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REVIEW ARTICLE

Biodetection Strategies for Selective Identification of Candidiasis

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Abstract Fungi are among the predominant pathogens seen in a greater proportion of infections acquired in healthcare settings. A common fungus that causes infections in medical settings is *Candida* species. Hospitalized patients who suffer from fungal diseases such as candidiasis and candidemia often have elevated rates of mortality and morbidity. It is evident that longer hospital stays have the possibility of bacterial and fungal recurrence and also have a negative economic impact. If left untreated, a *Candida* infection can spread to other organs and cause a systemic infection that can result in sepsis. Clinicians can treat patients quickly when fungal infections are timely detected, this enhances the results of clinical trials. Developing novel, sensitive, and quick methods for detecting *Candida* species is imperative. Conventional detection techniques are unsuitable for clinical settings and point-of-care systems as they require expensive equipment and take a longer detection time. This review examines a few of the most widely used biosensor systems for the detection of *Candida* species, their sensitivity, and the limit of detection. It focuses on various biorecognition elements used and follows utilization and advances in nanotechnology in the context of sensing. In addition to enabling general analysis and quick real-time analysis, crucial for detecting *Candida* species, biosensors provide an intriguing alternative to more conventional techniques.

Keywords Biosensors · *Candida* species · Nanomaterials · Invasive fungal infection · Detection · Biorecognition · Candidiasis

Abbreviations

ISFET	Ion-sensitive field-effect transistor
NAC	N-acetylcysteine
BMT	Bone marrow transplantation
OC	Oral candidiasis
BSA	Broad spectrum antibiotic
PNA-FISH	Peptide nucleic acid fluorescent in situ hybridization
SWCNTs	Single-walled carbon nanotubes
SPR	Surface plasmon resonance
FET	Field-effect transistor
SAM	Self-assemble monolayer
SERS	Surface-enhanced Raman spectral
NP	Nanoparticle
LOD	Limit of detection
AuNP	Gold nanoparticle
C. albicans	*Candida albicans*
NMR	Nuclear magnetic resonance

Introduction

Candida is a pathogen that is sometimes referred to as "opportunistic." Nonetheless, the word "opportunistic" might be interpreted to mean that the host immune system

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is a predisposing risk factor for candida infection. The significant role of *Candida* species as the major cause of hospital-acquired infections is becoming well-acknowledged [1]. *Candida* infections have lately emerged as a serious health problem for immunocompromised people, and their present diagnosis is accurate yet time-consuming. Fungi are part of the ubiquitous skin microbiome, although certain species are harmful. Fungal skin infections are thought to impact 20-25% of the world's population [2]. *Candida*-related diseases of the skin and superficial mucosal areas are caused by a symbiotic relationship between fungal virulence and host defenses. Moreover, *Candida* releases a peptide toxin called candidalysin which is the cause of pathogenesis [3]. Many *Candida* infections include the production of biofilms on surgical implants that consist of indwelling catheters or prosthetic heart valves [1]. Invasive candidiasis occurs when an infection spreads to the circulation and can spread across different body organs [4]. As a result, new approaches to treating *Candida* infections are required, as it appears unlikely that established conventional methods will significantly reduce the complications in mucocutaneous *Candida* infections along with the high death rate caused by invasive candidiasis [5]. Invasive candidiasis is a new illness that is intimately related to medical technological advancements. It is well acknowledged as a major source of mortality and morbidity in the health-care setting [6].

Various kinds of *Candida* species cause infection, particularly *Candida albicans (C. albicans)* is a major source of infections. It is an opportunistic infection that causes severe threats in immunocompromised people [4, 7]. There are around 350 distinct species of *Candida*, however only a few are linked to human disease: *C. albicans, C. parapsilosis, C. glabrata, C. dubliniensis, C. tropicalis, C. lusitaniae, C. utilis, C. kefyr, C. lipolytica, C. famata, C. haemulonii*, *C. krusei, C. rugosa,* and *C. guilliermondii* are all examples of *Candida* species. Antifungal medication resistance has emerged as a result of prolonged usage of antifungal medicines for the treatment of *Candida* species [5]. Prominent diagnostic techniques that are sold commercially have been created using fluorescent in situ hybridization (FISH), germ tube tests, PCR-based commercial systems, and the formation of chlamydospores. When it comes to identifying *Candida* species, conventional techniques have long been the gold standard. However, these techniques typically call for extra testing; they are tedious, time-consuming, and unreliable in detecting the wide range of *Candida* species [8]. Novel, sensitive, and quick approaches and techniques to detect *Candida* are highly needed.

The biosensor development technique focuses on sensitivity, specificity, early detection, non-toxicity, tiny molecule detection, and cost efficiency [9]. A better coupling of bio-fabrication and sensing with synthetic biology approaches based on optical, electrochemical, or bioelectronics principles, or a mix of all of these, will be critical for the effective creation of strong biosensors for the current period and day-to-day living. Biosensors have had a significant effect in a variety of sectors, including therapeutic applications, due to benefits such as high purity and sensitivity, miniaturization potential, mobility, low cost, and quick response. Recently discovered biomarkers and technological developments are increasingly illuminating the subtleties of many biological mechanisms in health and illness, indicating new targets for diagnostics and therapies [10]. A diagnostic test is any procedure for determining the ailment or condition of a patient. In the instance of infectious illnesses, it enables the identification of infection. The significance of simple, inexpensive, accurate, and speedy diagnosis tests is explained by their impact on clinical treatment since early detection impacts therapeutic success and prevents life-threatening complications and pathogen spread. Numerous papers on electrical approaches, growth rate, colorimetry, luminescence, fluorescence, and other fungal-based biosensors have been published. Thanks to recent advances in molecular biology, such as the insertion of novel coding sequences or the alteration of the fungal genome, more precise, accurate, and cost-effective techniques are now accessible [11].

New rapid and sensitive methodologies and procedures for detecting *Candida* species are desperately needed. Biosensor technology is continually advancing; this interdisciplinary industry was worth more than 25 billion USD the previous year and it is estimated to be worth 37 billion USD by 2026. The link between nanotechnology and biosensors improves responsiveness by improving electrochemical processes and signal amplification offered by nanoparticles. When coated with other metals, these nanoparticles perform better in immobilizing biomolecules. Encouraging their use in medicine, imaging, and biological sensing [11, 12]. Electrochemical biosensors are a great alternative to traditional approaches since they detect analytes quickly, are inexpensive, and can be miniaturized. *Candida* virulence is linked to its cell wall, which is flexible and responds to its genetics and adaption [12]. In this review, we look at the benefits and advantages of *Candida*-based biosensors for evaluating environmental samples quickly and accurately [13].

