Chapter

Application of Noble Metals in the Advances in Animal Disease Diagnostics

Gabriel Alexis S.P. Tubalinal, Leonard Paulo G. Lucero, Jim Andreus V. Mangahas, Marvin A. Villanueva and Claro N. Mingala

Abstract

The advent of molecular biology and biotechnology has given ease and comfort for the screening and detection of different animal diseases caused by bacterial, viral, and fungal pathogens. Furthermore, detection of antibiotics and its residues has advanced in recent years. However, most of the process of animal disease diagnostics is still confined in the laboratory. The next step to conduct surveillance and prevent the spread of animal infectious diseases is to detect these diseases in the field. Through the discovery and continuous development in the field of nanobiotechnology, it was found that incorporation of noble metal nanoparticles to biotechnology tools such as the loop-mediated isothermal amplification (LAMP), lateral flow assays (LFAs) and dipsticks provided a promising start to conduct point-of-care diagnostics. Moreover, the modification and application of nanoparticle noble metals has increased the stability, effectiveness, sensitivity and overall efficacy of these diagnostic tools. Thus, recent advances in disease diagnostics used these noble metals such as gold, silver and platinum.

Keywords: Animal Diseases, Biotechnology, Nanotechnology, Noble Metals

1. Introduction

The fastest growing and expanding agricultural sectors worldwide are the livestock, poultry and aquaculture industries. These industries need to grow and expand fast to sustain the needs of the growing population. However, this massive growth is in constant threat of outbreak of different infectious and/or zoonotic diseases [1]. Furthermore, the globalization of animal trade can further contribute to the spread of diseases such as spread of *Trypanosoma evansi* from the tse tse belt of Africa toward the rest of the world [2]. Thus, unforeseen entry of disease in a country or area may lead to rapid undetected spread of disease with late diagnosis. To prevent or slow down spread of animal diseases, the World Organization for Animal Health (OIE)

prescribed the use of rapid, accurate and highly sensitive identification and detection of these different infectious agents [1].

The application of molecular tool such as Polymerase Chain Reaction (PCR) has become one of the most important routine diagnostic procedure in the laboratory [3]. Furthermore, the development of Loop-mediated isothermal amplification (LAMP) by Japanese researchers further advanced disease diagnostics with its simplicity and cost-effectiveness [4]. However, even with the new PCR or LAMP techniques developed to detect different animal diseases, still, most of animal diseases are not properly diagnosed. Thus, development of methods and techniques that are more sensitive, specific, cost-effective, and can be used under field conditions are of paramount importance.

Noble metals are metals that have outstanding resistance to corrosion and oxidation at elevated temperature. These metals have a long and rich history and was reported to be used as early as the First Egyptian Dynasty. Noble metals include the metals of groups VIIb, VIII and 1b of the second and third transition series of the periodic table such as rhodium (Rh), ruthenium (Ru), palladium (Pd), silver (Ag), osmium (Os), iridium (Ir), platinum (Pt) and gold (Au) [5]. These metals belong to a group of elements with wide variety of use and applications in fields of aerospace, electronics and most significantly, health [6].

Nanotechnology is an emerging science and is the study of matter with one or more dimensions in between 1 to 100 nm. The combination of nanoscience and biotechnology has created a new growing field of research in the form of nanobiotechnology with massive opportunities [5] to further improve healthcare, medical treatments, therapeutics and biomedical [7] uses such as radiotherapy enhancers [8–10], drug and gene delivery vehicles, and highly specific and sensitive diagnostic assays [11, 12].

Among all noble metals, gold (Au) and silver (Ag) are the most extensively studied due to the well-established synthesis routes, their relatively higher content in the earth's crust and better safety profile. Furthermore, gold and silver nanoparticles demonstrated the most fascinating properties for biosensing. Gold nanoparticles (AuNPs), commonly known as colloidal gold or gold colloids, are the most stable metal nanoparticle. AuNPs present distinctive characteristics like size-related optical, electronic and magnetic properties, individual particle behavior and specially, compatibility with biomolecules [10, 11]. These characteristics of AuNPs attracted researchers from the field of human and animal medicine to apply these properties in a point-of-care or field diagnosis of various infectious diseases. In 1996, it was originally reported the capability of nucleotide functionalized AuNP can detect DNA colorimetrically [11, 13]. Moreover, AuNPs had been used for the detection of pathogenic DNA, single nucleotide polymorphisms and sequence discrimination [11, 14]. Researchers used AuNP in the development of numerous disease detection or screening platforms or techniques. This made gold as the most used noble metal in the field of point-of-care or field diagnostics [15].

AuNPs remain the most studied noble metal for disease diagnostics due to its biocompatibility and chemical stability [10, 16–18]. However, silver nanoparticles (AgNPs) are reported to habitually result in better sensitivity compared to AuNPs [18, 19]. Furthermore, Ag has higher thermal and electrical conduciveness, and more efficient to transfer electron than gold with shaper extinction band and AgNPs are more stable in water and air. Thus, the use of Ag has also attracted researchers to be used in drug delivery, environmental, electronics, antimicrobial agents and in diagnostics. Furthermore, AgNPs have been prominent in the field of biosensor and imaging [15].

Aside from Au and Ag, platinum (Pt) is another noble metal that has been noteworthy scientific tool explored by researchers in the field of biotechnology, nanomedicine and pharmacology [20].

In this book chapter, the different routes of synthesis and application of noble metal nanoparticles were discussed in order to give an overview on the recent advances and/or point-of-care animal disease diagnostics using these noble metals.

2. Advances in animal disease diagnostics

2.1 Synthesis of Noble metal nanoparticles

Throughout the emergence of nanotechnology, there have been many techniques developed on how to synthesize nanoparticles which include physical, chemical, and biological approaches. Among the three, synthesis of nanoparticles from physical and chemical methods are considered the best methods for they can provide more uniform-sized nanoparticles with long-term stability. Biological approach on the other hand is also used to lessen the production of toxic by-products from physical and mostly from chemical approaches [21].

2.1.1 The Turkevich method

The most common method of synthesis of nanoparticles is probably through the Turkevich method used to make spherical gold and silver nanoparticles [22]. This method is a chemical approach which makes use of a single phase water-based reduction where gold or silver salt undergo reduction by citrate (sodium tri-citrate) at boiling temperature (100°C). The citrate ions, which serves as both reducing and non-aggregation agent, stabilize the nanoparticles by providing negatively charged ions which gets absorbed onto the surface of each particle (see **Figure 1**). Individual particles which are now stabilized and surrounded by negative charges will tend to repel each other causing a more stable nanoparticle dispersion and preventing them from aggregation [23].

Furthermore, the concentration of the citrate ions used in the solution determines the average size of the nanoparticles. Higher concentration of citrate ions (citrate to gold ratio) produces smaller nanoparticle size (average of 10 nm) due to higher stabilization and particle repulsion. On the other hand, reducing the concentration of sodium tri-citrate limits the number of citrate ions that will stabilize the particles. This causes aggregation and forms bigger particles (>15 nm) [24].

