



Review Article



Application of Nanobiosensors in Detection of Pathogenic Bacteria: An Update

Peyman Ghafouri¹ , Bahare Kasaei² , Sara Aghili³ , Atefehsadat Monirvaghefi⁴ , Ahmad Mir Hosseini⁵ , Hora Amoozegar⁶ , Golnaz Mirfendereski⁷ , and Hamidreza Razzaghi^{8,*}

¹ Faculty of Pharmacy, Islamic Azad University Medical Sciences Damghan, Damghan, Iran

² Faculty of Pharmacy, Islamic Azad University Medical Sciences, Tehran, Iran

³ Rajiv Gandhi University of Health Sciences, Karnataka, India

⁴ Center for Drug Delivery and Nanomedicine, Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, Nebraska, United States

⁵ Medical doctor, Mashhad University of Medical Sciences, Mashhad, Iran

⁶ Department of Research and Development, Biopharmaceutical Company of Persisgen Par, Tehran, Iran

⁷ Department of Pharmaceutical Biotechnology, School of Pharmacy, Guilan University of Medical Sciences, Rasht, Iran

⁸ Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran

* **Corresponding author:** Hamidreza Razzaghi, Faculty of Pharmacy, Isfahan university of medical sciences, Isfahan, Iran. Email: hrazaghi1375@gmail.com

ARTICLE INFO

Article History:

Received: 20/10/2023

Revised: 21/10/2023

Accepted: 26/11/2023

Published: 25/12/2023



Keywords:

Bacterial pathogens

Detection

Nanobiosensors

Nanotechnology

Sensitivity

ABSTRACT

Bacterial infections remain a critical public health concern worldwide, necessitating the development of efficient and sensitive diagnostic tools. Nanobiosensors, comprising nanomaterials, offer a novel approach to bacterial pathogen detection. The present review aimed to explore the current research and applications of nanobiosensors for bacterial pathogen detection. Recent discoveries in nanotechnology have facilitated the development of nanobiosensors with remarkable sensitivity and specificity. These nanoscale sensors are designed to detect specific bacterial pathogens through various mechanisms, including aptamers, antibodies, and molecular recognition elements. Furthermore, miniaturization and integration with microfluidic systems have enabled the rapid and point-of-care detection of bacterial infections. Incorporating nanomaterials such as carbon nanotubes, quantum dots, and graphene into biosensing platforms has significantly enhanced their performance, leading to ultrasensitive detection of bacterial antigens and nucleic acids. Additionally, using nanobiosensors with advanced analytical techniques, such as electrochemical, optical, and piezoelectric methods, has expanded the possibilities for accurate and real-time monitoring of bacterial pathogens. Nanobiosensors represent a promising frontier in the battle against bacterial infections. Their exceptional sensitivity, rapid response times, and potential for multiplexed detection make them invaluable tools for the early diagnosis and monitoring of bacterial pathogens. Developing cost-effective and portable nanobiosensors for resource-limited settings becomes increasingly possible as nanotechnology advances.

1. Introduction

As a result of antibiotic (AB) discovery, bacterial infections in humans, livestock, and agriculture were controlled^{1,2}. However, multi-resistant bacteria (MDR) have become a global public health issue over the past few years due to the mismanagement of AB. This issue has challenged the use of AB³. Over 70% of bacteria are resistant to known anti-bacterial agents, making it

necessary to develop new antimicrobial agents or use highly toxic antimicrobial therapies to achieve effective treatment, especially in critically ill individuals⁴. Recent studies estimate that without the development of new molecules, antimicrobial drug-resistant infections will cause the death of 10 million people in the world every year and cost about USD 100 trillion by 2050^{4,5}. The World

► *Cite this paper as:* Ghafouri P, Kasaei B, Aghili S, Monirvaghefi AS, Mir Hosseini A, Amoozegar H, Mirfendereski G, Razzaghi H. Application of Nanobiosensors in Detection of Pathogenic Bacteria: An Update. Research in Biotechnology and Environmental Science. 2023; 2(4): 65-74. DOI: 10.58803/rbes.v2i4.22



The Author(s). Published by Rovedar. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Health Organization (WHO) has established measures to prevent the spread of MDR infections, including controls on AB sales, dosage, and administration^{6,7}. Most doses are currently uniformly administered to patients without considering infection progression or clinical characteristics, resulting in treatment failures, which may lead to subtherapeutic or toxic doses^{8,9}.

The use of therapeutic drug monitoring (TDM) is one of the solutions that measure drug toxicity by tracking changes in pharmacokinetic parameters (PK) of drugs that have narrow therapeutic index (TI)¹⁰. There are a variety of methods for monitoring, including single or mass-coupled chromatography with various detectors, such as ultraviolet detection, fluorescent detection (explained below), and immunoassays^{11,12}. The United States Food and Drug Administration (FDA) has approved several techniques¹³. Despite this, these expensive techniques require trained personnel and specialized laboratories. Nanobiotechnology can be used to overcome this problem, specifically biosensors that can measure drug concentration in body fluids (including blood, urine serum, and plasma)¹⁴. In addition to being sensitive, specific, and low-cost, these devices can also be miniaturized so that doctors and care providers can easily carry them to patients' bedsides^{15,16}.

Nanotechnology has received widespread interest in bioanalytical chemistry due to its prominent application¹⁷. A more efficient chemistry reduces reagent consumption and overall costs from an economic perspective¹⁸. Nanomaterials can enhance the performance of various bioassays, and improvements in micro- and nanofabrication techniques may facilitate the development of miniaturized devices that can be used in the field^{19,20}. Biosensors have several advantages, including low sample volume, reduced reagent consumption, minimal invasive sample collection methods, multiple analyte detection, and short analysis times²¹. In addition to these features, they provide real-time decision-making for individualized therapy²². Using nanobiosensors, health, and economic sectors benefit from shortened hospital stays, lower treatment costs, and reduced MDR strain infections that cost health systems millions of dollars annually^{23,24}. Consequently, biosensor monitoring offers many advantages, and these devices may one day become indispensable equipment, reducing hospital costs for the health system in the future²⁵. Nanobiosensors are extremely small devices, with dimensions of one billionth of a meter, capable of detecting and responding to physical stimuli²⁶. It is possible to use nanosensors for food analysis by using them for detecting pathogens, toxins, nutrients, environmental characteristics, heavy metals, particulates, and allergens²⁷. There have been several mechanisms reported to exploit nanosensor advances for food analysis.

Nanomaterials-based techniques are commonly used in combination with existing technologies, and their high level of compatibility may result in significant improvements^{28,29}. The current review aimed to focus on developments in sample preparation techniques and significant detection used in nanobiosensors and

nanobioassays for food pathogens.

2. Biosensors and nanobiosensors

Biosensors have proven an effective platform for identifying pathogenic bacteria in previous years³⁰. As a result of the advancement in bacterial sensing, microfluidic bioassays have been developed to detect pathogenic microorganisms rapidly³¹. Although these advancements have been made, commercial devices have yet to be demonstrated to work in real-world settings. In the ecological niche, bacteria are in low concentrations, and interfering components are present, sabotaging diagnostic performance. As nanotechnology progressed, researchers developed sensitive and effective detection techniques by studying the unique properties of nanomaterials (like their large surface area-to-volume ratio.). As a result, nanoscale materials make it possible to miniaturize sensing devices and build sensitive and rapid diagnostic systems for detecting pathogens³². As a result, it is essential to understand how nanobiosensors work.