Candidiasis

Almost in a healthy individual, some *Candida* species including *C. dubliniensis, C. albicans, C. parapsilosis,* and *C. glabrata* live as normal microflora of skin and surface of the mucosa (vagina, oral cavity, and gastrointestinal tract). In 71% of the healthy population, these yeast species can

be detected and diagnosed [14]. Patients in critical care have a heightened vulnerability to candida infection due to their extensive reliance on medical devices, including central venous lines, arterial lines, bladder catheters, hemodialysis, organ transplants, and indwelling catheters and devices. These small devices are all entry points for further infection and colonization of species [15]. Several *Candida* species are commonly isolated as well. The second most prevalent strain, *C. parapsilosis*, has been linked to bloodstream infections caused by hyperalimentation, preterm newborns, or contaminated prosthetic devices [16]. There are a lot of risk factors for some species of NAC (N-acetylcysteine): neonates, foreign body insertion and hyperalimentation are associated with *C. parapsilosis*; azoles prophylaxis, neutropenia, and BMT (bone marrow transplantation) are associated with *C. krusei*; surgery, azoles prophylaxis, and urinary or vascular catheters are associated with *C. glabrata*; prior polyene use (nystatin or amphotericin B) is associated with *C. lusitaniae* and *C. guilliermondii*; burns are associated with *C. rugosa* [16].

Oral Candidiasis

In healthy humans, *C. albicans* is the most frequently occurring species in humans. Oral candidiasis occurs in healthy oral mucosa because of its higher degree of pathogenicity and adhesion characteristics [17]. Among the other species of *Candida* are *C. glabrata, C. dubliniensis, C. parapsilosis, C. stellatoidea, C. krusei, C. kefyr and C. tropical, C. albicans* is the most pathogenic as it is found in 80% of oral lesions [18]. There are two ways that oral candidiasis (OC) can appear: white or erythematosus. Lesions that are white, such as hyperplasic; and pseudomembranous candidiasis are indicative of white OC. Red lesions are indicative of erythematosus OC [19].

Invasive Candidiasis

Although at least fifteen different species of *Candida* may infect humans, five pathogens account for the majority of invasive infections: *C. tropicalis, C. glabrata, C. albicans, C. parapsilosis*, and *C. Krusei* [20, 21]. The pathogenesis of IC involves three main elements: (1) an increase in fungal burden or colonization, usually due to the use of a wide range of antimicrobial agents; (2) a breakdown of normal skin and mucosal barriers due to recent trauma or surgery, prolonged indwelling intravascular devices, severe mucositis from cytotoxic chemotherapy, and radiation (3) immune dysfunction (e.g., neutropenia) that causes diffusion and the growth in deep tissues as shown in Fig. 1 [22, 23]. Increased fungal load along with modifications to the skin and mucous membranes to keep infections out are often the causes of the pathogenesis of IC. *Candida* is very skilled in adhering to surfaces and creating biofilms on human surfaces and prosthetic devices, such as intravascular and urinary catheters [24–26].

Systemic Candidiasis

Candida adherence and colonization of skin and vaginal mucosa as well as oropharyngeal and gastrointestinal mucosa are common causes of systemic infection [27]. Neutropenia alone is probably one of the worst factors in systemic candidiasis. Neutropenia severity and frequency seem to be highly related to candidiasis incidence in patients with solid tumours and hematologic malignancies [28]. Prolonged systemic candidiasis can impact the central nervous system (CNS) and cause widespread encephalopathy with reduced awareness, with microabscesses as the main lesions [29]. The diagnosis of CNS candidiasis is the current problem [30]. The prevalence of candidaemia varies according to age, location, local epidemiology, and other variables. Three to five cases for every 1,000 people in the overall population and one to two percent for all patients in the intensive care unit are reported by the majority of significant national surveys [31]. The types and pathogenesis of Candida is shown in Fig. 1.

Detection Strategies for *Candida* Species

In regular laboratory settings, the process of identifying *Candida* isolates involves a polyphasic method that involves the combination of morphological characteristics, assimilation and fermentation profiles, specific metabolite identification, and growth on differential media. These phenotypic techniques are inconsistent at times, sluggish, and may not be able to discriminate between closely related species. Moreover, not all clinically important species are listed in the databases [32–34]. Patients with immunosuppression resulting from many disorders, such as cancer, kidney transplantation, use of antibiotics with a wide spectrum (BSA), and other conditions are more prone to *Candida* as it is an opportunistic pathogen [35, 36]. When it comes to antifungal medications, some species like *C. albicans* are less susceptible to them than others, such as *P. kudriazevii*/*C. krusei*, and *C. glabrata*. Moreover, fluconazole resistance is higher in these species. Echinocampanoids and other azoles have become ineffective against *C. glabrata* [37, 38]. Some techniques take several days to evaluate biological reactions using quantitative testing, including the ID32C and VITEK systems [39]. Hibiscus sabdariffa (Hs) extract has been shown in research to have potential anti-microbial action. Hs is also a potential medication candidate and a stand-in for removing preformed biofilm and preventing the development of *C. albicans* [40]. Since different species of *Candida* have

