Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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A systematic review of the advancement on colorimetric nanobiosensors for SARS-CoV-2 detection

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ABSTRACT

The current pandemic of the acute severe respiratory syndrome coronavirus 2 (SARS-CoV-2) killed about 6.4 million and infected more than 600 million individuals by august of 2022, and researchers worldwide are searching for fast and selective approaches for this virus detection. Colorimetric biosensors are an excellent alternative because they are sensitive, simple, fast, and low-cost for rapid detection of SARS-CoV-2 compared to standard Enzyme-linked immunosorbent assay (ELISA) and Polymerase Chain Reaction (PCR) techniques. This study systematically searched and reviewed literature data related to colorimetric biosensors in detecting SARS-CoV-2 viruses, recovered from the Scopus (n = 16), Web of Science (n = 19), PubMed (n = 19), and Science Direct (n = 17) databases totalizing n = 71 articles. Data were analyzed for the type of nanomaterial, bio-recognition material at the detection limit (LOD), and devices designed for diagnostics. The most applied nanomaterial were gold nanoparticles, in their original form and hybrid in quantum dots and core-shell. In addition, we show high specificity in point-of-care (POC) diagnostic devices as a faster and cheaper alternative for clinical diagnosis. Finally, the highlights of the colorimetric biosensor developed for diagnostic devices applied in swabs, surgical masks, and lateral flow immunoassays were presented.

1. Introduction

The pandemic caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) infection resulted in the COVID-19 disease, killing about 6.4 million and infecting more than 600 million individuals by august 2022 [1]. Many deaths are due to cases of pneumonia and other complications, and the virus spreads from person to person, most commonly in hospitals and among families [2].

The virus's widespread transmission raises significant concerns about rapid detection methods. Among the techniques for detecting SARS-CoV-2 (diagnostic tests), Enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) are the most indicated because they have high sensitivity and precision. However, they are high cost and depend on complex equipment and trained technicians only viable in centralized laboratories. In addition, PCR may take a few days to obtain the results, and immunological assays are a complex reaction of antibodies with recombinant proteins. The need to produce faster devices with lower cost and reliability for detecting SARS-CoV-2 was observed [3].

Biosensors are simple, fast, low cost, sensitive, and specific, with good portability and miniaturization potential. Miniature devices with different sensing platforms that can detect SARS-CoV-2, for example, through colorimetric detections, are popular due to their ease of use and ability to capture images through electronic benchtops and portable devices [4–6]. However, when working with analyses in such low concentrations, these devices have limitations because it is often difficult to

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convert detectable signals into color readings, resulting in low sensitivity [5].

Nanomaterials can improve the sensitivity of biosensors based on the colorimetry detection method [7]. Compounds such as noble metal nanoparticles, including gold nanoparticles (AuNPs) [8–10], silver nanoparticles (AgNPs) [11,12], magnetic nanoparticles (MNPs) [13,14], carbon-based nanostructures [15–17], nanohybrids corel shell [18,19], quantum dots [20,21] and others can be used for this purpose. Because nanomaterials have different proprieties as the large surface area of contact, they can increase the number of conjugated receptors on their surface, increasing recognition events and improving detection performance [5]. Moreover, DNA, proteins, peptides [22], and enzymes responsible for detection can be attached to the surfaces of nanoparticles [23]. The use of nanomaterials for the fabrication technology of biosensor devices creates a new set of biosensors called nanobiosensors.

Prior amplification of genetic material also is an efficient approach that significantly improves the sensitivity of biosensors. Colorimetric biosensors associated with molecular biology techniques increased sensitivity and specificity to SARS-CoV-2 RNA [23,24]. Transcription Mediated Amplification (TMA), Rolling Circle Amplification (RCA), Clustered Regularly Spaced Short Palindromic Repeats (CRISPR), and Mediated Isothermal Amplification Loop (LAMP) are Isothermal amplification techniques that have gained popularity for their simplicity of execution and speed [23,24].

Given the current pandemic scenario, mass screening is critical to address the need for rapid diagnosis. The purpose of this study was to conduct a systematic search of four scientific databases relevant to the topic at hand, analyzing all articles published in the literature that experimentally developed a colorimetric biosensor for detecting SARS-CoV-2. The databases used were Scopus (n = 16), Web of Science (n = 19), PubMed (n = 19) and Science Direct (n = 17), totaling n = 71 articles that reviewed and discussed the most recent advances in colorimetric biosensors in the detection of SARS-CoV-2. The benefits of using nanomaterials in colorimetric biosensors to improve sensitivity, the use of gold nanomaterials, the innovation of ACE2 as a biorecognition element, and finally the biosensors that were applied to POC devices were discussed throughout the text. In addition, the devices that stood out for their innovations were discussed, such as application in surgical masks, Nano-Amplified Colorimetric Test (NACT), optodiagnostic and lateral flow immunoassay (LFIA).

2. Systematic methodology

This systematic review searched over four scientific databases (Web of Science, SCOPUS, PubMed, and Science Direct) about biosensors to SARS-CoV-2 detection with the colorimetric transducer. The search followed a four-phase flow diagram and guidelines for systematic review and meta-analyses (PRISMA) [24].

2.1. Focus questions

The focus questions agreed with the problem, intervention, comparison, and outcome method by PICO. The research questions were: What types of colorimetric biosensors can be used to improve the detection of SARS-CoV-2? Which nanomaterial is most used to detect SARS-CoV-2 using a colorimetric biosensor? Which nanomaterial has presented the best sensitivity? What are the types of samples analyzed by these biosensors?

