JOURNAL OF NANO- AND ELECTRONIC PHYSICS
Vol. **16** No 6, 06006(5pp) (2024)

ЖУРНАЛ НАНО- ТА ЕЛЕКТРОННОЇ ФІЗИКИ
Том **16** № 6, 06006(5cc) (2024)

REGULAR ARTICLE

Examining Ultrasensitive Nanobiosensors for Identifying Life-threatening Illnesses with Biological Objects

R.P. Singh[1,*] ✉, H. Kumar[2], S. Pandey[3], R.P. Verma[4], A.P. Srivastava[5], P.M. Pandian[6], Mr. A. Srivastava[7]

[1] *Department of Mechanical Engineering, GLA University, Mathura- 281406, Uttar Pradesh, India*
[2] *Chitkara Centre for Research and Development, Chitkara University, Himachal Pradesh,174103, India*
[3] *Centre of Research Impact and Outcome, Chitkara University, Rajpura- 140417, Punjab, India*
[4] *Department of Mechanical Engineering, Graphic Era Deemed to be University, Dehradun, Uttarakhand*
[5] *Lloyd Institute of Engineering & Technology, Greater Noida*
[6] *Department of Chemistry, Saveetha Engineering College, Thandalam, Chennai, Tamil Nadu, India*
[7] *Lloyd Law College, Greater Noida, India*

(Received 22 August 2024; revised manuscript received 15 December 2024; published online 23 December 2024)

The discovery of a new human coronavirus in 2019 and its rapid spread have led to a pandemic and increased morbidity. This has made it necessary to take more suitable action to improve the current diagnostic tools, which are labor-intensive, time-consuming, and immovable. In this situation, biosensors (BS) can be regarded as a means to surpass traditional methods and provide immediate diagnosis for multiple illnesses more effectively due to their rapidity, cost-efficiency, accuracy, selectivity, and sensitivity. Additionally, through effectively detecting a broad range of viruses, these BS have made it possible to give the proper treatment on time. This review attempts to examine the various types of BS that have been used to identify viruses. The area of nanotechnology has recently made significant advancements in diagnostic techniques with the invention of intelligent, small nanobiosensors (NBS) that have raised and revolutionized the diagnostic process. NBS are a suitable diagnostic tool for several types of viruses, such as COVID-19, due to their portability, durability, and cost. The current review has also thoroughly examined the function of these innovative NBS in the identification of COVID-19. Furthermore, this article has taken the difficulties and potential implications of creating such highly sensitive NBS before promoting these nano weapons as the ultimate, futuristic gold standard of diagnostics. This research can lead to significant advancements in medical diagnosis and treatment evaluation.

Keywords: Biosensors (BS), Nanotechnology, Life-threatening illnesses, Nanobiosensors (NBS).

DOI: 10.21272/jnep.16(6).06006 PACS number: 87.85.fk

1. INTRODUCTION

The combination of nanotechnology with biosensing has emerged as a significant paradigm in healthcare, leading to a new era of precise detection. Ultrasensitive NBShave generated a significant level of attention in the modern era of science for their unique ability to detect extremely small organisms, allowing for the early detection of life-threatening diseases. The combination of nanoscience and biosensing has great potential to transform disease identification, therapy, and patient outcomes [1].

NBS is the integration of nanotechnology and biological sensing principles, offering an environment that surpasses the constraints of traditional diagnostic procedures. These tiny marvels are able to identify biomolecules at previously unknown concentrations because they take advantage of the unique qualities of nanomaterials to attain extraordinary sensitivity [2]. The fundamental process frequently includes the relationship between these nanomaterials and organisms, leading to exceptionally regulated and responsive reactions that can be utilized for diagnostic purposes [3].

Ultrasensitive NBS are primarily powerful because of their unparalleled capacity to identify biomarkers related to severe disorders. These types of sensors can detect and strengthen signals coming from certain biological beings by utilizing the natural characteristics of nanomaterials like graphene, carbon nanotubes, or metal nanoparticles. This increased sensitivity enables the early identification of disorders, allowing medical professionals to respond at a stage when treatments are most important, thus significantly enhancing patient outcomes [4].