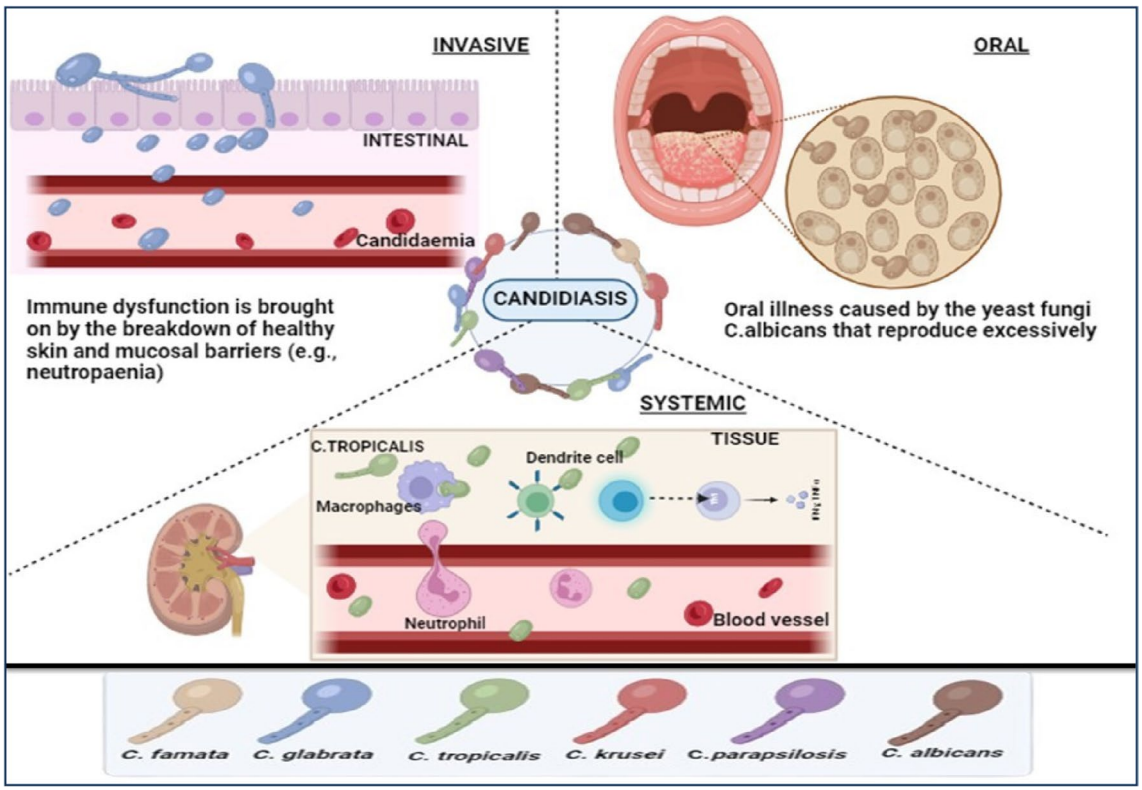

Fig. 1 Oral candidiasis is associated with aberrant yeast (*C. albicans*) production. Adhesion and penetration of hyphae invasive in the intestinal lining result in localized infection, while invasive infection and candidaemia are caused by invasive or seeded *Candida* into the bloodstream. Significantly sick individuals usually develop systemic candidiasis when *Candida* becomes an opportunistic infection that spreads by entering the blood circulation and mainly seeding the kidney

varying levels of resistance to antifungals, it is critical to quickly identify yeast at the species level to provide the optimal antifungal treatment and an early diagnosis.

A variety of molecular assays have been developed for diagnostic purposes, including peptide nucleic acid fluorescent in situ hybridization (PNA-FISH), matrix-assisted laser desorption/ionization, time-of-flight mass spectrometry (MALDI-TOF MS), and (PCR) polymerase chain reaction in different formats (real-time, multiplex, semi-nested, nested, simplex) directly linked to enzymatic restriction (PCR-RFLP) or enzyme immunoassay (PCR-EIA). MALDI-TOF and real-time PCR can accurately and broadly detect a wide variety of clinically significant pathogens at the species level [41–43]. Direct inspection along with traditional blood culture continues to detect through the gold standard of bloodstream fungal infections in laboratories, including candidaemia. These techniques, however, have limited therapeutic use since up to 50% of autopsy-confirmed cases of candidaemia have unfavourable outcomes. Furthermore, cultures could not turn positive until much later in the illness [44]. An easy and quick PCR-based multiplex technique that uses amplification of fragments of specific DNA from the regions ITS1 and ITS2, can identify eight clinically relevant *Candida* species including (*C. krusei, albicans, tropicalis, parapsilosis, glabrata, dubliniensis, lusitaniae, and guilliermondii*). Using a single PCR reaction, the approach combines two primers specific to yeast and eight primers unique to *Candida* species, producing 2 amplicons having varying sizes for each of the species. Furthermore, the following approach offers several benefits over existing methods: (1) It may be used to evaluate a variety of medical samples, like urine and blood culture bottles; (2) It is possible to add whole yeast cells directly in PCR mix; (3) limit of detection was 2.1590.25 cells/ml, makes it extremely sensitive and specific; (4) It can discriminate between distinct species of Candida that are involved in poly fungal infections at a maximum ratio of 1:10; (5) It is very reproducible in a variety of labs and PCR heat cycles. Taken together, the characteristics of this approach suggest a new and very beneficial use to identify *Candida* species in epidemiological research and medical diagnostics [45].

In various background species like *Malassezia furfur, Staphylococcus aureus, Penicillium citrinum, and Bacillus subtilis*, which are frequently found in hospital settings and skin flora, loop-mediated isothermal amplification can

be used to identify them. The ferredoxin oxidoreductase domain, which codes for pyruvate, is present in *C. auris* and it is swift, extremely perceptive, and precise [46]. *C. albicans, C. krusei, C. parapsilosis, and C. tropicalis* were all detectable using chromogenic media. The detection of "multi-species" yeast infections was also aided by chromogenic media [47]. Therefore, in the context of a hospital epidemic, the new chromogenic medium chromagartm *Candida* plus is a viable choice for the identification of additional yeasts as well as to identify and detect *C. auris* in colonization investigations [48]. Automated T2DX equipment is used to carry out a culture-independent test to identify *C. auris* in skin swabs [49].

A tiered statistical classification technique was applied to evaluate one-dimensional proton NMR spectra. When compared to traditional and DNA-based identification methods, NMR spectra analysis of *C. tropicalis, C. glabrata, C. krusei, C. parapsilosis, and C. albicans* produced a quick and accurate diagnosis. The five yeast species were classified using spectral areas that showed species-specific variations in the proportions of lipids, trehalose, polyols, and other metabolites. NMR spectroscopy usually combined with a quantitative segmentation method is a quick, harmless, moreover potentially beneficial technique that can be applied widely to fungus for chemotaxonomic characterization and identification [50]. According to the French Standard criteria, 143 strains of *C. auris* and non-auris were successfully verified using dried tubes (extracted DNA was added). GPS^{TM} MONODOSE canaur dtec-qpcr species-specific probes and primers showed satisfactory levels of specificity (exclusiveness/ inclusiveness), sensitivity, reliability (repeatability/ reproducibility), quantification and limits of detection [51].

The most common eight *Candida* species including *C. guilliermondii/M. guilliermondii*, *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. krusei/P. kudriazevii*, *C. dubliniensis*, *C. tropicalis*, and *C. lusitaniae* that cause infection can be specifically identified using the candf and candr oligonucleotides. Moreover, the PCR test employing the candr and candf primers' specificity, sensitivity, and negative and positive predictive value confirms its potential use in the diagnosis of systemic candidiasis [52]. In a study, they used the ribosomal DNA-coding regions that are unique from those of *Aspergillus* and *Penicillium* but conserved within *Candida* to construct pan-Candida primer sets in research. The final two sets of pan-Candida primers were demonstrated to be effective, with a detection sensitivity of as low as 10 fg of Candida genomic DNA, and they would not amplify *Aspergillus* DNA, to distinguish eight clinically significant *Candida* pathogens in real-time PCR assays based on their melting profiles [53]. According to the literature, various platforms demonstrated the accuracy and sensitivity of tub-simplex PCR targeting the beta-tubulin genes, and it has the potential to identify seven clinically significant species of *Candida* (*C. glabrata*, *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. tropicalis*, *C. dubliniensis*, *C. guilliermondii*) by use of seven pre-defined melting clusters. These characteristics of the tub-simplex PCR make it advantageous for use as a first-pass diagnostic supplement on blood culture bottles in microbiology laboratories or for direct whole blood testing, as they enable patient follow-up [43]. As a result, accurate and timely identification of *Candida* species can be crucial for managing infections and lowering death rates. These consist of quick processes like fluorogenic and enzymatic testing, commercially available procedures, automated systems, and recently developed molecular typing approaches. The germ-tube test, morphological analyses, and carbohydrate ingestion are examples of conventional techniques. However, accurately identifying every isolate from clinical samples can be difficult and time-consuming [54, 55]. Traditional methods have been the standard for identifying *Candida* species for a very long time. Nevertheless, these techniques typically call for extra testing and are time-consuming, and unreliable in detecting the wide range of *Candida* species.

