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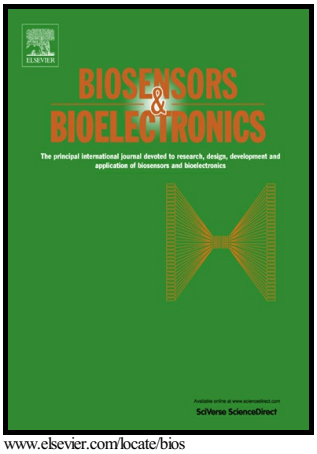

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Biosensors for rapid and sensitive detection of *Staphylococcus aureus* in food

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Abstract

Foodborne illness outbreaks caused by the consumption of food contaminated with harmful bacteria has drastically increased in the past decades. Therefore, detection of harmful bacteria in the food has become an important factor for the recognition and prevention of problems associated with food safety and public health. *Staphylococcus aureus* is one of the most commonly isolated foodborne pathogen and it is considered as a major cause of foodborne illnesses worldwide. A number of different methods have been developed for the detection and identification of *S. aureus* in food samples. However, some of these methods are laborious and time-consuming and are not suitable for on-site applications. Therefore, it is highly important to develop rapid and more approachable detection methods. In the last decade, biosensors have gained popularity as an attractive alternative method and now considered as one of most rapid and on-site applicable methods. An overview of the biosensor based methods used for the detection of *S. aureus* is presented herein. This review focuses on the state-of-the-art biosensor methods towards the detection and quantification of *S. aureus*, and discusses the most commonly used biosensor methods based on the transducing mode, such as electrochemical, optical, and mass-based biosensors.

Keywords: *Staphylococcus aureus*; Biosensor; Electrochemical; Optical; Mass-based

1. *Staphylococcus aureus*

A wide array of pathogenic bacteria usually found in the environment, food, water, and soil which may transmit foodborne illnesses to humans (Fleurot et al., 2014). Annually millions of people suffer from foodborne illnesses after consumption of food contaminated with 31 major identified pathogens (Scharff, 2012). There are an estimated 48 million cases of illnesses in the United States annually, resulting in 128,000 hospitalizations, and about 3000 deaths (Scallan et al., 2011; Rahman et al., 2012). Although the U.S Centers for Disease Control and Prevention report (2011), indicated that *Staphylococcus aureus* has dropped from the top of causal food agents to the fifth most common known pathogen caused foodborne illness, but still *S. aureus* is considered as one of the most significant threat to public health. Therefore, its detection is a key element to reduce the risks associated with public health and food safety. In this review, conventional and rapid detection methods are briefly described with special focus on biosensor based methods currently available for the detection of *S. aureus* and methicillin-resistant *S. aureus* (MRSA). The basic knowledge on the characteristics and bacterial functions of *S. aureus*, the emergence of antibiotic MRSA and current biosensor detection methods based on different transduction modes are also discussed.

S. aureus is a facultative, anaerobic, non-spore-forming, Gram-positive bacterium, ubiquitously found in the environment. *S. aureus* has a round shape with the size of about 1µm (Fig. 1). It was discovered by Dr. Alexander Ogston in 1880, but its origin is still not known (Alexander, 1984). The name *Staphylococcus* is originated from the two Greek words "*Staphyle*" and "*cocci*" that means "bunch of grapes" and the name "*aureus*" from Latin meaning "gold" because it grows in large yellow colonies (Koydemir et al., 2011). *S. aureus* is naturally present in human skin, mucous membrane, and nose flora (Argudín et al., 2012). It has been reported in literature that 30 to 50% of the general population is carrier of *S.*

aureus (Lowy, 1998). *S. aureus* is widely spread in the environment, capable to survive in hot and dry conditions and can flourish in saline environment too (Chaibenjawong et al., 2011; Shahbaz et al., 2016). As a potential pathogen, *S. aureus* causes foodborne infections ranging from mild infections of skin to post-operative wound infections (Zahoor and Bhatia, 2007). *S. aureus* is associated with several types of dermatitis and gastrointestinal tract infections and it is a leading cause of bacteremia and infective endocarditis. The symptoms of *S. aureus* infections may occur within 1-6 h post-consumption of contaminated food while duration of symptoms occurs within 24-48 h (Bohach and Foster, 2000).

S. aureus has the ability to produce a number of toxins both inside and outside of the cell and they cause damage to biological membranes by interacting directly with the host, leading to the cell death (Otto, 2014). These toxins include *Staphylococcal enterotoxins* (SEA, SEB, SEC, SED, SEE, SEG, SHE, and SEI), toxic shock syndrome toxin-1 (TSST-1) and leukocidin (Otto, 2014). Toxins are generally defined as infectious or poisonous object those are heat-resistant and survive even if bacteria are killed by heat treatment (Fleurot et al., 2014). They are also resistant to other environmental conditions like low pH, drying, and freezing (Hennekinne et al., 2012; Kadariya et al., 2014). Among these toxins, SEA is the most common toxin implicated with *Staphylococcal* outbreaks. Due to these characteristics and its toxins, *S. aureus* is considered as a significant threat in food industry.

Methicillin was introduced in 1959 to treat infections caused by penicillin-resistant *S. aureus*. In 1961, there were reports from the United Kingdom that *S. aureus* isolates had acquired resistance to methicillin (methicillin-resistant *S. aureus*, MRSA). Afterward, MRSA isolates were soon recovered from other European countries, and later from Japan, Australia, and the United States (Barber, 1961; Barrett et al., 1968). MRSA is a human pathogen and causes hospital-acquired and community-acquired infections (Ibelings and Bruining, 1998). During 1980's and 1990's, MRSA outbreaks caused repeated community-acquired infections

(Ayliffe, 1997; DeLeo et al., 2010; Johnson, 2011). It is difficult to efficiently treat the MRSA associated infections because they reflect the acquisition of resistance by the underlying pathogen to a wide range of commonly authorized antibiotics (Stevens, 2003; Broughan et al., 2011). MRSA has emerged in a wide range of animals from pets to food related animals and caused a number of infections in humans who are in direct contact with these animals (Van Loo et al., 2007; Leonard and Markey, 2008). MRSA clones have been isolated from meat, fish, milk and other dairy products around the world and considered as potentially harmful for consumers (Normanno et al., 2007; O'Brien et al., 2012; Parisi et al., 2016; Carfora et al., 2016). At present, MRSA is mainly associated with skin and soft tissue infections, and is less involved in lung infections (Zetola et al., 2005; Crago et al., 2012). MRSA deserves separate meditation in *S. aureus* pathogenesis due to its distinct epidemiology; specifically, morbidity and mortality (Liu, 2009).