The essential application of these NBS involves detecting life-threatening diseases, where early detection frequently leads to increased chances of survival [5].Ultrasensitive NBS has the potential to greatly help

* Correspondence e-mail: pratap.ravindra@gla.ac.in

Cite this article as: R.P. Singh et al., *J. Nano- Electron. Phys.* 16 No 6, 06006 (2024) https://doi.org/10.21272/jnep.16(6).06006

various health difficulties such as infections, cancer, and neurological disorders [6]. Detecting specific biomarkers related to these disorders in their early stages has a chance to significantly change the way diseases are managed, leading to a more aggressive and individualized approach [7].

Additionally, the adaptability of ultrasensitive NBS extends beyond their diagnostic capabilities. Their ability to interact effectively with different biological samples, such as saliva, blood, and urine, makes them highly useful in a wide range of clinical environments. The non-invasive characteristic not only facilitates the process of diagnosis but also encourages patients to cooperate and feel comfortable, thus promoting a patient-centered approach to treatment [8-10].

2. PRESENCE OF LIFE-THREATENING ILLNESSES

In recent years, there has been a rapid discovery of life-threatening illnesses, which have been responsible for numerous endemics, outbreaks, and epidemics throughout all demographic regions. These obligated organisms cause numerous diseases by entering host cells and utilizing receptor-ligand association chemistry. Prominent examples of human viruses that cause significant health issues include hepatitis B virus (HBV), hepatitis C virus (HCV) [11-12], and HIV. Likewise, several viruses such as Zika virus (ZKV), influenza, respiratory syncytial virus, astroviruses, rotavirus, and West Nile virus cause substantial harm to the organs they target, hence providing severe dangers to human health and resulting in illness and death [1]. Table 1 displays the various viruses identified at different times worldwide.

Table 1 – Different viruses identified at various times

Year	Virus	Location	Reference
2016, February	Zika Virus (ZKV)	Worldwide, Brazil	[13]
2015-2016	Zika Virus (Asian)	Western Hemisphere	[14]
1998	Nipah Virus	Malaysia	
2001 and 2007	Nipah Virus	Bangladesh	[15]
2001 and 2007	Nipah Virus	India (Kerala)	

At present, there are three very aggressive influenza viruses known as CoVs, including SARS-CoV-1, MERS-CoV, and the newly discovered COVID-19. These viruses have caused numerous respiratory disorders worldwide [16]. The initial influenza viruses, considered to have originated from bird species and subsequently transmitted to horses before infecting humans, were responsible for the 1918 outbreak. This catastrophic event claimed the lives of around 50 million individuals worldwide within two years. The “Asian flu” and the “Hong Kong flu," which occurred in the “1950s and 1970s”, resulted in the deaths of over 2 million individuals [17].

3. LIFE-THREATENING ILLNESSES

In December 2019, an increase in pneumonia cases with a mysterious cause occurred in the city of Wuhan, China. These cases were unusual and weren't reported before. The WHO has designated the illness as coronavirus disease-19. On “March 13, 2020”, the WHO stated Covid-19 was a worldwide outbreak. COVID-19 is a result of a new pathogen that shares 80% genetic similarity with an already-known virus called SARS-CoV, which was discovered in China in 2002. Additionally, it shares 50% genetic similarity with another virus called MERS-CoV. The International Viral Classification Commission has assigned the new pathogen COVID-19 because it resembles SARS-CoV more than any other pathogen. The global impact of COVID-19 leads to serious medical problems and subsequently imposes a socioeconomic impact. This is due to the fact that the virus has the ability to transmit between individuals, regardless of whether they exhibit symptoms or not [18].

3.1 Clinical Manifestations

The WHO has reported that individuals of every age category are prone to acquiring Covid-19. The spread of the virus typically occurs through indirect or direct contact with an affected individual. Life-threatening illness particles can be spread through droplets released during sneezing or coughing, as well as through contact with infected objects. RNA was identified in rectal samples, indicating the spread through the fecal-oral route is possible [19].