Even though these approaches have been widely used to identify *Candida*, their use is restricted, and certain species cannot be distinguished from one another [8]. Molecular approaches may offer an option for accurate and quick identification of *Candida* species as blood culture-based methods are insensitive and conventional methods for species-specific identification take a long time and sometimes result in misinterpretation within closely related species [56]. Nevertheless, the methodological difficulty of certain tests or the lack of necessary specialist infrastructure has limited its utilization in hospital laboratories. Therefore, it is imperative to create novel assays utilizing precise, easy-to-use, reasonably priced, and accessible procedures that may be used in any laboratory to accurately identify *Candida* species.

Biosensor Technology

A biosensor is an analytical tool that combines a particular biological component (which produces a recognition event) with a physical component (which transduces the recognition event) in a purposeful and personal way. The term "biosensor" designates a device that combines two components: a sensor element and a bio-element. The fundamental ideas behind how a biosensor works can be demonstrated. An enzyme or other specific bio element detecting a specific analyte triggers a sensor element, which then transforms the biomolecule's change into an electrical signal as shown in Fig. 2 [57]. The bio-element has an extremely narrow sensitivity to analytes. Other analytes are not recognized by it.

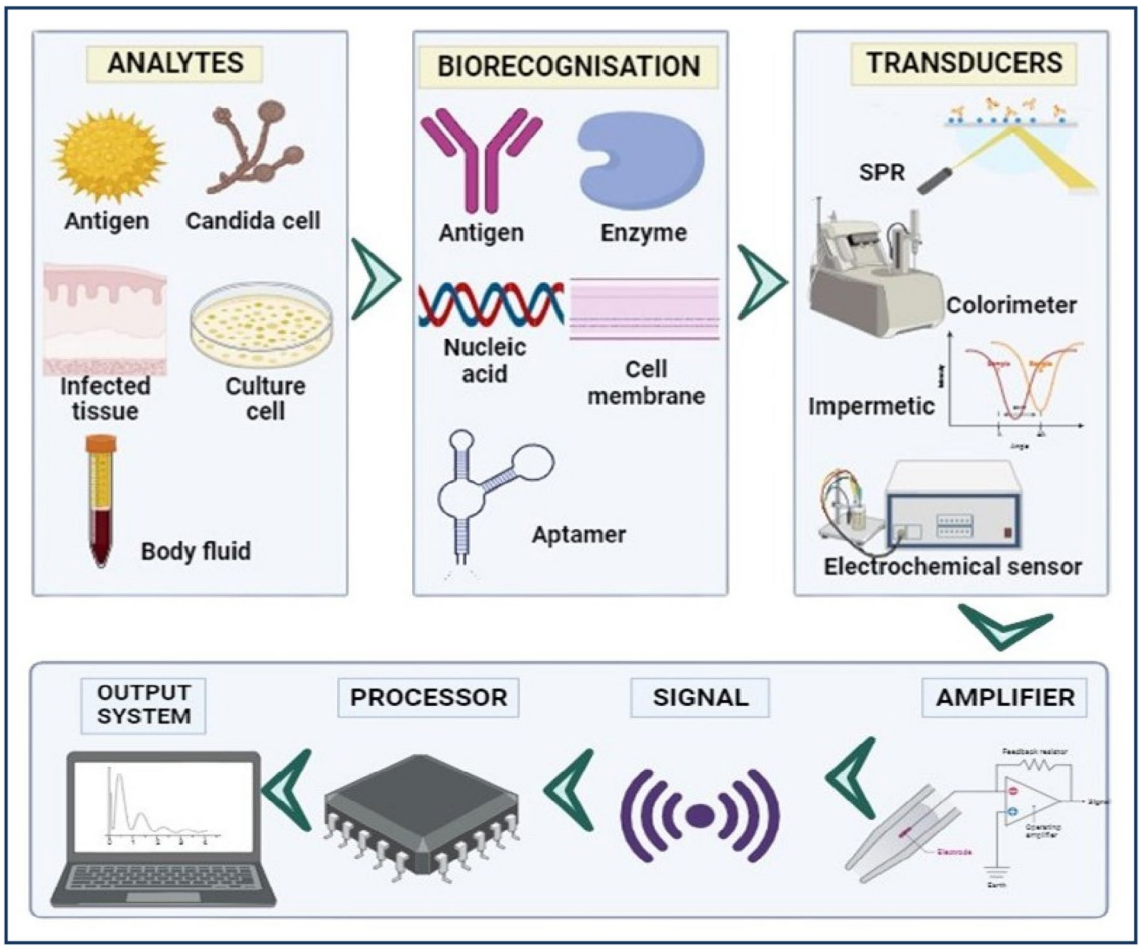

Fig. 2 Schematic and working of biosensors using different analytes and biorecognition elements

Biosensors may be classified into many varieties based on the transducing mechanism used.

These include thermal detection biosensors, optical detection biosensors, electrochemical biosensors, ion-sensitive field-effect transistor (ISFET) biosensors, and resonant biosensors [57, 58]. Compact analytical devices called optical-based biosensors have an integrated optical transducer and a bio-recognition component. These biosensors work on the principle that the amount of light absorbed or emitted is determined by changes in quantity analysis of the analyte being quantified, where molecules on the receptors and analyte interact to cause alteration in the medium's refractive index (RI) [59]. Another literature about brand-new Immuno-based microfluidic tool for quick *C. albicans* detection in whole human blood has been reported. Unfortunately, due to its less sensitivity, the technology of the microchip was able to capture *C. albicans* in the solution of phosphate buffer with an effectiveness of 61–78% for the cell concentrations ranging from 10 to 10^5 cfu/ml. Besides, the technology can be applied to other biosensors making it flexible approach and could also be further improved to provide greater specificity and sensitivity [59, 60].