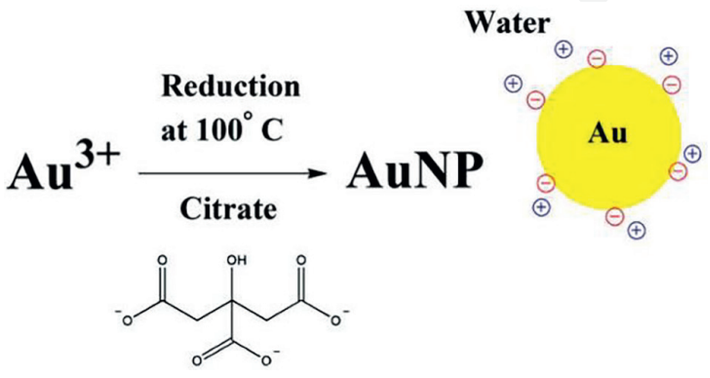

Figure 1.
Synthesis of AuNP using Turkevich method [23].

2.1.2 Physical methods of synthesizing nanoparticles

Several ways of producing nanoparticles using physical methods are already reported [25, 26]. Generally, some of these methods are using Plasma, Chemical Vapor Deposition, Microwave Irradiation, Pulsed Laser, Sonochemical Reduction and Gamma Radiation.

2.1.3 Green synthesis of nanoparticles

Green synthesis or biological synthesis are alternative pathways to produce nanoparticles in an eco-friendly way. This approach (in comparison with the physical and chemical methods) has lower energy consumption, lower cost, and less harmful to the environment. This pathway utilizes the use of microorganisms or plants (phytosynthesis) as source of reducing agents [26]. The main limitation of this approach is how to control the size and shape of the product. Different phyto-chemical compositions from organic sources have different influences on the particles' size and shape which can be attributed to purity of the extract used as reducing agents [27].

2.2 Characterization of synthesized gold nanoparticles

Synthesis of nanoparticles are verified mainly through their size and shape using Scanning Electron or Transmission Electron Microscopes (SEM/TEM). Additional characterization methods include spectroscopic analysis (UV–Vis Spectroscopy), dynamic light scattering (DLS), Zeta Potential, Inductively-coupled Plasma Mass Spectroscopy (ICP-MS), dark field microscopy, and more [28, 29]. Aside from their size and shapes, nanoparticles can have other unique properties based on their method of synthesis and precursor metals. These characteristics affect how they react with light due to surface plasmon resonance [30]. A good example on how to demonstrate the effect of size of nanoparticle on how they interact with light can be seen in **Figure 2** [31].

2.3 Advances in animal disease diagnostics using Noble metals

Serological (e.g. Enzyme-linked immunosorbent assay – ELISA) and molecular detection (e.g. PCR) of different animal pathogens has been one of the routine diagnostic techniques is most animal disease diagnostics. However, this requires well-trained laboratory technicians and expensive, sophisticated equipment [3]. Thus, the LAMP method developed by Japanese researchers that is claimed to be cost-effective without sacrificing sensitivity and specificity became a promising point-of-care molecular method [4]. However, this technique still has drawbacks such as less versatility compared to PCR, cannot be used in cloning purposes, limitation in multiplexing and difficulty in primer designing.

Colorimetric-based nanoparticle DNA detection is an eye-catching method due to its rapidity and cost-effectiveness compared to current generation of DNA detection or amplification. This method enables a direct or visual detection of amplified DNA even without expensive, sophisticated equipment. The incorporation of nanoparticles in platforms such as LAMP addresses the issue with regards to false positive results due to the addition of intercalating dyes as amplification indicators. Furthermore, hybridizations of nanoparticles with complementary DNA make this method more specific and overcoming the weaknesses of test format such as LAMP. Thus, LAMP and other

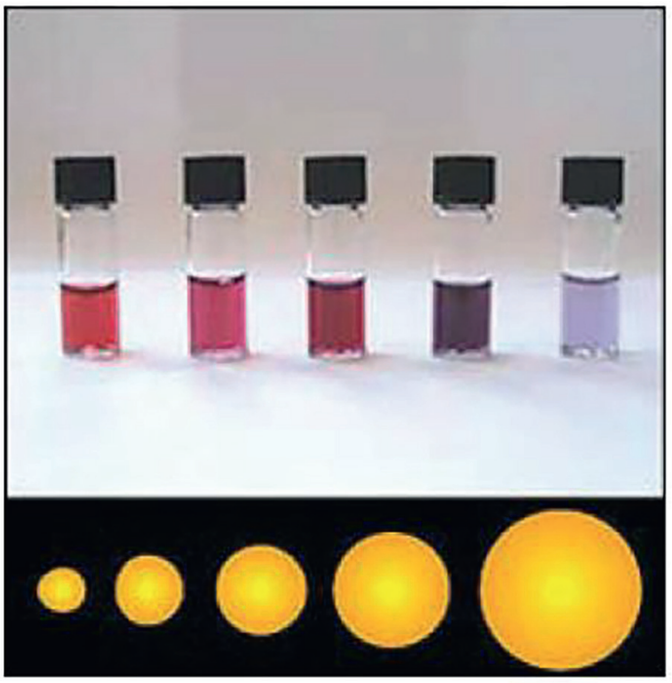

Figure 2.
Variations in color of gold nanoparticle suspension as particle size increases. Synthesized gold nanoparticles tend to have wine-red color (average size of 10–15 nm) and turns blue to purple as particles aggregate and get bigger.

point-of-care diagnostic tools coupled with nanoparticle has become a promising, sensitive, specific, cost-effective and rapid animal disease diagnosis techniques.

2.3.1 Point-of-care animal disease diagnosis using gold nanoparticles (AuNPs)

AuNPs are the most studied nanoparticle and has a fascinating property for biosensing. Furthermore, AuNPs can be synthesized to gold nanoprobes (AuPr) for detection of colorimetric detection of different animal diseases.

2.3.1.1 Bacterial diseases

Paratuberculosis or Johne's Disease, caused by *Mycobacterium avium subsp. paratuberculosis* (MAP), is a chronic gastro-enteric disease of ruminants marked with diarrhea and irreversible wasting leading to death [32, 33]. The problem with paratuberculosis is that it can exist in the herd for years and remain undetectable. However, recent reports reveal that an estimated 200–250 million USD is lost in US Cattle industry due to paratuberculosis [11]. Furthermore, sub-clinically infected cattle produce 15–16% less milk that amounts to 1300–1500 pound's loss in every lactation. In addition, there is no approved treatment for paratuberculosis and no effective vaccine available. Thus, screening and removal of the infected animal from the herd is the most effective way of controlling and preventing spread of paratuberculosis [33]. Ganareal *et al.* [11] developed a gold-nanoparticle based probe for the colorimetric detection of MAP DNA. The developed nano-probe was specific to detect MAP with a detection limit of 103 ng of MAP PCR product per reaction. Furthermore, UV–Vis and SEM showed dispersion and aggregation of the AuNPs for the positive and negative results with no observed particle growth.

