to attach to the cell surface of bacteria. Detection sensitivities were 68 CFU/mL in the phosphate buffer solution and had a range of $6.8 \times 10^2$ - $6.8 \times 10^3$ CFU/mL in food samples such as ground beef, milk, and vegetable. It was shown that the FNP-ELISA improved the detection sensitivity by two and four orders of magnitude compared to immunomagnetic separation ELISA (IMS-ELISA) and conventional ELISA (C-ELISA), respectively. Guo et al 2016, applied gold nanoparticles (AuNP) to the ELISA assay and improved the detection sensitivity of E. coli O157:H7 in whole milk by the magnitude of 185 compared to conventional ELISA [51]. Cross-interaction among the similar species in ELISA could lead to lower sensitivity and specificity in mixed cultures. Flow cytometry can perform single cell analysis and bacteria detection with high specificity and sensitivity. Yu et al 2018, presented a hybridization chain reaction, (HCR)-based, flow cytometric bead assay for the sensitive fluorescent detection of emetic B. cereus from milk. Under the optimum experimental conditions, the LOD of emetic B. cereus in pure culture and spiked milk were 7.6 cell/mL and $9.2 \times 10^2$ CFU/mL, respectively [44]. Flow cytometry analysis based on fluorescent signal readout demonstrated the high specificity of the designed primer towards emetic B. cereus detection in a mixture containing non-target bacteria, including non-emetic B. cereus, L. monocytogenes, S. aureus, S. Paratyphi, C. sakazakii, and B. subtilis [44].

**Biosensor based assays**

Biosensors have been introduced to address the conventional limitations associated with immunological and nucleic acid-based techniques such as need of expensive chemical and biological reagents, trained staff, and complex laboratory settings. There is also the possibility of getting false results because of interference between similar antigens, and inaccurate detection of dead cells [26]. A biosensor is an integrated receptor-transducer tool that converts a biorecognition or complementary biological binding event into electrical signal [52]. They are categorized based on the types of recognition element (enzymatic, nucleic-acid, aptamer, antibody, and whole cell) or transducer (optical, electrochemical, and piezoelectric) [53]. Biosensors with optimized and highly efficient interfaces could be connected to advanced equipment such as microfluidic devices to expand the detection capabilities. Liu et al 2018, developed an impedance based microfluidic biosensor to detect Salmonella serotypes B and D in turkey samples. The biosensor included two pre-functionalized microchannels with anti-Salmonella antibody serotype as detection regions with interdigitated electrode (IDE) arrays for the impedance measurements of bacteria. Detection sensitivity of Salmonella was reported as 300 CFU/mL in 1 hr. Author also demonstrated the ability of biosensor to differentiate live and dead Salmonella cells by observing very low detection signal when dead bacteria solution pumped into the sensor [54]. Surface Plasmon Resonance (SPR) is one of the most sensitive optical biosensor techniques that provides a real-time monitoring of the interactions between the target analytes and bioreceptors [55]. Antibodies are used extensively as an effective recognition element in SPR biosensors to address limitations regarding loss of sensitivity and specificity due to cross-reactivity in complex food matrixes [56]. Regarding that, Bhandari et al 2019, presented an SPR biosensor to detect the S. Typhimurium in romaine lettuce by using direct immunoassay, a pre-incubated one-step sandwich, and a two-step sandwich assay. Monoclonal antibodies for S. Typhimurium were used as a bioreceptor. The detection sensitivity for all three assay formats had bacteria concentration of 0.9 log CFU/gr. The processes revealed specific S. Typhimurium detection in the romaine lettuce samples including other bacteria such as Pseudomonas aeruginosa, Aeromonas salmonicida, and Enterobacter cloacae [57]. Compared to the optical biosensors, electrochemical-based biosensors offer lower cost and can handle many samples at once but are less specific [26]. Like antibodies, aptamers are considered to be promising bioreceptors in electrochemical biosensors because of their high stability and strong affinity. Use of an electrochemical biosensor with a biotin-modified aptamer allows for fast and efficient detection of E. coli in

Licorice extract as reported in the work of Wang et al 2019 [58]. The authors showed a detection sensitivity of 80 CFU/mL in bacterial solution with the buffer and $9.02 \times 10^4$ CFU/mL in Licorice extract samples in 2.6 hours [58].

## NANOMATERIAL-BASED FOODBORNE PATHOGEN DETECTION

Foodborne pathogens with a low infectious dose and harmful effects to the human body make the creation of sensitive, selective, fast, and reliable detection and isolation methods necessary to control infection. Current approaches are slow, show limited sensitivity, and mostly cannot detect the pathogens in real time. It can take several days to obtain correct information. There is a need to develop methods for sensitive and rapid isolation for culture-free detection of foodborne bacteria. A novel approach to address the challenges is the development of nanotechnology and nanomaterial-based detection techniques that are able to achieve the required criteria of this field. Nanotechnology proposes materials and devices in nanometric dimension (roughly 1–100 nm) offering functional properties, that first; because of their unique sizes, are able to provide high surface-to-volume ratio, and demonstrate physical strength, chemical reactivity, and excellent electrical and optical characteristics, and second; their physical properties and chemical functionality can be manipulated. Tuning the physicochemical behaviour of nanointerfaces can be done by engineering size, composition, shape, and chemical functionalization with different functional groups [59,60,61]. Recent developments in high-resolution synthesis and characterization of nanomaterials such as nanoparticles, nanotubes, quantum dots, and nanowires have motivated researchers to apply nanotechnology for use of bio-detection, drug delivery, and synthesis of functional devices [62]. Nanomaterials applied for detection of foodborne microbes offer unique identifying and detection mechanisms specific to the target and create differentiating signals from the analyte. The signal can be produced by nanostructures themselves or from immobilized biomolecules existing on the surface. Nanomaterials can be functionalized with a variety of targeting groups such as antibodies, aptamers, peptides, and ligands which enhances detection sensitivity and specificity. Nanomaterial-based detection techniques have shown a reduction in detection time and capability of performing high throughput and multiplexing screening [63,64]. Improving surface nanopatterning techniques, such as nanolithography and electron beam lithography, have led the generation of nanoscale arrays and nanopatterned interfaces for pathogen-targeting ligands that can greatly enhance the detection limits and accuracy of techniques designed for foodborne pathogen detection4. Nanopatterned and nanoarray interfaces provide the capability of special control and high throughput screening of bacterial pathogens in a small capture area [59].

