SYSTEMATIC REVIEW ARTICLE

Aptamer-based Strategies for COVID-19 Detection and Treatment: A Systematic Review Study

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Abstract: ***Background*:** Aptamer-based strategies have emerged as promising tools for the detection and treatment of COVID-19, offering advantages such as high specificity, sensitivity, and versatility. This systematic review aims to evaluate the effectiveness and innovation of aptamer-based approaches for COVID-19 detection and treatment.

***Methods*:** Following the guidelines of the Cochrane Handbook for Systematic Reviews and the PRISMA 2020 guidelines, a systematic search was conducted across multiple databases up to 2024. The search included studies that utilized aptamers for the diagnosis or therapy of COVID-19. Screening and selection of studies were performed independently by two reviewers, with any disagreements resolved by a third reviewer. Data were extracted regarding study characteristics, aptamer details, and outcomes.

***Results*:** In our systematic review, 98 studies from an initial pool of 1541 records met the inclusion criteria for analysis. Aptamers, single-stranded DNA or RNA molecules with unique three-dimensional (3D) structures, were extensively explored for COVID-19 detection and treatment. Various aptamer-based assays, including electrochemical sensors, surface plasmon resonance (SPR) biosensors, and lateral flow assays, demonstrated high sensitivity and specificity in detecting SARS-CoV-2 in clinical samples such as saliva, nasal swabs, and wastewater. Several aptamer structures targeting viral proteins like the spike and nucleocapsid proteins were employed. Nucleic Acid Amplification Techniques (NAATs) utilizing aptamers, such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based and Loop-mediated Isothermal Amplification (LAMP) assays, showed exceptional sensitivity in detecting viral genetic material. Aptamer-based therapeutic approaches showed potential by blocking viral protein activity or serving as delivery vehicles for therapeutic agents like small interfering RNAs (siRNAs). Despite their advantages, aptamer technologies face limitations such as susceptibility to nuclease degradation and rapid renal clearance, highlighting the need for further optimization.

***Conclusion*:** Aptamer-based strategies present promising avenues for COVID-19 detection and treatment. These approaches offer advantages such as high sensitivity, specificity, and rapid detection, making them valuable tools in combating the COVID-19 pandemic. Further research and development are warranted to optimize aptamer-based strategies for widespread application in clinical settings.

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1. INTRODUCTION

The COVID-19 pandemic has recently caused a global health crisis of unprecedented proportions [1, 2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significantly impacted people and communities worldwide. As of March 19, 2023, the global COVID-19 pandemic has resulted in 761,402,282 confirmed cases and 6,887,000 fatalities [3, 4]. The COVID-19 outbreak has also had a major impact on global health, the economy, and society as a whole [5]. The urgent need for accurate diagnos-

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tics, effective therapeutics, and preventive measures has spurred intensive research efforts to address this unprecedented challenge [6].

There are two widely used techniques for detecting the spread of these newly discovered viruses. Quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) is considered the most reliable method for identifying specific genes of SARS-CoV-2 due to its exceptional sensitivity and specificity [7]. However, the complete diagnostic procedure for this method, including sample preparation (including virus lysis and RNA extraction) and nucleic acid amplification, typically takes 3-4 hours. Furthermore, simplified and rapid detection of SARS-CoV-2 is achieved through the use of serological kits that detect viral antigens or immunoglobulin G and M (IgG/IgM) antibodies. Nevertheless, compared to nucleic acid techniques, this method exhibits significantly lower sensitivity and specificity [8, 9]. Recently, researchers have developed single-stranded DNA [ssDNA] aptamers that target specific human pathogens, including SARS-CoV-2 [10, 11].

Aptamers are short, single-stranded oligonucleotides capable of binding to a wide range of target molecules, including proteins, small molecules, and even intact cells [12]. Systematic evolution of ligands by exponential enrichment (SELEX) is a method used to select aptamers from a synthetic nucleic acid library. The SELEX process involves multiple stages: binding aptamers to a target, separating bound from unbound aptamers, retrieving the bound aptamers, amplifying them, and regenerating RNA or single-stranded DNA (ssDNA) aptamers [13]. The SELEX process typically comprises 6-13 rounds, where each round replaces the original nucleic acid library with a new set of aptamers exhibiting stronger binding affinity towards the target, while those with weaker affinity are removed. At the conclusion of the process, the enriched aptamers are cloned and sequenced for further examination [14]. Aptamers, like antibodies, exhibit high specific binding affinities and excellent target recognition capabilities. Aptamers, on the other hand, have distinct advantages over antibodies, including ease of synthesis, superior stability, lower immunogenicity, and the ability to target specific epitopes of a given target molecule [15]. SARS-CoV-2 virus utilizes two genetic information domains, the receptor binding domain (RBD) and the N-terminal domain (NTD), located in its S protein, to invade host cells and initiate antibody production. These domains play crucial roles in both the invasion process and the subsequent immune response. DNA-based aptamers have demonstrated the capability to bind to both the RBD and NTD domains [16].

This systematic review aims to investigate the application of aptamers in the context of COVID-19. The study provides a comprehensive analysis of aptamers' roles as diagnostic tools and therapeutic agents against COVID-19 through a systematic review of the current literature.

2. MATERIALS AND METHODS

The recommendations of the Cochrane Handbook for Systematic Reviews were followed to conduct this comprehensive review. Additionally, the PRISMA 2020 guidelines were adhered to in composing this review article. The protocol for the current study was registered in PROSPERO (Registration Code: CRD42023475474).

2.1. Search Strategy

A comprehensive and systematic search of reputable databases, including PubMed, Scopus, Web of Science, Embase, and Cochrane, was conducted for this systematic review. Gray literature and Google Scholar were also searched to ensure thoroughness. Additionally, reference lists of included articles were manually checked to prevent any omissions. Studies were conducted from 1950 to 2024. We used the following keywords for search without any time limitations: "SELEX Aptamer Technique" OR "Aptamers, Nucleotide" OR "Aptamers" OR "Aptamer*" OR "Aptamer-based technique" AND "coronavirus disease" OR "Severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "SARS-CoV-2 variants" OR "COVID-19" OR "COVID 19" OR "COVID*" OR "COVID-19 variants" (**Supplementary material**).

2.2. Study Screening

The final selection of articles for inclusion in this systematic review was based on the following criteria: 1. Original research articles utilizing aptamers as diagnostic methods or treatment agents for COVID-19, and 2. Written in English. Articles were excluded if they were conference papers, letters to the editor, review articles, preprints, did not report outcomes, or were not related to diagnostic methods for COVID-19 using aptamers. The articles identified through our systematic search were imported into EndNote version 11 software for screening. Two researchers independently conducted the screening process after removing duplicate records. Any disagreements between the two researchers regarding article selection were resolved by a third experienced reviewer. The screening was limited to publications in the English language.