3. Principle of nanobiosensors

Nanobiosensors were developed by combining traditional biosensors with nanotechnology, which is growing rapidly³³. Nanobiosensors have a biological recognition element and a transduction unit that detects biological molecules at the nanoscale. Nanobiosensors consist of physicochemical transducers and receptors. Molecule recognition is the basis of biosensors³⁴. The biological receptors can detect bacteria only when the receptor and the bacteria have a specific molecular recognition. In molecular recognition, lock and key models are the best examples of interaction between antibody and antigen. Bioreceptors are the parts of the sensor that interact with the target. There is an immovable fixation of bio-receptors on the surface of the transducer so that they can bind the target entity (enzymes, antibodies, deoxyribonucleic acid (DNA), cells, and aptamers) stable under various storage conditions³⁵. Various methods are employed to immobilize the biological recognition element, such as adsorption, entrapment, cross-linking, microencapsulation, and covalent bonding. In the preparation of nanobiosensors, immobilization of nano components is a challenge. Biologically originated molecules can replace biologically created receptors, including engineered artificial proteins, imprinted polymers³⁶ recombinant antibodies, synthetic catalysts, and ligands³⁷. The performance of these receptors determines a biosensor's selectivity and sensitivity³⁸. Transducers (electrodes, semiconductor pH electrodes, thermistors, photon counters, and piezoelectric devices.) detect molecular recognition effects (changes in heat, mass, light, pH, or electroactivity). Measurable signals are converted into energy from the receptor, acting as an interface. Transducers modified with nanoparticles are the highlights of nanobiosensors, allowing rapid detection in a short period. Compared to simple biosensors, nanobiosensors can

detect the quantity and presence of analytes³⁴.

Furthermore, a detector has an electronic component that amplifies or analyzes the electrical signals produced by the transducer and a microprocessor that measures it. Various amplifiers and filters are used to convert analog signals to digital signals. The data is displayed on the device as concentration units or stored as an image, numeric, graphic, or tabular. Detectors based on smartphones have been introduced for detecting analytes in nanobiosensors on-chip or at the point of care³⁹. As a result of the characteristics of nanobiosensors, their performance can be enhanced indirectly. They are selectivity, reproducibility, sensitivity, stability, and linearity. Selectivity refers to the ability of the sensor to identify a specific analyte among several others⁴⁰. The detection limits of nanobiosensors are determined by their sensitivity, which correlates with their robustness⁴¹. When repeated accurately and precisely, the reproducibility of a nanobiosensor result is correlated with its reliability. Working ranges or linear dynamic ranges where concentration is directly proportional to signals are indicators of linearity or accuracy. As a result of sensor stability, analytes can be quantified and detected under different conditions of measurement disturbances without compromising precision and accuracy.

4. Nanobiosensors for Pathogenic Agents Detection

The first biosensors were reported in the 1960s, and today they are predominantly utilized for biological detection and environmental monitoring purposes⁴². In biosensors, biological recognition is combined with digital signals, which are translated into information through software⁴³. Biosensors can detect substances present in living or non-living systems, the analytes, through their properties, such as electricity, magnetic, electrochemistry, chemicals, optical, or vibration⁴⁴. The device is usually composed of a biorecognition sensor and a transducer. An interaction between the bioreceptor and analyte will generate an electronic signal that can be measured by the transducer. It is achieved by immobilizing the biorecognition elements through covalent interaction, encapsulation, or adsorption⁴⁵. These biorecognition units, or receptors, found within cells (such as glycopeptides, lipoproteins, lipids, glycoproteins, carbohydrates, and receptor proteins), serve various roles. They play a part in infection processes, adhere to cell surfaces and non-cellular substrates, evade the immune system, and facilitate nutrient intake and transport⁴⁶. In addition to their extracellular exposure, receptors have one significant feature in common. They are used as biorecognition elements during the assembly of biosensors. Nanomaterials are used in the construction of biosensors to increase their detection limits. Large surfaces, high electronic conductivity, and plasmonic properties, such as the ability to store light in confined areas, contribute to this⁴⁷. Moreover, nanomaterials as biosensors are capable of transmitting optical or mechanical signals. In the context

of biosensors, a nanobiosensor is a material with a size of less than 100 nm⁴⁸. These operate using the fundamentals of optics, spectroscopy, and mechanics. Small detection surface, nanobiosensors require a smaller amount of analyte to detect a measurable result⁴⁹. It is generally more efficient for small spaces to allow higher-density arrays, which can detect more analytes in a single test by maximizing their density. Moreover, the intricacy and expenses associated with pathogen detection tests can be diminished through the use of nanobiosensors, which eliminate certain conventional sample processing steps⁴⁹. Nanobiosensors generally rely on interactions between enzymes, nucleic acids, cells, substrates, bacteria, antibody, and antigen interactions, using biomimetic materials replicating biological processes.

5. Nanobiosensors mechanism

Nanobiosensors (NanoBioSS) are analytical devices with a biological sensor and a physicochemical converter⁴⁷. As an essential function of NanoBioSS, it generates a digital electrical signal directly proportional to the sum of one or several molecules being analyzed⁵⁰. These NanoBioSS are assisting some key analytic advances that are being aided as well as supported by advances in nanotech, adding to the evidence that they are both expanding applications and facilitating machinery. This BioSS/ NanoBioSS can precisely and rapidly detect nanomaterials (NMs), making it useful in various industrial, ecological, agricultural clinical, biomedical /healthcare, and other scientific applications⁵¹. The NanoBioSS design/fabrication process is as diverse as its applications, with each NanoBioSS category containing its advantages and limitations as a result of limitations based on the applications and the parameters essential to their optimum performance. Therefore, BioSS/Nano-BioSS should be selected based on sensitivity, specificity, output mode, dynamic range, usage simplicity, activation time, and engineering simplicity⁵². The NanoBioSS is used in various human endeavors, including diagnosing and managing different diseases and quality environmental and food effluent^{53,54}. A significant difference exists between the surface dimension ratios of most commonly used nanomaterials in NanoBioSS, such as quantum dots (QD), noble metal nanoparticles (NPs), and carbon-based nanoparticles as opposed to their bulk arrangement, leading to different and better properties (electrical, chemical, and optical)⁵⁵. As a result of these NMs' enhanced properties, NanoBioSS can detect nanoparticles more rapidly and reproducibly. By incorporating NMs in these bioanalytical devices, NMs enhance the performance and quality of BioSS/NanoBioSS (ETC, magnetic, mechanical, and optical)⁵⁶. Thus, BioSS are more compact and sensitive⁵⁶. There have been several papers describing the use of nanotech BioSS/NanoBioSS in clinical, biomedical, and healthcare applications (for example, identifying pathogen microbes and viruses, detection of cancerous cells, and breath analysis mechanism), environmental science (detection of water, soil, and air pollution), and agricultural applications

(climate-smart organic agriculture and identification of animals, plants pests and diseases)⁵². In addition, modern materials science, particularly nanotech, has been suggested as a valuable tool used in COVID-19-related research because it has played a dynamic role in minimizing COVID-19 complications⁵⁷.

6. Nanobiosensors types

The categorization of nanobiosensors encompasses a broad spectrum, primarily contingent on the type of nanomaterials integrated into the biosensing process. In addition, the classification here is more complex than with biosensors. Biosensors can be classified based on two criteria, namely, the type of material being analyzed and the mechanism used for signal transduction. For instance, if researchers screen any enzyme or antigen through the biosensors, they can find electrochemical, calorimetric, optical, and acoustic sensors when researchers classify biosensors based on their sensing mechanisms⁵⁸. Each class is associated with various sensor categories overlapping according to the transduction mechanism. Potentiometric and Amperometric biosensors are electrochemical sensors, and optical biosensors are based on surface plasmon resonances or optical fibers⁵⁹. As we observe in classifying nanobiosensors, the criterion for classification is the type of nanomaterials used to improve their sensing abilities. An example of nanoparticle-based biosensors is metallic nanoparticles that enhance the detection of biochemical signals. A nanobiosensor in which carbon nanotubes are used as enhancers of the reaction's efficiency and specificity is called a nanotube sensor⁶⁰. In contrast, a nanowire biosensor uses nanowires as carriers and charge carriers⁶¹. Below are some of the significant nanobiosensors developed to date, along with those with no practical application. Quantum dots are employed as contrast agents in quantum dots-based sensors for improved optical responses

6.1 Nanoparticle-based sensors

6.1.1 Acoustic wave biosensors

Acoustic wave biosensors can increase the overall precision of biological detection limits by amplifying the sensing responses. With sensors like these, stimulus-based effects can occur in many ways. These sensors are designed to work with antibodies-modified sol particles, which can be conjugated with the electrode surfaces so that antibody molecules are immobilized over the electrode surface in a manner that binds themselves to the electrode surface, which has been complexed with analyte particles. By binding large amounts of particles to the antibody, the quartz platform is subjected to a change in vibrational frequency that serves to detect changes. It is typically preferred for antibody particles to have a diameter between 5 and 100 nm. The preferred particles are titanium dioxide, cadmium sulfide, platinum, and gold^{62,63}.

