Sensors International 5 (2024) 100253

Contents lists available at ScienceDirect

Sensors International

journal homepage: www.keaipublishing.com/en/journals/sensors-international

Diagnostic methods employing kidney biomarkers clinching biosensors as promising tools

Neelam Yadav [a,b], Jagriti Narang [c], Anil Kumar Chhillar [b], Jogender Singh Rana [d], Mohd Usman Mohd Siddique [e], El-Refaie Kenawy [f], Saad Alkahtani [g], Mohd Neyaz Ahsan [h], Amit Kumar Nayak [i,**], Md Saquib Hasnain [j,*]

[a] Department of Biochemistry, Central University of Haryana, Jant-Pali, Mahendergarh, 123029, India
[b] Centre for Biotechnology, Maharshi Dayanand University, Rohtak, Haryana, 124001, India
[c] Department of Biotechnology, Jamia Hamdard University, New Delhi, 110025, India
[d] Department of Biotechnology, Deenbandhu Chhotu Ram University of Science and Technology, Murthal, Sonepat, Haryana, 131039, India
[e] Department of Pharmaceutical Chemistry, Shri Vile Parle Kelavani Mandal's Institute of Pharmacy, Dhule, Maharastra, 424001, India
[f] Polymer Research Group, Chemistry Department, Faculty of Science, Tanta University, Tanta, Egypt
[g] Department of Zoology, College of Science, King Saud University, P. O. Box 2455, Riyadh 11451, Saudi Arabia
[h] Department of Medical Laboratory Technology, University Polytechnic, Birla Institute of Technology, Mesra, Ranchi, Jharkhand, India
[i] Department of Pharmaceutics, School of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, 751003, Odisha, India
[j] Department of Pharmacy, Palamau Institute of Pharmacy, Chianki, Daltonganj, 822102, Jharkhand, India

ARTICLE INFO

Keywords:
Kidney diseases
Biomarkers
Biosensors
Acute phase
Diagnosis

ABSTRACT

Worldwide, there has been an increasing prevalence of kidney disorders for several years. Kidney disorders are characterized by abnormal kidney biomarkers like uric acid, urea, cystatin C, creatinine, kidney injury molecule-1, C-related protein, *etc*., in the human body. A person suffering from kidney disorders is prone to several other serious health consequences, such as cardiac diseases and renal failure, which can lead to death. However, early diagnosis of kidney disorders requires effective disease management to prevent disease progression. Existing diagnostic techniques used for monitoring kidney biomarker concentration include chromatographic assays, spectroscopic assays, immunoassays, magnetic resonance imaging (MRI), computed tomography (CT), *etc*. They also necessitate equipped laboratory infrastructure, specific instruments, highly trained personnel working on these instruments, and monitoring kidney patients. Hence, these are expensive and time-consuming. Since the past few decades, a number of biosensors, like electrochemical, optical, immunosensors, potentiometric, colorimetric, *etc*., have been used to overcome the drawbacks of conventional and modern techniques. These biosensing systems have many benefits, such as being cost-effective, quick, simple, highly sensitive, specific, requiring a minimum sample amount, reliable, and easy to miniaturize. This review article discusses the uses of effectual biosensors for kidney biomarker detection with their potential advantages and disadvantages. Future research needs to be implicated in developing highly advanced biosensors that must be sensitive, economical, and simple so that they can be used for on-site early detection of kidney biomarkers to assess kidney function.

1. Introduction

Kidney diseases are characterized by abnormal concentrations of kidney biomarkers, such as urea, uric acid (UA), cystatin C (Cys C), creatinine, C-related protein (CRP), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid binding protein (LFABP), *etc*., in body fluids [1]. Consequently, the kidney loses its proper function. A person with a chronic kidney disorder suffers from glomerulonephritis, cardiovascular diseases like cardiac arrest, hypovolemic shock, and several intestinal issues [2,3]. Renal ailments in chronic conditions result in the inability of the kidneys to purify the body's wastes from the blood. Glomerular filtration rate (GFR) in kidney diseases/disorders is around <60 mL/min per 1.73 m^2 body surface area, and person die within three months [4]. According to

* Corresponding author.
** Corresponding author.
E-mail addresses: amitkrnayak@yahoo.co.in (A.K. Nayak), msaquibhasnain@gmail.com (M.S. Hasnain).