### Biofunctional nanomaterials for detection of targeted bacteria

Application of nanomaterials for providing a template for pathogen detection in conjugation with affinity ligands has led to enhance the pathogen detection sensitivity. Due to high surface area, nanomaterials are able to attach a large number and various types of biorecognition elements. This increases the interaction between bacterial pathogens and conjugated ligands which enhances the bacteria surface attachment and interface detection limit [65]. These recognition elements mainly include antibody/antigen [66,67], nucleic acids [68], enzymes/ligands, aptamers, peptides [69], carbohydrates [70], or synthetic bioreceptors which demonstrate strong affinity and specificity toward epitopes on bacteria surface structure [71,72]. Monoclonal, polyclonal, and recombinants antibodies conjugated on nanomaterials (nanoparticles, quantum dots, nanotubes, and etc.) are massively used as probe for highly selective, sensitive, capture and detection of foodborne pathogens. Literature reports use of antibody-conjugated nanomaterials for antigen interaction-based detection of E. coli O157:H7 and Salmonella sp. in food complexes such as hamburger and cucumber [73], S. Typhimurium which is typically found in ground beef and chicken rinse water [74], S. aureus in apple juice/lettuce [75], C. jejuni in poultry samples [76], and L. monocytogenes in sausage and pork [77]. Antibodies are selective, sensitive, and available for wide variety of pathogens. For instance Maurer et al 2012 reported that use of anti-E. coli coated gold nanoparticles could enhance the E. coli capture by the factor of 1.89 compared to uncoated particles [78]. However, antibodies are expensive, demonstrate nonspecific interactions, and normally are not able to differentiate between live and dead pathogens [79,80]. Carbohydrates (oligosaccharides or polysaccharides) are considered as another recognition

elements for pathogen detection and isolation. Compared to antibodies and nucleic acids, carbohydrates show more resistance against the denaturation. Higher density of carbohydrates on the surface is achievable because of their lower sizes, which provides higher multivalent interactions with the pathogen resulting in improve of the binding affinity [81,82]. Carbohydrate-mediated recognition occurs through the interaction with molecules present on the pathogen surface such as lipopolysaccharides, fimbriae, pili, capsules, lectins, glycocalx, adhesin, and mucin [83]. Carbohydrates can be considered as a potential option when antibodies and nucleic acids don't have the specific affinity to recognize mutants that differ slightly from the original target [68,84]. This has been mentioned in the research presented by El-Boubbou et al 2007, which demonstrated magnetic glyco-nanoparticles with the ability to differentiate between the three different E. coli strains. Silica-coated magnetite NP was functionalized with galactose (Gal) and D-mannose (Man) and the responses from the E. coli strains showed the capability of determining the strain identity: E. coli ORN178 (Man strong, Gal weak), E. coli ORN208 (Man weak, Gal weak), and E. coli ES (Man strong, Gal strong) [85]. Similar to carbohydrates, peptides and proteins demonstrate binding capability to multiple target pathogens including fungi and virus through interaction with surface components of the cells [86,87,88]. The use of functionalized peptide interfaces offers the opportunity to differentiate between dead and live pathogens in detection-based approaches [89]. Under equal conditions (considering same number of recognition molecules), peptide-based assays are able to detect larger number of target pathogens compared to antibodies since the binding event is semi-selective. Additionally, peptides can attach to different pathogens with different affinities [90,91,92]. There are several methods for immobilization of biomolecules onto nanomaterial surfaces, including electrostatic interaction, direct covalent attachment, and non-covalent interaction [93]. Electrostatic interaction is based on the charge difference between the particles surface and side chain of the biomolecules. Some biomolecules such as peptides can interact with the surface directly. Functional biomolecules can be attached to surface ligands using covalent bonds.

**Surface chemistry of nanomaterials designed to detect bacteria**

Although many biorecognition elements can be attached to the nanomaterial surfaces physically or by using bioaffinity immobilization, covalent immobilization is favored. Covalent attachment normally provides stronger bond and inhibits desorption as well as spatial modulation of the number and orientation of biomolecules. Modifying surface chemistry of nanomaterials with the desired chemical functional group(s) for covalent immobilization of bioreceptors such as antibodies, aptamers, peptides, proteins, nucleic acids is a critical step before doing biofunctionalization [94]. The type of the functional group is normally designated based on the physico-chemical characteristics of the nanomaterial, bioreceptor, and target pathogen [95]. Carboxyl [96], amine [97,98], epoxy [99], aldehyde [100,101], thiol [102], and succinimidyl esters [103] are commonly used as chemical groups functionalized on variety of substrates such as glass, silicon, gold, or carbon-based substrates which are then covalently reacted with biorecognition elements [104]. For instance, nanomaterials functionalized with carboxyl could be covalently coupled with biomolecules possessing amine such as proteins. Oligonucleotides can be immobilized on nanomaterials containing thiol through disulfide-coupling procedure. In addition, amine-modified nanomaterials are good candidates to be coupled to a broad range of drugs with succinimidyl esters and iso(thio)cyanates [94,105]. Not only the functionalizing surface with chemical groups provides a reactive platform for covalent bonds to form with biomolecules in the subsequent step, functional groups can also affect the surface properties of nanomaterials such as stability and dispersity. This emphasizes the importance of optimizing surface chemistry to generate high-efficient detecting interfaces. Viswanathan et al 2012, developed an electrochemical immunosensor for multiplexed detection of Salmonella, E. coli O157:H7, and Campylobacter and from spiked milk samples. A mixture of and anti-salmonella, anti-E.coli O157:H7, anti-Campylobacter antibodies (ratio 1:1:1) was used to immobilize antibodies on carboxylic acid-functionalized multiwall carbon nanotube-polyallylamine (MWCNT-PAH). Here MWCNT were functionalized with carboxylic groups in order to inhibit formation of aggregates