2. Various methods for detection of *Staphylococcus aureus*

Conventional culture methods have been used for decades in detection of *S. aureus* (Wang et al., 2015). However, there are drawbacks of using conventional detection methods as they require 3-5 days to yield results. Consequently, rapid detection techniques have been developed in recent years, such as polymerase chain reaction (PCR) (Alarcon et al., 2006; Trnčíková et al., 2009), enzyme linked immunosensor assay (ELISA) (Bennett, 2005), and nucleic acid-based molecular biology methods (Carroll, 2008). These advanced microbiological detection methods reduce the detection time from days to several hours although still there are some limitations, for example, these methods cannot be utilized as on-site detection methods because they need to be operated by trained personnel, require extensive sample preparation, and may also cause significant errors due to bacterial contamination during long and tedious procedures. Additionally, in developing countries, the high cost and confined resources limits the application of most rapid detection techniques.

Therefore, the approachable rapid detection methods are of great importance for the detection of *S. aureus* and MRSA with low cost. An overview of recent efforts using biosensors for the detection of *S. aureus* is presented afterwards.

3. Biosensors for detection of *Staphylococcus aureus*

In the last few decades, valuable efforts have been successfully made by scientists for the development of viable biosensors to propose a new analytical platform. The initial development in the field of biosensors was purposed to meet the clinical diagnostic demands but afterward biosensors made its way in the food industry due to their high sensitivity and earlier detection of bacteria. Biosensors can be defined as analytical devices, that transforms the biological response by incorporating bio-recognition element (e.g., antibodies, enzyme, nucleic acids, aptamers, bacteriophage, organelle, microorganism etc.), and biological material (e.g., antibody, enzyme, nucleic acids, cell-receptors, tissue, organelle, microorganism etc.) with a physical transducer (optical, electrochemical, or mass-based) to generate a measurable signal. Fig. 2 illustrates the schematic mechanism of biosensor. The classification of biosensors is discussed further according to their transduction mode.

The concept of biosensor was proposed more than four decades ago and the latest biosensors concept were found closely related to the ideas of Leland C. Clarke Jr. and his coworker (Clark Jr and Lyons, 1962). First biosensor was discovered in 1962, by Clark and Lyon for glucose detection and work was further broadened in 1975 to bring out commercialization of biosensors (Kumar et al., 2012). Biosensors are increasingly considered as the next generation detection devices and are viewed as an essentially important tool in food safety applications for routine surveillance in food processing and its usage in food defense emergencies (Leonard et al., 2003; Deisingh and Thompson, 2004). The performance of biosensors can be categorized in terms of specificity, sensitivity, assay time, detection limit, robustness, reproducibility, validation, and accuracy in results (Table 1).

A biosensor mainly consists of two components; bio-recognition element and physical transducer. Variety of bio-recognition elements are available; however antibodies, enzymes, and nucleic acids are the three mainly used elements in biosensor applications. Bio-recognition elements play an important role and their immobilization is the key to specific biosensor technologies. The choice of an appropriate technique for immobilization of bio-recognition element is essential for fabrication of useful biosensors (Leca-Bouvier and Blum, 2010). These techniques include: adsorption, microencapsulation, entrapment on the sensor surface (Sharma et al., 2003; Gupta and Chaudhury, 2007), covalent attachment and cross-linking methods (Arya et al., 2008; Sassolas et al., 2012).

Transducers also play an important role for the specificity and signal detection process of a biosensor. Transducer is a device which transforms the bio-recognition signal into measurable signals. In the past decade, a variety of transduction methods have been developed for the detection of foodborne pathogens. Transducers are mainly classified into three basic groups based on their mode of signal transduction; electrochemical, optical, and mass-based biosensors. These basic groups are further divided into sub-groups. Fig. 3 illustrates the classification of biosensors.

3.1. Electrochemical biosensors

Among different types of biosensors, electrochemical-based detection methods are the most prominent type of biosensors due to its multiple progressions leading to their well-known bio-interaction and inexpensive detection process. Electrochemical-based detection methods primarily depend on the observation of current or potential changes happening at the sensor surface due to the bio-chemical interactions. These methods are further classified into amperometric, impedimetric, potentiometric and conductometric categories based on the observed parameters, such as current, impedance, potential, and conductance, respectively

(Lazcka et al., 2007; Setterington and Alocilja, 2012). Electrochemical biosensors were the first scientifically nominated as well as commercialized biosensors and have been studied for prolonged period. The use of electrochemical-based transducers built is the basis for the most successful commercially available biosensors developed to date (Palchetti and Mascini, 2008; Viswanathan et al., 2009; Kimmel et al., 2011). However, electrochemical biosensors have a disadvantage similar to other biosensors, which is immobilization of bio-recognition element without denaturation or random orientation (Jung et al. 2008). Therefore, most of the biosensors use self-assembled monolayer (SAM) modified gold electrode surfaces as they provide novel substrates and assist for immobilization of bio-recognition element via anchor groups (such as thiols, disulphides, amines, salines or acids) in terms of chemical stability and leads them to work efficiently (Chaki and Vijayamohanan 2002; Vericat et al. 2010). Continuous efforts are still being undertaken on reducing the non-specific absorptions that occur at the electrode surfaces. However, owing to the numbers of publications over recent years, electrochemical biosensors are one of the most promising techniques within the field of foodborne pathogen detection. A list of applications of different modes of electrochemical-based detection methods for *S. aureus* are given in Table 2.

3.1.1. Amperometric methods

Amperometric based methods are quite sensitive and perhaps could be the most frequent electrochemical detection methods for foodborne pathogens and have superior sensitivity than potentiometric methods. The working principle of amperometric transducers rely on the linear relationship between the current and the analyte (substrate) concentration. The potential of the working electrode set at a value where the analyte directly or indirectly produced the current, in mean while amperometric transducers determine the presence of target material by measuring the changes in current resulting from the biochemical reaction

which takes place on the electrode surface. Many researchers have reported the application of amperometric method for the detection of *S. aureus* (Table 2).