2.2. Information sources

This systematic review was conducted on January 18, 2022, through research in the four previously cited databases. The study was realized with the search components *SC1* (Biosensor) AND *SC2* (Biosensor) AND *SC3* (SARS-CoV-2 OR COVID-19 OR coronavirus).

2.3. Selection criteria

This review considered original research articles and excluded revisions, thesis, and short communications. We first conducted the preliminary selection of abstracts, keywords, and titles identified independently. Articles were removed in this initial screening if the study did not investigate biosensors with colorimetric detection for SARS-CoV-2. Articles non-written in the English language were also excluded. After full-text reading, articles that did not meet any focus questions were rejected.

3. Dataset results

Data extraction and quality assessment were performed independently by three revisions. We only excluded studies after full-text reading discarded doubts about the study's eligibility. A total of 71 studies from the Scopus (n = 16), Web of Science (n = 19), PubMed (n = 19), and Science Direct (n = 17) databases were elected. The results of the systematic search are presented on the PRISMA flow chart, Fig. 1. After full-text reading of the articles, 17 were selected for quantitative analysis. All useful information obtained by each study were extracted and compiled in Tables 1 and 2, as presented in the following sections.

3.1. Colorimetric biosensors

Colorimetric biosensors are a promising diagnostic device, particularly in areas with limited resources, emergencies, and home care, where external devices and reagents are not required [5,25]. The advantage of this tool is its ability to provide a visible result to the naked eye, which overcomes the limitations of the gold standard, PCR, and ELISA techniques, regarding the time, cost, and techniques required for diagnosis [26]. Same with other biosensors that need expensive instruments to verify detection, such as electrochemical [17], SERS [27], and fluorescence [28], among others. Fast and easy detection systems are very desirable in the current pandemic scenario, where it is crucial to effectively detect the presence of viruses to combat and control the transmission of the SARS-CoV-2 that happens very quickly [29,30]. Fig. 2 shows a diagram of colorimetric biosensors.

Legend: (-) not reported; AuNPs (Gold nanoparticles); MNP (Magnetic nanoparticles); AuNPs-ACE2 (Gold nanoparticles with ACE2 protein acoplated); NBs (SiO2 @Au@QD nanobeads); mPEG-PCL (copolímeros dibloco de etileno glicol-caprolactona); AuNPs-N (Gold nanoparticles whit adsorbed nucleocapsid protein (N)); f-AuNPs (AuNPs functionalized with anti-SARS-CoV-2); SiO2 @Au/QD (gold nanoparticles and quantum dots on SiO2); mPEG–PCL (methoxy poly

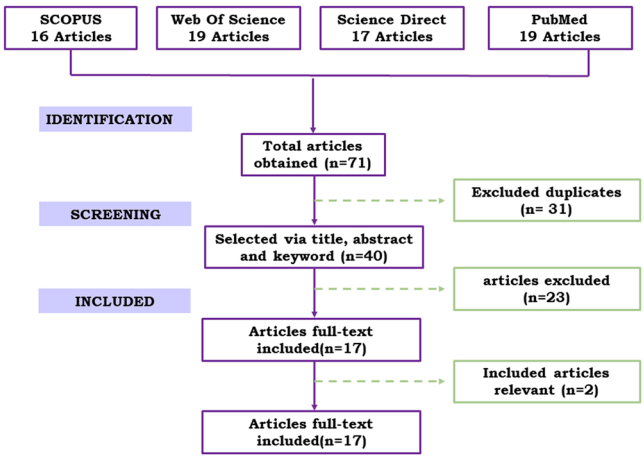

Fig. 1. The schematic diagram for the selection of articles included based on PRISMA methodology.

Table 1
Description of colorimetric biosensors for detection SARS-CoV-2.

Nanomaterial	Size	Target	Biological recognition element	LOD	Reference
Polymer mPEG-PCL-AuNP	222,1 nm	protein Spike	antibody	0,11 ng/mL	[31]
AuNPs-N	30 nm	IgG, IgM e IgA	protein N-antigen		[32]
MNP (γ Fe_2O_3)		protein Spike	ACE2 receptor	4,98 ng/mL	[33]
AuNPs-ACE2	7 nm	Protein Spike	ACE2 receptor	1.54×10^{-4} ng/mL	[34]
SiO2 @Au@QD NBs	~ 240 nm	Protein Spike	IgG and IgM	$1:10^{6}$ dilution	[35]
f-AuNPs	20 nm	spike, envelope, and membrane	antibody	Ct 7	[36]
NPs core–shell Au@Pt	25 nm	Protein spike S1	polyclonal antibodies	11 ng/mL	[37]
AuNPs	40 nm	Protein N	antibody rabbit IgG	3 ng/mL	[38]
AuNPs	–	Protein N	Antigen	150 ng/mL	[39]
SiO2 @Au/QD	~200 nm	Protein spike S1	antibody	1 ng/mL	[40]
AuNPs	17,7 nm	ORF1, ORF2, E1, and E2	cDNA	580 nM	[41]
AuNPs	16 nm	Protein Spike	antibody monoclonal (mAb)	48 ng/mL	[42]
AuNPs	–	Gene N	DNA+BoNT / A LC	1 copie/µL	[43]
Fe3O4/Au core-shell	30–80 nm	Protein Spike	anti-spike protein antibodies	1200 PFU/mL	[44]
AuNPs	80–120 nm	Gene N	ssDNA	10 copies/µL	[45]
Not applicated		–	DNA biotinilados	~1 nM	[46]
Not applicated		Gene N and E	ssDNA	10 copies	[47]

(ethylene glycol-block-caprolactone)diblock copolymers); ssDNA (DNA de fita simples); DNA+BoNT / A LC (botulinum neurotoxin type A light chain);.