https://doi.org/10.1016/j.sintl.2023.100253
Received 8 August 2023; Received in revised form 25 September 2023; Accepted 25 September 2023
Available online 27 September 2023

a report, in India, approximately seventeen individuals are suffering from chronic kidney disease (CKD) for every hundred individuals. Approximately 6% of people have been reported to be in the third stage of a kidney disease. Such individuals instantly require dialysis or kidney transplantation [5–7]. India has been reported as being second among the top 10 diabetic countries [8]. Diabetes and hypertension have accounted for 40–60% of kidney dysfunction. The chronic stage of kidney disorders has been treated using dialysis and kidney transplantation [9]. Kidney transplantation is very expensive, and therefore, every individual cannot afford its cost. So, it is necessary to diagnose kidney disorders in the acute stage [10]. In addition, differences from the expected ranges of particular physiological components in human bodily fluids can be used as signs of erratic kidney function. These components act as biomarkers for identifying any kidney disorder. Hence, biomarkers are the molecules acting as indicators for both healthy and abnormal physiological phenomena [11–13]. The response of biomarkers has also been investigated during diagnostic and therapeutic interventions. An abnormally high level of biomarkers leads to several human disorders. However, the risk of kidney function interruption depends on the extent of abnormal concentrations of kidney biomarkers that ultimately act as a deciding factor for acute and chronic kidney disorders, diabetic nephropathy, kidney cancer, an improper glomerular filtration rate, and preeclampsia [14]. Therefore, investigation of kidney biomarkers in various body fluids (like urine, tears, saliva, sweat, plasma, *etc*.) helps in diagnosis of kidney diseases/disorders in the acute stage to prevent the severity of diseases, ensure timely and effective treatment. This review article illustrates the significance of several different classes of biomarkers used for diagnostic applications in kidney diseases. Some of the ideal characteristics of biomarkers before recommending their use in the diagnosis of various kidney

