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Review Article

Optical Detection of the Viruses by Gold Nanoparticles (AuNPs)

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Viruses are dangerous pathogenic biological agents as they are highly infectious, very small in size, and have no real cure. Thus, early detection is the crucial step in defense against such threats. The optical biosensor is one of the appropriate approaches to the detection of viruses. An optical biosensor is a compact analytical device that contains a biorecognition sensing element integrated with an optical transducer system. This review is aimed at reporting the basic concept of optical biosensors with the recent biomedical applications of its varied forms briefly. Also, this paper focuses on the gold nanoparticles (AuNPs) based on optical biosensors and their few forms. Further, we discuss the varied forms of AuNPs-based biosensors in detecting various viruses in recent decades. This study has presented some recent achievements of AuNPs-based optical biosensors in virus detection in the last decade. Also, we have discussed some challenges being faced by the optical sensors and also their future prospects.

1. Introduction

There is a high demand for sensors that can detect small amounts of pathogenic biological agents in a populated area or field condition. Because of their great infectivity, small size, and lack of a viable cure, viruses are particularly deadly. It is extremely difficult to identify viruses in real time, so that a large network of sensors must be deployed in order to have any chance of early detection of this threat. The majority of currently used methods for detecting viral biomolecules rely on biochemical binding to functionalized surface [1]. Hemagglutinin inhibition, complement fixation, and Madin–Darby canine kidney cell culture are traditional techniques for viral detection. These techniques, while efficient, typically involve time-consuming laboratory processes and frequently call for experienced staff to carry them out. Designing and researching nanomaterials for biological and biomedical applications have advanced significantly in recent years [2]. Moreover, a label-free sensing technique is frequently utilized for biosensing, particularly when optical instruments are involved.

Nanomaterials have special physical, chemical, electrical, and optical characteristics that can be used in biosensors. Additionally, nanoparticles can be easily functionalized with target substrates and operate at the same scale as biological processes. Among various metals or metal oxides, gold nanoparticle-based techniques for the detection of pathogens gained the focus of the researcher [3]. The gold nanoparticles can be synthesized in the lab by chemical route [4], green synthesis [5], electrochemical method [6], bottom-up, and top-down method [7]. Since AuNPs have a high surface-to-volume ratio and a distinctive optical characteristic, they are very useful for pathogen identification [8]. It offers a variety of chances to create biosensors for pathogen detection because of its capacity to interact with the biomolecule [9]. Physical characteristics like size, shape, biocompatibility, and other factors influence the optical properties of AuNPs. AuNP is widely desired for optical biosensors due to its strong absorption coefficient, scattering flux, and luminescence characteristics [10]. Additionally, the surface plasmon resonance (SPR) is brought about by the oscillation of electrons on the surface of AuNPs, and this produces various absorption and scattering bands depending on the size,

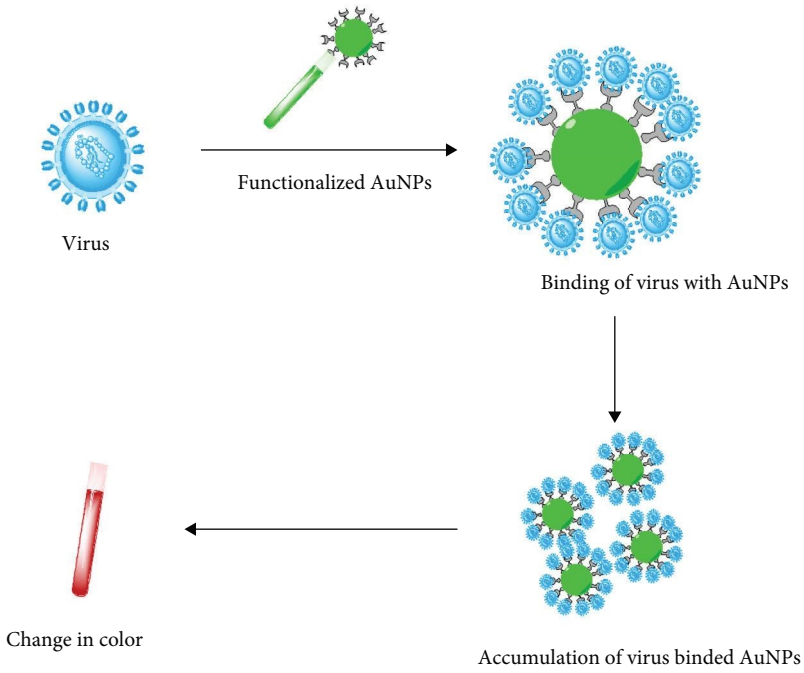

Figure 1: Schematic diagram representing the possible mechanism of optical detection of virus using AuNPs.

shape, and surface of AuNPs [11]. The resonance wavelength of SPR in a gold nanoparticle is highly dependent on the environment around the particles. When a nanoparticle binds with the biomolecule, the absorption and scattering properties of the nanoparticles change (Figure 1). The change in optical properties of nanoparticles according to the environment increases the demand for AuNPs to synthesize optical biosensors [12].