3.2. The role of nanomaterials in colorimetric biosensor

Nanomaterials have been used in biosensors (nanobiosensor) to improve sensitivity, especially colorimetric detection. Nanomaterials offer various physical and chemical properties and are easily functionalized with biomolecules [48]. Functionalization can happen with several biological structures, facilitating the capture of targets and amplifying the detection signal. Its works due to the greater contact area of the nanomaterials near the receptors. The more receptors in their surface area, the greater the chance of binding the target molecules and improving the sensitivity of the biosensor [14,49,50]. Among the selected studies that developed a colorimetric biosensor for detecting SARS-CoV-2, only two did not use nanomaterials (Table 1). This result shows that nanoparticles are already widely used as their benefits in detecting analytes with high sensitivity.

Nanomaterials are of interest in biosensing research because they can be exploited directly as signal reporters due to their inherent physical and optical properties. These characteristics include a high surface-to-volume ratio that enables suitable surface modification with bioactive compounds, an excellent capacity for reaction catalysis, electrical conductivity, excellent biocompatibility, a particularly high characteristic extinction coefficient in visible light, and a visual color transition resulting from the shift of surface plasma absorption as a result of varying size and shape. Using nanomaterials in colorimetric biosensors can dramatically magnify signal strength and increase the sensitivity of target biological molecules, including pathogenic bacteria and viruses, DNA, and proteins. Gold and silver nanoparticles are particularly intriguing among many nanomaterials due to their simplicity and sensitivity in producing a color response. Gold nanoparticles (AuNPs) are widely utilized in colorimetric biomedical assays because they are simple to produce, chemically and physically stable, biocompatible, exhibit a unique optoelectronic characteristic, and can be modified with bioactive and organic molecules [47]. Moreover, functionalization can occur with various biological configurations, facilitating target capture and amplifying detection signals due to the increased contact area of the nanomaterials near the receptors. The more receptors on their surface area, the better their chances of binding target molecules and improving biosensor sensitivity [14,48,49]. Due to these combined benefits, colorimetric biosensors have been used to detect SARS-CoV-2 antigens, antibodies, and/or their fragments at the molecular level. Table-1 demonstrates the application of these nanomaterials for the highly sensitive detection of SARS-CoV-2 spike protein [51]. Apart from the advantages, some technical issues need to be addressed right away with these nanomaterials for colorimetric detection of SARS-CoV-2, such as reliability and reproducibility in high ionic strength samples, such as in serum and urine, as well as lack of sensitivity is a concern in some applications because perceptible color change is difficult to measure, limiting their application to biological sample analysis in comparison to other analytical methods such as fluorescence and chemiluminescence [5].

SARS-CoV-2 detection can entail isolating and detecting nucleic acids in biological samples such as blood, feces, oral or nasal swab, tracheal, lung tissue, and sputum, which are used to investigate the level of infection during the pandemic. COVID-19 diagnostic methods must be effective, quick, and low-cost. Several biosensor improvements are being optimized and validated by researchers all over the world in order to meet the needs of the COVID-19 pandemic with faster detection and a low chance of false positive or false negative results [52,53].

Colorimetric reactions can be performed on various platforms, such as paper sheets, for a simple and quick approach to colorimetric detection at a low cost. Colorimetric detections generally use simple equipment or can be seen with the naked eye, such as when a color change is involved or by fluorescence and luminescence [54]. Thus, in asymptomatic cases or individuals at the beginning of the infection, rapid and sensitive tests for the diagnosis of COVID-19 are required; this allows health professionals to diagnose more accurately. Aside from the possibility of early detection, this is an effective strategy for reducing the spread of the SARS-CoV-2 virus, with several advantages over the standard gold test, RT-qPCR.

Colorimetric detection with gold nanoparticles is one example, in which the chromogenic effect (color appearance) is caused by the aggregation of the gold nanoparticles. Colorimetric detections based on gold nanoparticles have a number of advantages, including stability and ease of fabrication. Gold nanoparticles can be linked to biorecognition components like antibodies or antigens. This device produces results that can be evaluated without the use of instruments. Several brands of test kits are currently available on the market that is based on the reactions between antigens or human antibodies anti-SARS-CoV-2 detected by immunochromatography in the presence of gold nanoparticles [52].

3.2.1. Gold-based nanomaterials

Gold metal (Au) has unique optical nanobiosensors and electronic properties responsible for the high popularity of this metal used in nanomaterials in the biomedical field. The high extinction coefficient of

Table 2
Description of biosensors in terms of POCs developed, AFOM, analyze time, sample type, and confirmation technique.