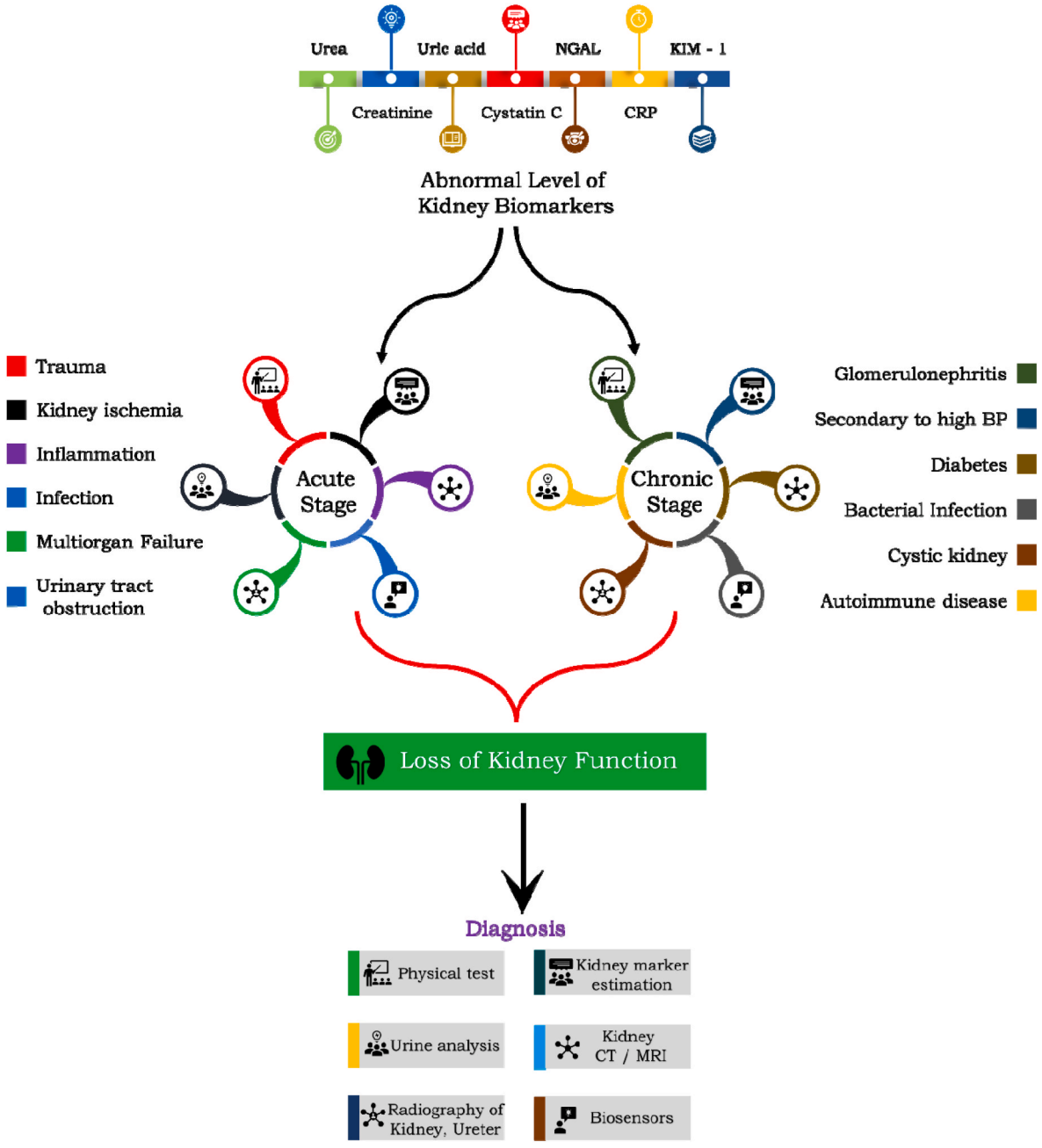

Fig. 1. Depiction of impact of various biomarkers on kidney function; The display of different types of chronic and acute diseases associated with various kidney biomarker; different test, techniques or biomarker used for detection of loss of kidney function.

diseases are [14].

(i) Biomarkers used for kidney diagnosis should be easily available in sources like blood or urine. They should be cost-effective, user-friendly, rapid, and non-interfering.
(ii) They must exhibit high sensitivity to avoid the similarity in concentration between diseased and healthy samples.
(iii) Furthermore, they must be specific and generate a fast and reliable analytical signal during the treatment of renal disorders.
(iv) Biomarkers must be plausible with the physiological phenomena and reveal enough to understand the process of associated diseases.

Numerous review articles have been published by compiling the different biomarkers used for the clinical diagnosis of different kidney diseases/disorders (acute as well as chronic) [15–17]. However, newer methodologies or tools have been invented for kidney biomarker detection due to emerging technologies and bioautomation in the health sector every year. Hence, we thought to compile all the recent updates in emerging biomarkers used for kidney diagnostics.

2. Emerging biomarkers used for kidney disorders diagnostics

To evaluate kidney function, numerous biomarkers have already been reported, *viz*. urea, UA, creatinine, Cys C, KIM-1, NGAL, LFABP, *etc* [18]. Nowadays, machine learning algorithm (MLA) also used to predict diabetic kidney disorders (DKD) [19]. Allen and co-researchers (2022) suggested that the developed MLA was capable of timely detection of the DKD in patients suffering from type-II diabetes mellitus [20]. Fig. 1 illustrates the impact of various kidney biomarkers on kidney function.

2.1. KIM-1

It is a well-known transmembrane protein. Due to kidney injury, its level increases in the proximal part of the kidney [21]. Normally, the level of this protein is low; however, it is elevated with the age of an individual. It has been found that the quantity of KIM-1 is higher in males in comparison to females [22]. During kidney failure, KIM-1 protein accumulates in epithelial cells, causing inflammation (fibrosis) and leading to kidney failure. Abnormal concentrations of KIM-1 also cause several other kidney disorders, including anaemia, proteinuria, hyperphosphatemia, and hypertension. It has been reported that the KIM-1 level is elevated in the patients with micro-albuminuric than in normal individuals [23]. The KIM-1 concentration in urine of a healthy person is < 1 ng/mL. It has been reported that the KIM-1 concentration gets considerably increased prior to measurable alterations in the expected glomerular filtration rate [24,25]. Hence, urinary KIM-1 is a potent biomarker candidate for kidney diseases because it damages interstitial cells of the kidney's proximal tubule.

2.2. Cys C

Cys C is another emerging endogenous biomarker, which is 13-kDa nonglycosylated protein and formed in the body by the nucleated cells [26]. Cys C acts as cysteine protease inhibitor. This biomarker is generally filtered in the glomerulus, and absorption occurs in cells of the proximal tubule; however, no secretion occurs in the tubules [27]. An increase in urine Cys C excretion indicates higher Cys C levels in the early stages of diabetes and nephropathy. Therefore, it has been recommended as one of the key biomarker candidates for glomerular as well as tubular damage [28]. Furthermore, it is more effective than creatinine for detecting death rates and cardiac ailments [29]. Hence, CysC has been found a sensitive biomarker for the evaluation of severity of kidney-related disorder [30]. This Cys C biomarker is used for the kidney dysfunction detection in the acute phase. It is illustrated by a drastic reduction in GFR [31]. Researchers have preferred to use Cys C in kidney diagnostics because its detection is not dependent on age, gender, or muscle mass [32]. It is also used in the diagnosis of cardiac disorders [33], neuronal diseases [34], cancer [35,36], death probability, and sepsis [37].