2.3. Data Extraction and Collection

After completing the aforementioned selection process, two independent reviewers meticulously evaluated the selected articles that met the predefined inclusion criteria. Relevant data for the systematic review were then extracted and compiled using a pre-designed data collection sheet. The extracted data included study characteristics (such as first author, publication year, and *in vivo*/*in vitro* methodology), details of the specific aptamer investigated, its nucleic acid sequence, the target molecule it binds to, its intended application (diagnosis or therapy of COVID-19), and its dissociation constant. Due to significant heterogeneity in study outcomes and methodological differences, conducting a meta-analysis was not feasible (Fig. **1**).

3. RESULTS

3.1. Study Selection

We initiated our search using a combination of techniques, resulting in a total of 1541 based on prisma studies in various databases. After removing duplicates, 821 based on prisma records underwent preliminary screening based on their titles and abstracts. From these, 131 based on prisma

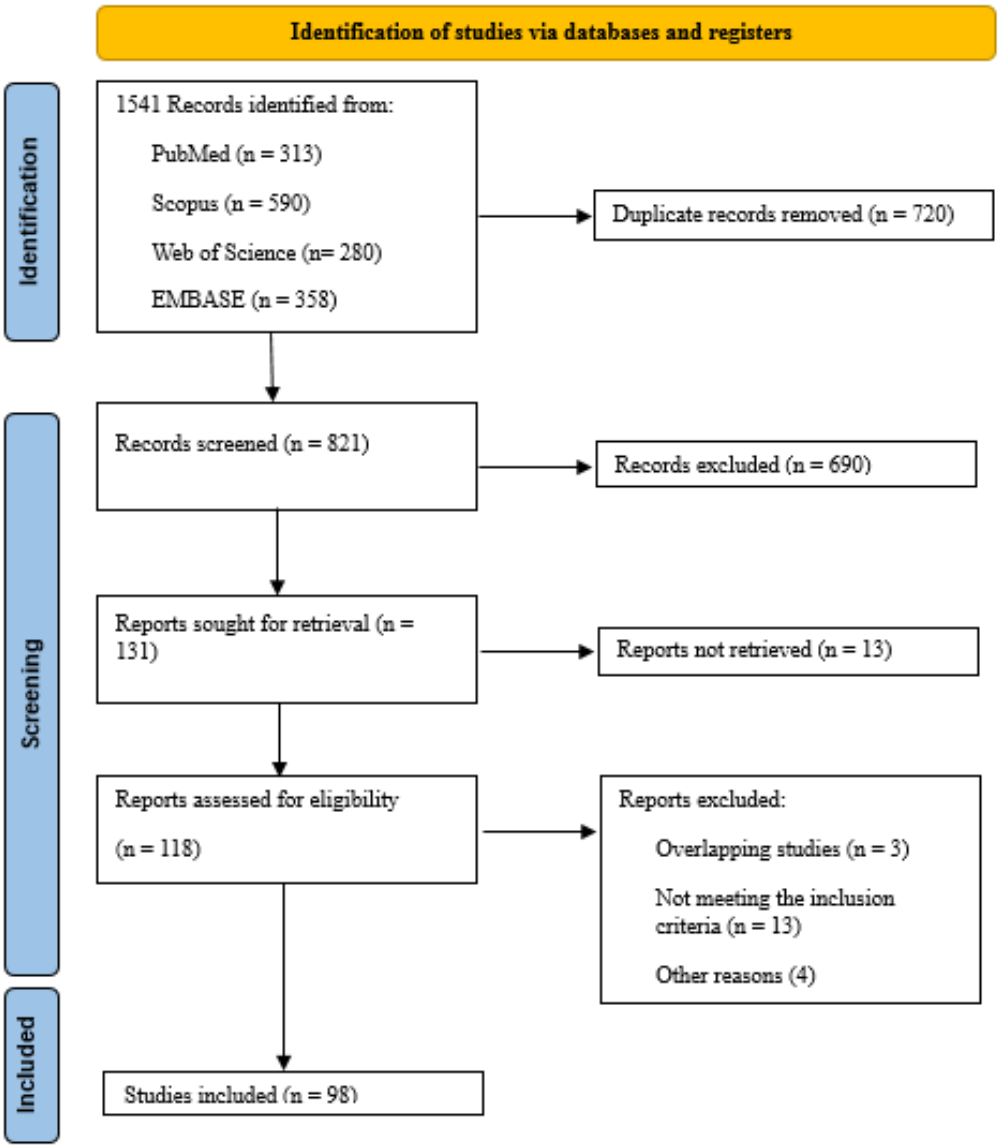

Fig. (1). Selection process for eligible studies from all identified citations.

records were selected for a comprehensive evaluation of their full texts. During the second screening phase, the complete texts of these studies were assessed, resulting in 98 studies deemed suitable for this systematic analysis, published between 2020 and 2024 [10, 17-113].

3.2. Aptamer's Structure

Aptamers are under investigation for their potential in both detecting and treating COVID-19. These molecules fold into unique three-dimensional structures that enable them to bind to specific targets with high affinity and specificity. The specific sequence and arrangement of nucleotides in an aptamer determine its unique conformation and its ability to bind to its target. [18, 38, 59]. Aptamers achieve their high affinity and specificity through their unique three-dimensional (3D) conformation [29, 31, 111]. The genetic makeup of SARS-CoV-2 encodes four distinct structural proteins: the envelope (E) protein, membrane (M) protein, nucleocapsid (N) protein, and spike glycoprotein (S) [30].

The spike glycoprotein (S) plays a crucial role in the viral entry process, making it a promising target for the development of both therapeutic drugs and diagnostic tests [32]. The spike glycoprotein (S) is composed of two distinct subunits: the receptor recognition S1 subunit and the membrane-bound S2 subunit. Within the S1 subunit, there are additional segments known as NTD and RBD. Activation of the S protein occurs through cleavage at the S1/S2 sites, facilitated by the transmembrane protease serine 2 (TMPRSS2), which ultimately facilitates viral entry into the host cell. Conversely, human angiotensin-converting enzyme 2 (ACE2) interacts with the RBD, enabling the entry of SARS-CoV-2 into host cells [49].

Since the onset of the COVID-19 outbreak, a multitude of aptamers have been developed specifically designed to bind to the S and N proteins of the SARS-CoV-2 virus (Table **1**). These aptamers have demonstrated exceptional specificity and affinity toward viral targets, suggesting their potential utility as tools for diagnosing and treating COVID-19.

Table 1. Various SELEX protocols have been employed to isolate potential diagnostic and therapeutic agents for COVID-19.