2.3.1.2 Viral diseases

Foot-and-Mouth Disease (FMD) is one of the most devastating and highly contagious disease of cloven-hoofed animals (e.g. ruminants and swine) that may threaten food security [34]. The causative agent, Foot-and-Mouth Disease virus (FMDV) has multiple modes of transmission, fast replication rate and viral excretion that makes FMD one of the acute and highly contagious diseases of cloven-hoofed animals [34, 35]. Southeast and East Asian countries such as Cambodia, Laos, Thailand, Vietnam and China show varying FMD prevalence [34]. Eradication and control strategy for FMD is mainly controlled by vaccination. However, discrimination between naturally infected versus immunized animals against FMD is a must especially in the event of mass importation of cloven-hoofed animals. Furthermore, the rapidity of development of antibody against FMD and the differentiation of naturally infected vs. immunized animals are important in the disease control and prevention strategies. Conventionally, serological methods such as FMD structural proteins (SPs)-based virus neutralization test (VNT), liquid phase blocking enzyme-linked immunosorbent assay (LPB-ELISA) and solid-phase competition ELISA (SPCE) can evaluate the antibody level and non-structural proteins (NSPs)-based ELISA can discriminate naturally infected from immunized animals. However, with the advent and success of immunochromatographic strip (ICS) in the field due to its high specificity, sensitivity, rapidity, low cost and portability for field detection and high sample throughput, Yang *et al.* [34] developed an immunochromatographic gold nanoparticle strip that can differentiate FMD type O-naturally infected from immunized animals using serum. Both epitopes of FMDVs SPs (T1) and NSPs (T2) were dispensed in the nitrocellulose membranes to be the two test lines and as for control line a goat anti-pig antibody IgG was used. The result of their experiment shows 95.17% and 100% specificities for T1 and T2, respectively with the sensitivity comparable to the commercial ELISA kits. Furthermore, the coincidence rate of the develop AuNP strip is 95.5% and 93.13% for 3ABC monoclonal antibody (Mab)-ELISA and LPB-ELISA, respectively. Thus, the developed AuNP strip can provide a point-of-care differentiation test between naturally-infected and immunized FMD animals that is easy-to-use, economical, faster without sacrificing sensitivity and specificity of the test.

Nam *et al.* [36] developed a bio-barcode amplification (BCA) and used to measure respective protein and nucleic acid targets of different living organisms. In 2011, Ding *et al.* [35] developed an AuNP improved immuno-PCR for the detection of FMDV. The target particles were captured using a polyclonal antibody on a microplate followed by the addition of primers with AuNP and FMDV Mab 1D11 to form the sandwich complex. Then, immuno-complex will be formed and the signal DNA will be released by heating and then characterized by PCR and real time PCR. The developed FMDV BCA has a detection limit of 10 fg/ml purified FMDV particles and can detect clinical samples of FMDV with high sensitivity as compared to the traditional ELISA techniques with 100 ng/ml. Thus, FMDV AuNP BCA provided a detection test for FMDV with high sensitivity.

Bluetongue disease (BTD) is an arthropod-borne viral disease that affects ruminants worldwide. Bluetongue can cause massive socio-economic effects and is one of OIE listed diseases [36, 37]. Diagnosis of BTD includes viral isolation, serology and molecular diagnostics. In 2011, Yin *et al.* [37] developed a BCA BTD VP7 test. However, traditional BCA is time-consuming and complex. Thus, Yin *et al.* [38] improved their previous BCA BTD VP7 [36] test by incorporating gold nanoparticle probe to make the test easy and more sensitive to detect BTD VP7. Their platform

captures the protein VP7 using AuPr coated with the anti-VP7 polyclonal antibodies and single-stranded signal DNA. Then, magnetic microplate (MMP) probes coated with the anti-VP7 monoclonal antibodies were added to form the sandwich immuno-complex. Using PCR and real-time fluorescence PCR using Taqman probe, the single-stranded signal DNA in the immuno-complex can be detected. This technique has a detection limit of 10^{-2} fg/ml which is 8 orders of magnitude (100,000,000x) greater than conventional antigen capture ELISAs and 1 order (10x) than conventional BCA. The developed AuNP BCA test is a highly sensitive and an easier detection test for VP7 protein of bluetongue. Furthermore, this technique can be modified to measure the presence of other proteins.

Caprine arthritis encephalitis virus (CAEv) is one of the economically important diseases of goats that causes mostly polyarthritis in adults and progressive paresis (leukoencephalomyelitis) in kids. However, other clinical manifestations include interstitial pneumonia, mastitis and chronic wasting diseases that lead to eventual death of the animal. Detection of CAEv infection is mostly done through serological testing such as Agar Gel Immunodiffusion (AGID) and Enzyme-linked immunosorbent assay (ELISA) [39, 40]. However, application of polymerase chain reaction to detect CAEv became a routine assay due to its rapidity and ability to detect CAEv in early stage of the disease [41]. Furthermore, Huang *et al.* [42] and Balbin *et al.* [41] optimized loop-mediated isothermal amplification (LAMP) to detect CAEv. Moreover, Balbin *et al.* [43] developed a LAMP test coupled with AuPr that can provide a specific colorometric detection CAEv. The specificity of this test was evaluated by subjecting other economically important small ruminant pathogens such as *Leptospira* spp., Bovine Leukemia Virus (BLV), *Trypanosoma evansi*, *Babesia* spp., *Anaplasma marginale,* and *Theileria* spp. The AuPr was not able to hybridize with the DNA amplification products of these pathogens, thus the designed oligonucleotide in the AuPr is only CAEv-specific. Furthermore, the result of AuPr colorimetric detection corroborated with the result of SYBR green and gel electrophoresis result of CAEv LAMP amplification.

Acute hepatopancreatic necrosis disease (AHPND) is one viral disease that causes devastating economic effects due to 100% mortality that occurs at 35 days after stocking of shrimp post-larvae in ponds [44–46]. De Guia *et al.* [12] developed a AuPr-based detection *pir*A^{vp} toxin gene that causes AHPND without PCR amplification. The sensitivity of the developed test was as low as 20 fg/μl of extracted genomic DNA and positive samples had decreased absorbance value of 0.048 from 0.210 as compared to the negative controls with 0.137 absorbance value. Thus, most of the AuNPs aggregated due to the presence of *pir*A^{vp} toxin in the samples. Furthermore, the sensitivity of this technique was tested with AHPND uninfected shrimp samples and non-vibrio DNA extracts of *Staphylococcus haemolyticus* isolate 1, *Staphylococcus haemolyticus* isolate 2, *Plesiomonas shigelloides, Staphylococcus arlettae, Edwardshiella tarda, Bacillus cereus* and *Citrobacter freundii*. The specificity and sensitivity of the test was conducted in 5 replications to assure the reliability of the test results. The positive result of the test will reveal a colorimetric change from pink red to purple, while negative will retain the pink red color.

2.3.1.3 Fungal diseases

Epizootic ulcerative syndrome (EUS) also known as mycotic granulomatosis, red spot disease or ulcerative mycosis is an economically important disease of wild and cultured fresh-water and estuarine finfish species [45]. This disease is caused by a fungus, *Aphanomyces invadans*. The conventional detection method for the

disease includes culturing of causative agent, gross observation of clinical signs and symptoms and histopathology [45]. Molecular techniques such as PCR and fluorescent *in-situ* hybridization (FISH) have also been used for diagnosis of EUS [47, 48]. Furthermore, electrochemical DNA biosensors have been used to detect diseases for their relatively lower cost, higher sensitivity and specificity, portability, greater analyte discrimination, fast result and easy-to-use [49]. Thus, application of noble metal nanoparticle on these electrochemical DNA biosensors have been used to further improve disease diagnosis [47, 48]. Kuan *et al.* [49] developed an EUS electrochemical genosensors for the detection of *18S rRNA* and the internal transcribed spacer (IRS) of *A. invadans.* Kuan *et al.* research group described their platform as novel application for the detection of PCR product from real sample of *A. invadans* using a premix of sandwich hybridization assay. This assay was easier to use and more specific and sensitive compared to conventional techniques. The limit of detection of the EUS-genosensor was 0.5 fM (4.99 zmol) of linear DNA target and 1 fM (10 zmol) of PCR product. The developed EUS-genosensor will be highly suitable for surveillance and diagnostics of EUS in the aquaculture industry worldwide.