2.3. CRP

The diagnosis of kidney-related disorders has been detected by measuring the inflammatory CRP biomarker level in serum samples. A high level of CRP has caused inflammation [38]. CRP comes under the pentraxin protein family and is produced by the liver by getting stimulus from cytokines, for example, TNF-α and interleukin-1 (IL-1) secreted by macrophages as well as adipocytes. A high level of CRP causes damage to endothelial cells and abnormal vasodilation in the kidney. Consequently, the progressive destruction of glomerular damage leads to abnormal kidney activity.

2.4. NGAL

NGAL is 25-kDa lipocalin protein. It is found in activated neutrophils. It acts as an innate antibacterial component [39]. In normal conditions, filtration of serum containing NGAL occurs by glomerulus and is followed by means of its reabsorption in the proximal tubule. However, individuals with CKD lost a large quantity of NGAL through the injured glomerulus. The concentration of NGAL helps in the independent estimation of the severity of kidney function abnormalities [40]. Hence, NGAL has become a promising next-generation biomarker for the clinical investigation of chronic kidney disorders.

2.5. Urea

Urea is formed as the end product of protein metabolic reactions. The urea concentration in the serum of healthy individual ranges between 3.3 and 6.7 mM, and when it rises up to or $>$30 mM, the person needs dialysis besides water lowering and damage to the gastrointestinal tract [41,42]. While declining urea concentration also impairs the normal function of the kidney. The decreased urea level is due to an imbalanced protein diet or a person abusing alcohol. Therefore, it is required to evaluate the urea concentration for the assessment of the functional status of the kidney. Clinically, investigation of urea in distinct sources includes urine, tears, saliva, sweat, plasma, *etc*.

2.6. UA

UA is formed from the purine metabolism occurring in the liver and excreted from the kidneys [43]. Its level in the blood of healthy males and females ranges between 3.50 and 7.50 mg/dL and 2.50–6.50 mg/dL, respectively [44]. Due to its insolubility in body fluids, it causes precipitation in connective tissue and the urinary tract. The elevated level of UA causes hyperuricaemia, Lesch-Nyhan syndrome, arthritis, urolithiasis, chronic kidney disease, gout, *etc* [44].

2.7. Creatinine

Chemically, creatinine is 2-amino-1-methyl-5H-imidazole-4-one that is formed in liver via the methylation of glycocyamine as end product of creatine metabolism. It is excreted through the kidneys during filtration. It is then translocated to several organs like the brain, muscles, and after phosphorylation, it is converted into a high-energy compound known as phosphocreatine [45]. The quantity of creatinine ranges between 45 and 140 l M in serum and 0.8–2.0 g/day in urine in normal individuals [46]. Furthermore, higher creatinine concentrations have been found in females than in males because of their higher muscular weight. Clinical estimation of creatinine levels has been carried out in both the urine and serum samples. A higher amount of creatinine causes kidney failure, urinary tract injury, preeclampsia, diabetic nephropathy,

glomerulonephritis, *etc* [47]. A decreased creatinine level in the blood also causes diseases like muscular dystrophy and myasthenia [48]. Spectroscopic techniques, photometric methods, chromatographic, and electrophoretic techniques were used for the creatinine detection in both the urine and serum samples [49]. Due to the drawbacks of these conventional techniques, researchers have designed biosensors to investigate the creatinine detection potentials in real samples, and they have shown better results [50]. Therefore, from the above-discussed biomarkers, the measurement of creatinine level in investigating samples has not been found reliable due to its variation with individual body mass, age, gender, amount of protein, and drug intake. Consequently, quantification of creatinine levels may generate false positive or false negative results. Like creatinine, the Cys C level also varies with body weight. On the other hand, detection of UA has also some negative consequences, such as aggregation of blood beneath the skin, patient discomfort, a mild headache, and infection at the needle pricking site. Researchers have also documented the complications associated with NGAL for kidney disorders because of biological alterations, less efficiency, instability, and interference tolerance [51]. Moreover, diagnostic applications of KIM-1 for kidney-related disorders in their acute phase have presented several benefits, like unique specificity and sensitivity, the ability to detect acute kidney injury in the early stage than the creatinine biomarker, and the fact that investigations can be carried out in urine, tissues, serum, or plasma. However, the detection of kidney disorders by using KIM-1 has shown several limitations, like its scarce availability, high cost, requirement for clinical authentication, and outcomes greatly affected by various confounding components [52]. From these aforesaid biomarkers, it can be concluded that urea can be an effective biomarker for the diagnostic application of kidney diseases. This is because urea is an abundantly produced physiological organic compound and is easily available in distinct types of body fluids, such as urine, saliva, sweat, serum plasma, *etc*. In future, the detection of urea for the diagnosis of kidney disorders in sweat samples will be more preferred because patients feel pain while collecting blood samples for the investigation. In addition to this, sweat has enough concentration of urea for the investigation of kidney disorders [53]. Fig. 2 depicts the mechanism of kidney dysfunction due to abnormal levels of kidney biomarkers.