Target	Types	Sequence [5′-3′]	Length	Kd [Measurement Method]	Partitioning Method	Selection Pool Regeneration Method	References
SARS-CoV Nucleocapsid (N) protein	RNA	GCCUGUCGUUCGCUGU GUCUUGCUACGUUAC-GUUAC ACGGUUGGCAU-AACCCAGAGGUCGAUG G	83	1.65 nM (ATPase assay)	Bead	-	[80]
N protein	ssDNA	CGA GGC TCT CGG GAC GAC NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN GTC GTC CCG CCT TTA GGA TT ACA G	NR	below 20 nM (SPR assay)	-	-	[26]
N Protein	ssDNA	GCAATGGTACGGTAC TTCCGGATGCGGAAA CTGGCTAATTGGTGA GGCTGGGGCGGTCGT GCAGCAAAAGTGCAC GCTACTTTGCTAA	45	-	-	-	[50]
S Protein	ssDNA	5'-AATGGATCCACATCTAC GA GCTCGAACGCCCG-GAGGAGACGGGGG-CAGGGCGTG TTCACTG-CAGACTTGACGAAGCT-3'	35	26 ± 6 pM (ELONAs)	-	Enzyme-linked oligonucleotide assays (ELONAs)	[31]
Spike	ssDNA	GGGAGAGGAGGGAGA TAGATATCAACCCAT GGTAGGTATTGCTTG GTAGGGATAGTGGGC TTGATGTTTCGTGGA TGCCACAGGAC	86	21 ± 4.6 nM (not reported)	Bead	Magnetic based SELEX, using S1 protein as the target	[56]
S_{RBD}	ssDNA	ATCCAGAGTGACGCAG-CAATTTACCGATGGCTT GTTT-GTAATGTAGGGTTCCGT CGGATTGGACAC GGTGGC	36	18 nM (Biolayer Interferometry)	Bead	RNA polymerase transcription	[67]
S Protein	ssDNA	ATCCAGAGTGACGCA GCATCGAGTGGCTTG TTTGTAATGTAGGGT TCCGGTCGTGGGTTG GACACGGTGGCTTAGT	40	28 nM (ELISA)	Bead	-	[42]
N Protein	ssDNA	ATCCAGAGTGACGCAG-CAAGGGTATT GGCAGTGG-TAGGTACTGCGTGCGTT GT GGTTCTAG-CATGTTTAATGGACAC-GGTGGCTTAGT	88	28.1 ± 0.2 nM (BLI)	-	Selection strategy that combined cell and protein SELEX.	[112]

(Table 1) Contd….

Target	Types	Sequence [5′-3′]	Length	Kd [Measurement Method]	Partitioning Method	Selection Pool Regeneration Method	References
Whole virus	ssDNA	CCCGACCAGCCAC-CATCAGCAAC TCTTCCGCGTCCATCCCT GCTG	45	79 ± 28 nM (ELONAs)	-	Viro-SELEX, using active pseudotyped SARS-CoV-2 with S protein as the target and counterselection against UV inactivated pseudotyped SARS-CoV-2, pseudotyped SARS-CoV-1 with S protein	[111]
S_{RBD}	ssDNA	CAGCACCGACCTT-GTGCTTTGGGAGTG CTGGTCCAAGGGCGTTA ATGGACA	40	5.8 nM (not reported)	Bead	Magnetic separation using streptavidin-coated bead	[53]
N protein	ssDNA	GCTGGATGTCGCTTAC-GACAATATTCCTTA GGGGCA	36	0.49± 0.05 nM (bead-based fluorescence binding assay)	-	-	[10]

3.3. Systematic Evolution of Ligands by Exponential Enrichment (SELEX)

The systematic evolution of ligands by exponential enrichment (SELEX) process is a robust and iterative method for the *in vitro* selection of aptamers, which are oligonucleotide sequences capable of binding with high specificity and affinity to various target molecules [32]. This technique leverages the principles of molecular evolution and combinatorial chemistry to identify aptamers from a vast library of nucleic acid sequences [47].

The SELEX process begins with the synthesis of a large oligonucleotide library containing approximately 10131013 to 10151015 unique sequences [28]. These sequences typically comprise randomized regions flanked by constant primer binding sites, facilitating amplification by PCR [50]. The initial library is incubated with the target molecule under conditions that favor the binding of aptamers to their target. Subsequent partitioning steps are employed to separate the bound sequences from the unbound ones. The bound sequences are then eluted, amplified by PCR, and subjected to further rounds of selection. Each iterative cycle enriches the pool with sequences that have higher affinity and specificity for the target. The process continues until sequences with desired binding characteristics are isolated [51-53].

The SELEX methodology has been modified and optimized over the years to improve efficiency and binding characteristics. Variants such as Capillary Electrophoresis-SELEX (CE-SELEX), High-throughput Sequencing-SELEX (HT-SELEX), and Cell-SELEX have expanded the utility of this technique, enabling the selection of aptamers against a wide range of targets, including small molecules, proteins, and even whole cells [29].

3.4. Importance of Dissociation Constant (Kd) and Aptamer Length

The dissociation constant (Kd) is a critical parameter in evaluating the binding affinity of an aptamer for its target. It is defined as the concentration of the ligand at which half of the available binding sites are occupied [32-35]. A lower Kd value indicates a higher affinity of the aptamer for its target, which is crucial for applications requiring high sensitivity and specificity, such as diagnostics and therapeutics. Typical aptamers selected *via* SELEX exhibit Kd values in the nanomolar to the picomolar range, reflecting their strong binding affinities [54].

Aptamer length is another vital factor influencing binding affinity and specificity. While longer aptamers have more nucleotides that can interact with the target, potentially enhancing binding affinity, they may also exhibit increased non-specific interactions and reduced stability. Conversely, shorter aptamers may have reduced binding affinity due to fewer contact points with the target. The optimal aptamer length is typically determined empirically during the SELEX process, balancing the trade-offs between affinity, specificity, and stability [46-48].

3.5. Aptamers Targeting SARS-CoV-2 Proteins Developed using SELEX

The COVID-19 pandemic has spurred significant research efforts to develop aptamers targeting SARS-CoV-2 proteins, with SELEX being a pivotal technique in these endeavors. For example, aptamers have been selected against the Spike (S) protein of SARS-CoV-2, which is crucial for viral entry into host cells. The Spike protein, specifically its receptor-binding domain (RBD), interacts with the human angiotensin-converting enzyme 2 (ACE2) receptor, making it an attractive target for therapeutic and diagnostic aptamers [55, 56].

In one study, researchers employed a modified SELEX approach to isolate DNA aptamers against the RBD of the spike protein [41]. These aptamers demonstrated high affinity with Kd values in the low nanomolar range, exhibiting potential for use in diagnostic assays and as therapeutic inhibitors of viral entry. Another study focused on developing

RNA aptamers targeting the nucleocapsid (N) protein of SARS-CoV-2, which plays a critical role in viral replication and assembly [47-49]. The selected RNA aptamers showed strong binding affinity and specificity, highlighting their utility in the development of rapid diagnostic tests for COVID-19 [36].