and to obtain better dispersion. Polyallylamine then was functionalized MWCNT surface followed by antibody immobilization through the reaction with amine group existing on the polymer chain [106]. In another work, Santra et al 2004, functionalized NPs with the negatively charged organosilane compounds containing phosphonate groups (3-(trihydroxysilyl) propylmethyl phosphonate (THPMP) to raise the repulsive forces among the NP and enhancing colloidal stability of NP in buffer [107]. As another direction, polyethylene glycol (PEG) linkers could also be functionalized on the surface of nanomaterials to perform as hydrophilic spacer and reduce the nonspecific binding and attachment of non-desired biomolecules [108].

**Nanoparticles for detection of foodborne microbes**

Different types of Nanoparticles (NPs) including, silica, gold, silver, and magnetic NPs have been used for the direct bacteria detection and screening. Detection techniques that use NPs for the capture of foodborne pathogens are rapid, sensitive, and specific [109,110]. The binding affinity between the target pathogen and NPs in detection methods depends on the immobilization of the NPs with the specific recognition elements (discussed in section 3.1) that motivate bioconjugation with target microbes and improve the NPs adsorption to pathogens [111]. Gold nanoparticles (AuNPs) offer unique optical properties dependent on NPs' size, shape, particle environment, and synthesis method [112]. These include a color changing property under aggregation-induced interparticle surface plasmon resonance or electron oscillation with light. The assay has a visible color change from red to blue (violet) that can be seen by the naked eye. Target detection may depend on AuNPs aggregation or re-dispersion, which may affect the color [113,114]. Ali et al 2014, developed a sensitive colorimetric method by using antibody conjugated with gold nanoparticles for detection of E. coli O157:H7 in yellow corn samples. An obvious change in the color from red to blue in sample solutions will occur because of binding between E. coli O157:H7 and specific sites of its antibodies. The visible change confirms the presence of bacteria. This technique can be performed within a few minutes without the need for feed sample enrichment [115]. AuNPs have been applied in many foodborne pathogen detection purposes because of their ability for various functionalization, easy-synthesizing, and introducing surface plasmon band localization in visible spectra [116]. For instance, an AuNPs functionalized with complementary DNA and aptamer for rapid and sensitive E. coli detection in water and food samples based on fluorescence resonance energy transfer was introduced by Jin et al 2017 [117]. Recently, the Lateral Flow Test strip (LFT) has been developed to be connected with AuNPs for providing the signal reporter for samples deposited on the LFT. The analyte of interest flows along the test strip and interacts with molecules on the test strip [118]. LFT and AuNPs have been used for detection of foodborne microbes including Campylobacter as reviewed by Singh et al., (2015) [119]. Several biological compounds for Campylobacter were immobilized on AuNPs to increase the sensitivity for detection of C. jejuni such as antibodies and DNA based aptamers [120,121]. Because of their unique optical properties, high surface to volume ratio, easy surface modification, low density, and low toxicity, silica nanoparticles (SNPs) have been extensively applied for detection of S. aureus [122], S. typhimurium [123], Campylobacter [124], and E. coli O157:H7 [125] in food samples. SNPs have been combined with a dye or Magnetic Nanoparticles (MNPs) to increase the functional stability of particles [126]. In the work of Tansub et al 2012, a fluorescent dye was added inside SNPs to provide a specific signal for C. jejuni detection. This method can detect C. jejuni from poultry samples in 60 min based on antigen-antibody interaction under a fluorescence microscope [127]. Poonlapdecha et al., 2018 reported that SNPs were conjugated with monoclonal antibody for detection of C. jejuni in poultry from slaughterhouse in Thailand. The relative sensitivity, relative accuracy, and relative specificity, and were determined as 94.87%, 95.67%, and 100%, respectively. The proposed method was able to detect C. jejuni within 30-45 min and appropriate for efficient detection of poultry products [124]. SNPs provide several advantageous compared to other polymeric NPs. Solution treatment steps, including separation of SNPs by using centrifuge is easier since silica is denser than many polymers like polystyrene. SNPs are also resistant against the change in solution pH that normally results in swelling or change in porosity of NPs [94]. In addition, nanoparticles with Magnetic Properties (MNP) generally are able to concentrate the target cells in any solution with easier purification procedures and