3. Detection methods for kidney biomarkers

Early diagnosis of kidney diseases helps avoid the several ills of human health discussed above. The function of the kidney in the diseased condition in the early stage has also been monitored by using a kidney function test [54]. Various conventional techniques used for the detection of abnormal concentrations of kidney biomarkers are discussed below.

3.1. Conventional detection methods for kidney biomarkers

Conventionally, a number of kidney function diagnostic tests have been used, including urinalysis, analysis of proteins in patient urine, GFR, serum creatinine, creatinine clearance, blood urea nitrogen (BUN), *etc* [55,56]. These tests use body fluids like urine, tears, sweat, saliva, *etc*. The most widely used kidney function tests include BUN and serum creatinine [54]. These tests have also been used before introducing the radiolabelled iodine and gadolinium that are required in the screening steps of MRI as well as CT. These are being performed to prevent the adverse effects of radiolabelled components, like nephropathy and nephrogenic systemic fibrosis [57]. Furthermore, kidney-related diseases have also been diagnosed calorimetrically by using the phenol-hypochlorite method, nesslerization method, or Berthelot method, and the diacetylmonoxime method [58,59]. Renal as well as pre-/post-renal hyperuremia of a patient can be checked by using BUN integrated with serum creatinine test. The nitrogen content in blood has been measured by BUN. The urea concentration in blood or urine samples has been monitored using BUN and glomerular filtration rate. Conventional techniques such as chromatographic,