S. aureus numbers were quantified in semi-skimmed milk using an amperometric immunosensor detection method by mercaptopropionic acid (MPA) self-assembled monolayer (SAM) modified electrodes for the immobilization of anti-RbIgG (anti-rabbit immunoglobulin) labeled with horseradish peroxidase with a detection limit of 1.6×10^5 CFU/mL (Escamilla-Gómez et al., 2007). Escamilla-Gómez et al. (2008a) improvised an amperometric immunosenor using covalent immobilization for anti-RbIgG at SAM modified gold electrodes by 3, 3'-Dithiodipropionic acid di (N-succinimidyl ester) (DTSP). The use of DTSP-SAM modified gold electrodes, reduced the detection limit up to 3.7×10^2 CFU/mL. Escamilla-Gómez et al. (2008b) reported another amperometric immunosensor for the detection of *S. aureus* which was based on co-immobilization for RbIgG and tyrosinase to modify the MPA-SAM gold electrode. This immunosensor showed a detection limit of 1.7×10^5 CFU/mL and remarkably improved the detection limit in food by exposing *S. aureus* cells to wall lysis using heat treatment (in a boiling bath for 30 min) to obtain a detection limit of 2.3×10^3 CFU/mL.

A disposable amperometric magneto-immunosensor was developed for the specific detection and quantification of *S. aureus* in raw milk based on the use of functionalized magnetic beads and gold screen-printed electrodes (Au/SPEs). This method was able to detect a very low detection limit up-to 1 CFU/mL in raw milk with a short analysis time of 2 h. Moreover, this technique showed a good selectivity against the most commonly involved foodborne pathogens originating from milk (de Ávila et al., 2012). In another study, an amperometric method was investigated for the detection of *S. aureus* in different food samples including milk, cheese, and meat. The detection method was based on immobilization of antibody on the platinum electrode surface modified with

polyethylenimine polymer via cross linkage by glutaraldehyde. The developed methodology showed a low detection limit of 10 CFU/mL of *S. aureus* in all tested food samples (Majumdar et al., 2013). A major drawback of these electrochemical biosensors is the generation of false current values by different electro-active compounds leading to a potential interference. However, this drawback may be overcome by using a selective membrane able to control the compounds access to electrodes based on weight or charge (Arora et al., 2011).

3.1.2. Impedimetric methods

This is a powerful sensing technique that has been applied for the detection of foodborne pathogens in electrochemical systems for many years and experienced a wide spread use in recent years due to its sensitivity, low cost, low power, and simplicity of the measurements (Yang and Bashir, 2008; Wang et al., 2012). Impedimetric biosensors work on the basis of electrochemical impedance spectroscopy (EIS) which is the most commonly used technique and plays an important role in development of a biosensor. Many researchers studied the impedimetric methods for the detection of foodborne pathogens but only a few published work on the detection of *S. aureus* (Table 2). Tan et al. (2011) investigated a microfluidic impedance immunosensor for the detection of *S. aureus* using the self-assembled (3-glycidoxypropyl) tri-methyoxysilane saline modified nanoporous membrane for the immobilization of antibody and the impedance was recorded with electrochemical impedance spectrum. This developed methodology showed a detection limit of 10^2 CFU/mL with a short analysis time of 2 h and minimal cross-reactivity. An easy-to-use electrochemical impedance spectroscopy (EIS) based detection method was used to detect *S. aureus*. This strategy used the SAM of 3-mercaptopropionic acid modified gold electrodes and showed a detection limit of 10 CFU/mL with good specificity and reproducibility (Braiek et al., 2012). Recently, a highly sensitive impedometric immunosensor method based on immobilization of antibody on modified gold electrodes using SAM method was evaluated by impedance spectroscopy

and observing the change in impedance caused by interaction of antibody and *S. aureus*. This method showed a detection limit of 10 CFU/mL with the advantage of detection in food samples even in stress conditions (Bekir et al., 2015). EIS offers a label-free detection compared to other electrochemical biosensor techniques, therefore, its detection limit is still not low enough (Lazcka e al., 2007).

3.1.3. Potentiometric methods

Potentiometric methods are the least common methods among electrochemical-based detection methods for the foodborne pathogens. Potentiometric methods usually use a high impedance voltmeter to measure the potential difference carried by the changes in the ionic nature of the two used electrodes (working electrode and reference electrode) under conditions of zero current flow (Velusamy et al., 2010). The basic concept of this method for the detection of foodborne pathogens is based on pH changes or ion concentration of the well-known glass electrode in an electrolyte solution. Zelada-Guillén et al. (2012) developed a label-free detection method for *S. aureus* detection in pig skin using a combined aptamer and potentiometric biosensor in which aptamer showed excellent recognition ability towards *S. aureus* and carbon nanotubes acted as a transducer. The biosensor compared two strategies; a covalent, and a non-covalent bond formation for adsorption of aptamers onto the electrode surface via network of single-walled carbon nanotubes (SWCNTs). The results showed that the non-covalently functionalized biosensors had higher sensitivity with a detection limit of 8×10^2 CFU/mL. In another, Hernández et al. (2014) demonstrated that the detection of *S. aureus* using aptamer based grapheme modified electrodes showed a high selectivity, reproducibility, and offer the ultra-low detection limit (1 CFU/mL) in a very short response time.

It has been reported that the speed of response, high sensitivity, and simplicity of electrochemical biosensors make it a promising device for rapid field-based detection of

foodborne pathogens toward the protection of the food supply chain. Moreover, the inter-digital gold electrodes could be easily regenerated and reused at least 10 times, but there is an issue with their marketability for in-field applications (Lian et al., 2015). Further, electrochemical biosensors have several disadvantages like sensitivity and selectivity of gold electrodes, ability to work with turbid samples, possible miniaturization, and integration system. The research to date is promising and developments are continuously progressing to improve the surface chemistry in terms of electrode stability, sensitivity, specificity, and speed of response of electrochemical biosensors (Caygill et al. 2010).

3.2. Optical biosensors

Optical biosensors have been widely used for detection of *S. aureus* after electrochemical-based detection methods. Optical biosensors are getting a substantial attention due to their high sensitivity, specificity, and relatively rapid detection. In addition to this, advantages of using fiber optics and integrated optical transducers have been visualized for the analysis of biological detection. Optical based detection techniques are mainly divided into two categories; label-free and near real-time detection. Optical biosensors are further classified into subcategories of the surface plasmon resonance (SPR), colorimetric sensors, surface enhanced Raman spectroscopy (SERS), fluorescence, and chemiluminescence based on the parameters such as absorption, reflection, refraction, and dispersion.