2.3.1.4 Parasitic diseases

Visceral Leishmaniasis, caused by *Leishmania infantum* that is transmitted by sandflies, is a fatal zoonotic diseases of domesticated dogs, wild canids and humans [50, 51]. Canine Leishmaniasis (CanL) can be diagnosed through the use of parasitological [52, 53], serological [50] and molecular testing approaches [54–58]. However, the limitations of using this test to diagnose CanL are reported to be the need to skilled workers/laboratory staff, expensive and the need to send samples to reference laboratories [50]. Furthermore, a lateral flow assay (LFA) test for the detection of CanL, however, the detection limit is the drawback as it cannot detect low level of CanL antibody in the blood [59–61]. Molecular tool, PCR, have proven effective as it is considered as the confirmatory and gold standard test. However, molecular diagnostic tool has its drawbacks like the need of expensive and sophisticated equipment for the precise and repeated heating required for amplification [50]. Thus, de la Escosura-Muñiz *et al.* [50] developed a point-of-care test kit for the detection of CanL using primers labeled by AuNPs and magnetic beads (MBs) using isothermally amplified DNA products. This test kit successfully discriminated CanL infected blood from healthy dog's blood. Further qualitative studies revealed that less than 1 *Leishamania* parasite can be detected per microliter of blood (8×10^{-3} parasites per isothermal amplification reaction). The result of study of de la Escosura-Muñiz *et al.* [50] provided a pioneering approach to advance diagnostic testing in animals using noble metals as it makes diagnostics faster, economical and easy-to-use.

2.3.1.5 Antibiotics and antibiotic residues

Antimicrobial resistance has emerged as one of the most essential problems in public health for the 21st century. This phenomenon is a threat to the effective disease prevention and treatment as increasing number of pathogens gain resistance to common medicines that used to treat them. In recent years, steady increase and intensification of animal production due to the increasing demand for animal protein has also lead to the increase in the use of antimicrobials as growth promoters in addition the specific use of antibiotics to treat specific diseases and to prevent the spread of particular diseases. This practice has been an essential contributor to the development

and spread of resistance. On the other side of the coin, the livestock industry cannot support the growing demand for animal protein to the growing population without this modern miracle – antibiotics.

Research groups around the world has developed aptamer nanoparticle-based detection of antibiotics and its derivatives. Point-of-care detection of antibiotics is important in One Health approach as tainted products with antibiotics and its derivatives can be intercepted before penetrating the market and table of consumers.

Oxytetracycline (OTC) is one of the most commonly used tetracyclines (TCs) in veterinary medicine. TCs are extensively used as growth promoters that can lead to bioaccumulation in livestock products and by-products. This bioaccumulation of antibiotics may lead to serious human health issues ranging from allergies to incurable disease such as aplastic anemia, however, still the greatest threat is antimicrobial resistance. Thus, point-of-care detection for antimicrobials and its derivative is important to prevent the development and spread of antimicrobial resistance. Kim *et al.* [62] developed a colorimetric aptasensor using gold nanoparticle for the detection of OTC. Using a highly specific ssDNA aptamer to bind to OTC that can discriminate to doxycycline (DOX) and tetracycline (TET), aggregation of AuNPs was specifically induced via desorption of OTC binding aptamers (OBAs) from the surface of AuNPs as a result of aptamer-target interaction, thus a colorimetric change from red to purple. Kim *et al.* [62] aptasensor can detect up to 25 nM of OTC which is 20-fold lower than the limit of USA-EPA regulations. Thus, this colorimetric aptasensor is advantageous over traditional methods with simple signal generation and detection with naked eye specially during on-site detection of antimicrobial agents.

Kanamycin is one the frequently used aminoglycoside antibiotics produced by *Streptomyces kanamyceticus* [63, 64]. The increasing use of kanamycin is a threat to human health due to is ototoxicity, nephrotoxicity and neurotoxicity due to its residue in animal-derived products [65, 66]. The European Commission has set the maximum residue limits (MRLs) or kanamycin in milk at 150 μg/kg [64, 67, 68]. Thus, a convenient, fast, economical, accurate and sensitive point-of-care detection test is vital to promote healthy and safe animal derived products [69, 70]. Ou *et al.* [64] developed an aptamer-based strip biosensor for visual detection of kanamycin. The strip design uses the easy separation of magnetic microspheres (MMS) with target-mediated chain displacement of ssDNA and capture of the visible DNA-functionalized AuNP probe. The presence of kanamycin will competitively bind to the aptamer and release the cDNA to the supernatant. The free cDNA concentration is directly proportional to the concentration of kanamycin. The capture of DNA functionalized AuNPs on the test zone is through cDNA-induced hybridization that provide visual detection signal or the presence of line in the test zone. The limit of detection of the aptamer test strip is 50 nM and 4.96 nM for visual detection limit by naked eye and quantitative determination, respectively. This lateral flow strip biosensor can detect presence of kanamycin in different food samples and has a potential in medicine and for everyday use. Furthermore, this is vital as kanamycin side effects from animal derived foods has become a serious public health issue on a global scale [68].

2.3.2 Point-of-care animal disease diagnosis using silver nanoparticles (AgNPs)

2.3.2.1 Antibiotics and antibiotic residues

Aminoglycosides (AMG) antibiotics are known for their broad-spectrum activities to gram-negative aerobic bacteria [71]. However, the discrepancy of administered

AMG and the presence in blood is an important concern [72]. Thus, emergence of AMG-resistant bacteria is a pressing concern due to its abuse in animal husbandry and agricultural practices [73–75]. One of the important AMG is Streptomycin, an effective antibiotic for gram-negative bacterial treatment and is used not only for human diseases but also for diseases of veterinary concern [76, 77]. The presence of streptomycin residues in animal-derived products is a threat to human health due to its nephrotoxicity, ototoxicity and allergic reactions [77, 78]. The European Commission has set a MRL for streptomycin of 500 and 200 μg kg^{-1} for meat and milk, respectively [77, 79]. Thus, development of sensitive and selective detection of streptomycin residues in animal derived products is vital to ensure food quality and safety and one health. Ghodake *et al.* [77] developed a silver nanoparticle (AgNP) probe for the colorimetric detection of picomolar-level sensitivity toward streptomycin in water, serum and milk samples. A color change of yellow to orange/red was observed in samples with streptomycin. A detection limit of 36 pmol L^{-1} was observed in the developed AgNP probe. The AgNP probe can successfully detect streptomycin residues in serum and milk and is a rapid and cost-effective detection of low molecular weight analytes. Thus, this method can provide practical application is the ultrasensitive detection of AMGs.