6.1.2 Magnetic biosensors

Specially designed magnetic nanoparticles are used in magnetic biosensors.

Materials based on ferrite are used either separately or in combination. Applications in biomedical science make these sensors very useful. Several analytical applications can be performed using magnetic materials. Because iron and other transition metals are paired, the magnetic compounds used in screening have different properties⁶⁴. Incorporating magnetic nanoparticles into conventional detection devices has enhanced their sensitivity and performance. A few transition metal alloys containing iron and other materials have unpaired electrons in their d-orbitals that have been widely studied for their magnetic properties⁶⁵. These are commonly used magnetic bioassay techniques to isolate magnetically labeled targets using magnetometers to isolate them from magnetically labeled targets as a new kind of material has emerged⁶⁶. The magnetic properties of magnetic nanoparticles enable them to rapidly detect biological targets through superconducting quantum interference devices. These devices can screen mixtures for specific antigens by binding antibodies to magnetic nanoparticles⁶⁷. Specifically, nanoscale particles exhibit superparamagnetic effects due to their magnetic properties.

6.1.3 Electrochemical biosensors

Biochemical reactions are facilitated or analyzed by these sensors using improved electrical methods. Nanoparticles are primarily used in these devices. It is possible to quickly and efficiently perform chemical reactions between biomolecules through metallic nanoparticles, which contribute significantly to the immobilization of a reaction product. By enabling these reactions to be very specific, unwanted side effects are eliminated⁶⁸. An overall biosensor is significantly enhanced by significantly lowering the detection limit using colloidal gold-based nanoparticles that enhance the immobilization of DNA in gold electrodes⁶⁹. It has been proposed to develop biosensors that identify glucose, xanthine, and hydrogen peroxide with enzyme-conjugated gold nanoparticles⁷⁰. A recent study by Xu et al. examined the electrochemistry of enzyme systems containing horse-reddish peroxidase immobilized on gold electrodes containing carbon nanoparticles⁷⁰. Based on the results of this study, horse reddish peroxidase showed a faster amperometric response and improved electrocatalytic reduction ability. This resulted in better sensitivity and smaller detection limits than those without nanoparticles in the biosensor.

6.2. Nanotube-based sensors

Carbon nanotubes are a popular nanomaterial in material science and optoelectronics. Because of their extraordinary properties, since their discovery in the 1990s, they have attracted worldwide attention. Among the

most important properties are their electronic conductivity, flexible geometries, and dynamic physicochemical properties, such as high aspect ratios, excellent functionalization capabilities, and high mechanical folding and strength properties. Due to these characteristics, single-wall and multi-wall nanotubes have been used to develop better biosensors⁷¹. In recent years, the design of glucose biosensors that utilize nanotubes as immobilizing surfaces for the enzyme glucose oxidase has become one of the most popular sensing advances. This enzyme is used to calculate glucose concentrations from several body fluids. Conventionally, enzyme-based sensors predicted glucose concentrations in significant body tissues, but nanotube assemblies have been successfully utilized to determine glucose concentrations even in scarce body fluids like tears and saliva⁷². Among such arrangements, single-walled nanotubes have been used to detect glucose enzymatically, and this innovation has improved enzyme activity significantly⁷³. Analyzed the biosensor and found its enhanced performance was mainly due to its high enzyme loading and improved electrical conductivity. The better and smoother electron transfer characteristics of carbon nanotubes have enabled carbon nanotubes to enhance structural flexibility and electrical detection of sensing phenomena. A particular investigation delved into notable enhancements achieved in catalytic biosensors. These advancements elevated oxidoreductase activity, enabling glucose oxidase and flavin adenine dinucleotide precursors to bind to substrates more efficiently and with enhanced control⁶⁰.

6.3. Nanowire-Based sensors

Nanowires are cylindrical arrangements and measure a few micrometers to centimeters in length and diameter. A nanowire is a one-dimensional nanostructure with excellent electron transport properties. A significant difference between bulk materials and nanowires is the motion of charge carriers. Nanowire sensors are very few, but literature has reported a few exciting examples of nanowires that have improved biological detection and performance. Using silicon nanowires doped with boron, Cui and Lieber reported the performance of biosensors for detecting biological and chemical species using silicon nanowires⁷⁴. The utilization of semiconductor nanowires has been investigated extensively, and they have also been applied to coupling a variety of biomolecules into specific substrates for identification⁷⁵. Streptavidin molecules from a mixture have been detected and isolated with silicon nanowires coated with biotin. In addition to their small size and ability to detect pathogens, these nanowires can also be used to analyze a wide range of biological and chemical data in real time, thus vastly improving the accuracy of current *in vivo* diagnostic procedures. The materials used for these sensing applications are exact in their dimensions, so they can be used within living cells and *in vivo* applications. Researchers have used nanosized fibers coated with antibodies in one study to detect toxicants within single

cells⁷⁶.

Cullum et al. used gold electrodes coated with ZnO nanowires to detect hydrazine using amperometric responses⁷⁷. Compared to conventional sensor systems, they propose high sensitivity, low detection limit, and much shorter response time than those reported at the time of the conventional sensor systems. Two significant advantages of nanowires over nanotubes are their versatility and their performance. By controlling their operational parameters during synthesis, they provide a range of design modifications. Additionally, their surfaces are compatible with a more excellent range of materials, which allows them to be further functionalized. Even though nanowires can be synthesized very quickly, their applications for sensing devices face several challenges. Many related studies report that adding nanowires to sensing systems is difficult, so overall electrical conductivity improvements cannot be realized⁷⁸. According to the Lieber group, semiconductor nanowires were synthesized using combinations of previously known methods in a very advanced study. To detect serum-bone cancer antigens at low levels, a sophisticated one-dimensional structure was devised, integrating a minimum of 200 distinct electrical nanowire assemblies⁷⁴ (Figure 1).

7. Advantages of nanobiosensors

Because of their nanoscale dimensions, nanobiosensors show remarkable sensitivity. Due to this sensitivity, bacterial pathogens can be detected at deficient concentrations, making them valuable diagnostic tools⁷⁹. High-specificity Bacterial pathogens can be identified by nano biosensors that recognize specific molecular markers or receptors. Ensuring a high specificity minimizes false-positive results, and accurate identification is achieved⁸⁰. Rapid detection As a result of their rapid detection capabilities, nanobiosensors often produce results within minutes of their use. This swift response is critical for timely intervention in bacterial infections or outbreaks⁸¹. Multiple biomarkers or bacteria can be detected simultaneously by nanobiosensors. In addition, modern materials science, particularly nanotech, has been suggested as a valuable tool used in COVID-19-related research because it has played a dynamic role in minimizing COVID-19 complications⁸².