without the need for enrichment processes. Biofunctionalized MNPs can capture the foodborne target pathogens with high specificity, improve the limit of detection, reduce the processing time, and eliminate interference from complex food matrixes for additional examination [75,128,129]. The review of Augustine et al (2016) [130] explains different aspects of using MNPs for monitoring and separation of foodborne pathogens. Bacteria isolation and enumeration by using MNPs occur by applying an external magnetic field after binding MNPs to the target bacteria following by performing various microbial techniques for quantification [111,131]. Poonlapdecha et al 2018, developed antibody conjugated MNPs for screening of C. jejuni in poultry samples. Amino-functionalized ferromagnetic nanoparticles (Amino-FMNs) were immobilized by a C. jejuni antibody. The C. jejuni detection limit of antibody-conjugated FMNs were then investigated. Here a standard plate count technique was applied to quantify the data and determine the limit of detection (102 CFU/ml) [76]. Yang et al 2007, proposed a technique that uses the combination of immunomagnetic nanoparticles (rabbit anti-L. monocytogenes as bioreceptor) and real-time PCR for simultaneous separation for the identification and quantification of L. monocytogenes in milk sample. The detection sensitivity was reported as 226 CFU/0.5 mL. They demonstrated the advantages of Immunomagnetic Separation (IMS) that allows the specific and sensitive isolation of L. monocytogenes from milk and the removal of inhibitors of the PCR amplification [132]. Regarding biorecognition of target pathogens, bioreceptors such as chemicals (dye), protein, nucleic acid, antibody, or aptamer may be conjugated on the MNP surface, or MNPs may be encapsulated with silica or another nanocomponents for forming a core and shell structure with SNPs, Quantom Dots (QDs) or AuNPs [133,134]. Biofunctional polymers like chitosan [44], Poly Methyl Methcrylate (PMMA) [27], and human serum albumin [43] can be used to cover MNPs as a core shell-like structure and improve the physico-chemical stability and water dispersity of particles in solution [135]. Chemical functional groups are functionalized on these polymers as well to provide a core/shell nanoparticle system with a wide range of bioconjugation activities. This combination system can exhibit several features and deliver more than one function simultaneously. Wei et al 2011, synthesized silver and iron oxide to generate Ag-Fe2O3 yolk–shell multifunctional magnetic nanoparticles following surface functionalization by conjugating dopamine (DA) and carbohydrates such as glucose and galactose. The E. coli ER2566 capture efficiency was reported as ≥ 99%. They also demonstrated that while NP is attached to the bacteria, the porous structure of iron oxide shells could allow silver nanoparticles to release from shells, interact with bacteria, destruct the bacterial cell walls, and membranes; leading to the death of bacteria [136]. The antibacterial activity of Ag-$Fe_2O_3$ yolk–shell nanoparticles in conjunction with their capture ability emphasizes the multifunctionality of these core/shell systems [137]. Besides the capability of silver nanoparticles (AgNPs) to be used in sensing and detecting applications [138,139], reports in the literature have also revealed their antimicrobial effectiveness [140,141]. This leads AgNPs to be considered as a promising alternative to alleviate the problem of multidrug resistance observed in bacterial strains and ultimately be replaced with antibiotics [142]. The aim of the work by Silvan et al. 2018 was to investigate the bactericidal properties of glutathione-functionalized silver nanoparticles (GSH-AgNPs) against Campylobacter strains demonstrating multidrug resistant and isolated from the chicken food. Very low concentration of GSH-AgNPs (9.85 µg/mL) could kill more than 60% of the tested Campylobacter strains [143]. In another work, Lok et al 2007, explained that oxidized AgNPs could deliver free Ag+ in solution that exert toxic to the cell membrane of E. coli K12 [144].

**Carbone nanotubes and nanowires for detection of foodborne microbes**

Carbon nanotubes (CNTs) have gained significant attention as one of the most novel and promising nanomaterials to be applied in biodiagnostics especially foodborne pathogen detection [106,145,146]. CNTs provide high length-to-diameter aspect ratios, easy chemical functionalization, established electrical transmission properties, and the capability of being directly integrated with other molecules [147]. Unlike other nanomaterials, CNTs have a large number of carbon atoms that reside on or near the nanotube surface, directly contacting the environment. This means nanotubes are able to offer maximum interactions with conjugated bioreceptors such as antibodies and proteins [148,149].

Bhardwaj et al 2017, developed a sensitive and low-cost electrochemical immunosensor for S. aureus detection by use of single wall carbon nanotubes (SWCNTs) covalently functionalized with Anti-S. aureus antibodies via a diimide-activated amidation technique. S. aureus screening in spiked milk occurred in 30 min with LOD of 13 CFU/mL. The enhanced bacteria sensing performance of the proposed SWCNT-based electrochemical immunosensor is attributed to several parameters including SWCNTs'size compatibility to antibodies due to small dimensions (diameter: 1–2 nm, length: 5–30 μm) and simple biofunctionalization resulting in high density of antibodies on the CNT surface [150]. Improved electrocatalytic functionality, minimum surface fouling, and capability of accumulating target analytes make CNTs as excellent candidates for electrochemical pathogen sensing [151]. Along with the ability of CNTs to be chemically functionalized and be used as carrier to incorporate biorecognition elements such as enzymes, antibodies, and aptamers, CNTs can also be associated with other nanomaterials. This further raises the amount of available attachment areas and enhances the detection sensitivity. In the work of Maurer et al 2012, CNTs were decorated with RNA-functionalized AuNPs. Sensor then was used to achieve highly sensitive capture of E. coli DH5a. When enhancing the surface area of CNT-NPs for additional analyte attachment sites, this resulted in the improvement of detection sensitivity for biosensor [152].