Applicated in POC	AFOM						Time	Samples	Confirmation thecnique	Reference
	Linear range	LOD	Sensitivity (%)	Recovery (%)	RSD (%)	Specificity (%)				
Colorimetric paper-based diagnosis	0.17–3 ng/mL	0,11 ng/mL			4.59 *		30 min	Serum human	RT-PCR and ELISA	[31]
Lateral flow immunoassay			89			100	20 min	Serum human	ELISA	[32]
Not applicated	4.98 – 1 13 ng/mL	498 ng/mL	97.56		3.16 *	90.24	30 min	Oropharyngeal and nasopharyngeal	RT-PCR	[78]
Optodiagnostic	10^{-3} – 10^{3} ng/mL	154 ng/mL	96		5.7%*	80	5 min	Nasopharyngeal and oropharyngeal	RT-PCR	[88]
Lateral flow immunoassay		1:10^{6} dilution	100			100	15 min	Serum human	RT-PCR	[35]
Not applicated		Ct 7	96			98	3 min	Nasal	RT-PCR	[36]
Not applicated	10 – 100 ng/mL	11 ng/mL	high			high	20 min	Not applicated	Elisa	[37]
Surgical face masks	0,3–10^{2} ng/mL	3 ng/mL	96,20			100	< 10 min	Face masks	RT-PCR	[38]
Not applicated	150–550 ng/mL	150 ng/mL				high	5 min	Not applicated	not applicated	[39]
Lateral flow immunoassay	0.1–100 ng/mL	1 ng/mL		> 92.98	3.92–5.19	high	30 min	Throat and nose swab	RT-qPCR	[40]
Not applicated	10–10^{-5} nM	580 nM					40 min	Simulated samples	RT-qPCR	[41]
Not applicated	250–1000 ng/mL	48 ng/mL		94.1 ± 2.1	2.2	high	10 min	Saliva	RT-qPCR	[42]
Not applicated		1 copies/µL					1–2 h	–		[43]
Lateral flow		10 copies				inconsistent	1 h	Swabs orofaríngeos e nasofaríngeos	RT-qPCR	[47]
'Nano-amplified colorimetric test'		10 copies/µL	> 96.6			100	< 1 h	Swabs orofaríngeos e nasofaríngeos	RT-qPCR	[45]
Not applicated	0–500 nM	~ 1 nM				high	2 h	Not applicated		[46]
Magnetic-focus-enhanced lateral flow assay	–	1200 PFU/mL	66.7			100	50 min	Saliva		[44]

Legend: (*) Relative standard deviation in relative to reproducibility; RSD (Relative standard deviation); LOD (Limite Of Detection); RT-PCR (Reverse.transcription polymerase chain reaction); RT-qPCR (Reverse transcription polymerase chain reaction in real-time quantitative)

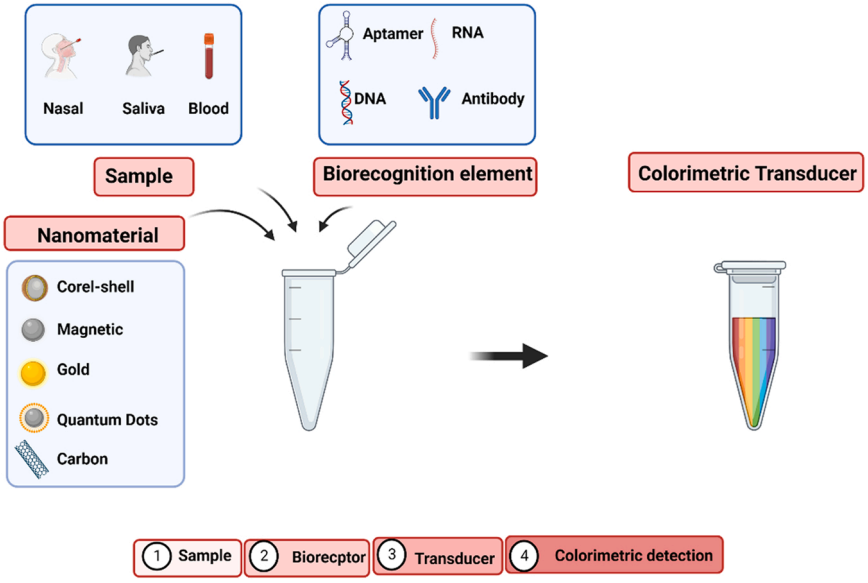

Fig. 2. Diagram of main elements of a colorimetric biosensor and the steps in the detection.

gold nanoparticles in 10^{10} M^{-1} cm^{-1} indicates that the metal strongly absorbs radiation [55,56]. This strong absorption generates intense bands of localized surface plasmonic resonance (LSPR), which is caused by the oscillation of free electrons on the surface of the metal under light stimulation [57]. Metals with intense SPR bands and absorption in the visible region are called noble metals, and gold is among them [58–61]. These optical characteristics and the fact that it is biocompatible and inert make gold the most used metal in biological sensors. The

biocompatibility of gold nanomaterials (AuNMs) was explored with functionalization for DNA detection as an alternative to replace radioactive markers that were the main ones used at the time [62].

The main advantage of AuNMs in optical biosensors is the possibility of visualizing the detection result with the naked eye [58]. An example is spherical AuNPs (Gold nanoparticles) which are the most used for displaying the SPR present in the visible region of 400–700 nm without enlargements. The solution color, blue or red, will depend on the interparticle distances when functionalized. The solution will be red if the distances are more significant than the average particle diameter; otherwise, it will be blue [63]. Confirmation of the AuNPs functionalization can also be observed by the displacement of the SPR absorption band. After detecting the target by the AuNPs, the solution will change color, being possible to visualize the positive result with the naked eye without the need for optical instruments [58]. In addition to the color change, the detection can be observed by the difference in the intensity of the SPR bands.