8. Limitations of nanobiosensors

Fabricating nanobiosensors can be time-consuming and technically challenging. Specialized expertise and equipment are required to manipulate nanoscale materials and integrate biological recognition elements⁸³. In some cases, cleanroom facilities are also necessary for producing nanobiosensors, which can be expensive. The high cost can prevent widespread adoption, especially in resource-constrained healthcare settings⁸⁴. By recognizing specific bacteria, the nanobiosensor's recognition elements may have to be customized to accommodate their unique molecular signatures or surface markers. Pathogen

Nanobiosensors variations

1. Nanoparticle-Based Sensors

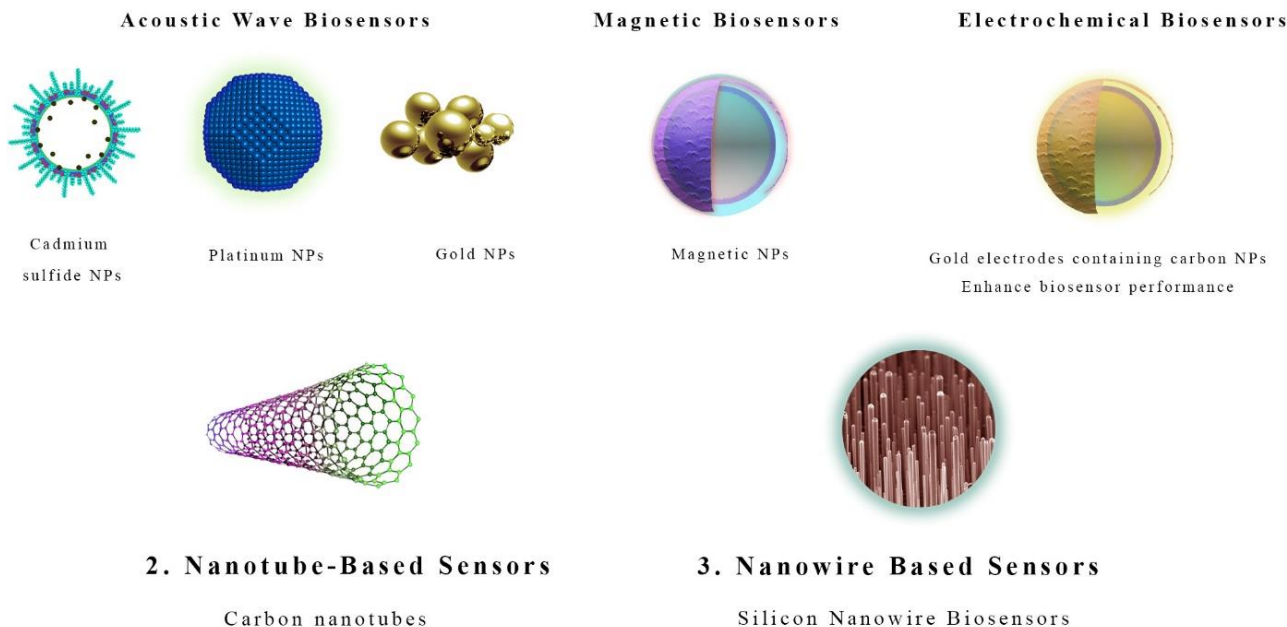


Figure 1. The diversity of nanoparticle-based sensors

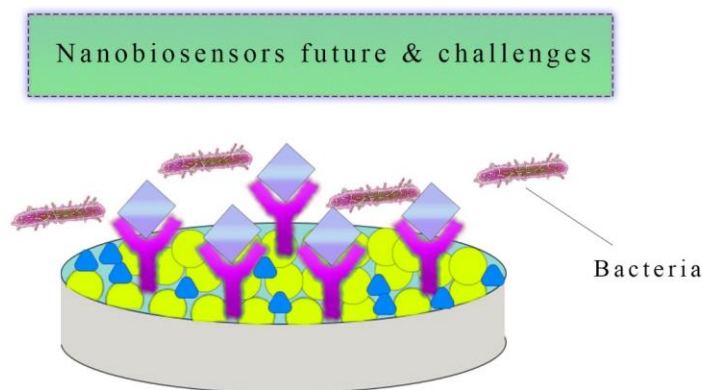
optimization is labor-intensive and requires thorough knowledge of the pathogen being targeted⁸⁵. There are some limitations to the shelf life of nanobiosensors, as well as their vulnerability to environmental factors, such as temperature or humidity. It is challenging to maintain their longevity and stability⁸³. Nanomaterials and Biorecognition elements are used in diagnostic devices, raising ethical and regulatory concerns regarding safety, data privacy, and environmental impact (Figure 2)⁸⁵.

9. Antibiotic quantification with nanobiosensors

Recently, biosensors have become an invaluable tool in various industries, such as agriculture and food, as well as clinical diagnostics⁸⁶. These devices are also easy to use, portable, automated, and can be miniaturized, as well as being durable and long-lasting. Sample analysis is inexpensive, requires no complicated pretreatment, and takes a short time^{87,88}.

Compound quantification with biosensors is made possible by these features. According to the International Union of Pure and Applied Chemistry (IUPAC), Biosensors detect chemicals via specific biochemical reactions mediated by isolated organelles, enzymes, or whole cells, immune systems, and tissues, usually through electrical, optical signals, or thermal⁸⁹. An analytical device called a biosensor incorporates a biological recognition element closely coupled to or

integrated with a transducer that allows signal processing based on the interaction between the ligand and the recognition element⁹⁰. Thus, biosensors are classified based on their biological components and transduction systems⁵⁸. Biocatalytic and affinity components are classified as biological components. There are various biocatalytic components, including whole cells, enzymes or multi-enzyme systems, organelles in cells, or tissues in plants or animals. Signals are obtained by measuring the products generated by catalyzed chemical reactions between enzymes and substrates⁹¹. The affinity bioreceptor generates an analyte-receptor complex through the interaction of the recognition element and analyte, which can be detected by labeling (fluorescent or enzymatic) or observing the transducer's physical-chemical properties. The most common biological components are an antibody, microorganism, aptamer, nucleic acid, and receptor protein⁹². As for transduction systems, it is the biosensor mechanism that converts changes in chemical or physical properties caused by analyte-ligand interactions into a signal. Transducers come in several types, including electrochemicals (amperometry, potentiometry, and impedimetry), opticals (fiber optics, biosensors using total internal reflection fluorescence (SERS), piezoelectrics (quasi crystal microbalances), surface-enhanced Raman scattering, and nanomechanicals (nanolevers)⁹⁰. An appropriate device can be selected based on the sample type and analyte-ligand interaction.



Advantages

1. High Sensitivity
2. High Specificity:
3. Rapid Detection
4. Multiplexing

Limitations

1. Complex Fabrication
2. Cost & Optimization
3. Sample Complexity
4. Regulatory Approval Hurdles

Figure 2. The advantages and limitations of using nanobiosensors for bacterial detection

10. Future

Many fields have benefited from nanotechnology's revolutionary potential. A novel analytical tool can be provided by nanomaterials in the detection of food pathogens, and their use can enhance existing methods. While nanotechnology has gained widespread popularity, many pathogen nanosensors or assays are still in their early stages of development. Despite this, nanotechnology has contributed to varying degrees of improvement. Some technologies demonstrate dramatic improvements, whereas others show only modest improvements, particularly in whole-cell detection due to fewer access points and bulkier geometry and reaction centers. As detection becomes more sensitive, matrix interference increases proportionally, compromising certain bacteria's specificity and sensitivity. This challenge further highlights the effective preparation of samples. In addition to the need for systematic studies focused on sample preparation techniques, few studies have examined how samples perform in natural food systems or contexts of competing bacteria. Nanotechnology is multidisciplinary, contributing to this deficiency. Researchers from engineering, chemistry, and material science have contributed the majority of publications on pathogen nanosensors and assays because they need more resources to evaluate and validate large-scale downstream methods. Despite this, advances in rapid detection will continue to be driven by nanotechnology as these issues are resolved. In the future, detection methods will boast high levels of sensitivity and specificity, high sample throughput, minimal instrumentation, robustness, and quantitative capabilities. The flexible nature of nanomaterials and nanofabrication could offer excellent solutions to a wide range of problems associated with the effective use of nanotechnology for foodborne pathogen detection. Two green methods for Ag-

GO nanocomposites were compared. Innovative approach Ag-GO-II exhibited superior anti-bacterial and cytotoxic behavior, controlling nucleation⁹³. Another study investigates the antioxidant and anticancer properties of black peel pomegranate extract and explores its potential as a dual reducing and stabilizing agent in biosynthesizing silver nanoparticles, expecting enhanced biological activity^{94,95}.