3.2 Virology

Coronaviruses are large, spherical viruses that are covered by a protective envelope. They possess a genome made up of a single strand of RNA, which is positive-sense and ranges in length from 27 to 32 kb. The family Coronaviridae comprises two subdivisions, namely Coronavirinae and Torovirinae. There has been the identification of four genera within the Coronavirinae family, namely Gamma coronavirus, Delta coronavirus, Alphacoronavirus, and Beta coronavirus. HCoV-229E and NL63 are classified as Alphacoronaviruses, while MERS-CoV, HCoV-OC43, Covid-19, SARS-CoV, and HCoV-HKU1 are classified as Beta coronavirus.

The genetic material of Covid-19 is primarily composed of 10 “open reading frames (ORFs)." The initial ORF includes approximately two-thirds of the RNA molecule and undergoes translation to produce two extensive polyproteins. The remaining ORFs contain the primary structural proteins of the RNA genome, which include the membrane envelope protein (E), nucleocapsid protein (N), spike glycoprotein (S), and glycoprotein (M). These proteins collectively cover one-third of the genome. In addition to these four primary protein structures, there are other auxiliary proteins whose activities remain unknown. They are not involved in the viral replication procedure. Multiple scientists have determined that

COVID-19 depends on “angiotensin-converting enzyme 2 (ACE 2)” as its sense organ for invading host cells. The interaction between the virus and cell sense organs is crucial for the development of infection. The spike protein connects the virus to the ACE 2 sense organ after endosome entry. Once viruses enter cells, their genomes are recovered and transformed into Polyproteins from viruses. The cytoplasm is the site of transcription and replication for both the capsid protein and virus RNA. The Golgi complex receives the remaining structural proteins after transcription and translation in the endoplasmic reticulum.

4. NANOBIOSENSORS: NEW DEVELOPMENTS IN QUICK IDENTIFICATION

BS has been utilized for nearly four decades. To enhance its development, researchers are currently concentrating on nanoscience and technologies. Nanomaterials are being utilized to develop NBS that can accurately and selectively diagnose nucleic acids, such as DNA or RNA.NBS are sensors composed of nanomaterials, as displayed in Fig. 1. Nanomaterials in BS are notable for their unique features, including mechanical, electrical, catalytic, magnetic, biological, optical, and surface. Whereas NBS perform identically to BS, their transducers are made from nanomaterials. NBS offers benefits over conventional approaches, including reusability, speed, low power usage, and enzyme insertion. The inclusion of nano-sized elements in NBS enhances sensitivity, enabling smaller sensors to reduce experimental space requirements. By using sophisticated technology, nanobiosensor manufacturing expenses can be decreased, leading to lower healthcare expenditures for illness identification and evaluation.

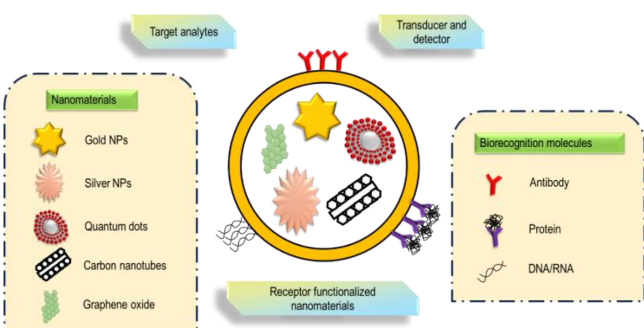

Fig. 1 – Diagrammatic representation of a nanobiosensor

NBS are a more appealing technological option for better illness detection because of their many benefits. “Human T-cell lymphotropic virus (HTLV-1)” and HIV-1 can both be detected early with the use of NBS.Identification using NBS is more precise, quick, sensitive, and economical. Recently, based on EC and optical approaches, nanomaterials were used to build genosensors for the diagnosis of HTLV-1 and HIV-1, improving clinical therapy and reducing virus proliferation. An EC-based DNA BS was developed for Ebola virus identification. Developed by modifying the gold electrode, the device utilized “single-strand DNA (ssDNA)” as a capturing test and hybridized using “biotinylated target nucleic acids."