Besides optical sensing properties, AuNPs can also be applied in various biological fields. AuNPs have been showing potential in cancer therapy. The conjugation of particular gold nanostructures with tumor-specific drugs enables more precise diagnosis and focused treatment. The use of AuNPs for the treatment of cancer has become more common, in addition to their application in tumor diagnosis [13, 14]. One of the most often used techniques is photothermal destruction of tumor tissues, which entails administering gold nanorods with an SPR frequency in the near-infrared spectroscopy region, followed by radiation exposure producing localized heating of cancerous tissue, ultimately leading to tumor elimination [15, 16]. Another application of AuNPs is the treatment of bacterial infections; in this case, antibiotic medications are coated on the AuNPs and tested against bacteria that are multidrug resistant. Also, some of the interesting and distinctive applications include imitating a virus, boosting the heart's electrical signaling, being used as a sterilizing system, and managing the development of blood vessels [16–19]. The most common metal employed in aggregation-based immunoassays is gold because it has the most plasmonic interaction with light of all metals and has the strongest localized surface plasmon resonance (LSPR) peak. Gold is also regarded to be innocuous and allows nanoparticle suspension to considerable scatter visible light, enabling visual detection [20].

This overview summarizes current optical biosensor research and development efforts. Including SPR, fluorescence, colorimetric, chemiluminescence (CL), and surface-enhanced Raman scattering (SERS), we will offer an overview of the functions of AuNPs-based optical biosensors for viral detection.

2. Main Text

2.1. Development of Optical Biosensor Production. Infectious diseases continue to be a constant threat to human health worldwide, particularly in rural cities. The lack of proper analytical techniques and subsequent treatment approaches as a result of the inadequately equipped health care facilities for diagnosis can be summed up as the underlying causes of such severe illnesses. Traditional viral detection techniques are time-consuming and costly, so there is a growing need for precise viral biosensors by rapid detection systems [21]. Biosensor research was first begun in 1962 when Clark and Lyons proposed the first glucose sensor at Children's Hospital in Cincinnati. Since then, the use of biosensors in several industries, including medicine, agriculture, food safety, environmental protection, biodefense, and many others, has increased [22]. Restructuring the sensing module of our current analytical procedures to detect biomolecules, particularly nanosized items like proteins and viruses, has a significant impact on turning them into diagnostic strategies. Since viruses mutate quickly and move primarily from person to person, there is obviously a need for constant modifications to present sensing platforms to handle these developing difficulties [23].

There is a lot of interest in creating sensors that can screen for viruses quickly and accurately with the least

amount of sample handling and laboratory expertise needed. One approach is to create single-step direct sensing techniques that do not require any signal-reporting agents to be separated, incubated, or combined [24]. One of the most often used types of biosensors is the optical biosensor, a small analytical tool with a biorecognition sensing component linked with an optical transducer system. It operates on the fundamental tenet that a signal is generated that is proportionate to the concentration of a measured substance when the interaction of the optical field with a biorecognition element is utilized (analyte). Label-free and label-based modes are the two broad categories into which optical biosensing can be divided. In the label-free mode, the contact of the sample with the transducer produces the signal directly, but in the label-based mode, the label is used, and the optical signal is then produced using a variety of additional techniques, including colorimetric, fluorescent, luminescent, and more. Optical biosensors can use a variety of biological components as biorecognition elements, including enzymes, antibodies, antigens, receptors, nucleic acids, entire cells, and tissues [25].

Because optical biosensors make it possible to detect various biological and chemical compounds directly, in real-time, and without the use of labels, they have significant benefits over traditional analytical methods. High specificity, sensitivity, compactness, and cost-effectiveness are only a few of its benefits. The development of new optical biosensors involves the use of numerous cutting-edge ideas and highly interdisciplinary methodologies from the fields of microelectronics, microelectromechanical systems, micro/nano-technologies, molecular biology, biotechnology, and chemistry. Over the past 10 years, optical biosensor research and technological advancement have grown exponentially. The evanescent field at the biosensor surface is used via optical waveguide interferometry, SPR, and evanescent wave fluorescence to detect the interaction of the biorecognition elements with the analyte [25, 26]. Optical biosensors based on colorimetry and chemiluminescence are further potential approaches.