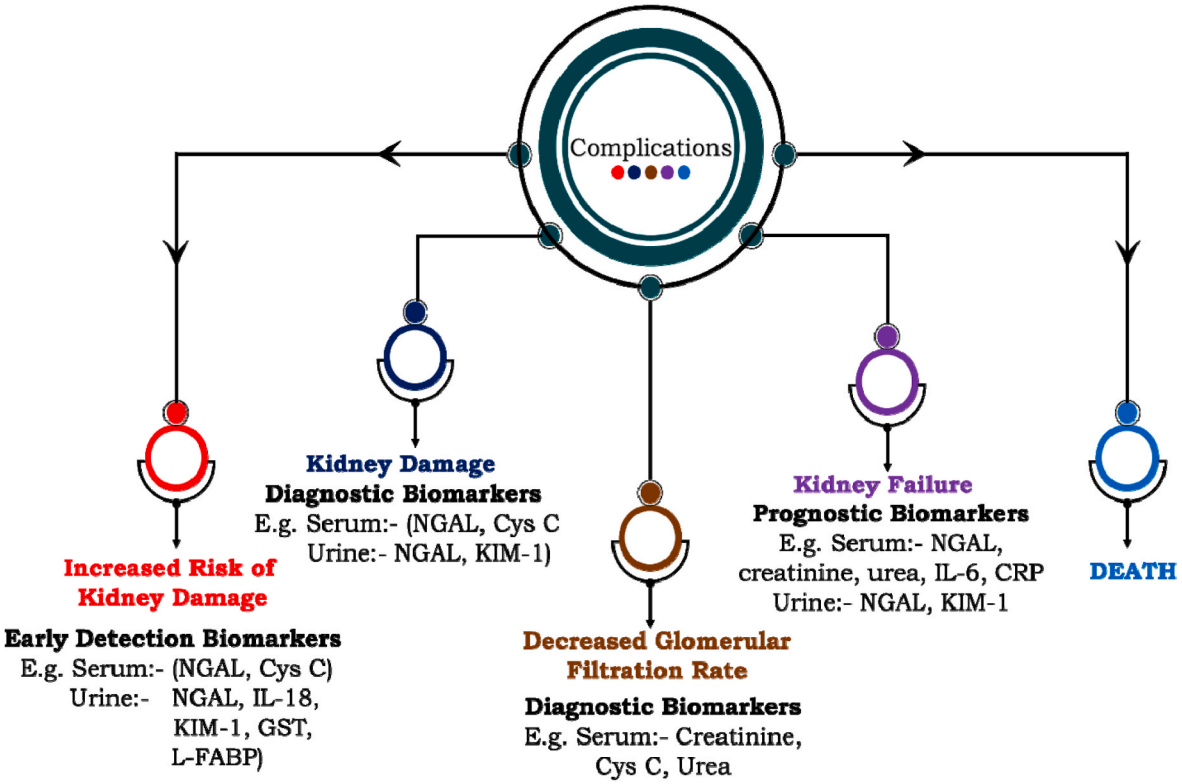

Fig. 2. Illustrative display of the impact of various biomarkers on renal function. The figure explains the elevated level of different biomarkers lead to increased risk of kidney damage or decreased glomerular filtration rate or kidney failure.

chemi-luminometric, colorimetric, spectrophotometric, and fluorimetric have been used. The measurement of UA concentration in blood or urine has been carried out by several conventional approaches, like spectroscopy, high-performance liquid chromatography (HPLC), phosphotungstic acid method, uricase-based photometric method, *etc* [60,61]. There are also some commercially available UA kits for the detection of UA. Due to costly instrumentation and complicated procedures that are more time consuming and less efficient, these above-mentioned approaches necessitate the search for some novel alternatives for UA quantification. NGAL concentration has been detected by using chemiluminescent micro-particle immunoassay (CMIA), particle-enhanced turbidimetric immunoassay (PETIA), and ELISA [62]. Methods for the detection of Cys C include enzyme immunoassays, nephelometry, turbidimetry [63], and electrospray chromatography [64].

3.1.1. Limitations of conventional detection methods

These immunoassays have shown better performance, unique sensitivity, and rapid detection. However, these conventional techniques have shown limitations like being tedious, time-consuming, painful blood extraction procedures, costly, and requiring skilled personnel for the operation and care of expensive instruments like microplate readers for the spectrophotometric detection [65]. Hence, researchers have shown their interest in biosensing technology. Biosensors employed for kidney diagnostic applications have overcome the limitations of conventional techniques as they are rapid, simple, reliable, cost-effective, highly sensitive, and efficient [13,17,66]. In addition, it requires a very small amount of sample for the investigation of kidney biomarkers.

3.2. Basis of biosensors in kidney biomarkers detection

Biosensors are electrochemical devices that incorporate recognition elements for biochemical processes [67,68]. These biosensors are integrated with a biorecognition element, transducer system, and detector (Fig. 3). A wide range of biorecognition elements, including enzymes, proteins, hormones, antibodies, cells, drugs, *etc*., have been used for the fabrication of a biosensing device [68–70]. Biorecognition elements have offered unique sensitivity for precise analytes, and thus, they have been used in the design of sensitive and specific biosensors [71]. Transducer transmits the analytical signals, *viz*. current, potential, absorbance, colour, heat, *etc*., which is dependent on the biosensor types [72]. Interaction involving the recognition element and the target analyte generates some alterations that are transformed into a measuring analytical signal by the detector. Intensities of generated signals depends on concentration of a biomarker in the investigating sample [73,74]. Biosensors are employed for the investigation of real samples to know composition, function, and precise detection of hazardous constituents in traces amounts in diverse fields like industries, environment monitoring, and diagnostic applications [69,75–78]. Researchers have designed distinct types of biosensors like immunosensors, glucometers, biochips, biocomputers, *etc* [1,78–81].

3.2.1. Classification of biosensors

Biosensors are well-acknowledged as ultrasensitive as well as quantitative analytical devices. Depending upon the type of transducing element, there are different biosensor-types, *viz*., optical, electrochemical, colorimetric, fluorescence, *etc* [82]. The analytical functioning of biosensors can be further enhanced by utilizing nanomaterials. Nanomaterials used in the designing of biosensors enhance the ratio of surface area-to-volume, improved catalytical, optical, electrical, and thermal characteristics of the biosensors [72,73]. Consequently, they enhanced the sensitivity, specificity, precision, rapidity, and accuracy of the biosensing device. Different types of nanomaterials, nanocomposites, and enzymatic nanoparticles of urease, creatinase, creatininase, sarcosine oxidase, *etc*., have been employed for the biosensors designing to detect kidney biomarkers [41,46]. The advantages and disadvantages of various biosensors used for kidney biomarker detection have been presented in Table 1.