11. Conclusions

The sensitivity and versatility of nanobiosensors make them useful in a wide range of fields, including clinical, environmental detection, and food safety. Two key factors determined nanobiosensors effectiveness. Firstly, advanced nanomaterials like carbon nanotubes, gold nanoparticles, and quantum dots offer functionalization potential. The second factor is unique properties and optimized biological recognition elements like aptamers and antibodies. Nanobiosensors are expected to become more sensitive, facilitate multiplexed detection, provide point-of-care diagnostics, and provide real-time monitoring in the future.

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

In the collaborative research project, the conceptualization phase was led by Hamidreza Razzaghi, while the methodology was crafted by a team comprising Peyman Ghafouri, Bahare Kasaei, and Ahmad Mir Hosseini.

The formal analysis and investigation aspects were diligently undertaken by Sara Aghili and Atefehshadat Monirvaghefi. The original draft of the document was skillfully prepared by Sara Aghili and Atefehshadat Monirvaghefi, and the subsequent review and editing were expertly handled by Hora Amoozegar and Golnaz Mirfendereski. Throughout the process, the project received valuable supervision from Hamidreza Razzaghi. All authors checked and approved the final version of the manuscript for publication in the present journal.

Funding

No funding was received for conducting this study.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical considerations

The authors checked for plagiarism and consented to publish the article. Furthermore, the authors reviewed the article for data fabrication, double publication, and redundancy.

Acknowledgments

Not applicable.

References

- Fedorenko V, Genilloud O, Horbal L, Marcone GL, Marinelli F, Paitan Y, et al. Anti-bacterial discovery and development: From gene to product and back. *Biomed Res Int.* 2015; 2015: 591349. DOI: [10.1155/2015/591349](https://doi.org/10.1155/2015/591349)
- Hassanshahian M, Bayat Z, Saeidi S, Shiri Y. Antimicrobial activity of *Trachyspermum ammi* essential oil against human bacterial. 2014; 2(1): 18-24.
- Chang HH, Cohen T, Grad YH, Hanage WP, O'Brien TF, and Lipsitch M. Origin and proliferation of multiple-drug resistance in bacterial pathogens. *Microbiol Mol Biol.* 2015; 79(1): 101-116. DOI: [10.1128/MMBR.00039-14](https://doi.org/10.1128/MMBR.00039-14)
- O'Neill J. Review on antimicrobial resistance. Antimicrobial resistance: Tackling a crisis for the health and wealth of nations. *Rev Antimicrob Resist.* 2014. Available at: <https://cir.nii.ac.jp/crid/1370857593729357568>
- Bush K, Courvalin P, Dantas G, Davies J, Eisenstein B, Huovinen P, et al. Tackling antibiotic resistance. *Nat Rev Microbiol.* 2011; 9(12): 894-896. DOI: <https://doi.org/10.1038/nrmicro2693>
- World Health Organization (WHO). Global antimicrobial resistance surveillance system (GLASS): GLASS manual for early implementation. 2015.
- Talebi Bezmin Abadi A, Rizvanov AA, Haertlé T, and Blatt NL. World health organization report: current crisis of antibiotic resistance. *BioNanoScience.* 2019; 9: 778-88. DOI: [10.1007/s12668-019-00658-4](https://doi.org/10.1007/s12668-019-00658-4)
- Touw DJ, Neef C, Thomson AH, and Vinks AA. Cost-effectiveness of therapeutic drug monitoring: a systematic review. *Ther Drug Monit.* 2005; 27(1): 10-17. DOI: [10.1097/00007691-200502000-00004](https://doi.org/10.1097/00007691-200502000-00004)
- Reeves D, Lovering A, and Thomson A. Therapeutic drug monitoring in the past 40 years of the *J Antimicrob Chemother.* 2016; 71(12): 3330-3332. DOI: [10.1093/jac/dkw408](https://doi.org/10.1093/jac/dkw408)
- Kim SW. Therapeutic drug monitoring (TDM) of antimicrobial agents. *Infect Chemother.* 2008; 40(3): 133-139. DOI: [10.3947/ic.2008.40.3.133](https://doi.org/10.3947/ic.2008.40.3.133)
- Garzón V, Pinacho DG, Bustos RH, Garzón G, and Bustamante S. Optical biosensors for therapeutic drug monitoring. *Biosensors.* 2019; 9(4): 132. DOI: [10.3390/bios9040132](https://doi.org/10.3390/bios9040132)
- Mabilat C, Gros MF, Nicolau D, Mouton JW, Textoris J, Roberts JA, et al. Diagnostic and medical needs for therapeutic drug monitoring of antibiotics. *Eur J Clin Microbiol.* 2020; 39: 791-797. DOI: [10.1007/s10096-019-03769-8](https://doi.org/10.1007/s10096-019-03769-8)
- Dasgupta A. Introduction to therapeutic drug monitoring: Frequently and less frequently monitored drugs. *Ther Drug Monit.* 2012; p. 1-29. DOI: [10.1016/B978-0-12-385467-4.00001-4](https://doi.org/10.1016/B978-0-12-385467-4.00001-4)
- Garzón V, Bustos RH, and Pinacho DG. Personalized medicine for antibiotics: The role of nanobiosensors in therapeutic drug monitoring. *J Pers Med.* 2020; 10(4): 147. DOI: [10.3390/jpm10040147](https://doi.org/10.3390/jpm10040147)
- Peloquin C. The role of therapeutic drug monitoring in mycobacterial infections. *Microbiol Spectrum.* 2017; 5(1): TNMI7-0029. DOI: [10.1128/microbiolspec.TNMI7-0029-2016](https://doi.org/10.1128/microbiolspec.TNMI7-0029-2016)
- Meneghello A, Tartaglia S, Alvau MD, Polo F, and Toffoli G. Biosensing technologies for therapeutic drug monitoring. *Curr Med Chem.* 2018; 25(34): 4354-4377. DOI: [10.2174/0929867324666170720101736](https://doi.org/10.2174/0929867324666170720101736)
- Fattahi Z, Hasanazadeh M. Nanotechnology-assisted microfluidic systems for chemical sensing, biosensing, and bioanalysis. *TrAC Trends Anal Chem.* 2022; 152: 116637. DOI: [10.1016/j.trac.2022.116637](https://doi.org/10.1016/j.trac.2022.116637)
- Sadr S, Lotfalizadeh N, Abbasi AM, Soleymani N, Hajjafari A, Roohbaksh Amooli Moghadam E, et al. Challenges and prospective of enhancing hydatid cyst chemotherapy by nanotechnology and the future of nanobiosensors for diagnosis. *Trop Med Infect Dis.* 2023; 8(11): 494. DOI: [10.3390/tropicalmed8110494](https://doi.org/10.3390/tropicalmed8110494)
- Lim JW, Ha D, Lee J, Lee SK, and Kim T. Review of micro/nanotechnologies for microbial biosensors. *Front Bioeng Biotechnol.* 2015; 3: 61. DOI: [10.3389/fbioe.2015.00061](https://doi.org/10.3389/fbioe.2015.00061)
- Sadr S, Lotfalizadeh N, Ghafari SA, Delrobaei M, Komeili N, and Hajjafari A. Nanotechnology innovations for increasing the productivity of poultry and the prospective of nanobiosensors. *Vet Med Sci.* 2023; 9(5): 2118-2131. DOI: [10.1002/vms3.1193](https://doi.org/10.1002/vms3.1193)
- Soleymani L, and Li F. Mechanistic challenges and advantages of biosensor miniaturization into the nanoscale. *ACS sens.* 2017; 2(4): 458-467. DOI: [10.1021/acssensors.7b00069](https://doi.org/10.1021/acssensors.7b00069)
- Noah NM, and Ndagili PM. Current trends of nanobiosensors for point-of-care diagnostics. *J Anal Methods Chem.* 2019; 2019: 2179718. DOI: [10.1155/2019/2179718](https://doi.org/10.1155/2019/2179718)
- Tekede RK, Maheshwari R, Soni N, Tekade M, and Chougule MB. Nanotechnology for the development of nanomedicine. Nanotechnology-based approaches for targeting and delivery of drugs and genes. 2017; p. 3-61. DOI: [10.1016/B978-0-12-809717-5.00001-4](https://doi.org/10.1016/B978-0-12-809717-5.00001-4)
- Somavarapu S, Ramesh B, Venkatrayulu C, and Subhosh Chandra M. Nanotechnology-a new frontier in medical microbiology. In: Maddela NR, Chakraborty S, Prasad R, editors. *Nanotechnology for advances in medical microbiology.* Singapore: Springer; 2021. p. 375-392. DOI: [10.1007/978-981-15-9916-3_16](https://doi.org/10.1007/978-981-15-9916-3_16)
- Kim J, Campbell AS, de Ávila BE, and Wang J. Wearable biosensors for healthcare monitoring. *Nat. Biotechnol.* 2019; 37(4): 389-406. DOI: [10.1038/s41587-019-0045-y](https://doi.org/10.1038/s41587-019-0045-y)
- Javaid M, Haleem A, Singh RP, Rab S, and Suman R. Exploring the potential of nanosensors: A brief overview. *Sens Int.* 2021; 2: 100130. DOI: [10.1016/j.sintl.2021.100130](https://doi.org/10.1016/j.sintl.2021.100130)
- Prado M, Espiña B, Fernandez-Argüelles MT, Diéguez L, Fuciños P, Vial S, et al. Detection of foodborne pathogens using nanoparticles. Advantages and trends. *Antimicrobial food packaging.* 2016. p. 183-201. DOI: [10.1016/B978-0-12-800723-5.00014-0](https://doi.org/10.1016/B978-0-12-800723-5.00014-0)
- Sadr S, Poorjafari Jafroodi P, Haratizadeh MJ, Ghasemi Z, Borji H, and Hajjafari A. Current status of nano-vaccinology in veterinary medicine science. *Vet Med and Sci.* 2023; 9(5): 2294-2308. DOI: [10.1002/vms3.1221](https://doi.org/10.1002/vms3.1221)
- Goh PS, and Ismail AF. Graphene-based nanomaterial: The state-of-the-art material for cutting edge desalination technology. *Desalination.* 2015; 356: 115-128. DOI: [10.1016/j.desal.2014.10.001](https://doi.org/10.1016/j.desal.2014.10.001)
- Xing G, Zhang W, Li N, Pu Q, and Lin JM. Recent progress on microfluidic biosensors for rapid detection of pathogenic bacteria. *Chin Chem Lett.* 2022; 33(4): 1743-1751. DOI: [10.1016/j.ccllet.2021.08.073](https://doi.org/10.1016/j.ccllet.2021.08.073)