Nanowires are also considered potential functional probes for detecting and isolating bacterial cells due to their unique physico-chemical characteristics such as long-term stability, sensitivity, and nanoscale dimensions (100−300 nm) [153,154]. Compared to the CNTs, nanowires are associated with two basic advantages. The oxide layer present on the surface of nanowires can be covalently reacted with various chemical groups expanding the functionality and applicability. In addition, physical structure and chemical properties of nanowires can be more accurately engineered with precisely ordered arrays by manipulating synthesis conditions in a relatively simple fabrication process [155]. Researchers used the advantages of nanowires over the CNTs in their work. As one of the most recent studies, Thiha et al 2018 [156], used the advantages of nanowires over CNTs regarding the ability of fabricating nanowires into any desired shape and integrated them with large-scale manufacturing techniques. They presented a lab on chip microfluidic device integrated with suspended carbon nanowires for label-free detection of S. Typhimurium. This is a typical example where the application of CNTs are limited. Here an amide-ended Salmonella-specific aptamer was immobilized on the functionalized nanowire surface by a carbodiimide crosslinker. Integrating carbon microelectromechanical fabrication methods with photolithography resulted in generating suspended carbon nanowire sensors (Diameter: sub-100 nm) on the support structure. Minimum sample volume (5 μL) was introduced to the microfluidic device and nanowire-bacteria interaction was monitored by observing the change in nanowires conductivity. The detection sensitivity reported 10 CFU/mL which was found in 5 min [156]. Simple fabrication and chemical functionalization of nanowires make them a good candidate for capture applications, where the main target is to combine nanotopography and surface chemical modification in order to enhance local topographic cell-surface interactions and attract components of the bacterial surface. Li et al 2014, introduced a synergistic strategy for improved S. aureus capture and detection using a lectin-functionalized three-dimensional (3D) nanowire substrate [157]. The fabrication of 3D nanowire substrates possessing nanowire arrays (Diameter: 100-250 nm, length: 8 μm, nanowire density: 15 per μm2) was done by silver assisted chemical etching. Chemical functionalization was performed by using 3-aminopropyltriethocysilane (APTES) and Bis (N-succinimidyl) carbonate followed by immobilization of Concoanvaline A (ConA) bacteria binding lectin on the modified surface. They showed that after 30 min of assay time, the number of bacteria capture by ConA functionalized 3D SiNW (SiNW-ConA) substrate is ten times more in comparison with the flat silicon-ConA substrate. These surfaces offered higher capture with the estimated LOD of 10 CFU/mL. Work of Borgne et al 2017 also demonstrates that 3D SiNW substrate functionalized with lysozyme (known for its ability to hydrolysis of the bacterial cell wall) achieve higher efficiency in killing of bacteria. This further emphasizes the effect of surface chemical modification on the bacteria cells [154].

**Quantum dots for labelling and detection**

Research of Kloepfer et al 2003 on conjugated-CdSe quantum dots with Wheat Germ Agglutinin (WGA) and transferrin

proteins for the labelling of microbial pathogens was one of the first studies established the application of QDs in microbiology [158]. Application of fluorescent labelling and fluorophores such as Fluorescein Isothiocyanate (FITC) and tetramethylrhodamine (TRITC) is a common method to identify biological cells and to visualize their interaction with capturing bioreceptors. However, these techniques are still relying on physico-chemical features of traditional dyes [159], that are associated with some limitations such as rapid photobleaching, low signal to noise ratio, and low photostability [160]. Application of nanometre-scale QDs as colloidal semiconductor crystals dots for the fluorescence labelling and detection has got many attentions since they possess characteristics of bulk semiconductors and single atoms [161]. Compared to the traditional dyes, QDs offer broad absorption spectra and narrow emission band which enables multicolour optical labelling and simultaneous excitation and detection [162]. They demonstrate high fluorescence stability, size-dependent distinct emission, and greater photobleaching resistance [163]. Hahn et al 2005, used QDs (CdSe/ZnS core/shell structure) functionalized with streptavidin for detection of E. coli O157:H7. QDs showed higher photobleaching resistance for hours while FITC dyes bleached within seconds. QDs improved the detection sensitivity by 2 orders of magnitude in comparison with organic FITC fluorophore [159]. Providing an outer shell consisting ZnS atomic layers on QD surface could improve the quantum yield and enhanced photostability. Improvement in in surface chemistry techniques facilitates conjugation of biomolecules such as antibodies and aptamers onto QDs and use them as probe for foodborne microbial pathogen detection [164,165]. Use of coating chemical groups such as PEG or hydroxyl on QDs surface could also raise their resistance against non-specific binding [166]. In a recent study, Yang et al 2019, presented amino-functionalized graphene quantum dots (af-GQDs) conjugated with antibody to detect E. coli O157: H7 in low-fat milk. Functionalization of anti-E. coli O157:H7 with NHS ester crosslinker was done by using EDC/NHS solution as well. Conjugation of QDs with antibodies was also performed with amine-ester coupling. The authors showed that labelled E. coli O157:H7 with af-GQDs immunofluorescence probe can be clearly seen under the fluorescent microscope with high detection sensitivity of 100 CFU/mL. Here the operation process from probe synthesis to testing data was shown to be performed in less than 3 hrs and it was applicable for detecting E. coli O157: H7 in drinks and drugs [163]. Due to their characteristics in providing broad range of excitation/emission wavelength, QDs are able to be applied in multiplex simultaneous detection purposes [167]. Wang et al 2015, presented an extensive work on developing a novel technique for sensitive and simultaneous detection of the three most prevalent foodborne bacteria such as E. coli., S. Enteritidis, and S. aureus by using multicolor QDs probes with various emission wavelengths (604, 557, and 504 nm). They were then functionalized with anti-E coli, anti-Salmonella, and anti-S. aureus, respectively. The food samples were apple juice and milk, mineral and soda water, and viscous foods including tomato and chicken sauce. The author provided extensive data on the detection sensitivity of each QD regarding specific bacteria in food samples and ultimately concluded that this technique is suitable for simultaneous detection achieving high accuracy and sensitivity [165].

**Nano/Micro patterned interfaces for bacteria detection**

Generating surfaces with micro/nanoscale patterns of specific biomolecule receptors with high resolution has been possible since the improvement in both nano/microfabrication techniques. This can include photolithography, dip-pen nanolithography, microcontact printing, inject printing, and surface modification techniques. These patterned interfaces introduce selective attachment of foodborne pathogens (based on the specificity of the biomolecule) within designated regions in a substrate and high resistivity by the other areas of surface. This allows cell spatial control and the capability of placing bacteria in predetermined locations and arrays, separated by defined distances. High throughput screening of various types of bacteria and target analytes such as DNA and proteins in a very small area is also achievable. Preparation of surface patterned bacteria microarrays is done with two major approaches. In the first approach, bacteria are directly immobilized on the surface in a predefined pattern. Dip-pen nanolithography (DPN) [168] and μCP [169] have been used to deposit single bacteria on the substrates but DPN requires complex instrumentation and μCP is associated with the possibility of damaging bacteria in the stamping step. The second approach uses surface patterning techniques following