The physicochemical properties of AuNPs allow adequate control of their size and shape in their synthesis and can generate different forms of AuNMs. Some forms most commonly used in sensors are nanorods [64,65], nanostars [66,67], nanoflowers [68,69], core-shell [70,71] and nanospheres [72,73]. However, gold nanospheres are the most commonly used form due to their isotropic structure [74]. A study by Mustafa et al. (2010) compared the SPR bands of AuNPs of spherical forms, nanorods, and nano octahedrons. The different forms investigated their SPR effects in different sizes in a fixed excitation wavelength of 670 nm with a fixed concentration of NPs. It was noted that nanospheres and octahedrons had the SPR signal affected by mass changes based on the refraction index. The mass effect of the sharpness of the corners and edges plays an important role in the field and, consequently, in the displacement response of the SPR angle. In this case, the gold nanorods produce an SPR signal almost twice the displacement of the SPR angle as the gold nanospheres. Conclusion affirmed that gold nanospheres should be preferred for marking sensors because there is no strong dielectric effect. Moreover, nanorods are very considerable because a double increase can be obtained compared to gold nanospheres [75].

For the same material, the optical properties of nanoparticles are directly influenced by their shape. Due to the atoms being in different faces and angles, metal nanoparticles of the same metal but with different shapes have different properties, allowing multiple surface plasmonic resonances [74,76]. Wiley et al. (2006) demonstrated how shape control can be used to adjust the optical properties of silver nanostructures using Mie's theory and Maxwell's equations calculations. Variations in the parameters: size, shape, or dielectric environment of the particles will result in the polarization change of its surface, affecting the resonance peak [59]. The spectrum of UV–vis extinction, absorption, and scattering obtained through theoretical calculations for different nanostructures: spherical, cube, tetrahedron, octahedron, and shell showed different absorption peaks [59]. The structures with sharp corners presented more peaks than the spherical shape because they had several distinct symmetries for dipolar resonance, and the loads accumulated in the corners of the structure. The hollow, spherical, or shells also present the plasmonic resonance peak diverted to red concerning a sphere because the loads on the inner and outer surface show the same signal for a given pole [59]. It concludes that the size and shape of the AuNPs and the dielectric constant of the surrounding environment have a high impact on the LOD [8]. All these factors make the spherical shape the most used.

Given the evidence discussed above, the data obtained by the articles selected in this systematic review did not let us establish any pattern between the nanomaterial size and the LOD obtained. The data showed the most varied sizes from 7 to 21 nm and LODs from 1 to 154 ng/L for studies that used nanomaterials. In 14 out of 17 studies (Table 1), gold was the most applied material/metal among the nanomaterials used to improve biosensor sensitivity.

The chromogenic effect (or chromatic alteration) produced by AuNPs explains their dominance in colorimetric biosensors. This effect is the aggregation of AuNPs, which results in a color change in virus detection. SARS-CoV-2 [77]. The interparticle distance is a critical parameter in nanoparticle aggregation and is responsible for the color displayed. Another important factor is particle diameter; NPs larger than 80 nm tend to shift their emission to the infrared region, making them impossible to detect with the naked eye. The fact that the gold nanoparticles present this effect offers an advantage compared to other nanomaterials. Of the published studies of colorimetric biosensors, only one study uses magnetic iron oxide nanoparticles (γ-Fe_3O_4), all other works use gold. In this single study, the visualization of color change is related to the oxidation of 3,3',5,5'-tetramethylbenzidine (TMB) in the presence of hydrogen peroxide (H_2O_2) and NPs of γ-Fe3O4 [78]. Unlike gold or nanoparticles of γ-Fe $_3O_4$ cannot cause color change with the detection of the target. This can be explained by the iron (Fe) not absorbing in the region of the visible, ~300 nm, causing the metal to have no SPR band [79]. Although iron nanoparticles are less expensive to synthesize, they do not detect the direct target, necessitating complementary reactions, making them less suitable for colorimetric biosensors. The sensitivity generated by the nanomaterial compared to the AuNPs is also an important issue. Büyüksünetçi et al., (2021) with γ-Fe3O4 nanoparticles present LOD 4.98 ng/mL, while Ferreira et al. [34] with AuNPs present LOD 1.54 × 10^{-4}, a detection of about 10^4 more sensitives, in which the two studies used ACE2 as a biorecognition element. These presented facts provided solid justifications for the popularity of gold-based nanomaterials for biosensors with colorimetric detection.

3.3. The innovation of ACE2 as a biorecognition element in colorimetric biosensors

The biosensor's precision and accuracy are directly linked to the biorecognition element and the detection region within SARS-CoV-2 DNA. Biorecognition elements also should be very specific. For SARS-CoV-2, biosensors, antibodies, and nucleic acid probes are the biorecognition elements most used [80]. According to reported publications (Table 1), most contained antibodies as biorecognition material, followed by nucleic acid, the human angiotensin-converting enzyme 2 (ACE2), antigen, and Protein N. They used monoclonal or polyclonal antibodies in biosensors and presented sensitive results with LOD 0.11 ng/L for detecting SARS-CoV-2 [31] in 150 ng/L [39]. Because of their high specificity and affinity binding properties, antibodies or immunoglobulins (Ig) are very popular in immunodiagnostic assays. Immunoglobulin A (IgA), Immunoglobulin D (IgD), Immunoglobulin E (IgE), Immunoglobulin G (IgG), and Immunoglobulin M are the five isotypes of immunoglobulins (IgM). The most common types are IgG and IgM, which work together to provide immediate and long-term protection against infections, while IgE is linked to allergies. [81,82]. Among the selected articles, we discovered that using aptamers in colorimetric detection was not observed among the biorecognition elements. cDNA or aptamers are gold standard diagnostic tools that use nucleic acids such as DNA (deoxyribonucleic acid) or RNA (ribonucleic acid). Nucleic acid-based biosensors are highly selective because they allow direct detection of a specific genetic fragment whose complementary sequence can be synthesized with high purity [83]. Because of this conjugation, they are highly specific for detecting SARS-CoV-2, for example. It can be tailored to a specific conserved genome region, avoiding regions where variants could result in false-negative detection [84]. Mutations occur naturally during virus replication within the host cell, and many mutations result in new variants. As a result, due to a high mutation rates of SARS-CoV-2, the correct selection of the detection region in the virus genome is critical for its identification [84]. Interestingly, the most significant number of mutations in SARS-CoV-2, about 4000, are encoded in the S gene, which is associated with viral entry into cells [85]. Despite the reported numerous mutations, more than half of the

included studies chose this gene as a detection region.