2.3.3 Point-of-care animal disease diagnosis using platinum nanoparticles (PtNPs)

2.3.3.1 Bacteria

Salmonella is one primary risk factor for bacterial food poisoning and can be transmitted via contaminated animal-derived foods like meats, eggs milk, etc. Millions of people are infected with *Salmonella* sometimes with severe and fatal results. Most highly developed countries have zero tolerance to *Salmonella* in foods, especially to ready to eat food. Thus, ultrasensitive detection is important. However, food testing is complex and usually low concentration of *Salmonella* is found in ready to eat foods [80]. The need for rapid, sensitive and cost-effective point of care *Salmonella* screening test is of great importance. Wang *et al.* [80] developed a *Salmonella* biosensor using a platinum nanoparticle loaded manganese dioxide nanoflowers (Pt@MnO_2 NFs) and thin-film pressure detector. The biosensor test starts by separating *Salmonella* from the sample using capture antibodies (CAbs) modified magnetic nanobeads (MNB) forming MNB-CAbs-*Salmonella* complex (magnetic bacteria). Then, detection antibodies (DAb) were used for labelling magnetic bacteria to form MNB-CAb-*Salmonella*-DAb-Pt@MnO_2 NFs complex (nanoflower bacteria). The nanoflower bacteria will be resuspended into H_2O_2 in a sealed centrifuge tube. H_2O_2 was catalyzed by $PtMnO_2$ to produce O_2 that results in increased pressure. This increased in pressure is monitored in real-time by piezoresistor-based pressured detector and transfer data to smartphone by Bluetooth for analysis and detection of *Salmonella* in the samples. The developed biosensor by Wang *et al* [80] can quantitatively detect *Salmonella* from 1.5 x 10^1 to 1.5 x 10^5 CFU/mL in 1.5 h with low detection limit of 13 CFU/mL.

2.3.3.2 Drug residues

β_2-adrenergic receptor agonists (β2-agonists) is a drug group which is usually used for the treatment of pulmonary diseases in animals [81, 82]. However, they can promote animal growth and increase feed efficiency by enhancing protein accretion and

reducing fat deposition producing "lean meats" [82–84]. The use of this drug group in veterinary medicine is illegal since prolonged consumption of residues in animal-derived products can cause headache, chest tightness, nausea, and more. One of this β2-agonists is ractopamine (RAC), however RAC is a derivative of clenbuterol which causes high blood pressure and heart disease in human. Thus, the use of RAC is illegal in Europe and China but RAC is still used around the world due to its effectiveness and low cost [82]. Thus, detection of RAC and its residue using simple and accurate method is important. Sun *et al* [82] developed a colorimetric immunosensor based PtNPs immobilized on Power Vision (PV) as signal probes and Fe_3O_4@β-cyclodextrin as capture probes for ractopamine detection in pork. PtNPs-PV double catalyzed the chromogenic substrate 3,3′-diaminobenzidine (DAB), which induced changes in DAB's color and chromogenic absorbance. Incubation temperature, pH, and incubation time were systematically optimized, and under optimum conditions, the measured absorbance values exhibited a linear relationship with the RAC concentrations in the range of 0.03 to 8.1 ng mL^{-1}. The detection limit was 0.01 ng mL^{-1}. The sensor exhibited high sensitivity and specificity, which was demonstrated by testing structurally similar organic compounds such as salbutamol (SAL), clenbuterol (CLE), and dopamine (DOA). The practicality of the developed colorimetric immunosensor was supported by the successful detection of RAC in pork samples with recovery ranging from 94.00% to 106.00%.

3. Conclusions

In conclusion, this review has provided the application of noble metals (gold, silver and platinum) in the advances in animal disease diagnostics. The versatility of these noble metals to be able to detect virtually all types of animal pathogens such as bacteria, virus, fungi, parasites to detecting drug and its residues is a promising foundation for point-of-care diagnostics/field diagnostics of animal diseases in the near future.

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Conflict of interest

The authors declare no conflict of interests.

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References

[1] Malik D, Yashpal S, Verma A, Naveen K, Deol P, Kumar D, Ghosh S, Dhama K. Biotechnological innovations in farm and pet animal disease diagnosis. Genomics and Biotechnological Advances in Veterinary, Poultry and Fisheries. 2020: 287-309. DOI: 10.1016/B978-0-12-816352-8.00013-8.

[2] Villanueva MA, Mingala CN, Tubalinal GAS, Gaban PBV, Nakajima C, Susuki Y. Emerging Infectious Diseases in Water Buffalo - An Economic and Public Health Concern. InTech. Janeza Trdine 9, 51000 Rjeka, Croatia, 2018.

[3] Valones MAA, Guimarães RL, Brandão RCL, De Souza PRE, De Albuquerque Tavares Carvalho P, Crovela S.Principles and applications of polymerase chain reaction in medical diagnostic fields: A review. Brazilian Journal of Microbiology. 2009: 40(1):1-11. DOI: 10.1590/S1517-83822009000100001.

[4] Notomi T, Okayama H, Masubuchi H, Yonekawa T, Watanabe K, Amino N. Loop-mediated isothermal amplification of DNA. Nucleic Acid Research. 2000: 28(12):e63

[5] Azharuddin M, Zhu GH, Das D, Ozgur O, Uzun L, Turner APF, Patra HK. A repertoire of biomedical applications of noble metal nanoparticles. Chemical Communications. 2019: 55(49):6964-6996. DOI: 10.1039/c9cc01741k.

[6] Begerow J, Neuendorf J, Turfeld M, Raab W, Dunemann L. Long-term urinary platinum, palladium, and gold excretion of patients after insertion of noble-metal dental alloys. Biomarkers. 1999: 4(1): 27-36. DOI: 10.1080/135475099230976.

[7] Sanvicens N, Marco MP. Multifunctional nanoparticles – properties and prospects for their use in human medicine. Trends in Microbiology. 2008: 26(8):425-433. DOI: 10.1016/j.tibtech.2008.04.005.

[8] Huang X, El-sayed IH, El-sayed MA. Gold nanoparticles : interesting optical properties and recent applications in cancer diagnostics and therapy. Nanomedicine. 2007: 2(5): 681-693.

[9] Hainfeld JF, Dilmanian FA, Slatkin DN, Smilowitz HM. Radiotherapy enhancement with gold nanoparticles. Journal of Pharmacy and Pharmacology. 2008:60: 977-985. DOI: 10.1211/jpp.60.8.0005.

[10] Hainfeld JF, Slatkin DN, Smilowitz HM. The use of gold nanoparticles to enhance radiotherapy. Physics in Medicine and Biology. 2004: 49:N309-N315. DOI: 10.1088/0031-9155/49/18/N03.

[11] Ganareal TACS, Balbin MM, Monserate JJ, Salazar JR, Mingala CN. Gold nanoparticle-based probes for the colorimetric detection of Mycobacterium avium subspecies paratuberculosis DNA. Biochemical and Biophysical Research Communications. 2018:496(3): 988-997. DOI: 10.1016/j.bbrc.2018.01.033.

[12] de Guia ACM, Fernando SID, Medina NP, Eugenio PJG, Pilare R, Velasco RR, Domingo CYJ, Monsarate JJ, Quiazon KMA. Gold nanoparticle-based detection of pirAvp toxin gene causing acute hepatopancreatic necrosis disease (AHPND). SN Applied Sciences. 2020:2(8):3-10. DOI: 10.1007/s42452-020-3073-9.

[13] Loiseau A, Asila V, Boitel-Aullen G, Lam M, Salmain M, Boujday S. Silver-based plasmonic nanoparticles for and their use in biosensing. Biosensors. 2019: 9(78). DOI: 10.3390/bios9020078.