31. Sharifi M, Hasan A, Haghighat S, Taghizadeh A, Attar F, Bloukh SH, et al. Rapid diagnostics of coronavirus disease 2019 in early stages using nanobiosensors: Challenges and opportunities. *Talanta*. 2021; 223(Part 1): 121704. DOI: [10.1016/j.talanta.2020.121704](https://doi.org/10.1016/j.talanta.2020.121704)
32. El-Safty S, and Shenashen M. Nanoscale dynamic chemical, biological sensor material designs for control monitoring and early detection of advanced diseases. *Mater Today Bio*. 2020; 5: 100044. DOI: [10.1016/j.mtbio.2020.100044](https://doi.org/10.1016/j.mtbio.2020.100044)
33. Debnath N, and Das S. Nanobiosensor: Current trends and applications. In: Saxena S, Khurana S, editors. *NanoBioMedicine*. Singapore: Springer; 2020. p. 389-409. DOI: [10.1007/978-981-32-9898-9_16](https://doi.org/10.1007/978-981-32-9898-9_16)
34. Christopher FC, Kumar PS, Christopher FJ, Joshiba GJ, and Madhesh P. Recent advancements in rapid analysis of pesticides using nano biosensors: A present and future perspective. *J Clean Prod*. 2020; 269: 122356. DOI: [10.1016/j.jclepro.2020.122356](https://doi.org/10.1016/j.jclepro.2020.122356)
35. Sadani K, Nag P, Thian XY, and Mukherji S. Enzymatic optical biosensors for healthcare applications. *Biosens. Bioelectron*. 2022; 12: 100278. DOI: [10.1016/j.biosx.2022.100278](https://doi.org/10.1016/j.biosx.2022.100278)
36. Erturk G, and Mattiasson B. Molecular imprinting techniques used for the preparation of biosensors. *Sensors*. 2017; 17(2): 228. DOI: [10.3390/s17020288](https://doi.org/10.3390/s17020288)
37. De Paepe B, Maertens J, Vanholme B, and De Mey M. Chimeric LysR-type transcriptional biosensors for customizing ligand specificity profiles toward flavonoids. *ACS Synth Biol*. 2018; 8(2): 318-331. DOI: [10.1021/acssynbio.8b00326](https://doi.org/10.1021/acssynbio.8b00326)
38. Bhattarai P, Hameed S. Basics of biosensors and nanobiosensors. In: Wu A, Khan WS, editors. *Nanobiosensors: From Design to Applications*, Chapter 1. 2020. p. 1-22. DOI: [10.1002/9783527345137.ch1](https://doi.org/10.1002/9783527345137.ch1)
39. Seo SE, Tabei F, Park SJ, Askarian B, Kim KH, Moallem G, et al. Smartphone with optical, physical, and electrochemical nanobiosensors. *J Ind Eng Chem*. 2019; 77: 1-11. DOI: [10.1016/j.jiec.2019.04.037](https://doi.org/10.1016/j.jiec.2019.04.037)
40. Denmark DJ, Mohapatra S, and Mohapatra SS. Point-of-care diagnostics: Molecularly imprinted polymers and nanomaterials for enhanced biosensor selectivity and transduction. *Eurobiotech J*. 2020; 4(4): 184-206. DOI: [10.2478/ebtj-2020-0023](https://doi.org/10.2478/ebtj-2020-0023)
41. Zhang Y, Duan B, Bao Q, Yang T, Wei T, Wang J, et al. Aptamer-modified sensitive nanobiosensors for the specific detection of antibiotics. *J Mater Chem B*. 2020; 8(37): 8607-8613. DOI: [10.1039/D0TB01441A](https://doi.org/10.1039/D0TB01441A)
42. Upadhyay LS, and Verma N. Role of biosensors in environmental monitoring. In: Sukla L, Pradhan N, Panda S, Mishra B, editors. *Environmental microbial biotechnology*. Springer, Cham; 2015. p. 77-90. DOI: [10.1007/978-3-319-19018-1_4](https://doi.org/10.1007/978-3-319-19018-1_4)
43. Byrne B, Stack E, Gilmartin N, and O'Kennedy R. Antibody-based sensors: principles, problems and potential for detection of pathogens and associated toxins. *Sensors*. 2009; 9(6): 4407-4445. DOI: [10.3390/s90604407](https://doi.org/10.3390/s90604407)
44. Fang Y, and Ramasamy RP. Current and prospective methods for plant disease detection. *Biosensors*. 2015; 5(3): 537-561. DOI: [10.3390/bios5030537](https://doi.org/10.3390/bios5030537)
45. Vo-Dinh T, and Cullum B. Biosensors and biochips: Advances in biological and medical diagnostics. *Fresenius J Anal Chem*. 2000; 366: 540-551. DOI: [10.1007/s002160051549](https://doi.org/10.1007/s002160051549)
46. Kaitanis C, Santra S, and Perez JM. Emerging nanotechnology-based strategies for the identification of microbial pathogenesis. *Adv Drug Deliv Rev*. 2010; 62(4-5): 408-423. DOI: [10.1016/j.addr.2009.11.013](https://doi.org/10.1016/j.addr.2009.11.013)
47. Welch EC, Powell JM, Clevinger TB, Fairman AE, and Shukla A. Advances in biosensors and diagnostic technologies using nanostructures and nanomaterials. *Adv Funct Mater*. 2021; 31(44): 2104126. DOI: [10.1002/adfm.202104126](https://doi.org/10.1002/adfm.202104126)
48. Beltrán-Pineda M, Peña-Solórzano D, and Sierra CA. Nanobiosensors for pathogenic agents detection. *J Braz Chem Soc*. 2021; 32(9): 1687-710. DOI: [10.21577/0103-5053.20210081](https://doi.org/10.21577/0103-5053.20210081)
49. Purohit B, Vernekar PR, Shetti NP, and Chandra P. Biosensor nanoengineering: Design, operation, and implementation for biomolecular analysis. *Sens Int*. 2020; 1: 100040. DOI: [10.1016/j.sintl.2020.100040](https://doi.org/10.1016/j.sintl.2020.100040)
50. Akkilic N, Geschwindner S, and Höök F. Single-molecule biosensors: Recent advances and applications. *Biosens Bioelectron*. 2020; 151: 111944. DOI: [10.1016/j.bios.2019.111944](https://doi.org/10.1016/j.bios.2019.111944)