SERS, SPR, fluorescent, luminescent, and other variations can all be used to build optical biosensors. In the past 20 years, sophisticated optical biosensors have been developed. Daniel et al. [27] created a whole-cell bioluminescent biosensor in 2008. Sensitive optical detection was accomplished using a single-photon avalanche photodiode (SPAD). The outcome demonstrated that the bioluminescence signal initially depends on the time square and that the spectrum's strength is inversely related to frequency [27]. By immobilizing two different hapten conjugates, MC-LR-OVA and NB-OVA, onto the same fiber-optic probe for the detection of tiny analytes. In 2010, Long et al. [28] created a unique optic fiber-based immunoassay biosensor. The detection thresholds for microcystin-LR (MC-LR) and trinitrotoluene (TNT) were determined to be 0.04 g/L and 0.09 mg/L, respectively, ensuring good regeneration performance, binding characteristics, and robustness of the sensor surface of the proposed immunoassay biosensor [28].

The fiber optic SPR biosensor with nanobead signal amplification was initially published by Pollet et al. [29]. The outcome demonstrated that applying magnetite nanoparticles as a supplementary label improved the detection limit for the bioassay of Ara h1 peanut allergens from 9 to 0.009 g/L. Additionally, a larger linear dynamic range, 0.1–2 g/mL, was discovered [29]. The ultra-sensitive colorimetric immunoassay biosensor for the detection of the influenza virus was developed by Ahmed et al. [30] using positively charged AuNPs that function as inorganic enzymes that imitate peroxidase. According to the findings, the linear range for H1N1 virus detection was up to 10 pg/mL, and for H3N2 virus detection, it was up to 10 plaque-forming units (PFU) per mL. The outcome also showed an improvement in sensitivity up to 500 times greater than that of commercial viral kits [30]. Tereshchenko et al. [31] created a photoluminescence-based biosensor for GVA-antigens in 2016 by studying the effects of immobilized grapevine virus A antibodies on the photoluminescence spectra on the ZnO. The biosensor's sensitivity was discovered to be between 1 pg/mL and 10 ng/mL [31]. Similarly, Viter et al. [32] also created a photoluminescence-based biosensor for the detection of Salmonella antigen in 2017 using TiO_2 nanoparticles. This designed biosensor's sensitivity was found to be between 10^3 and 10^5 cells/mL [32]. A fiber Bragg grating (FBG)-based optical sensors had a substantial market value because of a number of benefits including; their compact size, light, weight, lack of electrical connections, and compatibility with nonintrusive remote sensing [33]. A variety of wavelength of light was primarily flowed through the FBG, but one particular wavelength was reflected back [34].

A chemiluminescent-based DNA fiber optic genosensor for the detection of the hepatitis A virus (HAV) was developed by Ye et al. [35]. The result has shown that biosensors could detect at levels as low as 5 pg/L and as high as 50 pg/L for both cDNA and RNA [35]. In 2017, Durmanov et al. [36] developed a novel SERS substrate in the form of silver nanofilm through a physical vapor deposition method for the detection of four different species of viruses—Myxoma virus, Canine Distemper virus, Tobacco Mosaic virus and Potato Virus X [36]. Similarly, in 2019, Kukushkin et al. [37] successfully detected the influenza virus by applying the highly sensitive and rapid technology of the SERS aptasensor. The limit of detection was achieved as low as $1–10^{-4}$ hemagglutination units per probe for the H3N2 virus. This sensor was able to provide recognition of various influenza viral strains, including H1, H3, and H5 hemagglutinin subtypes thus could be applied for fast and low-cost strain-independent detection of influenza viruses [37].

2.2. Development of AuNPs-Based Optical Biosensors. Typically, photon and light output changes are measured by optical biosensors. The optical features of AuNPs-based optical biosensors, which result from the cooperative oscillation of conduction band electrons (plasmon) in response to electromagnetic radiation, offer a wide range of opportunities [38]. The technique of SPR has mostly been utilized to study the interaction of macromolecules with surface-bound ligands (e.g., proteins). Recently, the endeavor has been expanded to include large-size analytes including bacterial and viral disease [39] and cells [40, 41]. It is a type of optical sensing