Biosensors can be classified as either (i) optical, (ii) electrochemical, (iii) thermometric, or (iv) piezoelectric based on the kind of transducer used [61]. The primary components of the *Candida* cell wall include mannoproteins, enzymes, chitin, and -glucan, some of which have been studied before as potential intermediate targets for lipopeptide antimycotics [62]. The *Candida* species *C. tropicalis and C. albicans* displayed the greatest electrochemical response measured using the impedimetric method. One of the amphipathic amps, clavanin A, was discovered in the hemocytes of the marine organism Styela clava. Clavanin has shown antifungal effects, causing *C. albicans* transmembrane potential to rapidly dissipate [12]. Different methods, including counter immunoelectrophoresis and radioimmunoassay, are used in serological testing for *Candida*. But their specificity, as well as sensitivity, are uneven including up to 40% false positive and negative rates [63]. A *C. albicans* biosensor has been designed to improve the performance features of the currently accessible methods.

The fundamental concept behind it is a field-effect transistor (FET) with a conductor channel composed of a series of single-walled carbon nanotubes (SWCNTs). Adsorbed onto the SWCNT were anti-*Candida* monoclonal antibodies, which offered particular fungal antigen binding sites [64]. The major cause of candidiasis is an endogenous infection brought on by an excess of the body's fungus. While being subjected to *C. albicans* at different concentrations for just one hour, FET devices were able to determine at least 50 cfu (colony-forming units)/ml [64, 65].

Apparently, few biosensors have been designed that can identify *Candida* species. Furthermore, as described, they are coupled with technologies and approaches like microfluidics, nanomaterials, and lab-on-a-chip as summarized in Table 1. A potentiometric technique developed by Muramatsu et al. might be used in an immunoassay for *C. albicans*. For this, he utilized piezoelectric immunologic crystals coated in anti-*Candida* immunoglobulin that had been immobilized. The greatest amount of *C. albicans* cells (3.7 X 10^7cells cm^{-2}) were absorbed by the palladium anodically which oxidized at +1.4V vs. (Ag/AgCl) among the four electrode pretreatments [65]. In this study, they incorporated a monolayer that self-assembles (MBA) 4-mercaptobenzoic acid onto the electrode to bind amine-functionalized gold-capped magnetic nanoparticles (Fe_3O_4@Au). Synthetic temporin-PTA (T-PTA) was employed as a fungal biorecognition element. For *C. albicans*, a linear range of 10^1to10^5 cfu/ml and a detection of limit 10^1 cfu/ml were found. For the identification of *Candida*, the T-PTA biosensor platform is a useful and effective technique [11]. Sá et.al. developed the ConA and WGA lectin employed as recognition components in an electrochemical biosensor platform for the identification of infective species of *Candida*. With remarkable sensitivity, the sensor platform distinguished between live cells of *C. krusei*, *C. parapsilosis, C. tropicalis, and C. albicans*. All species of *Candida* evaluated in both lectin-based bioassay yielded a limit detection range from 10^2 to 10^6 cfu/ml. Depending on the lectin type, the biosensor displayed various responses, as seen below: Biosensor based on ConA (*C. parapsilosis* < *C. tropicalis* < *C. albicans* < *C. krusei*) and biosensor based on WGA (*C. tropicalis* <*C. albicans* <*C. parapsilosis* <*C. krusei*) [66]. This study uses electrochemical impedance spectroscopy to identify yeast cells that have been caught on electrodes that have been specially functionalized with anti-*Candida* antibodies. The membrane-based sensor will be further altered to allow for direct diagnosis of *C. albicans* infections from blood samples and blood processing through filtering. The biosensor was shown to have sensitivity down to 10 cfu/ml in a (PBS) sample, which is at clinically meaningful levels [67]. Another work aimed to detect *C. albicans* using the technique of surface plasmon resonance imaging, or SPR imaging. Covalent immobilization of the captured antibody was achieved on the mixed self-assembled monolayer (SAMs). SAMs ratio which was mixed between 3-mercaptopropanol and 11-mercaptoundecanoic acid was changed to discover the best ratio for usage as a sensor surface. The findings demonstrated that although mixed SAMs with the ratio 1:40 had a greater non-specific signal than mixed SAMs 1:0, the carboxylic SAM surface (mixed SAMs 1:0) was the most appropriate for *C. albicans* detection. For direct detection, the detection limit was 10^7cells/ml [68]. One novel application of citrate-reduced Ag nanoparticles via surface-enhanced Raman spectral biosensors approach based on a 514 nm laser enables quick and effective monitoring of highly concentrated scattered *C. albicans* cells (>10^8cfu/ml). The subsequent derivative and smoothing from the Savitzky-Golay algorithm preprocessed the principal component evaluation of a high-level frequency characteristic of the SERS from *C. albicans* and other micro-organisms [69]. In this study, they created a unique electrochemical signal for determining the quorum-sensing compounds (tryptophol) in the albicans fungal growth in the electrode matrix. The amount of tryptophol secreted into the *C. albican's* extracellular matrix as shown in Fig. 3b to be linked to the major precursor of tryptophol. The novel approach has been optimized after factors affecting test sensitivity were explored. The approach was used to measure tryptophol in *C. albicans* cultures [70].

This paper describes a new method that employs a fluorogenic nanosensor to identify *C. auris*. The technology consists of oligonucleotide-capped NAA mesoporous scaffolds that have been coated with a fluorophore. The capping oligonucleotides are released from the NAA surface when *C. auris* genetic DNA is present, which causes the pore to open and release the encapsulated fluorophore. In this study, a highly specific, and time-competitive biosensor constructed from oligonucleotide-gated nanomaterials for efficient detection of *C. auris* is reported. With clinical samples, *C. auris* may be found at concentrations as low as 6 cfu/ml, which allows for an hour-long diagnostic process [71]. In this study, the literature revealed that the identification accuracy of the approach will be determined by comparing the PCR-ESI/MS results with standard-of-care clinical microbiology findings from culture as well as analyte-specific molecular techniques. Both standard-of-care and PCR-ESI/MS data shall be contrasted to non-microbiological clinical findings to determine the relative utility of the two techniques for the identification and detection of etiologically relevant *Candida* species [72]. They demonstrate the use of two FRET-based biosensors to permit effective tracking of the pathogen's cAMP-PKA activity. Changes in cAMP concentration and protein kinase A(PKA) activity can be monitored in a time-resolved fashion, as demonstrated through glucose-induced pathway initiation. Also, they discuss how to manage and interpret the data correctly in a way that is both physiologically applicable and numerically accurate as they primarily