4.1 Variety of Nanobiosensors

Recently, BS have included a variety of nanomaterials to improve their accuracy and selectivity. The sections that follow address some of the more significant varieties of NBS.

4.1.1. Carbon-based Nanomaterials

Carbon Nanotubes

Medical applications include round carbon nanoparticles due to their basic geometry, non-immunogenicity, biocompatibility, and homogenous surface chemistry. They are less significant due to limited biomedical uses. Since 1991, there has been increased research on “carbon nanotubes (CNTs)” for use in NBS because of their strong mechanical properties, quick heterogeneous and extended electron transmission, large surface area, excellent electrical conductivity, and chemical durability.Distant electron transport, a large surface area, and rapid heterogeneity have made CNTs a popular choice in recent years. Adsorbing nucleic acids or biomolecules on enhanced CNTs and attaching them to functional structures enables fast and efficient label-free bioelectronic identification. Enhanced CNT-based electrodes with AuNP were created for detecting life-threatening Illnesses. Depositing metal nanoparticles on single-walled CNTs (SWCNTs) utilized electrical resistance. Viral nucleic acids can be mounted on SWCNTs/AuNP using probe DNA. This is useful in early medical identification.

Graphene-based Nanobiosensors

A popular carbon-based nanomaterial with unusual physical characteristics. NBS made from graphene oxide (GO) are produced using the reduction technique. NBS benefit from functionalized graphene sheets, also known as chemically reduced GO, due to their elevated “surface-to-volume ratio” and electron transferable ability. Their visible characteristics are unexplored. Specifically, graphene is used for EC identification of tiny biomolecules. Similar to CNTs, graphite coated with metallic nanoparticles improves virus detection accuracy compared to traditional approaches. Unique viruses have been identified using optical biosensing.

4.1.2. Metal-based Nanobiosensors

Silver Nanoparticles

The most commonly utilized metallic nanoparticles are silver nanoparticles (AgNP), especially in biological identification. They are employed in EC and SPR BS due to their physicochemical features, high adsorption, and excellent electric conductivity. A label-free fluorescent framework was designed using DNA-stabilized silver nanoclusters to identify two HIV DNAs together. An additional study was conducted that demonstrates the real-time detection of influenza viruses with a single virus labeled with AgNP.

Gold Nanoparticles (AuNP)

AuNP are easily synthesized, have a wide surface area, adsorb well, and conjugate to biomolecules. Due to these features, EC and optical nanobiosensor-based life-threatening illness detection methods are examined. AuNP serve as catalytic tags and electroactive for viral identification in EC experiments. The lateral-flow immuno chromatographic evaluation, which uses colloidal gold nanoparticles for the identification of "herpes simplex virus type 2", was developed. A test for identifying and measuring HCV by utilizing the unique physicochemical and visible characteristics of gold nanoparticles.

4.1.3. Electrospun Nanofibers

A standard nanotechnology procedure called electrospinning uses an electric field force to push a charged liquid jet toward an oppositely charged collector in a polymer solution, resulting in the deposition of small fibers. Electrospun nanofibers are employed in delivering drugs, biosensing, and tissue engineering structures. Benefits include substantial specific surface area, improved sensibility, and high permeability. NBS uses sensing concepts related to electric resistance, electric current, optical technology, photoelectricity, and vibration frequency.

DNA hybridization is detected by an extremely sensitive EC platform that uses electrospun semiconducting manganese oxide. This BS detects zeptomolar in "dengue consensus primer" using EC conversion with a 120×10^{-21} M detecting range.

4.1.4. RT-LAMP Mediated Nanoparticle-based BS

A highly accurate RT-LAMP examination employing nanoparticles as a BS has been designed to identify COVID-19. One stage amplifies and detects viral nucleoprotein genes, LAMP primer sets, and F1ab. A nanoparticle-based BS evaluates the results of detection. The 12 copies per reaction sensitivity renders this assay more sensitive and accurate. Also, they provide low false-positive outcomes. Just one hour was spent on detection.