model used for examining and describing physiochemical changes in a thin coating on a metal surface [38]. An inherent quality of AuNPs is SPR, which can be exploited to increase the sensitivity of gold-based sensors to detect biomolecules at low concentrations. Based on the development of a compound including gold nanorods and a particular specific antibody, this feature has been employed to produce sensors [42]. The dielectric constant of metallic films may change as a result of the binding of particular molecules to the surface, which may alter how laser light reflects off the metal–liquid interface. The SPR peaks of gold nanostructures can be tuned from the visible to the near-infrared region by controlling the shape and structure (solid vs. hollow). In this tutorial review, we highlighted this concept by comparing four typical examples: nanospheres, nanorods, nanoshells, and nanocages. A combination of this optical tunability with the inertness of gold makes gold nanostructures well-suited for various biomedical applications [33]. The LSPR refers to the attempt made by several studies to correlate the peak strength and location of the surface plasmon absorbance of AuNPs with the local reflecting index of the surrounding medium [21]. The biosensing event based on LSPR spectral shifts often referred to as "wavelength-shift sensing," is caused by the surrounding dielectric environmental change when a binding event occurs. These days, LSPR-based sensing systems are thought to be the plasmonic label-free techniques of the next generation [25].

Furthermore, fluorescence is one of the most commonly studied optical sensors and they typically use dyes, quantum dots, and fluorescent proteins as labels [43] because quantum dots have a narrow excitation wavelength that has been successfully used to simultaneously detect separate pathogens [11]. Fluorescence-based biosensors have been explored for various applications such as medical diagnostics, drug delivery, drug discovery, environmental monitoring, and food safety. Various working strategies are designed for fluorescence biosensors to detect different analytes. Numerous parameters can be explored in fluorescence biosensors such as fluorescence intensity, fluorescence anisotropy, decay time, energy transfer (radiative or nonradiative), quenching efficiency, and quantum yield [10]. Chemiluminescence (CL) is defined as material molecules generating optical radiation after absorbing chemical energy. The CL method has an attractive technique with a simple optical structure, low background, high sensitivity, and wide linear dynamic range nature; the intensity of the luminous radiation reflects the concentration of the analytes. In recent years, AuNPs were widely employed to amplify CL emission using catalysts, reductants, luminophores, or energy acceptors. For the CL enhancement mechanism, it was supposed that the AuNPs facilitated the radical generation and electron-transfer processes taking place on the surface of AuNPs [44]. Many researchers put continuous efforts into labeling biomarkers (e.g., proteins, genes, and chemiluminescent agents) onto the surface of AuNPs so as to improve the sensitivity of CL. All of these efforts are to develop rapid, sensitive, automatic, and point-of-care detection methods [45].

Colorimetric detection by using AuNPs have been widely studied because of their particular optical properties, i.e., LSPR, which represents a color with maximal absorbance wavelength. AuNPs have been utilized in colorimetric assays based on the distance-dependent optical property. AuNPs-based colorimetric detections were developed as rapid, visual assays that require little or no instrumentation for the detection of diverse biological molecules (e.g., proteins and nucleic acids), metal ions in which the change in particle color is generated by sensitive reactivity of nanosized particles to external condition. In addition, the dispersed state is adjustably modified from artificial electrostatic force control by ion, pH, biomacromolecules, and so forth [44, 46].

SERS has emerged as a promising spectroscopic technique for biosensing which enhances the single-molecule sensitivity, intrinsically sharp fingerprints, as well as availability of a wide range of photostable labels of the vibration spectra of a molecule by several orders of magnitude when it is in close proximity to nanoparticles made of gold or silver [25, 44]. It is an ultrasensitive signal amplification method that allows for detection and analysis at very low concentrations. In recent years, researchers have combined SERS with an immunochromatography system to explore high-sensitivity detection of low-level biomarkers of viruses and bacteria [47]. Typically, SERS enhancement comes from two mechanisms: chemical mechanism (CM) and electromagnetic mechanism (EM). The CM is based on a charge transfer between the molecule and the substrate and is a short-range effect that usually requires the molecule to be close enough to the substrate. While, the EM is concentrated on the "hotspots," which results from the coupling of the LSPR fields of AuNPs or AgNPs [44].

2.3. Characterization of AuNPs. Generally, the AuNPs synthesized by both chemical method or green synthesis method are characterized by various technique such as UV–visible spectroscopy (UV–vis), powder X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), energy dispersive spectroscopy (EDS), dynamic light scattering (DLS), Zeta potential, scanning electron microscopy, transmission electron microscopy, atomic force microscopy [48–50]. UV–vis spectroscopy is mainly used for the confirmation of formation of nanoparticles as well as to estimate the size of synthesized nanoparticles. The various metallic nanoparticles of different sizes ranging from 2 to 100 nm show absorbance peak between 300 and 800 nm in UV–vis spectra. Similarly, the AuNPs show UV–vis absorbance peak in the range of 500–580 nm. DLS analysis estimates the size distribution of nanoparticles and quantifies their surface charges. Element composition is determined by EDAX analysis [51, 52]. XRD technique is usually carried out for the determination of crystallite size [53]. The surface residues and functional groups such as flavonoid, phenol, and hydroxyls that attach to the surface of nanoparticles during their synthesis for efficient reduction and stabilization are identified by FTIR spectroscopy [54].