[14] Anker JN, Hall WP, Lyandres O, Shah NC, Zhao J, Van Duyne RP. Biosensing with plasmonic nanosensors. Nature Materials, 2008: 7:308-319

[15] Mayer K, Hafner JH. Localized Surface Plasmon Resonance Sensors. Chemical Reviews 2011: 111: 3828-3857. DOI: 10.1021/cr100313v.

[16] Doria G, Baumgartner BG, Franco R, Baptista PV. Optimizing Au-nanoprobes for specific sequence discrimination. Colloids Surfaces B: Biointerfaces. 2010:77(1)1:22-124. DOI: 10.1016/j.colsurfb.2010.01.007.

[17] Mirkin CA, Letsinger RL, Mucic RC, Storhoff JJ. A DNA-based method for rationally assembling nanoparticles into macroscopic materials. Nature. 1996:382(6592):607-609. DOI: 10.1038/382607a0.

[18] Tan P, Li HS, Wang J, Gopinath SBC. Silver nanoparticle in biosensor and bioimaging: Clinical perspectives. Biotechnology and Applied Biochemistry. 2020:1-7. DOI: 10.1002/bab.2045.

[19] Boisselier E, Astruc D. Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity. Chemical Society Reviews. 2009: 38(6):1759-1782. DOI: 10.1039/b806051g.

[20] Dreaden EC, Alkilany AM, Huang X, Murphy CJ,El-Sayed MA. The golden age: Gold nanoparticles for biomedicine. Chemical Society Review. 2012:41(7): 2740-2779. DOI: 10.1039/c1cs15237h.

[21] Rycenga M, Cobley CM, Zeng J, Li W, Moran CH, Zhang Q, Quin D, Xia Y. Controlling the synthesis and assembly of silver nanostructures for plasmonic applications. Chemical Review. 2011:111(6):3669-3712. DOI: 10.1021/cr100275d.

[22] Jeyaraj M, Gurunathan S, Qasim M, Kang MH, Kim JH. A comprehensive review on the synthesis, characterization, and biomedical application of platinum nanoparticles. Nanomaterials. 2019:9(12):2019. DOI: 10.3390/nano9121719.

[23] Augustine R, Hasan A. Chapter 11 - Multimodal applications of phytonanoparticles. In: Thajuddin N, Mathew SBPT, editors. Micro and Nano Technologies. Elsevier; 2020. p. 195-219.

[24] Kimling J, Maier M, Okenve B, Kotaidis V, Ballot H, Plech A. Turkevich Method for Gold Nanoparticle Synthesis Revisited. The Journal of Physical Chemistry B. 2006:110(32):15700-15707. DOI: 10.1021/JP061667W.

[25] Nayfeh M. Fundamentals and Applications of Nano Silicon of Nano Silicon in Plasmonics and Fullerines. Micro and Nano Technologies, Elsevier;2018:p. 169-203.

[26] Cele T. Preparation of Nanoparticles. Janeza Trdine 9, 51000 Rjeka, Croatia: InTech; 2020. DOI:10.5772/intechopen.90771

[27] Pal G, Rai P, Pandey A. Chapter 1 - Green synthesis of nanoparticles: A greener approach for a cleaner future. Shukla AK, Iravani S, editors. Green Synthesis, Characterization and Applications of Nanoparticles. Elsevier; 2019, p. 1-26.

[28] Khan A, Rashid R, Murtaza G, Zahra A. Gold Nanoparticles: Synthesis and Applications in Drug Delivery. Tropical Journal of Pharmaceutical Research.2014: 13(7):1169-1177. DOI: 10.4314/tjpr.v13i7.23.

[29] Mourdikoudis S, Pallares RM, Thanh NTK. Characterization techniques for nanoparticles: Comparison and

complementarity upon studying nanoparticle properties. Nanoscale. 2018:10(27):12871-12934. DOI: 10.1039/c8nr02278j.

[30] Pereira RMS, Borges J, Smirnov DV, Vaz F, Vasilevskiy MI. Surface Plasmon Resonance in a Metallic Nanoparticle Embedded in a Semiconductor Matrix: Exciton–Plasmon Coupling. ACS Photonics. 2019:6(1):204-210. DOI: 10.1021/acsphotonics.8b01430.

[31] Imbraguglio D, Giovannozzi AM, Rossi AM. Nanometrology. Proceeding of the International School of Physics "Enrico Fermi,". 2013:185(2018):193-220. DOI: 10.3254/978-1-61499-326-1-193.

[32] Facciuolo A, Kelton DF, Mutharia LM. Novel secreted antigens of Mycobacterium paratuberculosis as serodiagnostic biomarkers for Johne's disease in cattle. Clinical and Vaccine Immunology. 2013:20(12):1783-1791. DOI: 10.1128/CVI.00380-13.

[33] Hermon-Taylor J. Mycobacterium avium subspecies paratuberculosis, Crohn's disease and the Doomsday scenario. Gut Pathology. 2009:1(1):15. DOI: 10.1186/1757-4749-1-15.

[34] Yang S, Sun Y, Yang J, Liu Y, Feng H Zhang G. A gold nanoparticle strip for simultaneously evaluating FMDV immunized antibody level and discriminating FMDV vaccinated animals from infected animals. RSC Advances. 2019:9(52):30164-30170. DOI: 10.1039/c9ra04810c.

[35] Ding YZ, Liu YS, Zhou JH, Chen HT, Wei G, Ma LN, Zhang J. A highly sensitive detection for foot-and-mouth disease virus by gold nanopariticle improved immuno-PCR Virology Journal. 2011:8(148):1-5. DOI: 10.1186/1743-422X-8-148.

[36] Nam JM, Thaxton CS,Mirkin CA. Nanoparticle-Based Bio-Bar Codes for the Ultrasensitive Detection of Proteins. Science. 2003:203(5641): 1884-1884.

[37] Yin HQ, Jia MX, Shi LJ, Yang S, Zhang LY, Zhang QM. Wang SQ, Li G, Zhang JG. Nanoparticle-based bio-barcode assay for the detection of bluetongue virus. Journal of Virological Methods. 2011:178(1-2):225-228. DOI: 10.1016/j.jviromet.2011.05.014.

[38] Yin HQ, Jia MX, Yang S, Jing PP, Wang R, Zhang JG. Development of a highly sensitive gold nanoparticle probe-based assay for bluetongue virus detection. Journal of Virological Methods. 2012:183(1): 45-48. DOI: 10.1016/j.jviromet.2012.03.027.

[39] Herrmann-Hoesing LM. Diagnostic assays used to control small ruminant lentiviruses. Journa; of Veterinary Diagnostic Investigation. 2010:22(6):843-855. DOI: 10.1177/104063871002200602.

[40] Brinkhof JMA, van Maanen C, Wigger R, Peterson K, Houwers DJ. Specific detection of small ruminant lentiviral nucleic acid sequences located in the proviral long terminal repeat and leader-gag regions using real-time polymerase chain reaction. Journal of Virological Methods. 2008:147(2):338-344. DOI: 10.1016/j.jviromet.2007.10.013.

[41] Balbin MM, Lertanantawong B, Suraruengchai W, Mingala CN. Colorimetric detection of caprine arthritis encephalitis virus (CAEV) through loop-mediated isothermal amplification (LAMP) with gold nanoprobes. Small Ruminant Research. 2017:147:48-55. DOI: 10.1016/j.smallrumres.2016.11.021.