These examples underscore the versatility and efficacy of SELEX in generating high-affinity aptamers for emerging infectious diseases. The ability to rapidly produce aptamers against viral proteins holds promise for the development of novel diagnostics and therapeutics, offering a robust tool for responding to current and future pandemics [43].

3.6. Aptamer-Based Assays for COVID-19 Detection

The development of aptamer-based assays capable of detecting SARS-CoV-2 in clinical samples, including saliva, nasal swabs, and wastewater, has been demonstrated in several studies with high sensitivity and specificity [17, 28, 29, 44]. Idili *et al*. aimed to develop a rapid and sensitive method for detecting the SARS-CoV-2 virus in saliva using an electrochemical aptamer-based (EAB) sensor [55]. The EAB sensor achieved results within minutes of exposure to the SARS-CoV-2 spike protein. This rapid detection time is notably faster compared to traditional RT-PCR methods, which can take hours. These findings are consistent with results reported in other studies [42, 85]. One of the proposed advantages of aptamer compared to traditional methods in the diagnosis of SARS-CoV-2 virus is their simpler sample preparation [24, 41]. Unlike RT-PCR, aptamer-based assays for COVID-19 detection often require a significantly simplified sample preparation workflow [26, 33]. RT-PCR relies on the extraction of viral RNA from patient samples, which typically involves multiple steps such as lysis, homogenization, and purification using dedicated kits or columns. These steps can be time-consuming, labor-intensive, and prone to operator error, potentially affecting assay sensitivity and reproducibility. In contrast, aptamer-based assays often circumvent the need for RNA extraction. Aptamers can be designed to target various components of SARS-CoV-2, including viral proteins directly in solution [27, 38, 39].

Several studies have explored aptamers targeting various viral components, including the spike protein, nucleocapsid protein, and viral RNA [36, 51, 76]. These aptamers were incorporated into diverse detection methods such as electrochemical sensors, surface Plasmon resonance (SPR) biosensors, and lateral flow assays [78, 82, 90]. Sensitivity was also promising, with studies like Wu *et al*. reporting limits of detection in the Picogram per milliliter (pg/mL) range for SARS-CoV-2 viral proteins or RNA [18]. This exceptional sensitivity allows for detection at very low viral loads, potentially during the early stages of infection when viral shedding might be minimal [93, 95].

3.7. Different Types of Aptamer-based Assays for COVID-19 Detection

Aptamers are selected through a process called SELEX against specific targets on the virus, such as the spike protein, nucleocapsid protein, or receptor-binding domain [72]. SELEX can rapidly identify aptamers with high affinity and specificity for SARS-CoV-2 from a vast library. Other techniques, such as capillary electrophoresis (CE-SELEX), can also be employed. The study by Liu *et al*. describes the development of DNA aptamers targeting the SARS-CoV-2 receptor-binding domain using SELEX with magnetic bead separation [42]. These aptamers demonstrated high affinity and specificity for the virus. In another study in 2021, CE-SELEX was employed to identify RNA aptamers targeting the nucleocapsid protein. These aptamers exhibited high sensitivity in detecting SARS-CoV-2 in clinical samples [53, 73].

Aptamers can be incorporated into various assay formats, each with its advantages and limitations. The N protein has been predominantly chosen as the target in most studies because it is the most commonly encountered structural protein during the initial phase of infection [26, 31, 46]. In some studies, researchers have targeted the S1 domain [21, 38] or RBD [17, 18]. Aptamers can effectively target viral proteins such as S and N as suitable targets. For SARS-CoV, it has been previously demonstrated that during the first 10 days of infection, the sensitivity of detecting the virus's genetic material and antibodies is significantly lower compared to detecting the viral antigen, specifically the viral N protein [29]. It has been determined that antigen testing has nearly 94% sensitivity in detecting the early stages of infection. Using aptamers for direct detection of viral antigens in diagnostic samples could potentially reduce the need for expensive and complex tests like real-time RT-PCR. Additionally, it could eliminate the requirement to wait for the infected host to produce antibodies, which is necessary in serological tests [67]. Furthermore, aptamers possess a remarkable capability to detect even the slightest quantities of virus particles, thanks to their exceptional sensitivity and specificity. This capability could potentially enable the use of saliva as a determinant agent, which alternative would provide greater ease or comfort for the patients. Additionally, aptamers could potentially identify individuals who contract SARS-CoV-2 during the pre-symptomatic period [19, 20].

3.8. Biosensors for COVID-19 Detection

Comparison of different diagnostic methods for COVID-19 is provided in Table **2**. Numerous studies have focused on developing aptamer-based biosensors for accurate and rapid detection of SARS-CoV-2. Xing *et al*. demonstrated the customization of aptamers to create a CRISPR/Cas12a-derived ultrasensitive biosensor, showcasing its potential for precise detection. Their biosensor achieved remarkable sensitivity, with a limit of detection (LOD) as low as 1.5 femtomolar and a dynamic detection range spanning several orders of magnitude. This capability enables early and accurate identification of SARS-CoV-2 [17].

Biosensors are analytical devices that combine biological recognition elements with a physicochemical transducer [22]. The biological component, such as antibodies, enzymes, or aptamers, specifically binds to the target analyte (viral RNA, proteins, or antigens). The transducer converts this biorecognition event into a measurable signal, like an electrical current, light, or mass change. Various biosensor types are being investigated for COVID-19 detection, including electrochemical biosensors that utilize electrodes to measure changes in electrical current upon target-receptor

Table 2. DNA Aptamers usage for SARS-CoV-2 detection.