2.4. Current Situation of Optical Biosensor Using AuNPs and Its Application for Virus Detection. Because of its distinctive optical feature, high density, high atomic number, ease of synthesis, characterization, surface modification, outstanding stability, biocompatibility, and exceptionally high absorption

coefficients, AuNP is one of the top nanostructures that are used extensively around the world for the detection of pathogens. Furthermore, the ability to control the size and structure of AuNPs as well as their chemical stability and water solubility make them well-known. With sizes ranging from 1 to 800 nm and a range of morphological morphologies, including spheres, rods, prisms, tetrapods, dog bones, cubes, shells, and different hollow structures, AuNPs are a perfect instrument for viral detection [8]. Due to their high sensitivity, optical biosensors are able to overcome the drawback of the traditional method of virus detection. The viral gene or entire virus cell can be diagnosed using modified and unmodified AuNPs. The AuNPs are functionalized using a variety of biomolecules, including enzymes, antibodies, proteins, nucleic acids, receptors, and antigens. AuNPs are being employed in nanohybrids with nanoscale particles like carbon nanotubes [30], AgNPs [55], graphene [56], quantum dot [57], and MNP [58] for virus diagnosis. Nanoparticle-based biosensors are sensitive and fast methods so it has been developed as an alternative method for virus diagnosis during a global pandemic. Table 1 displays the various viruses' diagnostic methods using gold nanoparticles.

Besides AuNPs, Au-doped other nanoparticles are also able to detect some viruses. Lee et al. [73] prepared the hybrid Au/MNP_CNT sensing platform and successfully conducted the research for the detection of influenza (H1N1) virus with the detection limit of ∼8.4 pM. In addition to this, with great sensitivity and selectivity and a LOD of about 8.8 pM, norovirus DNA was also successfully detected by the Au/MNP-CNT sensing channel. A research team successfully improved an interdigitated electrode (IDE)-based nanobiosensor for electrochemical impedance spectroscopy-based biorecognition of HPV-16-infected cervical cancer cells. The system was developed by coating the surface of IDE chips with gold (Au) doped zinc oxide nanorods interfaced with HPV-16 viral DNA bioreceptors. Au-doped ZnO-nanorod biosensors showed outstanding HPV-16 E6 oncogene detection. By identifying viral E6 gene targets at as low as 1 fM, this sensor demonstrated significant levels of sensitivity. Additionally, the sensor demonstrated significant discriminatory abilities against HPV-16, good repeatability, and a steady functional life span of more than 5 weeks [74].

Using a lateral flow immunoassay biosensor, a new research team developed a sensitive, quick, and accurate method to concurrently detect SARS-CoV-2 antibodies (IgM/IgG) based on a spike protein coupled to a SiO_2@Au@-quantom dot. The lateral flow immunoassay took 15 min to complete and required a serum sample of 1 mL [75]. The new coronavirus known as SARS-CoV-2 is responsible for the COVID-19 disease. First reported in China, has traveled all over the world, the WHO has declared a global pandemic because of COVID-19 disease [76]. A reverse transcription real-time polymerase chain reaction (real-time PCR) is the gold standard for identifying COVID-19 infection. Real-time PCR tests are performed in certified laboratories due to their complexity, are time-consuming, necessitate experienced workers, and are hardly suitable for mass screening [77]. The rapid diagnostic assay is therefore required. Biosensors based on AuNPs are often proposed because of their unique optical properties. Furthermore, AuNPs are clearly visible as labeling agents due to their intense color, and they are known to form stable and highly active bioconjugates with commonly targeted biomolecules including DNA and proteins, allowing for very sensitive and specific sensing and detection applications [8].