3.2.1. Surface plasmon resonance methods (SPR)

Among optical based detection methods, SPR based methods are most commonly used for the detection of *S. aureus*. In 1983, SPR biosensor was introduced for bio-sensing for the first time (Liedberg et al., 1983). SPR is the oscillation phenomenon (resonant oscillation of conduction electrons) that occurs at the interface between positive and negative permittivity materials by incident light. The resonance intensity is dependent on the type as well as

dielectric function of metal and surrounding of the metal surface. The plasmon resonance changes when target analyte binds on the sensor surface which in result changes the refractive index of the metal surface (Cooper, 2003). SPR biosensors are able to measure these changes as a result of change in resonance angle which causes a shift in the wavelength of absorbed light. However, pathogen size can interfere in some measurements and limit of detection has been often too high which is unsatisfactory for food safety applications of SPR biosensors. SPR biosensors for the detection of *S. aureus* are summarized in Table 3.

Subramanian et al. (2006) developed a SPR method by employing mono- and di-thiol based SAM for immobilization of antibody on the sensor surface to detect *S. aureus* at a level of 10^5 CFU/mL along with good specificity and rapidity. Moreover, SPR biosensors has the advantage of commercial applications for the detection of foodborne pathogens (Byrne et al., 2009). BIAcore™ SPR series and Lytic-phage combined SPR are the most popularly commercialized biosensors (Hoa et al., 2007). Balasubramanian et al. (2007) used SPREERA™ sensor, using lytic-phage as a bio-recognition element for label-free detection of *S. aureus* at low concentrations. However, in general these SPR machines (BIAcore™ series, and Texas instrument SPREERA™) are quite expensive (Abdulhalim et al., 2007).

Several efforts have been undertaken to deploy fluorescent-tagged bacteriophages and phage-displayed peptides for the detection of foodborne pathogens. However, involvement of complex labeling and detecting procedures make these approaches time-consuming and complicated. The use of lytic-phage is highly specific and selective bio-recognition element for detection of *S. aureus* with a detection limit of 10^4 CFU/mL. It has been suggested that using lytic-phage combined SPR platform has the potential for rapid and label-free detection of different foodborne pathogens. Tawil et al. (2012) reported a SPR method by employing T4 bacteriophage (which had been used to detect *Escherichia coli*) as a bio-recognition element for the detection of MRSA. This method allowed label-free, real-time, specific and

rapid detection with a limit of 10^3 CFU/mL in a short analysis time of less than 20 min. Tawil et al. (2013) reported another SPR method by using penicillin binding protein 2a (PBP2a) at SAM modified gold electrodes for the detection and differentiation of MRSA. It has reduced the detection limit up to 10 CFU/mL in less than 20 min. It should be noted that SPR is the most commonly used method among optical biosensors and it has the advantage of label-free detection, multiplexing and quantification capability; however, SPR has some drawbacks such as low sensitivity (generally limit of detection, 1×10^3 CFU/mL) in terms of limitations to detect relatively large objects (whole microbial cell). In addition, SPR biosensors still require complex, large and expensive pieces of equipment for laboratory-based tests (Yoo and Lee, 2016).

3.2.2. Colorimetric based optical methods

Colorimetric based method is an attractive optical method because it can instantly detect the presence of pathogens in the sample through the color change. The response signals are visible to naked eye for quantification without the need of any analytical instrument to read out the results. Colorimetric based methods are further classified into two formats; flat substrate based and solution based formats. Flat substrate based formats usually use paper or glass as a substrate and lateral flow immunoassay (LFA) is a representative example of this format. Li et al. (2011) used a LFA based biosensor for the detection of *S. aureus* with immune disc which was used as substrate modified with gold nanoparticles and antibody immobilized on the nanoparticles. By taking the advantage of optical properties of gold nanoparticles, *S. aureus* can be detected by the color change in the region within 5 min of the sample application with a detection limit of 5.0×10^2 to 5.0×10^3 CFU/mL. It is likely that LFA based colorimetric methods give the advantage of fast processing time but have a major drawback of low sensitivity and gives semi-quantitative results (Pohlmann et al. 2014). Solution based formats use nanoparticles and have the advantage of simple and rapid analysis

of large volume of samples and usually use colloidal gold nanoparticles (Au NPs). Bio-recognition element immobilized on Au NPs react with the corresponding pathogen and the pathogen bio-recognition element interaction leads to a visible change in color from red to purple and this change can be detected via aggregation of Au NPs (Yoo and Lee, 2016). Sung et al. (2013) investigated efficiency of the solution based colorimetric biosensor using antibody/AuNP/MNP nanocomposite for detection of *S. aureus* in phosphate buffer saline (PBS) and milk. The capture efficiency of antibody/AuNP/MNPs increased significantly compared to antibody-coupled MNPs without AuNP. By taking the advantage of AuNP, a detection limit of 1.5×10^3 and 1.5×10^5 CFU/mL was obtained in PBS and milk, respectively with a short analysis time of 40 min. Another colorimetric method was reported for the selective and sensitive detection of *S. aureus*by modifying AuNPs with cysteamine (CS) bifunctional nanoprobe instead of magnetic nanobeads. This method showed higher functionality of CS-stabilized AuNPs with an improved detection limit (19 CFU/mL) and analysis time (30 min) (Liu et al., 2016a). Recently, a colorimetric method was reported using magnetic nanobeads and *S. aureus* peptide as a bio-recognition element (Suaifan et al., 2017). *S. aureus* peptides immobilized on the magnetic nanobeads and color changes when test sample (pure culture, and food sample) were dropped on the sensor surface. The color change was detected by the naked eye and analyzed using ImageJ software for the quantitative measurement without any amplification step. The detection limit was reported as low as 7 CFU/mL and 40 CFU/mL of *S. aureus* in pure culture and inoculated food samples (ground beef, turkey sausage, lettuce and milk) respectively. Some other colorimetric methods are also summarized in Table 3.