Study	Types	Target	LOD	Detection Method	Findings	References
Xing *et al.*2023	ssDNA	S protein (RBD)	1.5 pg/mL for the spike protein 1 (S1) of SARS-CoV-2	CRISPR/Cas12a-derived electrochemical aptasensor	- SARS-CoV-2 S1 can be detected at very low levels, with a limit of 1.5 pg mL^{-1}. - The new aptasensor based on CRISPR/Cas12a technology is highly effective at detecting the Beta, Delta, and Omicron variants	[17]
Wu *et al.*2023	ssDNA	S protein (RBD)	Wuhan Strain: 4.80×10^{-1} copies/mL Omicron Strain: 1.95×10^{-2} copies/mL	An integrated microfluidic system	newly created aptamer could detect inactive SARS-CoV-2 viruses, eight SARS-CoV-2 pseudo-viruses	[18]
Wang *et al.* 2023	ssDNA	S protein (RBD)	NR	Robust Covalent Aptamer Strategy	Covalent aptamers have the ability to transform aptamer-protein complexes from a state of dynamic equilibrium to a state of stable and irreversible covalent complexes, even under harsh conditions	[19]
Torun *et al.* 2023	ssDNA	RBD-4C	NR	Rapid Nanoplasmonic-Enhanced Detection	This method achieves a sensitivity and specificity rate of 95.2%	[20]
Sullivan *et al.* 2023	ssDNA	S1 domain	NR	Hybrid aptamer-molecularly imprinted polymer (aptaMIP)	This work illustrates that by immobilizing the aptamer within a polymeric framework, its ability to selectively identify its intended target is enhanced. This suggests a potential approach for achieving highly specific molecular recognition with exceptional affinity for various targets.	[21]
Poolsup *et al.* 2023	ssDNA	N protein	1.61 pg/mL	Label-free optical aptasensor fabricated with a novel single-stranded DNA aptamer	The researchers found that the tNSP3 aptamer, which is 44 nucleotides long, has a strong affinity for the N protein of both the wild type and Delta and Omicron variants.	[24]
Park *et al.* 2023	ssDNA	S protein (RBD)	2 pg/mL	Label-free optical aptasensor fabricated with a novel single-stranded DNA aptamer	The aptasensor, which combined label-free surface-enhanced Raman spectroscopy (SERS), was able to accurately detect SARS-CoV-2, including its variants of concern such as the wild-type, delta, and omicron variants, even in clinical samples.	[25]
Neff *et al.* 2023	ssDNA	N-protein	NR	Enzyme-linked aptamer sorbent assay (ELASA)	The DNA aptamers demonstrated the ability to detect very low levels of the protein, as low as 150 pg/mL, and under 150 k copies of the inactivated SARS-CoV-2 Wuhan Alpha strain in a viral transport medium.	[26]
Moshref *et al.* 2023	ssDNA	RBD	NR	Aptamer-based assays	Aptamer 91 was able to identify different strains of the virus in more than 97% of clinical samples. Aptamer 52 was capable of detecting the SARS-CoV2 virus.	[27]

(Table 2) Contd….

Study	Types	Target	LOD	Detection Method	Findings	References
Le *et al*. 2023	ssDNA	N-protein	1.77 pg/mL	Label-free optical aptasensor fabricated with a novel single-stranded DNA aptamer	K1 and M40, which were discovered through target-alternating selection, exhibited extremely strong binding to the spike protein of both the wild-type and Alpha variants.	[31]
Chen *et al*. 2023	ssDNA	RBD	400 copies per mL	Aptamer-based assays	Scientists identified two aptamers that have the ability to differentiate between the Omicron and Delta variants.	[35]
Yu *et al*. 2022	ssDNA	N Yprotein	NR	DNA tetrahedron-tethered aptamers	The electrochemical aptamer can improve the early detection of SARS-CoV2 virus.	[37]
VarnBuhler, *et al*. 2022	RNA	N protein	1.5 pg/mL	A fluorogenic DNA aptamer named Lettuce	This research explains a straightforward method for detecting RNA using DNA oligonucleotides without any modifications, which can rebuild the Lettuce aptamer that is guided by RNA	[39]
Martínez-Roque *et al*. 2022	ssDNA	S1 domain	NR	By Two non-competing DNA aptamers, C7 and C9	The DNA aptamers C7 and C9, which do not compete with each other, were effectively utilized as precise and selective biological recognition components to create electrochemical and fluorescent aptasensors for the SARS-CoV-2 Spike glycoprotein. These aptasensors were able to detect the protein with high sensitivity, with detection limits of 0.07 fM and 41.87 nM for the electrochemical and fluorescent methods, respectively.	[41]
Liu *et al*. 2022	circular DNA template (c-DNA)	N-protein	NR	By Synthetic ssDNA aptamers	The electrochemical signal is amplified when using an RCA-DNA reporter compared to a regular ssDNA reporter.	[11]
Ge *et al*. 2022	RNA	N protein	NR	ELISA method	The digital method using femtoliter-sized wells was able to detect N protein at a limit of 33.28 pg/mL, which is 300 times more sensitive than the traditional ELISA method based on a double-antibody sandwich and enzyme-linked immunosorbent assay.	[43]
Daniel *et al*. 2021	RNA	N protein	NR	Nanoparticles based method	In under 5 minutes, an electronic gadget that comprises DNA-based aptamer functionalized AuNPs can identify SARS-CoV-2 RNA.	[44]

Abbreviations: aptaMIP; hybrid aptamer-molecularly imprinted polymer; NR, Not reported.

binding [22, 37]. Electrochemical aptasensors have emerged as a promising approach for COVID-19 diagnosis due to their ability to achieve high sensitivity and label-free detection. These assays rely on the principle that the interaction between an aptamer and the SARS-CoV-2 virus alters the electrical properties of an electrode surface. In some studies, interdigitated gold electrodes (IDEs) have been utilized to maximize the surface area for improved sensitivity [90, 91, 93, 100]. In this technique, aptamers are immobilized on the electrode surface using linker molecules such as thiol groups (for gold electrodes) to create a capture layer for the virus. Additionally, in some studies, researchers employed electrochemical impedance spectroscopy (EIS) techniques [18, 22, 27]. This technique measures the impedance of the electrode-electrolyte interface, with increased impedance upon aptamer-virus binding. In one of the included studies, researchers employed EIS and achieved a limit of detection (LOD) of 0.4 pg/mL for the SARS-CoV-2 Spike glycoprotein (S) within 20 minutes of incubation [100]. Moreover, differential pulse voltammetry (DPV) is another technique that measures the current at various applied voltages, where a change in the peak current reflects the binding event [98].

Other types of biosensors evaluated in several studies are aptamer-based biosensors and SPR biosensors. SPR biosensors offer a powerful technique for label-free, real-time detection of biomolecular interactions. These intricate devices exploit the phenomenon of surface plasmons, which are collective electron oscillations that arise at the interface between a metal film and a dielectric medium, often a liquid sample [34]. When biomolecules like antibodies bind to target analytes on the sensor surface, the interaction alters the refractive index of the local environment, consequently affecting the SPR conditions [84]. This alteration can be measured through changes in the reflected or transmitted light, providing a highly sensitive readout of the biorecognition event. In the context of COVID-19 diagnosis, SPR biosensors present a compelling approach for detecting the SARS-CoV-2 virus. SPR can detect minute changes in refractive index, enabling the sensitive detection of low viral loads, potentially even at early stages of infection. Despite these significant advantages, SPR biosensors for COVID-19 diagnosis still face some challenges. SPR instrumentation can be expensive and require trained personnel to operate, potentially limiting their accessibility in resource-limited settings. Also, while offering high sensitivity, current SPR setups might require further optimization for high-throughput sample analysis, which is crucial for large-scale testing needs [84].