[42] Huang J, Sun Y, Liu Y, Xiao H, Zhuang S. Development of a

loop-mediated isothermal amplification method for rapid detection of caprine arthritis-encephalitis virus proviral DNA. Archives of Virology. 2012:157(8):1463-1469. DOI: 10.1007/s00705-012-1322-y.

[43] Balbin MM, Belotindos LP, Abes NS, Mingala CN. Caprine arthritis encephalitis virus detection in blood by loop-mediated isothermal amplification (LAMP) assay targeting the proviral gag region. Diagnostic Microbiology and Infectious Disease. 2014:79(1):37-42. DOI: 10.1016/j.diagmicrobio.2013.12.012.

[44] SirikharinR, Taengchaiyaphum S, Sanguanrut P, Chi TD, Mavichak R, Proespraiwong P, Nuangseng B, Thitamadee S, Flegel TW, Sritunyalucksana K. Characterization and PCR detection of binary, pir-like toxins from vibrio parahaemolyticus isolates that cause acute hepatopancreatic necrosis disease (AHPND) in shrimp. PLoS One. 2015:10(5):1-16. DOI: 10.1371/journal.pone.0126987.

[45] Te Lee C, Chen IT, Yang YT, Ko TP, Huang YT, Huang JY, Huaag MF, Lin SJ, Chen CY, Lin SS, Lightner DV, Wang HC, Wang AHJ, Wang HC, Hor LI, Lo CF. The opportunistic marine pathogen Vibrio parahaemolyticus becomes virulent by acquiring a plasmid that expresses a deadly toxin. Proceedings of the National Academy of Sciences of the United States of America. 2015:112(39):E5445. DOI: 10.1073/pnas.1517100112.

[46] Boys CA, Rowland SJ, Gabor M, Gabor L, Marsh IB, Hum S, Callinan RB. Emergence of epizootic ulcerative syndrome in native fish of the murray-darling river system, Australia: Hosts, Distribution and Possible Vectors. PLoS One. 2012:7(4). DOI: 10.1371/journal.pone.0035568.

[47] Vandersea MW, Litaker RW, Yonnish B, Sosa E, Landsberg JH, Pullinger C, Moon-Butzin P, Green J, Morris JA, Kator H, Noga EJ, Tester PA. Molecular Assays for Detecting *Aphanomyces invadans* in Ulcerative Mycotic FIsh Lesions. Applied and Environmental Microbiology. 2006:72(2):1551-1557. DOI: 10.1128/AEM.72.2.1551.

[48] Phadee P, Kurata O, Hatai K, Hirono I, Aoki T. Detection and identification of fish-pathogenic Aphanomyces piscicida using Polymerase Chain Reaction (PCR) with species-specific primers. Journal of Aquatic Anial Health. 2004:16(4):220-230. DOI: 10.1577/H03-047.1.

[49] Kuan GC, Sheng LP, Rijiravanich P, Marimuthu K, Ravichandran M, Yin LS, Lertanantawong B, Surareungchai W. Gold-nanoparticle based electrochemical DNA sensor for the detection of fish pathogen Aphanomyces invadans. Talanta. 2013:117:312-317. DOI: 10.1016/j.talanta.2013.09.016.

[50] De La Escosura-Muñiz A, Baptisa-Pires L, Serrano L, Altet L, Francio O, Sanchez A, Merkoci A. Magnetic Bead/Gold Nanoparticle Double-Labeled Primers for Electrochemical Detection of Isothermal Amplified Leishmania DNA. Small. 2016:12(2):205-213. DOI: 10.1002/smll.201502350.

[51] Chappuis F, Sundar S, Hallu S, Ghalib H, Rijal S, Peeling RW, Alvar J, Boelaert M. Visceral leishmaniasis: What are the needs for diagnosis, treatment and control?. Naturet Reviews Microbiology. 2007:5(11):873-882. DOI: 10.1038/nrmicro1748.

[52] Solano-Gallego L, Fernandez-Bellon H, Morell P, Fondevila D, Alberola J, Ramis A, Ferrer L. Histological and immuno-histochemical study of clinically normal

skin of Leishmania infantum-infected dogs. Journal of Comparative Pathology. 2004:130(1):7-12. DOI: 10.1016/S0021-9975(03)00063-X.

[53] Xavier SC, De Andrade HM, Monte SJH, Chiarelli IM, Lima WG, Michalic MSM, Tafuri WL, Tafuri WL. Comparison of paraffin-embedded skin biopsies from different anatomical regions as sampling methods for detection of Leishmania infection in dogs using histological, immunohistochemical and PCR methods. BMC Veterinary Research. 2006:2:1-7. DOI: 10.1186/1746-6148-2-17.

[54] Reithinger R, Dujardin JC. Molecular diagnosis of leishmaniasis: Current status and future applications. Journal of Clinical Microbiology. 2007:45(1):21-25. DOI: 10.1128/JCM.02029-06.

[55] Srividya G, Kulshrestha A, Singh R, Salotra P. Diagnosis of visceral leishmaniasis: Developments over the last decade. Parasitology Research. 2012:110(3):1065-1078. DOI: 10.1007/s00436-011-2680-1.

[56] Lombardo G, Pennisi MG, Lupo T, Migliazzo A, Caprì A, Solano-Gallego L. Detection of Leishmania infantum DNA by real-time PCR in canine oral and conjunctival swabs and comparison with other diagnostic techniques. Veterinary Parasitology. 2012:184(1):10-17. DOI: 10.1016/j.vetpar.2011.08.010.

[57] Naranjo C, Fondevilla D, Altet L, Francino O, Rios J, Roura X, Peña T. Evaluation of the presence of Leishmania spp. by real-time PCR in the lacrimal glands of dogs with leishmaniosis. The Veterinary Journal. 2012:193(1):168-173. DOI: 10.1016/j.tvjl.2011.10.001.

[58] Van Der Meide W, Guerra J, Schoone G, Farenhorst M, Coelho L, Faber W, Peekel I, Schallig H. Comparison between quantitative nucleic acid sequence-based amplification, real-time reverse transcriptase PCR, and real-time PCR for quantification of Leishmania parasites. Journal Clinical Microbiology. 2008:46(1):73-78. DOI: 10.1128/JCM.01416-07.

[59] Chappuis F, Mueller Y, Nguimfack A, Rwakimari JB, Couffignal S, Boelaert M, Cavailler P, Loutan L, Piola P. Diagnostic accuracy of two rK39 antigen-based dipsticks and the formol gel test for rapid diagnosis of visceral leishmaniasis in northeastern Uganda. Journal Clinincal Microbiology. 2005:43(12):5973-5977. DOI: 10.1128/JCM.43.12.5973-5977.2005.

[60] Salotra P, Sreenivas G, Ramesh V, Sundar S. A simple and sensitive test for field diagnosis of post kala-azar dermal leishmaniasis. British Journal of Dermatology. 2001:145(4):630-632. DOI: 10.1046/j.1365-2133.2001.04434.x.

[61] Sundar S, Maurya R, Singh RK, Bharti K, Chakravarty J, Parekh A, Rai M, Kumar K, Murray HW. Rapid, noninvasive diagnosis of visceral leishmaniasis in India: Comparison of two immunochromatographic strip tests for detection of anti-K39 antibody. Journal Clinincal Microbiology. 2006:44(1):251-253. DOI: 10.1128/JCM.44.1.251-253.2006.