51. Carpenter AC, Paulsen IT, and Williams TC. Blueprints for biosensors: Design, limitations, and applications. *Genes*. 2018; 9(8): 375. DOI: [10.3390/genes9080375](https://doi.org/10.3390/genes9080375)
52. Ukhurebor KE, Onyancha RB, Aigbe UO, Uk-Eghonghon G, Kerry RG, Kusuma HS, et al. A methodical review on the applications and potentialities of using nanobiosensors for disease diagnosis. *Biomed Res Int*. 2022; 2022: 1682502. DOI: [10.1155/2022/1682502](https://doi.org/10.1155/2022/1682502)
53. Kerry RG, Ukhurebor KE, Kumari S, Maurya GK, Patra S, Panigrahi B, et al. A comprehensive review on the applications of nano-biosensor-based approaches for non-communicable and communicable disease detection. *Biomater Sci*. 2021; 9(10): 3576-602. DOI: [10.1039/D0BM02164D](https://doi.org/10.1039/D0BM02164D)
54. Singh S, Kumar V, Dhanjal DS, Datta S, Prasad R, Singh J. Biological biosensors for monitoring and diagnosis. In: Singh J, Vyas A, Wang S, Prasad R, editors. *Microbial biotechnology: Basic research and applications*. Singapore: Springer; 2020. p. 317-335. DOI: [10.1007/978-981-15-2817-0_14](https://doi.org/10.1007/978-981-15-2817-0_14)
55. Debnath N, Das S. Nanobiosensor: Current trends and applications. In: Saxena S, Khurana S, editors. *NanoBioMedicine*. Singapore: Springer; 2020. p. 389-409. DOI: [10.1007/978-981-32-9898-9_16](https://doi.org/10.1007/978-981-32-9898-9_16)
56. Mehrotra P. Biosensors and their applications—A review. *J Oral Biol Craniofac Res*. 2016; 6(2): 153-159. DOI: [10.1016/j.jobocr.2015.12.002](https://doi.org/10.1016/j.jobocr.2015.12.002)
57. Weiss C, Carriere M, Fusco L, Capua I, Regla-Nava JA, Pasquali M, et al. Toward nanotechnology-enabled approaches against the COVID-19 pandemic. *ACS Nano*. 2020; 14(6): 6383-406. DOI: [10.1021/acsnano.0c03697](https://doi.org/10.1021/acsnano.0c03697)
58. Kaur H, Bhosale A, and Shrivastav S. Biosensors: Classification, fundamental characterization and new trends: A review. *Int J Health Sci Res*. 2018; 8(6): 315-33. Available at: https://www.ijhsr.org/IJHSR_Vol.8_Issue.6_June2018/46.pdf
59. Kimmel DW, LeBlanc G, Meschievitz ME, and Cliffel DE. Electrochemical sensors and biosensors. *Anal Chem*. 2012; 84(2): 685-707. DOI: [10.1021/ac202878q](https://doi.org/10.1021/ac202878q)
60. Wang J. Carbon-nanotube based electrochemical biosensors: A review. *Electroanalysis*. 2005; 17(1): 7-14. DOI: [10.1002/elan.200790029](https://doi.org/10.1002/elan.200790029)
61. Patolsky F, Zheng G, and Lieber CM. Nanowire-based biosensors. *Anal Chem*. 2006; 78(13): 4260-4269. DOI: [10.1021/ac069419j](https://doi.org/10.1021/ac069419j)
62. Su X, Chew FT, and Li SFY. Design and application of piezoelectric quartz crystal-based immunoassay. *Anal Sci*. 2000; 16(2): 107-114. DOI: [10.2116/analsci.16.107](https://doi.org/10.2116/analsci.16.107)
63. Liu T, Tang Ja, and Jiang L. The enhancement effect of gold nanoparticles as a surface modifier on DNA sensor sensitivity. *Biochem Biophys Res Commun*. 2004; 313(1): 3-7. DOI: [10.1016/j.bbrc.2003.11.098](https://doi.org/10.1016/j.bbrc.2003.11.098)
64. Giakissikli G, and Anthemidis AN. Magnetic materials as sorbents for metal/metalloid preconcentration and/or separation. A review. *Anal Chim Acta*. 2013; 789: 1-16. DOI: [10.1016/j.aca.2013.04.021](https://doi.org/10.1016/j.aca.2013.04.021)
65. Alonso JA. Electronic and atomic structure, and magnetism of transition-metal clusters. *Chem Rev*. 2000; 100(2): 637-678. DOI: [10.1021/cr980391o](https://doi.org/10.1021/cr980391o)
66. Richardson J, Hawkins P, and Luxton R. The use of coated paramagnetic particles as a physical label in a magneto-immunoassay. *Biosens Bioelectron*. 2001; 16(9-12): 989-993. DOI: [10.1016/S0956-5663\(01\)00201-9](https://doi.org/10.1016/S0956-5663(01)00201-9)
67. Chemla Y, Grossman H, Poon Y, McDermott R, Stevens R, Alper M, et al. Ultrasensitive magnetic biosensor for homogeneous immunoassay. *PLoS Comput Biol*. 2000; 97(26): 14268-14272. DOI: [10.1073/pnas.97.26.14268](https://doi.org/10.1073/pnas.97.26.14268)
68. Cai H, Xu C, He P, and Fang Y. Colloid Au-enhanced DNA immobilization for the electrochemical detection of sequence-specific DNA. *J Electroanal Chem*. 2001; 510(1-2): 78-85. DOI: [10.1016/S0022-0728\(01\)00548-4](https://doi.org/10.1016/S0022-0728(01)00548-4)
69. Yanez-Sedeno P, and Pingarron J. Gold nanoparticle-based electrochemical biosensors. *Anal Bioanal Chem*. 2005; 382: 884-886. DOI: [10.1007/s00216-005-3221-5](https://doi.org/10.1007/s00216-005-3221-5)
70. Xu X, Liu S, and Ju H. A novel hydrogen peroxide sensor via the direct electrochemistry of horseradish peroxidase immobilized on colloidal gold modified screen-printed electrode. *Sensors*. 2003; 3(9): 350-360. DOI: [10.3390/s30900350](https://doi.org/10.3390/s30900350)
71. Gupta S, Murthy CN, and Prabha CR. Recent advances in carbon nanotube based electrochemical biosensors. *Int J Biol Macromol*. 2018; 108: 687-703. DOI: <https://doi.org/10.1016/j.ijbiomac.2017.12.038>
72. Koklu A, Ohayon D, Wustoni S, Druet V, Saleh A, and Inal S. Organic Bioelectronic devices for metabolite sensing. *Chem Rev*. 2022; 122(4): 4 581-635. DOI: [acs.chemrev.1c00395](https://doi.org/10.1021/acs.chemrev.1c00395)