Jia *et al*. developed an aptasensor for detecting the SARS-CoV-2 virus utilizing a novel generation of aptamers. The aptasensor consisted of key components including RNA and DNA aptamers, as well as optical microfibers coated with graphene oxide. This configuration enabled the detection of the purified viral N protein at extremely low thresholds. Specifically, the detection limit was 6.25×10^{-18} M when using an RNA aptamer as the detection element, and even lower at 6.25×10^{-19} M when using a DNA aptamer [113]. As aptamers bind to their targets, they undergo a conformational change from relaxed states to hairpin or G-quadruplex structures. This structural transformation correlates with changes in electrochemical current signals, providing an indication of target concentration [44].

3.9. Immunoassays Utilizing Aptamers for COVID-19 Detection

Immunoassays employing aptamers as recognition elements have gained significant attention in COVID-19 diagnostics. These assays capitalize on aptamers' unique properties, including high affinity and specificity for their targets, to detect SARS-CoV-2 antigens or antibodies. Numerous studies in the reviewed literature have investigated the development of immunoassays using aptamers for COVID-19 detection, each demonstrating distinct approaches and promising results [10].

The development of immunoassays incorporating aptamers as recognition elements represents a significant advancement in the field of biosensors, particularly for the detection of SARS-CoV-2 [28-30]. Aptamer-based biosensors, or aptasensors, offer distinct advantages over traditional antibody-based assays, including greater stability, ease of synthesis, and the potential for rapid and cost-effective production [32].

For instance, electrochemical aptasensors have been developed to detect the Spike protein of SARS-CoV-2. These sensors utilize an aptamer immobilized on an electrode surface. When the Spike protein binds to the aptamer, it induces a change in the electrochemical signal, which can be quantified to determine the viral load. Such aptasensors offer high sensitivity, specificity, and the potential for miniaturization and integration into portable diagnostic devices [45-47].

Optical aptasensors, another class of aptamer-based biosensors, employ techniques such as fluorescence resonance energy transfer (FRET), surface plasmon resonance (SPR), and colorimetric assays to detect SARS-CoV-2 proteins. These methods rely on changes in optical properties upon aptamer-target interaction, enabling real-time and label-free detection of the virus [39].

Mass-sensitive aptasensors, such as those utilizing quartz crystal microbalance (QCM) technology, measure changes in mass on a sensor surface due to aptamer binding. The binding event alters the resonant frequency of the crystal, providing a quantitative measure of the target protein concentration [34]. The integration of aptamers into biosensors for COVID-19 detection not only enhances the performance of diagnostic assays but also facilitates the development of point-of-care testing devices. These devices are crucial for rapid and widespread testing, enabling timely identification and isolation of infected individuals, and thereby contributing to the control of the pandemic [49-51].

Zhang *et al*. developed an aptamer-based fluorescence immunoassay for the detection of N protein of SARS-CoV-2 in clinical samples. Their assay achieved a limit of detection (LOD) of 0.05 ng/mL and demonstrated excellent sensitivity and specificity in distinguishing COVID-19 positive and negative samples. This study underscores the potential of aptamer-based fluorescence immunoassays as reliable tools for COVID-19 diagnosis [49, 79]. In another study, Chen *et al*. devised an aptamer-linked immunosorbent assay (ALISA) for detecting the SARS-CoV-2 spike protein in patient

samples. Their assay showed a LOD of 0.1 ng/mL and achieved a sensitivity of 95% and specificity of 97% during clinical validation [35]. The ALISA platform provides a robust and scalable approach for the accurate detection of viral antigens, essential for effective COVID-19 surveillance and management [99]. Similar findings have been reported in some other studies [78, 103]. Yang *et al*. designed a colorimetric immunoassay based on aptamers for detecting SARS-CoV-2 antigen in respiratory specimens. Their assay demonstrated an LOD of 0.2 ng/mL and enabled rapid detection within 30 minutes, making it suitable for point-of-care testing. This approach offers a straightforward and cost-effective method for COVID-19 diagnosis, particularly advantageous in resource-limited settings. [72, 110]. Collectively, these studies underscore the versatility and effectiveness of aptamer-based immunoassays for detecting COVID-19. They offer a variety of platforms and techniques that enable sensitive and specific identification of viral antigens and antibodies.

3.10. Nucleic Acid Amplification Techniques in COVID-19 Diagnosis

Nucleic Acid Amplification Techniques (NAATs) have emerged as pivotal tools in combating the COVID-19 pandemic, providing sensitive and specific methods for detecting the genetic material of the SARS-CoV-2 virus [39]. These techniques encompass various molecular biology methods designed to amplify viral nucleic acids, thereby enabling accurate diagnosis of infected individuals. NAATs include a diverse array of molecular techniques such as PCR, RT-PCR, Loop-mediated Isothermal Amplification (LAMP), and CRISPR-based assays. These methods leverage the unique genetic signature of SARS-CoV-2 to amplify viral RNA or DNA, facilitating sensitive detection even at low viral loads. NAATs offer exceptional sensitivity, capable of detecting even trace amounts of viral genetic material present in clinical samples. This attribute is crucial for early diagnosis and containment of COVID-19 outbreaks [45, 46]. VarnBuhler *et al*. detected SARS-CoV-2 RNA using a DNA aptamer that mimics green fluorescent protein. They developed a DNA aptamer named "Lettuce", specifically designed to bind to SARS-CoV-2 RNA. The study showed that Lettuce can selectively bind to SARS-CoV-2 RNA and induce fluorescence in the presence of DFHBI-1T. They also employed a strategy involving split Lettuce molecules, where two separate DNA strands assemble to form the complete aptamer structure only upon binding to the target RNA. This approach facilitated sensitive and specific detection of SARS-CoV-2 RNA fragments [39]. However, NAATs, especially those employing PCR, can be costly due to the requirement for specialized equipment, reagents, and consumables. Additionally, NAATs are vulnerable to contamination, which may result in false-positive outcomes and undermine diagnostic precision. Strict adherence to quality control measures is crucial to minimize this risk [86].

3.11. Using Aptamers for the Management of SARS-CoV-2 Infection

Critical components of the SARS-CoV-2 viral entry pathway, such as the viral S protein and the host ACE2 protein, are therefore compelling targets for aptamers, as illustrated in Table **3**. There are medical procedures that utilize nucleic acids as therapeutic agents, including RNA interference, particularly with small interfering RNAs (siRNAs) molecules, as well as ribozymes, antisense oligonucleotides, and aptamers [112]. The therapeutic potential of aptamers is underscored by their ability to adopt a precise 3D structure that facilitates strong binding to specific targets. Furthermore, aptamers are increasingly recognized as a promising class of pharmacological agents due to several notable characteristics. Their compact size, approximately 2 nanometers, is significantly smaller than antibodies, which typically measure around 10 nanometers. This size advantage allows aptamers to access and bind to binding sites that may be difficult for larger molecules to target [14]. Furthermore, aptamers exert minimal impact on the immune system, and their high programmability enables structural modifications post-SELEX to enhance stability in diverse physiological conditions. These unique attributes position aptamers as promising candidates for treating various illnesses [65]. One example is the FDA's approval of pegaptanib, the first RNA aptamer, for treating ocular vascular diseases by targeting vascular endothelial growth factor (VEGF) [106].