3.2.3. Fluorescence-based optical method

Fluorescence is a powerful and relatively easy to construct bio-sensing technique with great potential for application in food safety. Fluorescence is one of the most sensitive

techniques and widely used to detect a very low concentration of analyte. Fluorescence based detection methods often use combination of fluorescent bio-recognition element associated with an optical transducer. Many researchers have reported fluorescence based optical biosensors for the detection of *S. aureus* (Table 3). Zuo et al. (2013) developed a polydimethylsiloxance (PDMS)/paper/hybrid microfluidic system integrated with aptamer-functionalized graphene oxide for the multiplex detection of *S. aureus* in one step. The microfluidic systems were fabricated from two PDMS layers as top layer (reagent delivery microchannel and inlet reservoirs), middle layer (incubation micro-array) and a piece of circular chromatography paper which was placed inside each micro well and serves as a platform for immobilization of the aptamer functionalized graphene oxide. Presence of *S. aureus* in the sample releases the fluorescently labeled aptamer from graphene oxide, resulting in enhanced fluorescence intensity with a detection limit of 8×10^2 CFU/mL. The fluorescence-based optical biosensors require sample labeling with a fluorescent reagent which increases the time and cost of the procedure. He et al. (2104) demonstrated that a dual-color flow cytometric detection strategy employing a combination of bioconjugated fluorescent silica nanoparticles (FSiNPs) and SYBR Green I dye for the specific and sensitive detection of *S. aureus*. This strategy used aptamer-FSiNPs as a bio-recognition element and the nucleic acid intercalating SYBER Green I (dye used for the staining of nucleic acid) to monitor the decreased false-positives of dual flow cytometry. The detection limit was determined as low as 1.5×10^2 and 7.6×10^2 CFU/mL of *S. aureus* in buffer and milk samples, respectively.

Another biosensor method was developed using aptamer-fluorescent silica nanoparticles (Apts/FNPs) combined with positive dielectrophoresis (pDEP) driven on-line enrichment for the detection of *S. aureus* in spiked water sample through fluorescence microscopy imaging. Firstly, the target sample was incubated with $Apt_{S.\ aureus}$/FNPs and then directly injected into

the microfluidic channel for the pDEP on-line enrichment and fluorescence detection. After that, an AC voltage applied in pDEP frequency region to the electrodes in the presence of an electric field gradient, the $Apt_{S.\ aureus}$/FNPs labelled *S. aureus* moved towards the strongest electric field region and get enriched in the electrode gap due to pDEP force. The accumulated *S. aureus* was then detected by fluorescence microscope imaging system. The detection limit was determined as low as 9.3×10^1 and 2.7×10^2 CFU/mL of *S. aureus* in deionized water and spiked water samples, respectively (Shangguan et al., 2015).

3.2.4. Surface-enhanced Raman spectroscopy methods (SERS)

Surface-enhanced Raman spectroscopy (SERS) is the less commonly used method for the detection of foodborne pathogens and mainly developed for the detection of protein biomarkers. SERS is basically a combination of two techniques, Raman spectroscopy and nanotechnology. There are two sets of theories endorsed by the scientific community attributed to the SERS effect; electromagnetic and chemical theory, whilst, the exact mechanism is not clearly understood (Pang et al., 2016). Electromagnetic theory is the widely accepted one for the scattering enhancement of Raman signal (Schatz et al., 2006; Smolsky et al., 2017). According to the electromagnetic theory, SERS working principle is based on the plasmon-assisted scattering of molecules on the nanomaterial surface by the excitation of the localized surface plasmon resonance (LSPR) when an incident light strikes on the surface of target analyte which is near to the nanomaterial. Very few SERS biosensors have been reported for foodborne pathogens and especially for the detection of *S. aureus* (Table 3).

Zhang et al. (2015) developed a SERS-based biosensor combined with aptamer for the quantitative detection of *S. aureus*. Gold nanoparticles modified with Raman signal molecule and aptamers of *S. aureus* are immobilized on the gold electrode are utilized as the signal probe and modified gold electrode immobilized with aptamer used as a capture probe. This SERS-based biosensor showed that the detection limit of 35 CFU/mL with high sensitivity,

selectivity, and short analysis time of 3 h. Wang et al. (2015) applied the same strategy and used the silver magneto nanoparticles modified with DTNB-labeled inside-and-outside plasmonic NPs (DioPNPs) instead of gold with improved detection limit and a good linear relationship from 10^1 to 10^5 CFU/mL. Furthermore, this method offers the advantage of single-cell detection of *S. aureus*. Even though, SERS has been used in various biosensors for foodborne pathogens detection, it still has some limitations, such as, limited quantification capability and complex system. In addition, the currently available SERS biosensors require bulky instruments, such as optical microscopes, lasers, monochromators, and detectors (Yoo and Lee, 2016).

3.3. Mass-based biosensors

Mass-based detection offers direct label-free analysis with increased specificity and sensitivity. Transduction is based on sensing the small changes in mass on the sensor surface using resonance phenomenon (Turner et al., 2001). The resonance phenomenon can be measured by various parameters such as frequency, amplitude and phase (Ferrari et al., 1996). Mass-sensitive biosensors are cost-effective and relatively easy to operate. However, foodborne pathogen detection based on mass-based sensors is limited in contrast to electrochemical and optical-based biosensors. Mass-based sensors, on the basis of transducer type are further classified into piezoelectric (PZ) and magnetoelastic (ME) biosensors.

3.3.1. Piezoelectric methods (PZ)

In 1880, Pierre Curie discovered the piezoelectric effect which was introduced in the sensing applications in the 1950's (Karunakaran et al., 2015). The working principal is based on the use of PZ crystals that can be made to vibrate with an electrical signal at a specific frequency under the influence of an electrical field. The frequency of the vibration is dependent on the frequency of applied electrical frequency to the crystal as well as on the

mass of crystal. Therefore, when chemicals bind on the crystal surface, the crystal's mass increases (the thickness of crystal changes due to the antibody-antigen reaction) as well as the vibration frequency of the crystal changes which can be measured by electrical signals to calculate the additional mass of the crystal (Velusamy et al., 2010). Quartz is the main type of PZ biosensor commonly used. Quartz crystal microbalance are very attractive systems which are capable of sensitive detection of minute amounts of analytes according to a linear relationship between the deposited mass and its frequency response. The general idea is based on coating the surface of the PZ crystal with a selectively binding substance, for example, antibodies to bacteria, and then placing it in a solution containing bacteria. The bacteria will bind to the antibodies and the mass of the crystal will increase while the resonance frequency of oscillation will decrease proportionally. This sensing technology is not currently suitable for on-site applications, it is valuable for laboratory based methods. A limited number of researchers reported PZ based methods for detection of *S.* aureus (Table 4).

He et al. (2007) demonstrated that a PZ biosensor using interdigitated electrode and quartz crystals in series gave a good linear relationship in the range of 10^1-10^6 CFU/mL. The detection limit was determined as 10 CFU/mL. Recently, a further modification of the surface functionalization of the ME biosensor has been reported by Lian et al. (2015) which includes usage of graphene-modified interdigitated gold electrode. Aptamer immobilized on the graphene-modified gold electrode providing an efficient way to capture *S. aureus* to the surface of ME biosensor. The purposed biosensor showed a good linear relationship in the range of 4.1×10^1 to 4.1×10^5 CFU/mL due to the specific binding between *S. aureus* and aptamer. This leads to the substantial improvement in the detection limit with a value of 41 CFU/mL within 60 min.