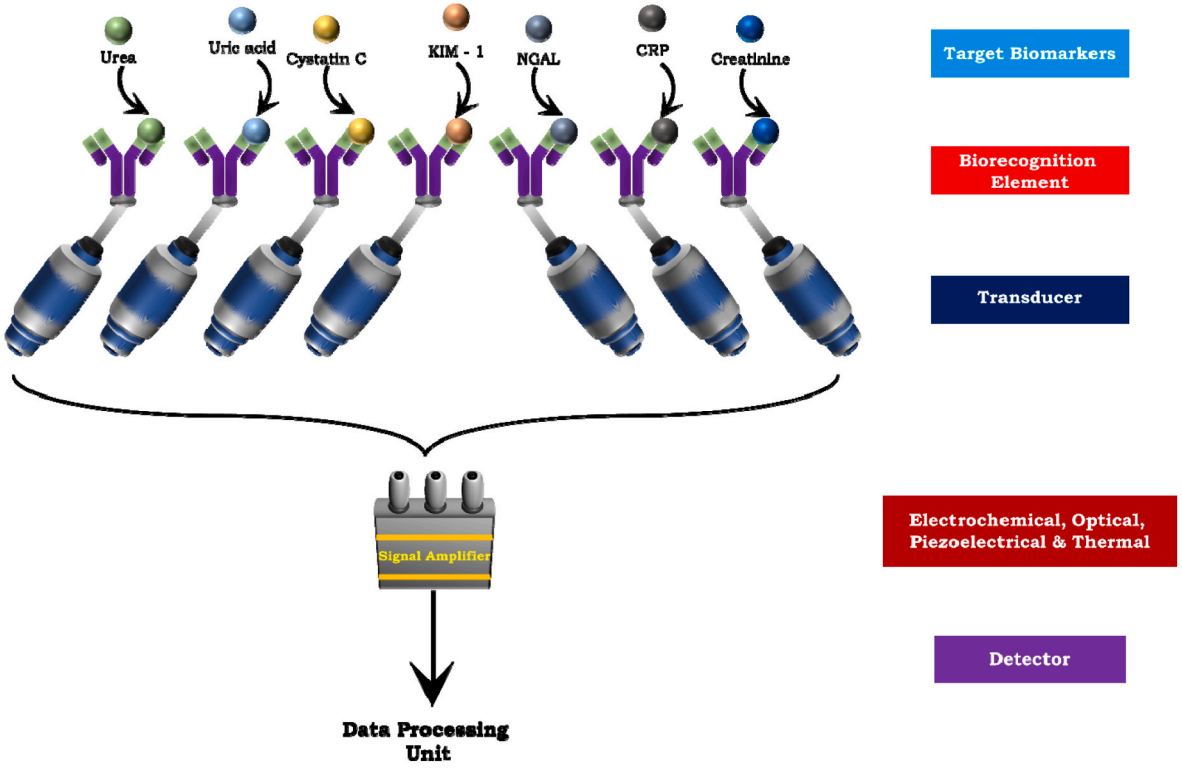

Fig. 3. Schematic illustration of working principle of a biosensor.

Table 1
Advantages and disadvantages of various biosensors for kidney biomarker detection.

Types of biosensors	Advantages	Disadvantages	Reference
Amperometric	These are fast, inexpensive, reproducible, specific, sensitive, and involve a simple fabrication procedure.	These biosensors are less stable, and their performance depends on several factors, including temperature, pH, ionic concentration, and chemical inhibition.	[46,83,84]
Immunosensor	Such biosensors are highly sensitive, specific, economical, and quick diagnostic devices.	The results obtained from these biosensors are greatly varied when multiple samples are analysed simultaneously.	[85,86]
Potentiometric	These devices are highly selective, user-friendly, quick, sensitive, and economical for kidney biomarker detection in real samples.	These are less stable and need a reaction buffer with a precise pH and temperature for the investigation of kidney biomarkers. Furthermore, ionic drift in the reaction buffer also alters the analytical signal.	[83,87]
Optical	These biosensors are marker-independent, sensitive, and stable.	These optical biosensors cannot be easily miniaturized like electrochemical biosensors.	[88,89]
Colorimetric	These biosensors are simple, consistent, and inexpensive for kidney biomarker detection.	The detection of kidney biomarkers using colorimetry requires a modification in the pH of the sample to near 12 for the aggregation. These biosensors require costly reagents or fluorescent dyes for the detection of kidney biomarkers (analytical signals) in real samples. Furthermore, the response time of these biosensing devices is longer, and sometimes they produce false signals during detection.	[90,91]
Point of care (POC) devices	These POC devices are convenient and therefore, these can be used in the near vicinity of kidney patients. These devices are simple, produce a fast response, are highly sensitive, and only require a drop of sample for investigation.	These devices produce semi-quantitative results and require clinically skilled personnel to work on them.	[53,92]