To utilize aptamers in COVID-19 treatment, there are three potential approaches: (a) blocking protein activity, such as viral or cellular receptor proteins like the RBD of S protein, M protein, or N protein of SARS-CoV-2, or ACE2 receptors; (b) initiating signaling pathways by binding to cell receptors to induce an immune response; and (c) employing aptamers as targeted carriers of therapeutic substances to deliver them specifically to infected cells [60]. In the study by Villa *et al*., a SELEX technique was employed to discover two aptamers that specifically bind to the region surrounding K353, a crucial residue in human ACE2 that interacts with the N501 amino acid of SARS-CoV-2 S. Sources indicate that these aptamers bind to the specified region and effectively inhibit the interaction between SARS-CoV-2 S and human ACE2, thereby hindering viral infection at a nanomolar level [62]. Rahman *et al*. explored the potential of aptamers to inhibit the COVID-19 virus. Their study indicated that the first aptamer obstructs the ACE2-binding site in the receptor-binding domain (RBD), thereby impeding the binding of ACE2. The second aptamer inhibits ACE2 allosterically by attaching to a different side of the RBD [63]. Similar findings were reported in another study [64]. Also, Sun *et al*. found that a spherical cocktail neutralizing aptamer-gold nanoparticle (SNAP) could inhibit the interaction between the Omicron RBD and ACE2 [65].

SARS-CoV-2 gains entry into human host cells by binding the RBD of the spike glycoprotein to the ACE2 receptor, which serves as the virus's entry point. Given the pivotal role of RBD in the mechanism of SARS-CoV-2 infection, it represents a promising target for developing drugs and vaccines against the virus. Aptamers bind to the three-dimensional structure of the RBD, preventing the viral spike protein from attaching to ACE2 receptors on human host cells, thereby blocking viral entry [62]. Scientists have developed a stable RNA aptamer capable of preventing viral entry by binding efficiently to the RBD of the COVID-19 spike protein at picomolar levels. This aptamer holds promise as a candidate for inhibiting the interaction between host receptors and the SARS-CoV-2 spike protein [66]. To enhance its chemical

Table 3. Compilation of high-affinity ssDNA and RNA aptamers as prospective therapeutic agents for COVID-19.

Study	Target	Sequence [5′-3′]	KD [nM]	Selection Method	Partitioning Method	Main Results
Schmitz *et al*. [56] 2021	S Protein	GGGAGAGGAGGGAGATAGA-TATCAACCCATGGT AGGTATTGCTTGGTAGGGA-TAGTGGGCTTGATG TTTCGTGGATGCCACAGGA	21±4.6	Lambda exo-nuclease digestion	Bead	The study identified a DNA aptamer that binds to the SARS-CoV-2 spike protein and inhibits pseudovirus infection without interfering with the S protein or block-ing the virus's interaction with ACE2
Liu *et al*. [42] 2022	S Protein	ACGCAGCATCGAGTGGCTT-GTTT GTAATGTAGGGTTCCGGTCGTG GGTTGGACACG GTGGCTTAGT	28	-	Bead	The study developed syn-thetic ssDNA aptamers that can specifically target the SARS-CoV-2 related S protein, effectively blocking the virus's ability to bind to ACE2 receptors on human cells and preventing infec-tion
Sun *et al*. [65] 2022	S_{RBD}	CGCAGCACCCAA-GAACAAGGACTGCTTAGGATT GCGATAGGTTCGG	44.78±9.97	-	Bead	The study presents a spheri-cal cocktail neutralizing aptamer-gold nanoparticle [SNAP] that effectively blocks the SARS-CoV-2 Omicron variant by binding to its receptor binding do-main [RBD] with high affin-ity
Valero *et al*. [67] 2021	S_{RBD}	GGCACTATTTATATCAAC-CTCTTCC TGACGGAAGTATCGGTCCAG-GAATTACAAATGTCG TTGGTGGCCC	18	RNA poly-merase tran-scription	Bead	Researchers developed a serum-stable RNA aptamer called RBD-PB6. This ap-tamer binds with high affini-ty to the receptor binding domain [RBD] of the SARS-CoV-2 spike protein, preventing its interaction with the host receptor ACE2.
Villa *et al*. [62] 2022	ssDNA	GGCGTGCTTGACAGCAACAC-GAAC ACTGAACGTTCTTAACAA-GCCTGGCAGAGCAGG TACGGTGTCA	33	Denaturation and rapid cooling	Bead	These aptamers efficiently prevent the SARS-CoV-2 spike protein from interact-ing with the human angio-tensin-converting enzyme 2 [ACE2] receptor, inhibiting viral infection in the nano-molar range.

stability and resistance to degradation by viral nucleases, the RNA aptamer was modified by incorporating 2-fluoropyrimidine [67]. The use of these aptamer agents against COVID-19 has recently been evaluated in human studies. According to the study by Haberland *et al*., the BC 007 aptamer adopts a quadruplex structure, enabling it to bind specifically with high affinity [68]. Two studies have investigated the use of aptamers targeting the NSP10 protein of the SARS-CoV virus. NSP10 plays a crucial role in various stages of the SARS-CoV virus infection cycle, including replication and recombination, due to its NTPase/Helicase activity. Research suggests that inhibiting this protein with aptamers can restrict the unwinding of the virus's genetic material. Therefore, it is pertinent to explore whether aptamers could potentially attenuate SARS-CoV-2 infection progression due to similarities in gene and protein sequences between SARS-CoV and SARS-CoV-2 [112].