The ACE2 enzyme also can be used as a biorecognition element, and this use is highlighted as an innovation in colorimetric biosensors for diagnosing COVID-19. The diagnosis is possible because ACE2 is found in the membranes of the lungs, arteries, heart, kidney, and bowel cells and acts as an entry point for some coronaviruses, such as SARS-CoV and SARS-CoV-2 [78,86,87]. SARS-CoV-2 is an enveloped RNA virus containing crown-shaped tips on the outer surface called protein (S) Spike. The infection in human cells happens by the interaction of protein S with the ACE2 cell receptor [78,86,87]. After this contact with the cell receptor, the virus can release its genetic material into the cell, infecting it. Based on this interaction, recent studies use ACE2 as a biorecognition element in colorimetric biosensors to detect SARS-CoV-2 [78,88]. In addition to protein S, there are three other main proteins: membrane (M), envelope (E), and nucleocapsid (N) [87], as represented in Fig. 3.

Ferreira et al. (2021) developed optodiagnosis for COVID-19, a colorimetric biosensor in the form of swabs made of gold nanoparticles (7 nm) modified with ACE2. The test had a low production cost of about 15 cents and a 5-minute detection time. The excellent sensitivity of this biosensor, capable of detecting very low viral particle loads, LOD 1.54×10^{-4} ng/mL, makes it an excellent choice. The optadiagonotic was applied to 100 nasopharyngeal and oropharyngeal clinical samples obtaining sensitivity, specificity, and accuracy values of 96%, 84%, and 90%, respectively [34]. Büyüksünetçi et al. (2021) also used ACE2 as a biorecognition element in its colorimetric biosensor. The enzyme was functionalized to a solution containing magnetic nanoparticles γ Fe_2O_3 and 3,3',5,5'-tetramethyl benzidine (TBM) oxidized, presenting a blue color. The change in coloration to colorless/transparent indicated the presence of spike protein (S), consequently detecting SARS-CoV-2. This method was applied to 40 real clinical samples and presented 90.24% specificity when tested with H1N1 and H3N2 influenza viruses and excellent sensitivity (LOD 4,98 ng/mL) [78]. The novelty of the optodiagnosis method is that ACE2 is the specific detection target rather than

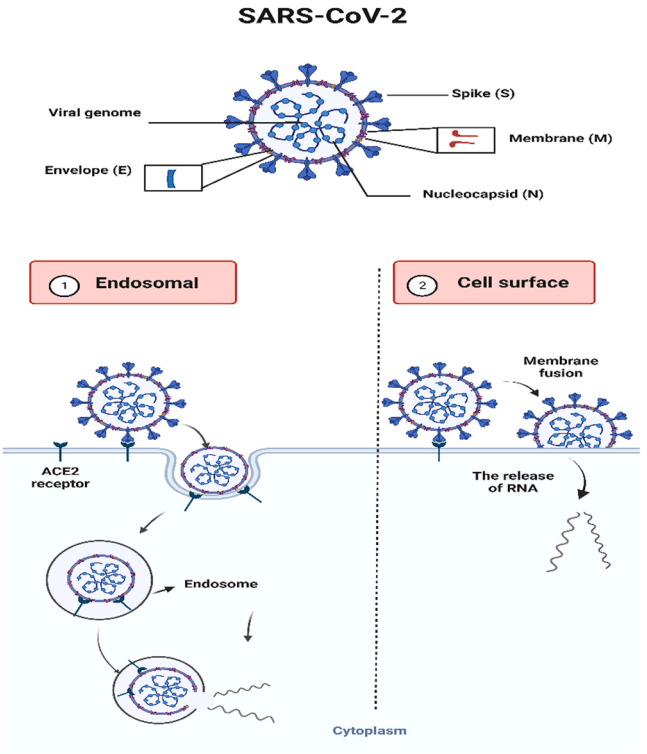

Fig. 3. Description of the proteins mainly found in SARS-CoV-2 and the two routes of entry into human host cells. 1) The SARS-CoV-2-ACE2 complex can be internalized in lysosomes by endocytosis. 2) SARS-CoV-2 membrane fusion by action of host cell proteins and releasing RNA.

SARS-CoV, so virus mutations or antigen changes have little or no effect on detection efficiency. Furthermore, given the virus mutations reported thus far, this system may not require updates in other reagents such as primer and aptamers.

According to the literature, the ability to interact with all virus variants is the main advantage of using ACE2 as a biological element of recognition. The emergence of new variants in various genes may have an impact on biosensors that use RNA or antibodies. Wei et al., (2023) published a critical review in which its advantages over other elements were well established using various types of transduction [52]. Our main concern is the specificity of ACE2 to other viruses. Because the genome of the SARS-CoV-2 virus resembles SARS-CoV by 80%, an interaction with other viruses from the same family is very likely, resulting in false positives. Furthermore, we believe that additional research with other viruses, such as influenza, norovirus, and others, is required to confirm the specificity of ACE2.