by chemical functionalization to provide surfaces including patterns of bioreceptor molecules or chemicals surrounded by passive or blocked areas. Bacteria then attaches to those specific patterns [170]. Dos Santos et al 2013, applied microcontact printing to covalently immobilized antibody patterns onto the gold electrodes functionalized with self-assembled monolayer of mercaptohexadecanoic acid (MHDA). A printing method was applied to generate anti-E. coli microarrays onto the COOH-functionalized gold substrate. PEG3-thiol was also used to minimize non-specific interactions in non-patterned areas. The height difference between PEG3-thiol regions and antibody spots was measured around 5nm. Gold electrodes were used in an Electrochemical Impedance Spectroscopy (EIS)-base sensor for detection of Escherichia coli O157:H7 with very high sensitivity (2 CFU/mL) [171]. In a similar work, authors used microcontact printing to pattern anti-Ecoli O157:H7 antibodies on Indium Tin Oxide (ITO) surfaces and reached a detection sensitivity of 1 CFU/mL with the ability for selective detection of E. coli in the mixture containing ratio of 500:1 S. typhimurium to E. coli O157:H7 [172]. The authors mentioned the excellent capability of patterned surfaces that provide dense antibody spots in a very small capture area. This feature allows the improved detection sensitivity with several orders of magnitude. Demers et al 2002, also generated covalently bonded nanoscale patterns of proteins and oligonucleotides on gold and silicon oxide by using direct-write Dip-Pen Nanolithography (DPN). Low-resolution DPN provided spot sizes of 200×200 μm2 consisting of 50000 proteins with diameter of ~250 nm, while high-resolution DPN provided 13000000 spots in the same area. This is a great ability of DPN to create the reactive patterns with specific chemical functionality and high density of biomolecules with excellent control over the feature size [173]. In addition to capture and detection, surfaces possessing well-controlled patterns of bacteria provide the potential in a wide variety of applications such as single cell analysis, study of bacteria behavior after altering the environment, disease diagnostics [6], microbial ecology [7] and environmental monitoring [8]. These demand high throughput and sensitive patterned interfaces. Arnfinnsdottir et al 2015, used μCP to generate pillars of adhesive polydopamine (PD) (3.5 μm diameter, 10 nm height) on glass surfaces that are pre-functionalized with the bacteria-resistant polymer Polyethylene Glycol (PEG). As a positively charged polymer, PD can bind to the negatively charged bacteria through electrostatic interactions. A solution of Pseudomonas putida KT2440 in LB was then incubated on the surfaces. Results showed 97-100% of spots were immobilized with one or more bacteria, whereas the fraction of spots occupied with single bacteria was 21.4-62.2%. Cell viability analysis of bacteria after attachment was reported as 99.1% [170].

## LECTINS-CARBOHYDRATES INTERACTIONS FOR BACTERIA DETECTION

Carbohydrates (oligosaccharides or polysaccharides, glycolipids, glycoproteins) are important elements present on almost all bacterial cell structures. One detection approach is to use biomolecules and ligands as the biomarkers with the capability of recognising and binding with specific carbohydrates presenting on the bacteria surface [80,82]. This marker-carbohydrate interaction can be used for specific detection and identification of target bacterial pathogens [171]. Lectin, as a group of carbohydrate binding proteins, specifically interact with carbohydrates in a reversible and noncovalent manner. Interaction can occur through van der Waals forces, hydrophobic interactions, hydrogen bindings, and metal coordination [174]. Detection approaches based on lectin-carbohydrates interactions have several advantages in comparison with antibody and nucleic acid methods. Lectins are less expensive and their agglutination with bacteria occurs quickly [175]. They show higher resistance in extreme conditions such as basic and acidic environments [176]. Their molecular size is smaller than antibodies, which allows them to be functionalized on the interfaces with higher densities per unit area leading to an increase of multivalent interactions with bacteria cell constituents. This achieves higher detection sensitivities in biosensing approaches. In terms of carbohydrate binding specificity and affinity, lectins are mainly classified in five categories including, N-acetylglucosamine galactose/N-acetylgalactos amine, mannose, sialic acid, and fucose [177,178]. Due to the high affinity, they are able to detect and recognize broad range foodborne bacterial pathogens. Wheat Germ Agglutinin (WGA), Concanavalin A (ConA), Lens Culinaris Agglutinin (LCA), Peanut Agglutinin (PNA), Maackia Amurensis (MAL), and Elex Europaeus Agglutinin (UEA) are the