73. Li W, Ouyang R, Zhang W, Zhou S, Yang Y, Ji Y, et al. Single walled carbon nanotube sandwiched Ni-Ag hybrid nanoparticle layers for the extraordinary electrocatalysis toward glucose oxidation. *Electrochim Acta*. 2016; 188: 197-209. DOI: [10.1016/j.electacta.2015.12.003](https://doi.org/10.1016/j.electacta.2015.12.003)
74. Cui Y, and Lieber CM. Functional nanoscale electronic devices assembled using silicon nanowire building blocks. *Science*. 2001; 291(5505): 851-853. DOI: [10.1126/science.291.5505.851](https://doi.org/10.1126/science.291.5505.851)
75. Zhou W, Dai X, and Lieber CM. Advances in nanowire bioelectronics. *Rep Prog Phys*. 2017; 80(1): 016701. DOI: [10.1088/0034-4885/80/1/016701](https://doi.org/10.1088/0034-4885/80/1/016701)
76. Nikoleli GP, Nikolelis DP, Siontorou CG, Karapetis S, and Varzakas T. Novel biosensors for the rapid detection of toxicants in foods. *Advances in Food and Nutrition Research*. 2018. p. 57-102. DOI: [10.1016/bs.afnr.2018.01.003](https://doi.org/10.1016/bs.afnr.2018.01.003)
77. Cullum BM, Griffin GD, Miller GH, and Vo-Dinh T. Intracellular measurements in mammary carcinoma cells using fiber-optic nanosensors. *Anal Biochem*. 2000; 277(1): 25-32. DOI: [10.1006/abio.1999.4341](https://doi.org/10.1006/abio.1999.4341)
78. Pham TA, Qamar A, Dinh T, Masud MK, Rais-Zadeh M, Senesky DG, et al. Nanoarchitectonics for wide bandgap semiconductor nanowires: Toward the next generation of nanoelectromechanical systems for environmental monitoring. *Adv Sci*. 2020; 7(21): 2001294. DOI: [10.1002/advs.202001294](https://doi.org/10.1002/advs.202001294)
79. Swierczewska M, Liu G, Lee S, and Chen X. High-sensitivity nanosensors for biomarker detection. *Chem Soc Rev*. 2012; 41(7): 2641-55. DOI: [10.1039/C1CS15238F](https://doi.org/10.1039/C1CS15238F)
80. Weng X, Zhang C, and Jiang H. Advances in microfluidic nanobiosensors for the detection of foodborne pathogens. *Lwt*. 2021; 151: 112172. DOI: [10.1016/j.lwt.2021.112172](https://doi.org/10.1016/j.lwt.2021.112172)
81. Ahangari A, Mahmoodi P, Mohammadzadeh A. Advanced nano biosensors for rapid detection of zoonotic bacteria. *Biotechnol Bioeng*. 2023; 120(1): 41-56. DOI: [10.1002/bit.28266](https://doi.org/10.1002/bit.28266)
82. Pradhan A, Lahare P, Sinha P, Singh N, Gupta B, Kuca K, et al. Biosensors as nano-analytical tools for COVID-19 detection. *Sensors*. 2021; 21(23): 7823. DOI: [10.3390/s21237823](https://doi.org/10.3390/s21237823)
83. Kaur R, Sharma SK, and Tripathy S. Advantages and limitations of environmental nanosensors. *Advances in nanosensors for biological and environmental analysis*. 2019. p. 119-132. DOI: [10.1016/B978-0-12-817456-2.00007-3](https://doi.org/10.1016/B978-0-12-817456-2.00007-3)
84. Ali Q, Zheng H, Rao MJ, Ali M, Hussain A, Saleem MH, et al. Advances, limitations, and prospects of biosensing technology for detecting phytopathogenic bacteria. *Chemosphere*. 2022; 296: 133773. DOI: [10.1016/j.chemosphere.2022.133773](https://doi.org/10.1016/j.chemosphere.2022.133773)
85. Karim ME. Biosensors: Ethical, regulatory, and legal issues. In: Thouand G, editor. *Handbook of cell biosensors*. Springer, Cham; 2021. p. 679-705. DOI: [10.1007/978-3-030-23217-7_23](https://doi.org/10.1007/978-3-030-23217-7_23)
86. Haleem A, Javaid M, Singh RP, Suman R, and Rab S. Biosensors applications in medical field: A brief review. *Sens Int*. 2021; 2: 100100. DOI: [10.1016/j.sintl.2021.100100](https://doi.org/10.1016/j.sintl.2021.100100)
87. González-Fernández E, de-los-Santos-Álvarez N, Lobo-Castañón MJ, Miranda-Ordieres AJ, and Tuñón-Blanco P. Impedimetric aptasensor for tobramycin detection in human serum. *Biosens Bioelectron*. 2011; 26(5): 2354-2360. DOI: [10.1016/j.bios.2010.10.011](https://doi.org/10.1016/j.bios.2010.10.011)
88. Shou D, Dong Y, Shen L, Wu R, Zhang Y, Zhang C, et al. Rapid quantification of tobramycin and vancomycin by UPLC-TQD and application to osteomyelitis patient samples. *J Chromatogr Sci*. 2014; 52(6): 501-507. DOI: [10.1093/chromsci/bmt069](https://doi.org/10.1093/chromsci/bmt069)
89. Zhao J, Guo W, Pei M, and Ding F. GR-Fe 3 O 4 NPs and PEDOT-AuNPs composite based electrochemical aptasensor for the sensitive detection of penicillin. *Anal Methods*. 2016; 8(22): 4391-4397. DOI: [10.1039/C6AY00555A](https://doi.org/10.1039/C6AY00555A)
90. Jahanbani S, and Benvidi A. Comparison of two fabricated aptasensors based on modified carbon paste/oleic acid and magnetic bar carbon paste/Fe3O4@ oleic acid nanoparticle electrodes for tetracycline detection. *Biosens Bioelectron*. 2016; 85: 553-562. DOI: [10.1016/j.bios.2016.05.052](https://doi.org/10.1016/j.bios.2016.05.052)
91. Ismail F, and Adeloju SB. Comparison of single layer and bilayer biosensors based on crosslinking of penicillinase for potentiometric detection of penicillin in milk and antibiotics. *Electroanalysis*. 2015; 27(6): 1523-1531. DOI: [10.1002/elan.201500037](https://doi.org/10.1002/elan.201500037)
92. Almeida SA, Truta LA, Queirós RB, Montenegro M, Cunha AL, and Sales MGF. Optimizing potentiometric ionophore and electrode design for environmental on-site control of antibiotic drugs: Application to sulfamethoxazole. *Biosens Bioelectron*. 2012; 35(1): 319-326. DOI: [10.1016/j.bios.2012.03.007](https://doi.org/10.1016/j.bios.2012.03.007)
93. Khorrami S, Abdollahi Z, Eshaghi G, Khosravi A, Bidram E, and Zarrabi A. An improved method for fabrication of Ag-GO nanocomposite with controlled anticancer and anti-bacterial behavior; a comparative study. *Sci Rep*. 2019; 9(1): 9167. DOI: [10.1038/s41598-019-45332-7](https://doi.org/10.1038/s41598-019-45332-7)
94. Khorrami S, Zarepour A, and Zarrabi A. Green synthesis of silver nanoparticles at low temperature in a fast pace with unique DPPH radical scavenging and selective cytotoxicity against MCF-7 and BT-20 tumor cell lines. *Biotechnol Rep*. 2019; 24: e00393. DOI: [10.1016/j.btre.2019.e00393](https://doi.org/10.1016/j.btre.2019.e00393)
95. Ganjuzadeh F, Khorrami S, and Gharbi S. Controlled cytotoxicity of Ag-GO nanocomposite biosynthesized using black peel pomegranate extract against MCF-7 cell line. *J Drug Deliv Sci Technol*. 2022; 71: 103340. DOI: [10.1016/j.jddst.2022.103340](https://doi.org/10.1016/j.jddst.2022.103340)