Another mechanism involves the effects of siRNAs on SARS-CoV-2 infection. Aptamers can hinder the infection and replication of SARS-CoV-2, while siRNAs have the capability to cleave the viral RNA genome, thereby impeding its propagation. It has been reported that aptamer-siRNA chimeras can serve as targeted antiviral therapy, combining the abilities to obstruct viral replication and counteract the virus effectively [70]. SiRNAs achieve high specificity by cleaving and obstructing the expression of their target genes through complementary sequences. This prevents the mRNA from being translated, resulting in reduced protein levels [112]. Alternatively, aptamers can serve as targeting ligands and delivery systems, enabling them to direct siRNA to the specific location in the viral infection cycle and reduce the risk of off-target effects. A recent study conducted in a severely ill patient demonstrated that lipid nanocarriers functionalized with aptamers and encapsulating RNAi could effectively treat SARS-CoV-2. The patient's lung ground-glass opacity showed improvement after six days of treatment [69]. Although aptamers offer numerous benefits and are highly effective in treating COVID-19, they also have limitations. The development and clinical use of aptamer drugs may face obstacles due to their susceptibility to nuclease cleavage and rapid renal filtration. To address these challenges, recent studies have focused on modifying aptamers using compounds such as 2'-fluoro, 2'-amino, or thiol-phosphate substitutions in the 2'-position or phosphate backbone [10]. Moreover, the utility of aptamers as molecular recognition agents may be limited by their susceptibility to degradation by nucleases. However, this issue can be addressed by employing mirror-image aptamers, also known as Spiegelmers. These mirror-image counterparts retain the specific binding properties of aptamers while demonstrating resistance to degradation by nucleases [67].

4. DISCUSSION

Our analysis of the existing literature indicates that aptamers hold promise as diagnostic tools for COVID-19. Due to their high specificity and affinity, aptamers can effectively bind to viral proteins such as the N protein, RBD, and NTD, thereby enabling the detection of viral antigens in diagnostic samples. These aptamers have shown exceptional sensitivity, allowing for the detection of even small quantities of the virus [114]. Moreover, aptamers have the potential to identify individuals in the early stages of infection, even before symptoms appear. The development of aptamer-based diagnostic methods, such as aptasensors, including electrochemical aptasensors, has shown promising results in terms of sensitivity and specificity [53].

In addition to their diagnostic potential, aptamers also show promise as therapeutic agents against COVID-19. Their exceptional specificity and affinity make them suitable for targeting viral proteins involved in viral entry and replication, such as the S protein and its RBD and NTD domains [107]. Aptamers possess the potential to inhibit viral entry into host cells and interrupt viral replication, thereby reducing the viral load and mitigating the severity of the infection. Furthermore, aptamers can be engineered to deliver therapeutic payloads, such as antiviral drugs or neutralizing agents, directly to the infected cells. The advancement of aptamer-based antiviral therapies presents significant promise for effectively treating COVID-19 [46].

One of the strengths of aptamer-based strategies for COVID-19 detection and treatment lies in their high specificity and affinity, which enable precise and targeted interventions. Aptamers are readily synthesized, and their production costs are relatively lower compared to antibodies. They also demonstrate superior stability and lower immunogenicity. Moreover, aptamers can be modified and engineered to improve their properties, such as enhancing resistance to nucleases and optimizing binding affinity [110]. However, aptamer-based strategies also face limitations and challenges. One such limitation is the potential emergence of genetic variations in the SARS-CoV-2 virus, which could impact the binding affinity and effectiveness of aptamers. Ongoing surveillance and adaptation of aptamers to accommodate new viral variants may therefore be necessary to uphold their diagnostic and therapeutic efficacy [103]. Another challenge involves optimizing aptamer selection processes, such as SELEX, to improve efficiency and enhance the generation of high-affinity aptamers. Furthermore, despite promising results in experimental models and *in vitro* studies, additional research is necessary to evaluate the efficacy of aptamers in clinical settings and to assess their long-term safety and potential side effects. Given the rapid evolution of SARS-CoV-2, with new variants like Omicron spreading globally, ongoing adaptation of aptamers to these changes is crucial [114]. However, aptamer selection is a time-consuming and resource-intensive process. Moreover, only a limited number of laboratories possess the requisite facilities and resources for conducting SELEX experiments. Redoing SELEX for each new variant may not be necessary. Instead, bioinformatic tools can be employed to repurpose existing aptamers originally designed against the wild-type (WT) virus to combat SARS-CoV-2 variants. Currently, SELEX coupled with high-throughput sequencing has emerged as a popular method for screening aptamers, yielding numerous potential candidate sequences [51, 114].

Based on our knowledge, the present study is the first systematic review study that investigated the use of aptamer and aptamer-related technologies in the diagnosis and treatment of COVID-19. The current study had several strengths such as conducting a systematic and detailed search in reliable databases, evaluating and screening studies by two researchers in a detailed manner, and also examining the use of aptamer in both phases of prevention and treatment of COVID-19. However, due to some limitations, the results of this study should be interpreted with caution. Firstly, due to the very high heterogeneity between the studies in terms of the examined outcomes and the design of the studies, it was not possible for us to perform meta-analysis and quality assessment. Secondly, some studies had investigated the effect of aptamer-based technologies on some strains of COVID-19, but this had not happened in other studies, and this was also a source of heterogeneity.

CONCLUSION

The use of aptamers as detection and therapeutic agents has garnered significant attention recently. Aptamers show

promise as therapeutic agents by targeting specific viral proteins or host cell receptors. The ongoing mutations in SARS-CoV-2 pose challenges affecting the efficacy of COVID-19 vaccines and treatments. Aptamers' unique characteristics make them attractive for adapting to viral mutations and developing advanced antiviral therapies for SARS-CoV-2. Additionally, aptamers have been successfully utilized in early COVID-19 detection in certain studies. However, challenges and limitations in their application for COVID-19 diagnosis and treatment need thorough investigation and resolution. Further human studies are essential to advance our understanding and utilization of aptamers in combating COVID-19.

AUTHORS' CONTRIBUTIONS

MN and MRZR conceptualized the study, oversaw the search conducted analysis/synthesis, led the drafting of the first draft of the review, and addressed comments received. ZG played a leading role in literature screening and conducted analysis. JC, FS, and NA participated in the development of the search strategy and contributed to the drafting of the first draft of the full review. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

LIST OF ABBREVIATIONS

3D	=	Three-dimensional
ACE2	=	Angiotensin-converting Enzyme 2
CRISPR	=	Clustered Regularly Interspaced Short Palindromic Repeats
DPV	=	Differential Pulse Voltammetry
EAB	=	Electrochemical Aptamer-based
EIS	=	Electrochemical Impedance Spectroscopy
FRET	=	Fluorescence Resonance Energy Transfer
LOD	=	Limit of Detection
NAATs	=	Nucleic Acid Amplification Techniques
NTD	=	N-terminal Domain
QCM	=	Quartz Crystal Microbalance
qRT-PCR	=	Quantitative Real-time Reverse Transcription Polymerase Chain Reaction
RBD	=	Receptor Binding Domain
SARS-CoV-2	=	Severe Acute Respiratory Syndrome Coronavirus 2
SELEX	=	Systematic Evolution of Ligands by Exponential Enrichment
SPR	=	Surface Plasmon Resonance
VEGF	=	Vascular Endothelial Growth Factor

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA guidelines and methodology were followed.

AVAILABILITY OF DATA AND MATERIALS

The data produced or examined in this study are incorporated in this article and can be obtained from the corresponding author upon reasonable inquiry.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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