3.3.2. Magnetoelastic methods (ME)

Recently, magnetoelastic (ME) sensor platforms are gaining high attention in chemical and biological sensing. ME sensors are constructed with amorphous ferromagnetic ribbons or wires which are analogous and complementary to PZ acoustic wave sensors (Grimes et al., 2002). ME sensors influenced by magnetic alternating current and, in turn, generate magnetic fluxes that can be detected with a sensing coil from a distance making these sensors highly attractive for wireless biosensing. These sensors have a high tensile strength and they are highly cost-effective which makes them appealing for biosensor platform. The fundamental operating principle of the ME sensors involves a change in sensor resonance frequency due to mass loading of the sensor. In biosensing, the change in mass is associated with the binding of a target analyte to a bioreceptor immobilized on the surface of the ribbon-like ME sensor. The ME sensor can be coated with various probe molecules in order to target analytes. The change in resonant frequency can be observed if an analyte binds to the magneto elastic sensor which can be measured rapidly and accurately.

Hiremath et al. (2015) developed a ME biosensor using a lytic-phage as a bio-recognition element for the detection of MRSA. The detection limit was obtained as 10^3 CFU/mL by taking the advantage of lytic-phage as a novel bio-recognition element. Another ME biosensor has been reported using lytic-phage for the detection of MRSA spiked on spinach (Byeon et al., 2015). When the incubation time and temperature were optimized, the performance of lytic-phage and detection of MRSA was improved. The developed methodology showed the detection limit of 1.76×10^2 CFU/mL. An aptamer immobilized ME sensor was reported for the detection of *S. aureus*. The developed biosensor showed the detection limit as low as 5 CFU/mL with good sensitivity and selectivity (Rahman et al., 2015).

5. Conclusion and future perspectives

Biosensors provide an astonishing alternative to the traditional and rapid microbial detection methods, allowing rapid on-site, real-time, and multiple analyses that are mandatory for the detection and identification of bacteria in food, especially in perishable or semi-perishable foods. Over the recent years, significant research work has been undertaken in the development of biosensors in the field of food industry and the time has come to bring this technology to the forefront and make it commercially accessible. An overview on recent advances in the development of biosensors for detection of *S. aureus* based on electrochemical, optical, and mass-based analyses was discussed. Biosensors have been emerged as practical devices for foodborne pathogen detection, especially, electrochemical biosensors which took the leading position and grow rapidly due to their advantages. Electrochemical biosensors are portable and can be used to detect bacteria in situ compared to optical and mass-based biosensors. Electrochemical-based detection methods are widely investigated for the detection of foodborne pathogens due to the highly elaborated theoretical background and exclusive properties in terms of rapid response and cost-effective instrumentation. Compared to optical and mass-based biosensor, electrochemical biosensors have shown the capability of miniaturization and potential for the fabrication of regeneratable biosensors. In addition, electrochemical biosensors are not affected by sample turbidity and exhibit excellent sensitivity and a large linear detection range with a low detection limit in a wide range of solvents, electrolytes, and temperature etc. Based on the reported detection limits, electrochemical detection methods were more sensitive (with detection limit of 1 CFU/mL) than optical and mass-based biosensors (with the detection limit of 8 and 5 CFU/mL, respectively). However, few of the optical and mass-based biosensors were also employed in biological samples because of a low concentration of target analyte and intricacy of biological environments which influences the detection process.

Thus, it is recommended that the formerly fabricated biosensor techniques which have been discussed in this review for detection of *S. aureus* can be used as an appealing choice for future development and on-site application. Though the field of biosensors has enormously expanded but development of biosensor is still an open field for improvement and much remains to be done, for example, functionality of biosensors depends on the sample conditions. In addition, non-interactions of the bio-recognition element with target analytes is a major problem which may cause the inaccurate results in the detection process. Therefore, selection of more specific bio-recognition elements is one of the aspects needs attention.

The fusion of biosensor technology with other disciplines such as nano-technology exhibited unique advantages for constructing biosensors with more cost-effective signal transduction, efficient support for bio-recognition elements, and the possibility of multiplex simultaneous detection of several foodborne pathogens. To become a commercial product, the reliability of the developed biosensors should be further studied. Over the long run, it is expected that further research in the development and advancements of modern biotechnology and biomolecular engineering, biosensors will have a promising and sparkling future for development of foodborne pathogen detection and surveillance system to control and prevent foodborne outbreaks.

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Figure Captions

Fig. 1. Scanning electron microscopic image of *Staphylococcus aureus.* From Centers for Disease Control and Prevention. Color image is online.

Fig. 2. Schematic diagram of biosensing principle of biosensor.

Fig. 3. Components and classification of biosensor.