3.4. Biosensors applied to point-of-care (POC) diagnostic devices

Point-of-care (POC) diagnostic devices have emerged as an excellent option for diagnosing various infectious diseases, particularly in the current pandemic scenario. This testing entails gathering detailed clinical data and parameters about the patient. POCs are very popular because they allow patients to be treated in the right direction as soon as possible [89] due to their detection speed, simplicity, and robustness [23,90]. Lateral flow immunoassay (LFIA), colorimetric paper-based diagnosis, optodiagnostic, applicated surgical face masks, Nano-Amplified Colorimetric Test (NACT), and origami were the biosensors developed as POCs in the included studies. Table 2 shows their Analytical Figures of Merit (AFOM) in terms of LOD, sensitivity, recovery, RSD, and device specificity.

The lateral flow immunoassay (LFIA) was the most commonly used device with colorimetric biosensors to detect SARS-CoV-2 in the studies included in our systematic review (Table 2). This assay detects antigens in the early stages of infection, making it ideal for field use. Following that, we summarized the general aspects of three studies that focused on the most efficient application of LFIA to diagnostic POC devices.

Han et al. [40] created an LFIA based on rapid antigen detection of S protein, employing SiO2 @Au/QD fluorescent, colorimetric NPs as a quantum dots probe that can be viewed in two modes: naked eye and fluorescence. The sample is not pre-treated and can be directly placed on the device. The LOD showed 33 pg mL-1 and 1 ng mL^{-1} in fluorescence and naked eye detection, respectively. It was shown to be selective/specific when placed with interfering in a high concentration of SARS-CoV (100 ng/mL), MERS-CoV (100 ng mL^{-1}), Influenza H1N1 (5×10^6 copies mL^{-1}), Influenza-B (5×10^4 copies mL^{-1}), Respiratory syncytial virus (5×10^5 PFU mL^{-1}) and Adenovirus (5 μg mL^{-1}). The recovery assay proved accuracy $> 92.98\%$, and the device's RSD of 3.92–5.19%. This study confirmed that the new biosensor has excellent accuracy and applicability for detecting SARS-CoV-2 in real samples [39].

Cavalera et al. [32] developed a device that detect the total antibodies produced by COVID-19. It is a dual-line LFIA in which both test lines could connect to various immunoglobulin classes (IgG, IgM, and IgA). The biosensor detects specific anti-SARS immunoglobulins with 100% specificity (95.75–100, 95% IC; n = 85 healthy individuals with other infections) and 94.6% sensitivity (84.9–98.9, 95% IC; n = 62 SARS CoV −2 infected individuals). The method also succeeded as a standard serological ELISA reference technique [31].

Ren and Irudayaraj's [44] study reported an improved lateral flow assay with magnetic focus (mLFA) detecting SARS-CoV-2 in non-inoculated saliva. Magnetic nanoparticles (MNPs) (Fe3O4/Au core-shell) conjugated with anti-spike protein antibodies were used to identify the SARS-CoV-2 virus in saliva samples during target detection. The higher concentration of the virus in the capture antibody region is due to the use of the magnet, and also the longer insertion time

significantly improves the capture efficiency, resulting in high sensitivity capable of detecting 400 PFU mL^{-1} in buffer PBS and 1200 PFU mL^{-1} in saliva samples with sensitivity of 66.7% and 100% specificity without the prior need for amplification of genetic material [43].

Despite its broad applicability and sensitivity, LFIA detection of host immune response cells may be detrimental. This occurs because the time required for the host to produce antibodies can result in false negative results. Methods that detect the virus directly are alternatives for reducing this bias. In this context, we will discuss two of the most innovative studies in which researchers developed point-of-care (POC) devices capable of detecting SARS-CoV-2 directly in host samples.

Vaquer et al. (2021) pioneered the development of an antibody-decorated gold nanoparticle transfer biosensor for the non-invasive detection of SARS-CoV-2 antigens trapped in surgical masks of patients. Direct contact transfers AuNPs from the biosensor to the mask, emitting colorimetric signals that are later quantified using a mobile app. This requires the surgical mask be used for less than 10 min and be applied to 27 patients with mild or no symptoms. The analytical parameters presented by the authors were excellent: LOD 3 ng mL^{-1}, sensitivity 96,2%, and specificity 100%. The high sensitivity, even for samples of asymptomatic patients, mobile detection, and non-invasive sample collection procedure, makes this biosensor ideal for mass triage [37].

Alafeef et al. (2021) created a test that combines two steps: amplifying viral RNA using the LAMP method and detecting SARS-CoV-2 in the same device. The nano-amplified colorimetric test does not require RNA extraction, and the sample can be placed crudely on the device before amplification and detection. AuNPs were coated with antisense oligonucleotides (ASOs), which served as a colorimetric reporter for detecting virus RNA. ASOs are specific to the N gene, which allowed a high specificity of 100%, accuracy $> 98.4\%$, and sensitivity $> 96.6\%$ and with a detection limit of 10 copies μL^{-1} showing the optimal analytic results of the device and with response time < 1 h. The test is effective in viral detection and can be applied to other targets, changing the sequence of primers used in the LAMP amplification technique [44].