Table 1 Biosensors used for the detection of *Candida* species

S. No	Species	Platform	Biorecognition element	Nanoparticle	Limit of detection	Purpose	Refer ences
1	*C.kursei, C.tropicalis, C. albicans, C. parapsilosis*	Impedimetric Biosensor	Concanavalin A (ConA) wheat germ agglutinin (WGA)	AuNPs and MBA-AuNPs	10^2 cfu/ml	Identification of pathogenic *Candida* species	[66]
2	*C. albicans*	Electrochem ical Impedance Spectroscopy	Anti-Candida antibodies	NA	10^1 cfu/ml	High sensitivity and specificity towards *C.albicans*	[67]
3	*C. albicans*	SPR (surface plasmo resonance) Imaging Biosensor	Antibody mixed with self assembles monolayers (SAMs)	NA	10^7cells/ ml (direct assay)10^6 cells/ml (sandwich assay)	Identify C. albicans from the blended microbial mixture without the need for a proficient professional	[68]
4	*C. albicans*	Surface-Enhanced Raman Spectroscopy (SERS)	Surface of cells cultured	Ag nanoparticles	10^8 cfu/ml	Ag nanoparticles can be used to detect large amounts of dispersed *C. albicans* cells quickly and sensitively	[69]
5	*C. albicans*	Electrochemicalsensor	Cyclic macromolecule	NA	1 µg/ml	An electrochemical method that is both specific and sensitive for tryptophol in yeast cultures	[70]
6	*C. auris*	Oligonucleo tides-capped nanoporous anodic alumina biosensor	Oligonucleotide	oligonucleotid e-gated	6 cfu/ml (0.3 pg/µl)	Fast and reliable diagnosis	[71]
7	*C. krusei C.guilliermondii*	PCR Electrospray Ionization-mass Spectrometry (ESI-MS)	NA	NA	100 cfu/ml	For detection and identification of *C. albicans*	[72]
8	*C. glabrata*	FRET-based Biosensors	cAMP-PKA activity	NA	NA	Screening of cAMP-PKA in *C. glabrata*	[73]
9	*C. dubliniens*	SPR Biosensor	Concanavalin A (Con A) lectin	NA	0.1 nM	To estimate the efficiency of the immunization against *C. dubliniensis*	[74]
10	*C. tropicalis*	Amperometric biosensor	Glutaraldehyde	NA	0.5–7.5 mM	The biosensor response may be affected by interference, substrate accuracy, or certain chemicals	[75]
11	*C. tropicalis*	Microbial Biosensor,	L-Ascorbic acid	NA	62 µM	Fast, effective and sensitive	[77]

Table 1 (continued)

S. No	Species	Platform	Biorecognition element	Nanoparticle	Limit of detection	Purpose	Refer ences
12	*C. albicans*	Chip biosensor	Enzyme aspartyl proteinase	NA	NA	As a cutting-edge detection technique for the quick and accurate identification of fungal infections in immunocompromised patients' plasma samples	[78]
13	*C. albicans*	(2D) Photonic Crystal (PC) Sensor	Con A	NA	32 cfu/ml	Differentiates between E. coli, a gram-negative bacteria, and *C. albicans*, which do not have cell-surface mannan	[79]
14	*C. albicans*	Microchip Biosensor	Antigen	NA	10 cfu/ml	Technique will be helpful in clinical and point-of-care settings to screen for different infections	[80]
15	*C. albicans, C. tropicalis*	Electrochem ical impedance spectroscopy (EIS) and cyclic voltammetry (CV)	Temporin-PTA (T-PTA)	And gold-capped magnetic	10^1 cfu/ml	This platform is an efficient and promising instrument for microbiological identification	[11]
16	*C. albicans*	Piezoelectric immunosensor	Anti-*Candida* antibody	Palladium-plated	NA	The sensor's viability in identifying *C. albicans*	[65]

NA, not applicable

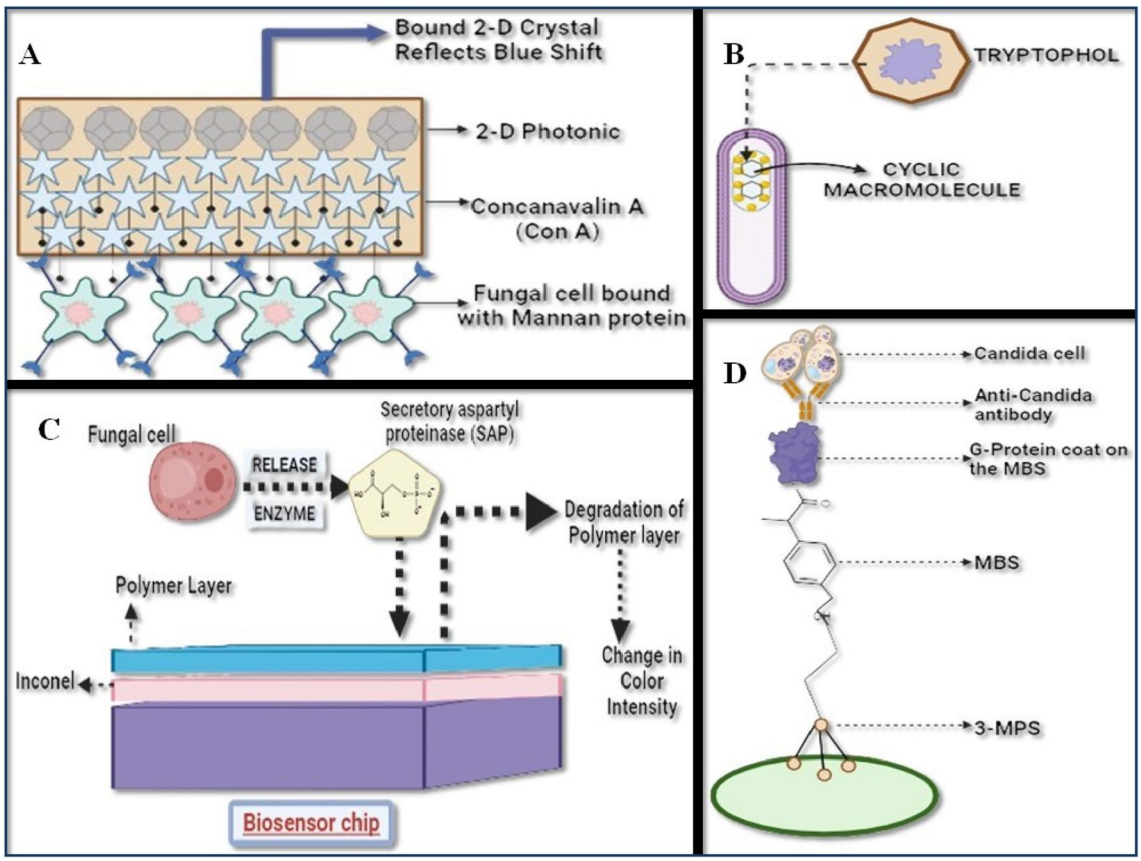

Fig. 3 Principle of biosensors used in *Candida* detection. **a** The Con-A hydrogel protein binds with the mannose of *C. albicans*, cross-linkage leading to a reduction in the level of 2D particle spacing, which causes a 2D array diffraction blue-shift giving *C. albicans* concentration; **b** working electrode surface with multi-walled carbon nanotube and 12-crown-4 that interact selectively with quorum sensing molecule, tryptophol; **c** fungal cell release enzyme like phospholipase/aspartyl proteinase which causes degradation of the biodegradable polymer resulting in a change in colour intensity; **d** the protein G-based on surface chemistry was used for the immobilization of the anti-*Candida* antibody on the surface