SPR = Surface Plasmon Resonance; SERS = Surface Enhanced Raman Spectroscopy

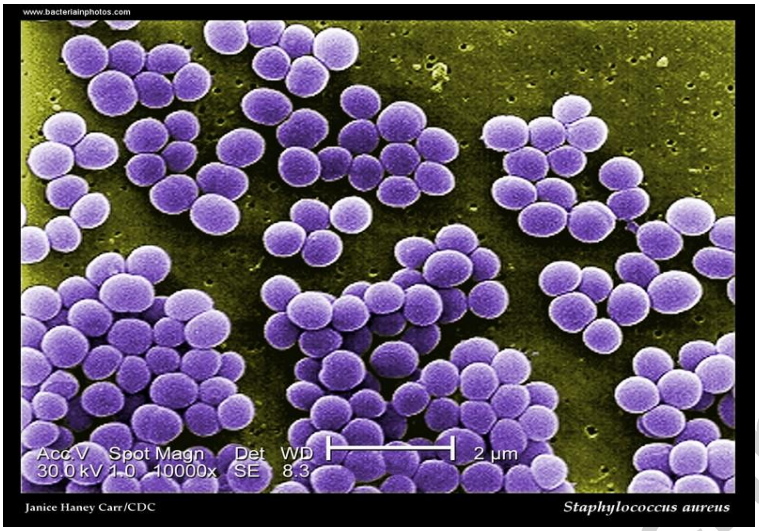

Fig. 1

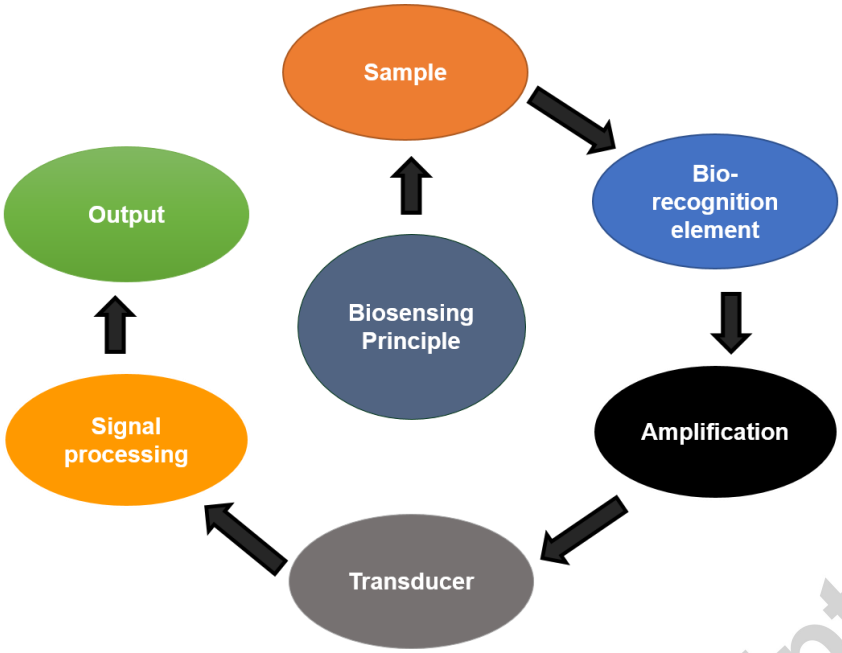

Fig. 2

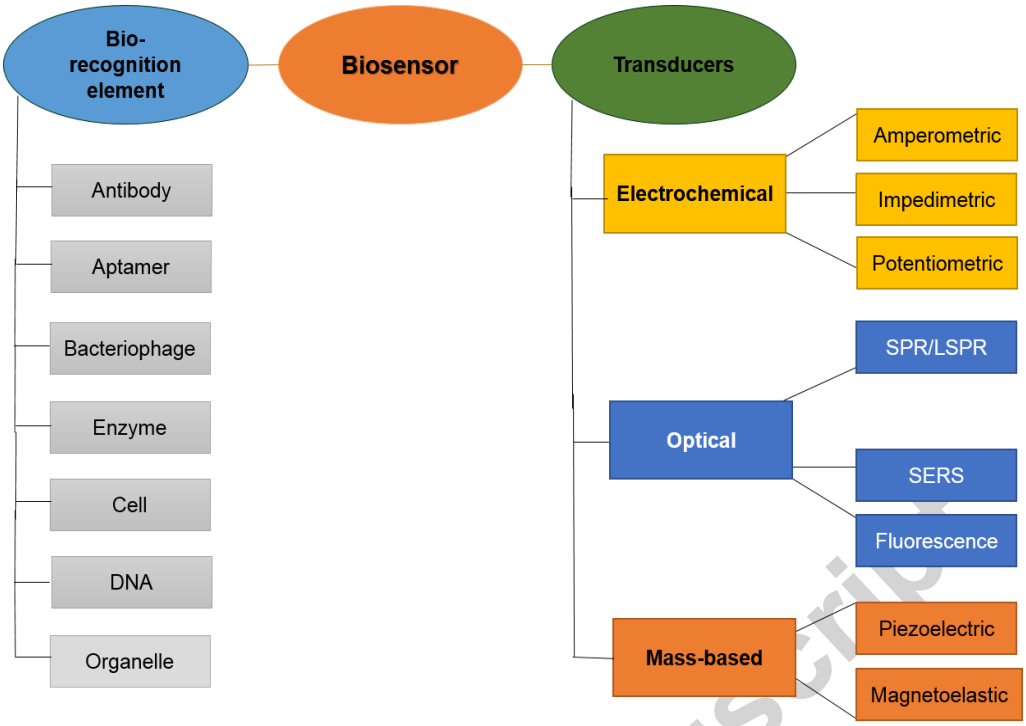

Fig. 3

Table 1. A summary of the biosensor requirements for detection of pathogenic microorganisms in food.

Attributes	Definition	Requirement
Accuracy	Degree of correctness	False-negative and false-positive results must be low or ideally zero and especially when pathogenic microorganisms are detected
Specificity	Selectivity	The biosensor should easily differentiate between the target analyte/organism and other organisms or toxins
Sensitivity	Response per mass/area, slope of calibration curve	Deficit or not able to detect false-negative results, lowers the sensitivity is not bearable in the biosensors
Assay time	Detection time	The biosensor should produce "real-time" response means a definite time period for the 95% of the response
User friendly	Ease of use	The assay should be fully automated and does not require operator skills for routine detection
Robust	Durability	The biosensor must be able to withstand the adverse conditions like changes in the surrounding environment like, pH, temperature and sterilization
Reproducibility	Series of observations	Each step should be easy to calibrate and reproducible over a period of time
Validation	International acceptance/ Sensor cost	The biosensor should fill full the current requirements of the standard obtained limit of detection

Table 2. Electrochemical biosensor techniques used for the detection of *Staphylococcus aureus*.

Transducer	Bio-recognition element	Sample	Detection limit (CFU/mL)	Linear range (CFU/mL)	Ref.
Amperometric	Antibody	Milk	3.7×10^2	1.3×10^3 - 7.6×10^4	Escamilla-Gómez et al. (2008a)
Amperometric	Antibody	Culture, milk, cheese and goat meat	10.00	10^1-10^8	Majumdar et al. (2013)
Amperometric	Antibody	Raw milk	1.00	-	de Ávila et al. (2012)
Amperometric	Antibody	Culture, milk	1.7×10^5	4.4×10^5- 1.8×10^7	Escamilla-Gómez et al. (2008b)
Amperometric	Antibody	Culture	1.6×10^5	2.2×10^5– 9.2×10^5	Escamilla-Gómez et al. (2007)
Impedimetric	Antibody	Culture	240	-	Tang et al. (2011)
Impedimetric	Antibody	Culture	10^2	10^2–10^7	Tan et al. (2011)
Impedimetric	Antibody	Culture	10.00	10–10^6	Braiek et al. (2012)
Impedimetric	Antibody	Culture	10.00	10^1–10^7	Bekir et al. (2015)
Impedimetric	Antibody	Culture	10.00	10–10^6	Jia et al. (2014)
Impedimetric	Peptide	-	10^2	-	Liu et al. (2016b)
Electrochemical	-	Culture	6.5×10^2	-	Morales et al. (2007)
Electrochemical	-	Culture	10^2	-	Chen et al. (2015)
Electrochemical	-	Culture	10.00	-	Yoo et al. (2016)
Electrochemical	Antibody	Culture	3.1×10^2	1.0×10^3 – 1.0×10^9	Yue et al. (2016)
Electrochemical	Aptamer	Culture	1	10^1–10^6	Abbaspour et al.