4.1.5. FET-based BS

A BS based on FETs detects Covid-19 in clinical samples. This device utilizes graphene for extremely accurate evaluation. Appropriate antibodies were combined with graphene sheets in the FET to produce BS. The evaluation was conducted using nasopharyngeal swab samples from infected individuals. The FET BS is capable of detecting the Covid-19 spike protein in self-culture media with a limit of detection of 1.6×10^1 plague forming units/ml (pfu/mL) and in "nasopharyngeal swab samples" using an identification limit of 2.42×10^2 copies/ml (copies/mL). The device exhibited a high level of sensitivity and quick identification of a small amount of the target material without causing any interaction with the MERS-CoV antigen.

4.1.6. Drawbacks of Nanobiosensors

NBS can detect a wide variety of viruses, however, multiple constraints limit their utility in medicine. Some NBS are unaffordable due to the expensive nature of raw ingredients like CNTs. It limits large-scale nanobiosensor manufacture and commercialization. NBS' dimensions and sensitivity to synthesis methods make producing them challenging.

Additionally, the negative and cytotoxic consequences of NBS are not widely recognized. Toxic nanomaterials are primarily influenced by their composition, dimension, form, surface chemistry, appearance, and protein absorption gradient. Therefore, manipulating physicochemical features can reduce toxicity. Additionally, the effect of NBS in biological environments is not widely recognized. It is crucial to research the biological significance of NBS before building them for widespread utilization.

5. CONCLUSION

NBS with exceptional sensitivity detects severe diseases by interacting with biological entities, providing unmatched sensitivity. Modern technology provides quick and accurate detection of health risks, transforming diagnostic capacities and enhancing timely intervention for crucial medical diseases. This review analyzed the wide variety of BS employed for life-threatening illness detection. Nanotechnology has recently made substantial progress in diagnostic approaches with the development of intelligent, compact NBS, which have greatly enhanced and transformed the method of diagnosis. NBS provides the necessary characteristics of portability, durability, and cost-effectiveness, making them an appropriate diagnostic tool for several viruses, including COVID-19. The present review further comprehensively investigated the role of these advanced NBS in the detection of Covid-19. The difficulties involve interference with signals, strength, and scalability. The accuracy of practical applications may be affected by sensitivity to atmospheric circumstances and complicated biological systems. The future aspects depend on improving the accuracy of resolving interference with signals, strength difficulties, and scalability problems. It can lead to significant advancements in medical diagnosis and treatment evaluation.

REFERENCES

1. A. Alba-Patiño, A. Vaquer, E. Barón, S.M. Russell, M. Borges, R. de la Rica, *Microchimica Acta* **189** No 2, 74 (2022).
2. M. Kumari, V. Gupta, N. Kumar, R.K. Arun, *Mol. Biotechnol.* **66**, 378 (2023).
3. M. Hegde, P. Pai, M.G. Shetty, K.S. Babitha, *Monitor. Manag.* **18**, 100756 (2022).
4. S. Padma, P. Chakraborty, S. Mukherjee, *Next-Generation Nanobiosensor Devices for Point-Of-Care Diagnostics,* 79 (2022).
5. N. Panchal, V. Jain, R. Elliott, Z. Flint, P. Worsley, C. Duran, T. Banerjee, S. Santra, *Anal. Chem.* **94** No 40, 13968 (2022).
6. X. Zhang, Y. Shi, G. Chen, D. Wu, Y. Wu, G. Li, *Small Meth.* **6** No 10, 2200794 (2022).
7. A.D. Teklemariam, M. Samaddar, M.G. Alharbi, R.R. Al-Hindi, A.K. Bhunia, *Mol. Cellular Probes* **54**, 101662 (2020).
8. M. Sadeghi, S. Sadeghi, S.M. Naghib, H.R. Garshasbi, *Biosensors* **13** No 4, 481 (2023).
9. N.M. Noah, P.M. Ndangili, *J. Anal. Meth. Chem.* **2019**, 2179718 (2019).
10. Y. Fu, Q. Ma, *Nanoscale* **12** No 26, 13879 (2020).
11. R. Samson, G.R. Navale, M.S. Dharne, *Biotech.* **10** No 9, 385 (2020).
12. R. Torabi, R. Ranjbar, M. Halaji, M. Heiat, *Mol. Cellular Probes* **53**, 101636 (2020).
13. D. Baud, D.J. Gubler, B. Schaub, M.C. Lanteri, D. Musso, *Lancet* **390** No 10107, 2099 (2017).
14. F. Javed, K.N. Manzoor, M. Ali, I.U. Haq, A.A. Khan, A. Zaib, S. Manzoor, *J. Basic Microbiol.* **58** No 1, 3 (2018).
15. D.U. Ehichioya, S. Dellicour, M. Pahlmann, T. Rieger, L. Oestereich, B. Becker-Ziaja, D. Cadar, Y. Ighodalo, T. Olokor, E. Omomoh, J. Oyakhilome, *J. Virology* **93** No 21, 10 (2019).
16. A. Audi, M. AlIbrahim, M. Kaddoura, G. Hijazi, H.M. Yassine, H. Zaraket, *Front. Public Health* **8**, 576 (2020).
17. R. Noor, S.M. Maniha, *Virusdisease* **31**, 441 (2020).
18. M. Srivastava, N. Srivastava, P.K. Mishra, B.D. Malhotra, *Sci. Total Environ.* **754**, 142363 (2021).
19. W. Wang, Y. Xu, R. Gao, R. Lu, K. Han, G. Wu, W. Tan, *JAMA* **323** No 18, 1843 (2020).