[62] Kim YS, Kim JH, Kim IA, Lee SJ, Jurng J, Gu MB. A novel colorimetric aptasensor using gold nanoparticle for a highly sensitive and specific detection of oxytetracycline. Biosensor and Bioelectronics. 2010:26(4):1644-1649. DOI: 10.1016/j.bios.2010.08.046.

[63] Chen J, Li Z, Ge J, Yang R, Zhang L, Qu LB, Wang HQ, Zhang L. An aptamer-based signal-on bio-assay for sensitive and selective detection of Kanamycin A by using gold nanoparticles. Talanta. 2015:139:226-232. DOI: 10.1016/j.talanta.2015.02.036.

[64] Ou Y, Jin X, Liu L, Tian Y, Zhou N. Visual detection of kanamycin with DNA-functionalized gold nanoparticles probe in aptamer-based strip biosensor. Analytical Biochemistry. 2019: 587:113432. DOI: 10.1016/j.ab.2019.113432.

[65] Robati TY, Arab A, Ramezani M, Langroodi FA, Abnous K, Taghdisi SM. Aptasensors for quantitative detection of kanamycin. Biosensors and Bioelectronics. 2016:82:162-172. DOI: 10.1016/j.bios.2016.04.011.

[66] Song HY, Kang TF, Li NN, Lu LP, Cheng SY. Highly sensitive voltammetric determination of kanamycin based on aptamer sensor for signal amplification. Analytical Methods. 2016:8(16):3366-3372. DOI: 10.1039/c6ay00152a.

[67] European Commission. COMMISSION REGULATION (EU) No 37/2010. Official Journal European Union. 2010: L 15/1:1-72.

[68] Xing YP, Liu C, Zhou XH, Shi HC. Label-free detection of kanamycin based on a G-quadruplex DNA aptamer-based fluorescent intercalator displacement assay. Sciemtific Reports. 2015:5:14-16. DOI: 10.1038/srep08125.

[69] Zhu Y, Chandra P, Song KM, Ban C, Shim YB. Label-free detection of kanamycin based on the aptamer-functionalized conducting polymer/gold nanocomposite. Biosensors and Bioelectronics. 2012:36(1):29-34 DOI: 10.1016/j.bios.2012.03.034.

[70] Wang H, Wang Y, Liu S, Yu J, Guo Y, Xu Y, Huang J. Signal-on electrochemical detection of antibiotics at zeptomole level based on target-aptamer binding triggered multiple recycling amplification. Biosensensors and Bioelectronics. 2016:80:471-476. DOI: 10.1016/j.bios.2016.02.014.

[71] He X, Han H, Liu L, SHi W, Lu X, Dong J, Yang W, Lu X. Self-Assembled Microgels for Sensitive and Low-Fouling Detection of Streptomycin in Complex Media. ACS Applied Materials and Interfaces. 2019:11(14):13676-13684. DOI:10.1021/acsami.9b00277.

[72] Mahmoudi L, Nikman R, Mousavir S, Ahmadi A, Honarmand H, Ziaie S, Mojtahedzadeb M.Optimal aminoglycoside therapy following the sepsis: How much is too much?. Iranian Journal of Pharmaceutical Research. 2013:12(2):261-269. DOI: 10.22037/ijpr.2013.1298.

[73] Schwake-Anduschus C, Langenkämper G. Chlortetracycline and related tetracyclines: detection in wheat and rye grain. Journal of the Science of Food and Agriculture. 2018:98(12): 4542-4549. DOI: 10.1002/jsfa.8982.

[74] Chander Y, Gupta SC, Kumar K, Goyal SM, Murray H. Antibiotic use and the prevalence of antibiotic resistant bacteria on turkey farms. Journal of the Science of Food and Agriculture. 2008:88:714-719.

[75] Ben Said L, Klibi N, Dziri R, Borgo F, Boudabous A, Slama KB, Torres C. Prevalence, antimicrobial resistance and genetic lineages of Enterococcus spp. from vegetable food, soil and irrigation water in farm environments in Tunisia. Journal of the Science of Food and Agriculture. 2016:96(5):1627-1633. DOI: 10.1002/jsfa.7264.

[76] Krause KM, Serio AW, Kane TR, Connolly LE.Aminoglycosides : An Overview. Cold Spring Harbor Perspective in Medicine. 2016 pp. 1-18, 2016: 6(a2729):1-18.

[77] Ghodake G, Shinde S, Saratale RG, Kadam A, Saratale GD, Syed A, Marraiki N, Elgorban AM, Kim DY. Silver

nanoparticle probe for colorimetric detection of aminoglycoside antibiotics: picomolar-level sensitivity toward streptomycin in water, serum, and milk samples. Journal of the Science of Food and Agriculture.2020:100(2):874-884. DOI: 10.1002/jsfa.10129.

[78] Ramatla T, Ngoma L, Adetunji M, Mwanza M. Evaluation of antibiotic residues in raw meat using different analytical methods. Antibiotics. 2017:6(4):1-17. DOI: 10.3390/antibiotics 6040034.

[79] Zhao J, Wu Y, Tao H, Chen H,Yang W, Qiu S. Colorimetric detection of streptomycin in milk based on peroxidase-mimicking catalytic activity of gold nanoparticles. RSC Advances. 2017:7(61):38471-38478. DOI: 10.1039/ c7ra06434a.

[80] Wang L, Hao L, Qi W, Huo X, Xue L, Liu Y, Zhang Q, Lin J.A sensitive Salmonella biosensor using platinum nanoparticle loaded manganese dioxide nanoflowers and thin-film pressure detector. Sensors and Actuators B: Chemical. 2020:321:128616. DOI: 10.1016/j.snb.2020.128616.

[81] Chen C, Meng L, Li M, Zhu Z. Simultaneous separation and sensitive detection of four β2-agonists in biological specimens by CE-UV using a field-enhanced sample injection method. Analytical Methods. 2015:7(1):175-180. DOI: 10.1039/c4ay02385d.

[82] Sun Y, Du T, Chen S, Wu Z, Guo Y, Pan D, Gan N. A novel colorimetric immunosensor based on platinum colloid nanoparticles immobilized on Power Vision as signal probes and Fe_3O_4@β-cyclodextrin as capture probes for ractopamine detection in pork,. Journal of the Science of Food and Agriculture. 2019:99(6):2818-2825. DOI:10.1002/ jsfa.9492.

[83] Schiavone A, Tarantola M, Perona G, Pagliasso S, Badino P, Odore R, Cuniberto B, Lussiana C. Effect of dietary clenbuterol and cimaterol on muscle composition, β-adrenergic and androgen receptor concentrations in broiler chickens. Journa of Animal Physiology and Animal Nutrition. 2004:88(3-4):94-100. DOI:10.1111/ j.1439-0396.2003.00464.x.

[84] Li Z, Wang Y, Kong W, Li C, Wang Z, Fu Z. Highly sensitive near-simultaneous assay of multiple 'lean meat agent' residues in swine urine using a disposable electrochemiluminescent immunosensors array. Biosensors and Bioelectronics. 2013:39(1):311-314. DOI: 10.1016/j.bios.2012.07.007.