detect *C. glabrata* [73]. Fabrication and evaluation of an SPR-based biosensor chip on precipitated mannan derived from the species *C. dubliniensis* for applications such as determining the capability of generated antibodies attached to their antigen to gauge the effectiveness of vaccination reviewed in this paper [74]. The study revealed that a microbial biosensor created based on *C. tropicalis* cells may be utilized for the effective detection of ethanol levels even in the availability of other alcohols that may be discovered to be found in the same solution as ethanol. Yet no research in the literature on building a microbial biosensor for ethanol detection based on the *C. tropicalis* cells suspended in the gelatin was found [75]. Wang el. at. describe *C. tropicalis* was detected using a combination of lateral flow biosensors (LFB) and multiple cross displacement amplification (MCDA). As a result, the best reaction temperature for the MCDA test of C. tropicalis was 30 minutes at 64°C and each reaction required 10fg of DNA. The results reported for 300 sputum samples showed that all 28/300 *C. Tropicalis*-positive samples discovered using the gold-standard method could be rapidly and effectively diagnosed by the MCDA-LFB test [76]. O-aminophenol was used to immobilize lyophilized *C. tropicalis* yeast cells by electropolymerizing an acrylic sheet on an electroplated platinum surface. L-ascorbic acid was measured using the biosensor utilizing differential pulse voltammetry (DPV) and amperometric methods [77]. This study created a sensor chip on the polymer polylactic-co-glycolic acid (PLGA) as a substitute diagnostic tool for the quick and accurate identification of fungal infections in immune-compromised people's plasma samples. Through matrix manipulation, the double-layered, biomimetic biosensor-based device may simultaneously eliminate potential bacterial co-infection and identify the yeast's aspartyl proteinase enzyme. The biosensor structure comprises a polymer layer coated with a thin covering of metal dubbed Inconel, which is vulnerable to breakdown by lytic enzymes such as aspartyl proteinase. The thickness of the polymer layer is shown by the colour shift on the

biosensor's surface that is apparent to the unaided eye as shown in Fig. 3c [78]. Zhongyu Cai et al. offers a novel detection approach that uses two-dimensional (2D) photonic crystal (PC) sensing materials to detect *C. albicans* alone. These sensors use Concanavalin A (Con A) protein hydrogels, which have a 2D PC implanted on the surface of the hydrogel. Mannan on the surface of *C. albicans* binds to the Con A protein hydrogel surface multivalently and selectively to generate crosslinks. The ensuing crosslinks cause the light diffracted from the PC to change blue, the Con A protein hydrogel to contract, and the 2D PC particle spacing to decrease as shown in Fig. 3a. Through the use of a spectrometer, visual monitoring, or the Debye diffraction ring diameter, one may determine the diffraction shifts. For *C. albicans*, our hydrogel sensor is unoptimized and has a threshold for identification of about 32cfu/ml [79]. Asghar et al. designed an innovative immune-based microfluidics technology that can quickly detect and extract *C. albicans* from human whole blood and phosphate-buffered saline (PBS). With an effectiveness of 61–78% at concentrations that vary between 10^1 and 10^5 cfu/ml, their microchip technique demonstrated three microchannels that were equipped with surface chemistry based on protein G as an effective capture of *C. albicans* in the PBS solution. The surface was treated using surface chemistry based on protein-G to immobilize anti-*Candida* antibodies as shown in Fig. 3d. Comparing polyclonal antibodies to monoclonal antibodies, they found that the former collected a noticeably higher quantity of *Candida* cells. Testing for potential medication resistance and susceptibility is made possible by the technique that is being described, which enables the capture and isolation of entire *Candida* cells [80].

Nanomaterial Used in *Candida* Detection

The area of biosensors is revolutionized by nanomaterials. Due to its industry-leading position, nanotechnology has developed several cutting-edge applications in recent decades for use in nanomedicine and nanobiotechnology, including drug delivery systems, biosensing and biodetection, and the development of novel treatments for incurable diseases like cancer [81, 82]. Since nanoparticles exhibit exceptional sensitivity for chemical and biological sensing, there has been a lot of interest in the subject of biosensors as a result of recent breakthroughs in nanotechnology [83]. Biosensors have made use of a wide range of nanoparticle types, including metal, oxide, semiconductor, and even nano-dimensional conducting polymers. For instance, multiple laboratories have reported using hybrid nanostructures of silver and silica or gold and silver nanoparticles as biosensor substrates [84, 85]. To enhance real-time, wireless monitoring and analysis of environmental and food conditions, further integration of electrical engineering, functional nanomaterials, microfabrication, and materials science with sensor technologies will be needed. It will be necessary to determine the detection levels appropriate for these practical applications to ensure the assurance and security of the environment and food, even though various detection limits at parts per trillion, femtomolar, or even small amounts have been described in the literature. Setting up detection limits is going to be essential for risk assessments. The ideal sensors would detect certain types of pollutants in food and environmental samples [86].

Several nanomaterials that are utilized in chemical compound identification are depicted schematically. Carbon-based materials comprise graphene, fullerenes (e.g., C60), single-walled carbon nanohorns (SWCNHs), multiwalled carbon nanotubes (MWNTs), single-walled carbon nanotubes (SWNTs), and among many more nanomaterials [87]. Recent research has suggested that nanomaterials represent a novel class of biological receptors. As nanotechnology and nanoscience have advanced, several nanomaterials have been employed as biorecognition systems [88]. NPs offer a wider variety of biosensing technology applications. In addition to transducers, NMs can function as bioreceptors. For instance, the biomimetic catalytic activity of NMs based on cerium oxide is beneficial for bioreceptors. Due to their strong conduction skills, a variety of inorganic materials, including graphene and CNT-based NMs, quantum dots, and noble metal NPs have been used as transducers [89]. Among the NPs are metal and noble metal NPs, which offer superior optical, electrical, magnetic, chemical, mechanical, and catalytic capabilities. Examples of these metals include silver (Ag), platinum (Pt), palladium (Pd), gold (Au), copper (Cu), iron (Fe), palladium (Pd), and cobalt (Co); also, metal oxide NPs, such as MnO_2, TiO_2, ZnO, and SnO_2, are included. Coating with different matrices, such as metal oxides, silica networks, graphene, polymers, fibres, and dendrimers, can customize the performance of NP biosensing [90].