Вивчення ультрачутливих нанобіосенсорів для ідентифікації небезпечних для життя хвороб за допомогою біологічних об'єктів

R.P. Singh[1], H. Kumar[2], S. Pandey[3], R.P. Verma[4], A.P. Srivastava[5], P.M. Pandian[6], Mr. A. Srivastava[7]

[1] *Department of Mechanical Engineering, GLA University, Mathura- 281406, Uttar Pradesh, India*
[2] *Chitkara Centre for Research and Development, Chitkara University, Himachal Pradesh,174103, India*
[3] *Centre of Research Impact and Outcome, Chitkara University, Rajpura- 140417, Punjab, India*
[4] *Department of Mechanical Engineering, Graphic Era Deemed to be University, Dehradun, Uttarakhand*
[5] *Lloyd Institute of Engineering & Technology, Greater Noida*
[6] *Department of Chemistry, Saveetha Engineering College, Thandalam, Chennai, Tamil Nadu, India*
[7] *Lloyd Law College, Greater Noida, India*

Виявлення в 2019 році нового коронавірусу людини та його швидке поширення призвели до пандемії та зростання захворюваності. Це призвело до необхідності вжиття більш відповідних заходів для вдосконалення поточних діагностичних інструментів, які є трудомісткими, забирають багато часу та є нерухомими. У цій ситуації біосенсори (БС) можна розглядати як засіб, який перевершує традиційні методи та забезпечує ефективнішу негайну діагностику багатьох захворювань завдяки їх швидкості, економічності, точності, вибірковості та чутливості. Крім того, завдяки ефективному виявленню широкого спектру вірусів ці БС дають змогу вчасно призначити належне лікування. У цьому огляді зроблено спробу вивчити різні типи БС, які використовувалися для ідентифікації вірусів. Сфера нанотехнологій нещодавно досягла значного прогресу в діагностичних методах завдяки винаходу інтелектуальних малих нанобіосенсорів (НБС), які підняли та революціонізували діагностичний процес. НБС є придатним діагностичним інструментом для кількох типів вірусів, таких як COVID-19, завдяки своїй переносимості, довговічності та вартості. У поточному огляді також було ретельно вивчено функцію цих інноваційних НБС у ідентифікації COVID-19. Крім того, у цій статті розглянуто труднощі та потенційні наслідки створення такого високочутливого НБС перед тим, як просувати цю нанозброю як остаточний футуристичний золотий стандарт діагностики. Це дослідження може призвести до значного прогресу в медичній діагностиці та оцінці лікування.

Ключові слова: Біосенсори (БС), Нанотехнології, Небезпечні для життя хвороби, Нанобіосенсори (НБС).