Spike (S) glycoprotein, small envelope (E), matrix (M) protein, nucleocapsid (N) protein, and numerous other accessory proteins make up the structural protein components of SARS-CoV-2. S and N proteins are two of the main antigen biomarkers for coronavirus disease diagnosis [78]. Most of the biosensors are based on marking the antigen–antibody, protein, nucleic acid, and other biomolecules related to the coronavirus. Indirect immunochromatography was used by Huang et al. [2, 79] to create the colloidal gold nanoparticles-based lateral flow (AuNP-LF) assay for quick diagnosis and on-site detection of the IgM antibody against the SARS-CoV-2 virus. The SARS-CoV-2 nucleoprotein was coated on an analytical membrane for sample collection, and antihuman IgM was coupled with AuNPs to make the detecting reporter. This process was used to create the AuNP-LF strips. Sensitivity and specificity of the AuNP-LF assay were found to be 100% and 93.3%, respectively. Only 10–20 L of serum were needed for each test using the newly invented AuNP-LF assay, which could deliver results in just 15 min [79]. Li and Rothberg [80] developed a rapid and simple point-of-care lateral flow immunoassay with the application of AuNPs that can detect immunoglobulin M (IgM) and IgG antibodies against the SARS-CoV-2 virus in human blood within 15 min, allowing them to detect patients at various stages of infection. The test strip's main body is made up of five parts: a plastic backing, a sample pad, a conjugate pad, an absorbent pad, and an NC membrane. The mixture of AuNP-COVID-19 recombinant antigen conjugate and AuNP-rabbit-IgG was sprayed in the conjugate pad. The assay had an overall testing sensitivity of 88.66% and specificity of 90.63% [80].

With the help of isolated RNA samples, Moitra et al. [62] created a colorimetric assay based on gold nanoparticles that could identify COVID-19 positive patients within 10 min. The antisense oligonucleotides (ASOs) specifically targeted to the N-gene (nucleocapsid phosphoprotein) of SARS-CoV-2 were used to cap the AuNPs in the experiment. The SPR of the thiol-modified ASO-capped AuNPs shifts and they aggregate preferentially in the presence of the SARS-CoV-2 target RNA sequence. Furthermore, the presence of RNaseH causes the RNA strand from the RNA DNA hybrid to be broken, which is mediated by increased agglomeration among the AuNPs and causes a plainly detectable precipitate to form from the solution. The developed assay's limit of detection was 0.18 ng/L [62].

In order to quickly identify the COVID-19 virus in nasal and throat swabs, Ventura et al. [77] demonstrated a colorimetric biosensor that is based on a colloidal solution of gold nanoparticles. AuNPs are functionalized with antibodies against one of the three SARS-CoV-2 surface proteins in

Table 1: The diagnostic approach of different viruses using gold nanoparticles.

Viruses	Detection method	LOD	Diagnostic approach	References
1. Influenza (H1N1) virus	DLS-based technique	8.6 TCID/mL	AuNPs were functionalized by mAb clone IC5-4F8 (antibody of H1N1) with a DTSSP crosslinker and bound with the H1N1 virus, which was detected by DLS equipped with He–Ne laser and a photodiode detector	[59]
2. MERS COV	Colorimetric detection of target DNA	6×10^{11} copies/μL	Target DNA was attached with thiol-modified ds-DNA-AuNP and formed a complex which was detected by observing the UV absorption	[60]
3. HIV	DLS-based method to detect the target gene complex with AuNP	16 pM	AuNPs were linked with an antibody of HIV with carboxymethyl cellulose (CMC) from AuNP–CMC–PolyArg–AbHIV complex, which was detected by the DLS method.	[61]
4. SARS-CoV-2	Colorimetric detection of target gene	1 ng/mL	Antisense oligonucleotide (ASO) functionalized AuNPs were bonded with SARS-CoV-2 RNA and formed a complex. The addition of RNase cleaves the phosphodiester bond of RNA and aggregation of AuNPs ASO complex, which was detected by observing the color of the solution	[62]
5. SARS-CoV-2	Colorimetric detection of viruses	1 pg/mL	Antibody of SARS-CoV-2 virus functionalized GNP binds with the antigen of COVID-19 and forms complex	[63]
6. Hepatitis C virus	Colorimetric detection of Viral RNA	50 copies/reaction	Extracted RNA, hybridized buffer containing PBS, and primer targeting 5′UTR of HCV were mixed. Viral RNA was confirmed by observing the change in color of the solution	[9]
7. Hepatitis B virus	Fluorescence-based detection of viral gene	4.6×10^{-9} ng/mL	GNP-TH-Ab was used as the fluorescence signal generator. GNP-TH-Ab and MNP-Ab mixed in phosphate buffers along with HBsAg formed a sandwich complex. The fluorescence of the solution was measured	[64]
8. Dengue-1	Colorimetric lateral flow technique to detect viral RNA	0.01 μM	Dextrin-capped AuNPs were functionalized by thiolated rDNA loaded to the conjugated pad, and viral antigen was placed and lateral flow was observed. The presence of an antigen formed a dark band on the test line	[65]
9. Human papillomavirus	Fluorescence-based nanochip of AuNP and quantum dot for virus detection	10 copies/μL	AuNPs of diameter (16 nm) were functionalized with HRP and thiolate oligonucleotide; these microbeads form a sandwich with a target gene. Streptavidin labeled quantum dots allowed to bind with Au complex to form a chip. The target gene was detected by analyzing fluorescence	[66]
10. Norovirus	LSPR-based technique for the detection of norovirus capsid protein	10 copies/mL	Immobilized AuNPs were functionalized by peptide (specific for norovirus) and mixed with different concentrations of norovirus. The absorbance of LSPR was observed. It was found that the absorbance increases with the increase of viral capsid protein concentration	[67]
11. Ebola virus	Fluorescence-based technique	3–50 pM	Thiol-modified oligonucleotides were used to functionalize the AuNPs and combined with UCNPs and nanoporous alumina (NAAO) membrane to form a probe which mixed with viral RNA and fluorescence intensity was measured	[68]
12. Variola virus	Raman spectroscopic technique	20 fM	AuNPs (13 nm) were functionalized with Raman dye-labeled oligonucleotide from nanoprobe, Ag particles were used for enhancing the SERS signals and analyzed	[69]
13. H5N1 influenza	SPR-based technique	50 TCID/mL	Gold chip was functionalized by primary oligonucleotide then binds with target H5N1 which mixes with AuNPs conjugated with secondary (reporter) oligonucleotide form sandwich-type SPR-based assay. The target virus was detected by analyzing the SPR signal	[70]
14. Zika virus	LSPR-mediated fluorescence-based detection of viral RNA	1.7 copies/mL	Citrate-capped AuNPs and AgNPs nanoparticles were synthesized and conjugated with CdSeSQdots formed alloyed AuAgNP-Qdot646 nanohybrids mixed with molecular beacon (MB) formed NP-Qdot-MB probe this probe mixed with EDTA buffer and viral RNA. The fluorescence intensity of the solution was analyzed to detect viral RNA	[71]