The application of colorimetric biosensors as POCs devices has become an excellent tool for detecting SARS-CoV-2 due to its speed in diagnosis, practicality to be performed in the field, and low production cost. They are easily handled without requiring highly qualified personnel, as demonstrated by the LFIA-based methods and surgical masks developed by Vaquer et al. (2021). The main advantage of these devices is that they do not require prior RNA amplification, as Alafeef et al. (2021). Fig. 4 depicts the diagnostic devices discussed above. In summary, they proved to be inexpensive, robust, and portable for diagnosing COVID-19 and assisting in virus control strategies.

4. Final remarks

This systematic review selected remarkable studies of colorimetric biosensors developed to detect SARS-CoV-2. Most of them used nanomaterials in their construction to improve sensitivity. The predominant use of AuNPs, due to their unique optical properties, showed excellent sensitivity LOD (1–154 ng/mL) without RNA amplification, even placing the sample raw. Nanohybrids were also used in the core-shell (Au@Pt), and quantum dots (SiO2 @Au/QD) outs contained gold and the polymer mPEG-PCL. The sensitivity of the biosensor is directly linked to the type of nanomaterial employed and the type of transducer. The reported biosensors were applied to POCs of different configurations as an alternative to diagnostic devices. The most used model was the LFIA which has popularity due to its use in pregnancy tests. A highlighted model was manufactured by Ferreira et al. (2021) with swabs functionalized with ACE2 enzymes, which after nasopharyngeal, are placed in a solution containing AuNPs for visualization of results. However, the use of aptamer biorecognition element was not observed within the articles found during the investigation. The use of MNPs by Ren and Irudayaraj [44] was also highlighted as it can be applied

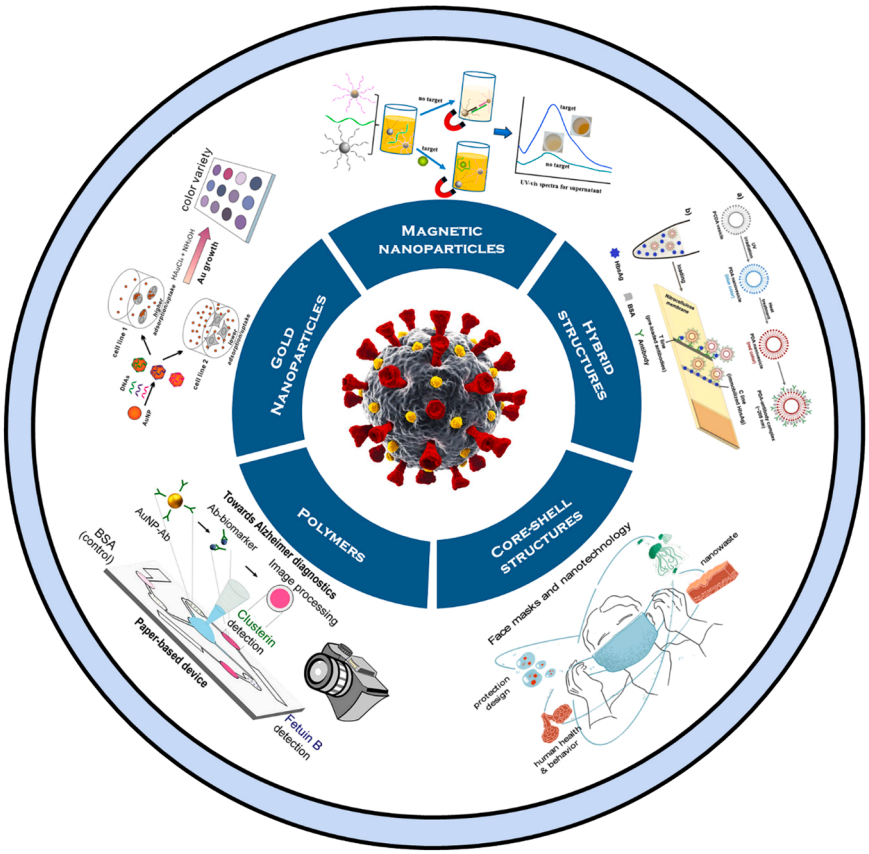

Fig. 4. Major diagnostic devices include lateral flow immunoassay (LFIA), colorimetric paper-based diagnosis, optodiagnostic, applicated surgical face masks, and Nano-Amplified Colorimetric Test (NACT) based on different nanomaterials.
(a) Reproduced with permission from Palmieri et al., [91] Copyright 2021 Elsevier. (b) Reproduced with permission from Bahadır and Sezgintürk [92] Copyright 2022 Elsevier. (c) Reproduced with permission from Brazaca [93] Copyright 2019, ACS. (d) Reproduced with permission from Ng Copyright 2016, ACS. (e) Reproduced with permission from Roh et al., [94] Copyright 2017, Asian Chemical Editorial Society. (f) Reproduced with permission from Loiseau et al.,[96] Copyright 2014, ACS. (g) Reproduced with permission from Yang et al., [95] Copyright 2019, ACS.

directly to raw samples. Here we presented the latest advances in colorimetric biosensors used to develop devices capable of clinical diagnoses and provide information on exposure to the SARS-CoV-2, making them useful for a pandemic scenario. Biosensors proved themselves towards the alternative of fast, robust, and inexpensive detection methods, particularly for environments with limited resources, in controlling the spread of the virus in a pandemic state, such as COVID-19.

CRediT authorship contribution statement

Leticia Tessaro: Conceptualization, Methodology, Writing – review and editing. **Adriano Aquino:** Conceptualization, Writing – review and editing. **Pedro Panzenhagen:** Conceptualization, Writing – review and editing. **Nirav Joshi:** Conceptualization, Writing – review and editing. **Carlos Adam Conte-Junior:** Supervision, Project administration, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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