The impedimetric responses' distinctive patterns were established by examining the lectins' selectivity to certain sugars on the surface of *Candida* spp. Sensitive detection and differentiation of live cells of *C. tropicalis, C. parapsilosis, C. krusei, and C. albicans* was achieved using the sensor platform. Using UV–Vis spectrophotometry, absorption of radiation by the synthesized nanoparticles (MBA-AuNPs and AuNPs) was evaluated, with a hypochromic shift taking place following the measurement of the wavelength transmittance band measurements of λ ¼ 533 nm and λ ¼ 524 nm. The absorption peaks line up with colloidal gold's surface plasmon resonance. The MBA structure's thiol group binds to the surface of AuNPs with a high affinity, leaving the COOH functional group open for posterior connections [66, 91]. Surface-enhanced Raman spectral biosensing

technique, which uses a laser of 514 nm and nanoparticles based on citrate-reduced Ag, may be used to quickly and sensitively detect liquid-phase microorganisms, including an elevated focus on suspended *C. albicans* cells ($>10^8$ CFU/ml). The citrate-reduced Ag nanoparticles that interact with yeast cells may display localized surface plasmon resonance (LSPR), corresponding with the field-enhanced mechanism [69]. The addition of 10% of each crown ether (12-crown-4) and carbon nanotubes to the electrode matrix produced a unique electrochemical indication that could be used to identify the (tryptophol) quorum sensing molecule of *C. albicans* culture. Ultimately, using MWCNTs and 12-crwon-4-ether together, the sensitivity and selectivity were improved [70]. An efficient biosensor for the detection of *C. auris* is built on oligonucleotide-gated nanomaterials and it is specific, selective, and time-competitive. The article offers an alternative viewpoint for the detection of *C. auris* utilizing a fluorogenic nanosensor. NAA mesoporous support that have been loaded with a capped and fluorophore with an oligonucleotide make up the system [71]. New nanostructures are frequently integrated into biosensor designs to improve sensitivity (i.e., the rate at which the target analyte is correctly identified), specificity (i.e., the capacity to separate the target analyte from other sample components), and the lowest limit of detection (LOD). The lower quantity of a compound that can be identified from a sample without the analyte at a certain degree of confidence is known as the LOD of a biosensor [92, 93]. Materials that are inorganic, organic, or hybrid can be employed to create nanostructures for biosensors. The material selection is determined by the purpose of the component (such as electrode components or biosensor recognition elements) inside the biosensor device [94, 95]. Because inorganic materials can transmit, amplify, and modify electrical signals, they are frequently used in the production of electrical biosensors. Examples of these materials are metals and metal oxides [96–98]. Both SERS and LSPR biosensors frequently use the functionalization of NPs onto a sensor platform to boost target-binding capacity [99, 100]. The findings demonstrated that all positive samples of *C. tropicalis* found through the gold-standard technique could be quickly and successfully identified by the MCDA-LFB assay. In this study, they effectively created an MCDA-LFB assay for the quick, easy, and accurate detection of *C. tropicalis*. In contrast to culture-based techniques and molecular detection tests, the MCDA-LFB assay eliminates the need for complex procedures, costly equipment, and highly qualified technical staff [76]. The synergistic properties of aptamer and gold nanoparticles are present in aptamer-conjugated gold nanoparticle complexes, such as strong binding affinity, high biocompatibility, improved target selectivity, and long circulation half-life [101]. Even at low concentrations, AuNPs have demonstrated strong effectiveness and selectivity toward their targets. AuNPs may enhance both the conductivity of the electrode and the mechanisms involved in charge transfer [65, 102]. There has been discussion of the broad use of nanomaterials, including freshly created ones in electrochemical and optical biosensing. This review addressed a range of nanomaterials and several infectious *Candida* species detection systems.

Challenges

Biosensor development for the determination and recognition of the species of *Candida* was started in 1986 earlier [103]. Biosensors have been employed in the medical profession for a long time, and this field is undoubtedly the one that benefits the most from the most commercially available devices, including those for the detection of harmful bacteria and other uses. The capability to make disposables on an extensive basis at a cheap price, notably with acceptable precision and repeatability, is the fundamental obstacle for biosensors to become essential analytical instruments for medicine. For instance, immunosensors are biosensors that can quickly identify antibodies (or antigens, depending on their size and configuration) in samples like blood, serum, saliva, urine, plasma, etc. They are crucial tools for the development of rapid test kits, particularly for infectious diseases. These innovative tools, which have a great deal of promise for point-of-care diagnostics, include optical, electrochemical, piezometric, and surface Plasmon resonance (SPR) sensors in addition to fluorescence-based technologies to detect biomolecular interactions efficiently [103]. The piezoelectric platform acts as a sensor element under the law of oscillations transform when a collecting leap develops on the surface of a piezoelectric crystal. Many biosensors may be developed for many additional species of *Candida* similarly. Artificial biosensors have made significant progress in terms of functioning, design, and applications to continuous advancements in chemical science and bioengineering [104]. The literature states that biosensors were primarily created to detect *C. albicans*, while other species that cause severe infections; it is essential to build biosensors that identify those species. Numerous applications of biosensors and bioelectronics have been made in the fields of life science, healthcare research, military, agriculture, and environment. These sensors can also be improved using nanobiotechnology and other prominent advances in sensing [105]. There are still many more species that can be quickly identified; we can process and find candidiasis with these biosensors.

Conclusion and Future Perspective

Innovative biosensing technologies with enhanced selectivity, sensitivity, and speed of response have come a long way in the previous several years. In conclusion, molecular investigations based on ITS sequencing are required for the identification of closely related and emerging species, even if traditional approaches may be utilized to accurately identify the most prevalent *Candida* species. The main *Candida* species infections are endogenously acquired. Thus, whereas species mostly linked to exogenously acquired illnesses, including *C. parapsilosis*, displayed minimal intraspecific variability, *C. glabrata, C. albicans, C. lusitaniae, and C. tropicalis* displayed considerable genetic variety. Biosensor technology will detect illness and perhaps prevent it. Biosensors may be able to detect an illness at its earliest stages, according to research from Stanford University. Sensing technology has benefited greatly from nanotechnology; the application of quantum dots, carbon nanotubes, and nanoparticles has helped to improve the consistency of biosensors. This paper describes the existing state of affairs and makes recommendations for future sensor research because there hasn't been much done on the utilization of certain nanomaterials for the detection of *Candida* species. It is crucial to keep in mind to conduct and track the progression of infectious illnesses, resource-constrained towns require an evidence-based decision-making tool that is standardized, and capable of attaining extremely low levels of detection. Looking ahead, potential developments in biosensing technology cleared the path for the introduction of more robust, convenient, scalable, affordable, and versatile devices that fit in with ease in daily activities. Wearable technology integration with biosensors will provide personalized healthcare delivery. Furthermore, advancements in synthetic biology and nanotechnology will open up new possibilities for developing more creative biosensing frameworks with unmatched sensitivity and specificity.

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Declarations

Conflict of interest None.

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