Table 1: Continued.

Viruses	Detection method	LOD	Diagnostic approach	References
15. H3N2 influenza	Colorimetric detection of Influenza using Au-CNT nanohybrid	10 PFU/mL	Au-CNT was prepared and functionalized by anti-H3N2-HA MAb antibody and mixed with TMB H_2O_2. Finally, the AuNP biosensor was mixed with different concentrations of the influenza virus. Viruses were detected by the change in color of the solution	[30]
16. Avian influenza H7N9	Colorimetric detection of virus cells	1.25 pg/mL	Ab2-ALP-MB modified AuNPs were mixed with different concentrations of virus solution, and the color of the solution of AuNPs changed from wine red to blue. The color of the negative sample remained red	[72]

this developed biosensor (spike, envelope, and membrane). The biosensor can be utilized for mass screening because it relies on interactions between virions and pAb-functionalized AuNPs for detection. According to the author, the biosensor could detect viral loads as low as 0.1 with a detection limit that was comparable to real-time PCR. Additionally, the biosensor's sensitivity depends on infecting viral particles rather than its RNA, boosting the effectiveness of its virus detection [77].

According to Pramanik et al. [63], a colorimetric assay using an antispike antibody bound to gold nanoparticles has been developed for the quick diagnosis of a specific COVID-19 viral antigen or virus within 5 min. Using 4-aminothiophenol as a reporting molecule coupled to the gold nanoparticle via an Au-S link, SERS was used for quick and accurate identification. According to the authors, the antigen–antibody interaction that occurs when COVID-19 or a virus is present causes the AuNPs to aggregate, changing their hue from pink to blue. This enables quick detection of antigen or virus presence using only one's eyes, even at low concentrations of 1 nanogram of COVID-19 antigen or 1,000 virus particles per milliliter. SARS-CoV-2 spike protein baculovirus pseudotype. Additionally, the Raman analyzer's use improved the ability of the created antibody and 4-aminothiophenol-attached gold nanoparticle-based SERS probe to identify COVID-19 antigen even at a very low concentration of 4 pg/mL and virus at a concentration of 18 virus particles per mL within a 5-min time frame [63].