most common lectins used in detection of foodborne pathogens. Mikaelyan et al 2017, used anisotropic silver nanoparticles (AgNPs) functionalized with LCA and WGA for quantitative detection of E. coli and S. aureus. Detection sensitivity was measured by translating the changes in optical spectrum obtained during the interaction of lectin-functionalized nanoparticles with E. coli and S. aureus. The sensitivities were reported as $10^3$ and $3\times10^3$ CFU/ml. The authors mentioned the thicker proteoglycan structure of S. aureus (Gram-positive) compared to E. coli (Negative-positive) as the reason for the lectin-proteoglycan interaction and increased detection sensitivity. The detection sensitivity data obtained from WGA-functionalized nanoparticles was one order of magnitude less than LCA-functionalized nanoparticles [179]. In addition to capture, lectins can also be applied to amplify the bacteria detection signal. In the work of Li et al 2015, WGA was used as a signal amplifier in an electrochemical impedance immunosensor designed for E. coli O157:H7 detection. Biotin-antibodies were immobilized on the microelectrode surface followed by using BSA to inhibit physical adsorption. Bacteria solutions were incubated on the surface of electrodes followed by use of WGA to amplify the signal. Impedance measurements were performed before and after WGA incubation. The impedance value determined for WGA-incubated detection improved compared to the detection based on just antibody. The results demonstrated the capability of using WGA for signal amplification as high number of lectin-binding locations present on the surface E. coli O157:H7 enhances impedance signals [180]. Concanavalin A (ConA) is one of the most famous mannose binding lectins that can interact with wide range of foodborne pathogens such as E. coli O157:H7, B. subtilis. In a very recent work, Kaushal et al 2019, used lectins to develop a novel platform for simultaneous photothermal ablation and detection of foodborne microbes. Gold nanorods (AuNRS) functionalized with ConA and PNA were applied for optical detection and photoablation of E. coli and P. aeruginosa in spiked RO water and coconut water. TEM images showed the aggregation of ConA-functionalized AuNRS around the surface of E. coli, while there was no aggregation around the P. aeruginosa surface. PNA-functionalized AuNRS demonstrated strong aggregation around the P. aeruginosa surface. These observations revealed the sugar specificity of lectins through the carbohydrate molecules existing in bacterial cell wall. Selective photothermal killing of bacteria was also performed by exposing NIR light (200 mW, 808 nm) to the bacteria attached to glycoconjugates coated gold nanorods. AuNRs were able to adsorb light and emit heat to their surroundings which lead the destruction of bacteria membranes [181]. Lectin-carbohydrate interactions can be applied to identify different isolates and strains of a specific bacteria. This is an advantage compared to antibody and nucleic acids-based detection systems that need prior knowledge regarding target bacteria. Dechtrirat et al 2014, reported the specific affinity of ConA lectin with E. coli DH5α while it does not bind to E. coli HB10 [182]. In the work of Safina et al 2008, series of lectins including Con A and LCA (specific to glucose and mannose), MAL (β-N-acetylglucosamine) , WGA (sialic acid), and UEA (specific fucose) have been studied to identify and differentiate seven strains of C. jejuni, 3 strains of Helicobacter pylor, and E. coli presence. This was done based on different carbohydrate constituents existing in their cell surface using a lectin-functionalized Quartz Crystal Microbalance (QCM) sensor. Con A was shown to be specific to wide range of the pathogens examined, especially strains of C. jejuni. UEA demonstrated limited specificity, only binding to one strain of H. pylori and C. jejuni. The detection sensitivity of C. jejuni strain HS:3 by Con A-functionalized sensor reported as $10^3$ CFU/mL in 30 min assay [182]. In a similar approach, Wang et al 2013, targeted the detection of E. coli O157:H7 and L. monocytogenes in cucumber and ground beef by using a SPR. SPR response demonstrated higher sensitivity of WGA and UEA compared to Con A for recognizing and detection of E. coli O157:H7 [183]. Although lectin-carbohydrate based detection techniques offer several advantages, there are still some limitations. Compared to antibody–antigen interaction, equilibrium dissociation constant (KD) for the binding of an individual lectin to a monosaccharide is usually higher by 2-3 orders of magnitude [21]. Functionalized interfaces with improved lectin density could overcome this limit by providing maximized multivalent lectin-carbohydrate interactions, leading to binding through enhanced avidity [184]. This is based on the theory introduced by Lee et al and is called “glycoside cluster effect” describing the advantageous of presenting multiple binding sites specific to the receptor to increase the avidity

[185,186]. Immobilization techniques should also be able to tune the spatial arrangement, orientation, and prevent denaturation of lectins which is critical for lectin-carbohydrate binding events [187,188,189]. Considering that, bio-functional polymers have attracted considerable attention as a template for lectin-based detection approaches because of their excellent ability to tune the physico-chemical properties of interfaces.

## BIOFUNCTIONAL POLYMER INTERFACES AS TEMPLATE SUPPORT FOR LECTINS

Synthetic polymeric materials are used as the perfect support template for lectin covalent immobilization. They can tune the physical and chemical properties of surfaces such as cross-link density and wetting behaviour. They are able to extend chemical functionality and reactivity of interface as well. Biofunctional polymers can manipulate the concentration of lectins on the surface during the post-functionalization while retaining their biological functionality. Covalent immobilization of lectin receptors occurs through the coupling of lectin with polymer reactive groups. Polymers containing active functional such as lysine, ethylene glycol, methacrylate, ethyleneimine, and azlactone have obtained broad potential applications in biotechnology, biodiagnostics, and biomedical fields [190,103]. Polymer brushes have been used to improve the orientation, accessibility, and loading of lectins, as demonstrated in the work of Pan et al 2013 [191]. Here surface initiated atom transfer radical polymerization (SI-ATRP) of a methacrylate functionalized polymer (2-methyl-acrylic acid 3-(2,4,5-trihydroxy-6- hydroxymethyl-tetrahydro-pyran-3-ylamino)-propyl ester) (GMA-G) on silica microparticle was applied to synthesize a core–shell structure "polymer-brush shell hybrid silica microparticles (PSHSM)". Sodium periodate oxidation converted vicinal diols of GMA-G to aldehyde followed by immobilizing ConA, WGA, and ricinuscommunis agglutinin (RCA120) lectins. A traditional approach for immobilization of a single layer of lectins on aldehyde functionalized microparticles was also performed and lectin loadings obtained from both approaches were evaluated. Compared to the single layer method, the use of polymer brushes increased the ConA, WGA, and RCA120 loading density on microparticles by the factor of 4.8, 4.2, and 4.8, respectively. According to authors, this was because polymer brushes could provide 3D structure support and huge number of binding locations for lectin immobilization. In another work, Woller and Cloninger 2001, used a thiourea linkage to functionalize sixth generation PAMAM dendrimer polymers with mannose and demonstrated an improvement in ConA binding compared to methyl mannose. It was shown that dendrimers can provide multiple reactive sites available for ConA functionalization [192]. Woller et al also revealed that the degree of ConA clustering and the strength of ConA binding interactions can be tuned by controlling; (1) the number of sugar (mannose) present on the surface of PAMAM dendrimer polymers, and (2) dendrimer polymer diameter [186]. Controlling the density of other types of biomolecules such as peptides and enzymes is also possible by using biofunctional polymers. The epoxy-based polymer supports can generate stable chemical bonds with amino, thiol, and phenolic groups of proteins and peptides in mild reaction environments. (e.g. natural pH) [193]. In the work of Bayramoglu et al 2003, film supports of poly (2-hydroxyethyl methacrylate-co-glycidyl methacrylate) (poly(HEMA–GMA)) synthesized by using different ratio of HEMA/GMA immobilized covalently with invertase using the strong epoxy-amine interaction. Results showed roughly 230% increase in immobilized enzyme density by increasing GMA density in polymer films from 0.58 to 2.33 mmol/gr. This clearly confirmed the capability of poly(HEMA–GMA) films to modulate the enzyme density since GMA density can be simply tuned to a desired value via manipulating the ratio of monomer to comonomer in polymerization step [193]. The role of GMA block as an anchor to provide covalent immobilization of proteins was shown by Liu et al 2009 as well. In their work, poly(GMA)-grafted PET (PGMA-PET) surfaces were used to immobilize high density of Immunoglobulin G (IgG) with protein detection sensitivity of 10 pg/mL. The reported LOD and detection dynamic range were better or comparable compared to other commercialized protein microarrays [194]. In addition to the capability of controlling protein density to prepare a template for bacteria detection and isolation approaches, synthesized biofunctional glycopolymers containing carbohydrate moieties can also be directly used as bacteria probe [195,196]. In the work of Wang et al 2014, Raft-based glycopolymers, Polymethacrylamide/acrylamide, 2-Melibionamidoethyl,