					(2015)
Electrochemical	Antibody	Culture	4.4	-	Wu and Chai (2017)
Electrochemical	Antibody	Milk	13	$10–10^7$	Bhardwaj et al. (2017)
Potentiometric	-	Pig	8×10^2	2.4×10^3–2.0×10^4	Zelada-Guillén et al. (2012)
Potentiometric	-	-	1.00	-	Hernández et al. (2014)

Table 3. Optical biosensor techniques used for the detection of *Staphylococcus aureus*.

Transducer	Bio-recognition Element	Sample	Detection limit (CFU/mL)	Linear range (CFU/mL)	Ref.
SPR	Antibody	Culture	10^5	$10–10^8$	Subramanian et al. (2006)
SPR	Antibody	Culture	10^6	$1.0 \times 10^6–1.0 \times 10^7$	Chen et al. (2007)
SPR	Bacteriophage 14	Culture	10^3	-	Tawil et al. (2012)
SPR	Antibody	Culture	1.0×10		Tawil et al. (2013)
SPR	Lytic phage	Culture	10^4	$10^3–10^6$	Balasubramanian et al. (2007)
SPR	Antibody	Culture	-	10^5-3.2×10^7	Tokel et al. (2015)
LSPR	Antibody	Culture	1.2×10^2	$10^3–10^5$	Verdoot et al. (2017)
SERS	Aptamer	Culture	35.00	$10^2–10^7$	Zhang et al. (2015)
SERS	Aptamer	Culture	10.00	$10^1–10^5$	Wang et al. (2015)
SERS	Antibody	Spinach solution	10^3	-	Wang et al. (2011b)
Fluorescence	Catalase	Culture	2×10^2	-	Abdelhamid and Wu (2017)
Fluorescence	-	Culture	10^2	$10^2–10^7$	Xue et al. (2009)
Fluorescence	Aptamer	Culture	8×10^2	-	Zuo et al. (2013)
Fluorescence	-	Milk	50.00	$10–10^5$	Miao et al. (2011)
Fluorescence	Aptamer	Buffer	1.5×10^2	-	He et al. (2014)
Fluorescence	Aptamer	Milk	7.6×10^2	-	He et al. (2014)
Fluorescence	Aptamer	Deionized water	93.00	-	Shangguan et al. (2015)
Fluorescence	Aptamer	Spiked water	270	-	Shangguan et al. (2015)

Fluorescence	Aptamer	-	8.00	10^1–10^5	Duan et al. (2012)
Fluorescence	Aptamer	Culture	25.00	50–10^6	Wu et al. (2014)
Fluorescence	Antibody	-	9×10^2	10^3–10^7	Wang et al. (2011a)
Optical	-	Culture	2×10^2	-	Chai et al. (2011)
Optical	-	Culture	10^3	10^3–10^6	Adak et al. (2013)
Colorimetric	Phage	Culture	19.00	1×10^3–1×10^6	Liu et al. (2016a)
Colorimetric	Antibody	Culture	5.0×10^2–5.0×10^3	-	Li et al. (2011)
Colorimetric	Aptamer	Milk	9.00	10–10^6	Yuan et al. (2014)
Colorimetric	Antibody	Milk	1.5×10^5	1.5×10^4–1.5×10^8	Sung et al. (2013)
Colorimetric	Antibody	PBS, Culture	1.5×10^3	1.5×10^4–1.5×10^8	Sung et al. (2013)
Colorimetric	-	Culture	7.00	-	Suaifan et al. (2017)
Colorimetric	-	Ground beef, turkey sausage, lettuce, milk	40.00	-	Suaifan et al. (2017)
Colorimetric	-	Water	10^2	-	Suaifan et al. (2017)
Colorimetric nano-bead based immune-biosensor	Antibody	Chicken	10.00	10–10^8	Alamer et al. (2017)

SPR = Surface Plasmon Resonance; SERS = Surface Enhanced Raman Spectroscopy

Table 4. Mass based biosensor techniques used for the detection of *Staphylococcus aureus.*

Transducer	Bio-recognition element	Sample	Detection limit (CFU/mL)	Linear range (CFU/mL)	Ref.
QCM-D	Antibody	Culture	10^5	10^5–10^8	Boujday et al. (2008)
QCM-D	Phage 12600	Culture	10^4	-	Guntupalli et al. (2012)
QCM-D	Phage 12600	Culture	-	-	Guntupalli et al. (2013)
Piezoelectric	*S. aureus*aptamer	Culture, Milk	41, 4.1×10^1, respectively	4.1×10^1 – 4.1×10^5	Lian et al. (2015)
Piezoelectric	-	Culture	10.00	10–10^6	He et al. (2007)
Magnetoelastic	Phage (12600)	Spinach	1.76×10^2	1.0×10^1– 1.0×10^8	Byeon et al. (2015)
Magnetoelastic	Lytic phage	Culture	10^3	1.0×10^1– 1.0×10^8	Hiremath et al. (2015)
Magnetoelastic		Culture	10^3	3×10^3– 2×10^7	Huang et al. (2010)
Magnetoelastic	-	Milk	10^4	10^4–10^7	Huang et al. (2010)

Magnetoelastic	Aptamer	Water	5	$10^1 – 10^{11}$	Rahman et al. (2015)
Magnetoelastic	-	Milk	-	10^3–10^7	Huang et al. (2008)
Magnetoelastic	Antibody	Culture	10^4	10^4–10^8	Menti et al. (2017)

QCM-D: Quartz Crystal Microbalance with Dissipation

Highlights

- Recent advances in development of biosensors for detection of *S. aureu*s are discussed
- An overview of biosensors based on transducing mode is presented
- Electrochemical, optical, and mass-based biosensors are mainly discussed