2.5. Challenges (Drawbacks). AuNPs can have morphological shapes such as spheres, rods, prisms, tetrapods, dog bones, cubes, shells, and various hollow structures, and their sizes can range from 1 to 800 nm, AuNPs-based optical biosensors have been somewhat ideal biosensors in the detection of various kinds of viruses. They have shown great effective abilities to detect and recognize the disease-causing viruses in living beings. However, there are major challenges that these sensors have been facing in recent decades. In general, a biosensor should be affordable, sensitive, specific, user-friendly, rapid/robust, equipment-free, and deliverable to the end-user, to be an ideal biosensor [46]. Recent days, optical biosensors have most of these characteristics. But still, these AuNPs-based optical biosensors possess some challenges. One of the challenges includes the generation of AuNPs. In general, the process seems simple, easy, and involves benign chemistry; however, it requires great precaution too in the generation of required-size nanoparticles. The concentration of reducing agents greatly affects the generation of AuNPs. The lower concentration of reducing agents (e.g., HCOONa) is insufficient to reduce Au^{3+} to AuNPs. This results in the bigger-sized and nonspherical AuNPs, which in turn form poor optical biosensors [8]. In some cases, the generation of optical biosensors involves the use of cross-linkers between the nanoparticles. The size of these cross-linkers also plays an important role in the precision of detection. Generally, the larger cross-linkers are needed to be chosen to overcome the errors created by the randomness of the binding virus particles. The smaller size cross-linker between two nanoparticles shows poor precision of detection because the space of the approaching virus is extremely concise, thus creating difficulties in the generation of good optical biosensors [57].

In the case of CdSe and AuNPs-based sensors, one of the challenges is to maintain the good selectivity of the sensors because these groups have soft interaction with the thiol group of the systems which affects the sensing signal significantly. Similarly, the sensitivity of AuNPs-based optical biosensors is greatly affected by the number of interferences. The larger number of interferences results in poor sensing performance of the sensors due to nonspecific adsorption with nanoparticles [57]. In some sensors, the concentration of primer used also plays a significant role in the sensitivity and reliability of the sensors. For instance, in the absence of a target, a very low primer concentration gives false-positive results as it will be insufficient to prevent aggregation. But, in presence of the target, a very high primer concentration prevents the aggregation leading to false results. Thus, an appropriate primer concentration is required [9].

Another challenge that AuNPs-based biosensors face is durability of the sensors. In some cases, the performance of the sensor has a negligible effect over the first 3 weeks. But, after the third week, the performance is found to be decreasing significantly [57]. In other cases, there is no record of the good durability of the sensors. Most of the biosensors are generated by the chemical approach methods. Fully green chemistry approaches for designing and developing enzyme-free immunosensors based on AuNPs are yet to be flourished.

2.6. Conclusions and Model for Future Perspectives. The idea of employing biosensors to detect viruses and viral components is one that is still in its infancy, as are many of the techniques mentioned. Because conventional viral detection techniques are time-consuming and expensive, there is a

growing need for precise viral biosensors using quick detection systems.

Because they are so little and contagious, viruses are one of the true risks to people and other living things. Several viruses, including the influenza virus, HIV, hepatitis virus, SARS-CoV-2, MERS-CoV, Ebola virus, Zika, and others, have been discovered to be deadly and life-threatening. In addition, the COVID-19 virus, which has killed millions of people worldwide and spread pandemics, is the most current virus threat to humanity. The key to defending against such assaults is early viral identification. Virus identification is a difficult task due to their small size and lack of quick and effective diagnostic tools. This contributes to the spread of viruses among those who are already ill. Therefore, a better, quicker, more sensitive, focused, affordable, and user-friendly sensor are needed for the detection of viruses. AuNPs-based optical biosensors can be created and used in such a situation. The sensitivity of these sensors has been demonstrated in numerous tests to be great, and they also have better detection limits that range from femtometer to picometer. These sensors are extremely accurate and have a large range. This has the potential to assist in preventing the transmission of viruses because it can be used to speedily, robustly, and accurately identify viruses at an early stage. However, since most of the generation processes use chemical methods and some molecules are lost during generation, these AuNPs biosensors need to be improved. One such enhancement is the prevention of contamination. In order to prevent chemical pollution in the future, entirely green chemistry procedures must be developed. It is important to carefully choose a biorecognition sensing component that has a significant affinity for AuNPs. For user convenience, these biosensors must be made available in kits. Optical biosensors based on AuNPs might be the best choice in light of this. These biosensors are the sensors of the future for biomedical applications. We have essentially covered the capabilities of AuNPs-based optical biosensors in this review. This paper first covered the fundamental ideas and variants of optical biosensors before moving on to the application of AuNPs in optical biosensors. In addition, this work has shown some new developments in viral detection using optical biosensors based on AuNPs. Additionally, we discussed about certain difficulties that optical sensors are currently facing as well as their potential in the future.

Data Availability

Data are available if needed.

Conflicts of Interest

No conflict of interest for this study.

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