methacrylamide (PMA-MAEMA) possessing α-galactose residues, and Polymethacrylamide/acrylamide, 2-Allolactobionamido ethyl, and methacrylamide (PMA-ALAEMA) possessing β- galactose as the pendant sugar were employed to bind with P. aeruginosa and S. aureus. Same polymers without sugar moieties were also used as negative control. The results for glycopolymers containing corresponding pendant sugars showed a dramatic increase in number of attached bacteria to the polymers compared to controls (~10 times more for P. aeruginosa and ~ 8 times more for S. aureus) [70].

Among various classes of biofunctional polymers, use of azlactone-based polymers to generate reactive platforms for biological applications such as bacteria detection and capture has gotten attention [197,198]. Azlactones go through the byproduct-free ring opening nucleophilic reactions with broad range of nucleophiles such as amines, thiols, and alcohols to make strong covalent amide/amide, amide/thioester, and amide/ester crosslinks, respectively [199]. These reactive polymers can be functionalized with different chemicals to introduce new chemical functionality, surface interfacial characteristics, and to modulation of biomolecule density [200]. Azlactone-functionalized interfaces are considered as excellent platforms for post-fabrication immobilization with a variety of biomolecules such as lectins [201], proteins [202,104], peptides [203], and nucleotides through fast binding with amine or thiol groups [204]. Hansen et al. 2013, created 3D structures of WGA by using an azlactone-based block copolymer poly(glycidyl methacrylate)-block-poly(vinyl dimethyl azlactone) (PGMA-b-PVDMA) for capture of Pseudomonas fluorescens. The results revealed the capability of polymer to couple high density lectins, leading to a significant improvement in bacteria capture compared to surfaces containing physisorbed lectins [205]. When using PGMA-b-PVDMA, our group has been recently reported a systematic investigation on the experimental and interface parameters that affect the lectin-VDMA coupling reaction such as pH and polymer chain density and applied the findings to generate surfaces with highest lectin density. Optimized interfaces obtained by more simple procedure demonstrate higher hydraulic stability and a 41.9% increase in lectin density compared to EDC−NHS cross-linking protocol. We combined obtained surface chemistry knowledge with the nanoscale structure to the surfaces and detection sensitivity and capture efficiency of the E. coli K12 were then evaluated. Functionalizing VDMA polymers to the flat surfaces enhanced the detection sensitivity by one order of magnitude, whereas using nanostructured surfaces increased the detection sensitivity by a factor of two.206 One-step and hydrolytically stable reactions of azlactone-based polymers with other biomolecules have also been reported in the works of Kratochvil et al 2017 [207] and Cullen et al 2008 [208]. Interface properties of azlactone polymer films could be adjusted through post-fabrication with molecules that can promote or inhibit bacterial cells attachment. Buck et al 2009, functionalized glass surfaces with poly(ethylene imine) and poly(2-vinyl-4,4′-dimethylazlactone) (PEI/PVDMA) films followed by coupling with amine-functionalized small molecules such as decylamine and D-glucamine to tune the interface properties. P. aeruginosa solution was then incubated over the functionalized surfaces. The results demonstrated that D-glucamine-treated polymers inhibit P. aeruginosa cells adhesion and growth while decylamine-functionalized polymers promoted adhesion and growth [209]. Due to their versatile functionality, azlactone-containing polymers have been used in various environmental, biomedical, and biological approaches such as design of anti-fouling/anti-adhesive interfaces [210] and cell adhesion and growth in tissue engineering [203,211].

## CONCLUSION

The nanomartials were developed to apply for foodborne pathogen detection that had been reviewed. In addition, methods for bacterial isolation and detection that included conventional methods and alternative method were reported to compare to efficacy of each assay. A conventional method for bacterial detection is actually required biochemical confirmation, large sample volume, long incubation time, and significant technician labor. Currently, alternative methods have been selected to reduce the detection time and these assay can also increase limit of detection. Several nanomartials were developed as biosensor that could attach bacterial target via the biological reaction such as attaching with antigen- antibody and nucleotide. The synthesis and function of nanoparticles are related to the properties of materials. For example, light expression, magnetic capturing, and transmission for drug delivery was a functional activity of nanoparticles. The chemical modifications for connecting NPs and biological

molecules were applied to increase the usefulness of the NPs. These particles would be attached with several biomolecules for conjugation to bacterial target after chemical surface modification. In this review mentioned chemical reagents and cross-linked for surface modification as well.

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## CONFLICTS OF INTEREST

"The authors declare no conflict of interest."

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