3.2.1.1. Electrochemical biosensors for kidney biomarker detection. Since past few years, electrochemical biosensors are receiving more attention because of their unique benefits like simplicity, selectivity, high sensitivity, reproducibility, rapidity, *etc* [92,93]. These electrochemical biosensors have achieved significance in the detection of kidney biomarkers. In these biosensors, the analyte (biomarker) to be detected is coated on the surface matrix or bound covalently with the immobilizing material. Interaction between analyte and matrix material generates an electrical analytical signal either in terms of altered current, voltage, conductance, or impedance. The intensity of the analytical signal is generally proportional to the binding of analytes with their specific substrate. The electrical signal produced during electrochemical reactions by these biosensors is due to the absorption of ions or electrons that causes electrical alterations in the reaction solution [65]. Therefore, depending upon the kind of analytical signals, different electrochemical biosensors are further categorized as: amperometric biosensors, immunosensors, and potentiometric biosensors.

3.2.1.1.1. Amperometric biosensors. In amperometric biosensors, an electrochemical signal is produced due to interactions among the analyte (biomarker) and the bio-recognition element immobilized onto the working electrode [67,73]. These electrochemical interactions usually produce an analytical signal in terms of altered electric current peaks on the standard potential of the working electrode. A number of amperometric biosensors have gained significance in the diagnostic applications of kidney diseases. For instance, an amperometric biosensor to be employed for the UA determination in urine and blood samples was designed by Fukuda et al. (2020) [94]. They drop-casted the uricase enzyme in combination with carboxy methylcellulose (CMC) along with conjugate of carbon nanotubes, and a gold film on the gold electrode. CMC was used as a surfactant to provide the hydrophobic environment. Moreover, it also enhanced the surface area for efficient redox reactions on the gold working electrode and consequently accelerated the electrical conductivity of the working electrode. Its sensitivity and linearity were 233 μA/mM/cm^2 and 0.02–2.7 mM, respectively. The limit of detection (LOD) of this amperometric biosensor was 2.8 μM. Kumar and co-researchers (2019) detected creatinine in real samples by fabricating an amperometric biosensor using enzymatic nanoparticles containing creatinase, creatininase, and sarcosine oxidase [95]. They immobilized these enzymatic nanoparticles onto the electrode made of gold. Based on cyclic voltammetry, creatinine estimation in the real samples was done. The aforesaid biosensor exhibited a 0.1 μM LOD, a 2 s response time, better stability (180 days), and a wider working ranging (0.1–200 μM).

Thakur and co-researchers (2013) have electrochemically investigated the UA determination in sera of human blood by depositing conjugates of polyaniline and prussian blue (PB) at the platinum electrode surface [96]. The linearity ranges were found between 10 and 160 μM. Furthermore, the sensitivity of the aforesaid amperometric biosensor was 160 μA/mM/cm^2. Shukla et al. (2014) have amperometrically detected the urea by constructing a amperometric biosensor integrated with the nanocomposite of zirconia-polypropylene imine (ZrO_2-PPI) dendrimer onto the screen printed carbon electrode [84]. Zirconia (ZrO_2) nanoparticles were synthesized via a modified sol–gel technique, dispersed in a polypropylene imine (PPI) solution, and then, electro-codeposited via cyclic voltammetry technique onto a screen-printed carbon electrode surface. The synergistic action of ZrO_2 and PPI was found to produce a notable enhancement in the electrocatalytic characteristics of the developed biosensor, which helped in urease immobilization. The schematic diagrams of ZrO_2-PPI dendrimer/screen-printed carbon electrode designing, and urease immobilization by a nanocomposite electrode of ZrO_2-PPI dendrimer are presented in Fig. 4.

Jirakunakorn et al. (2020) have detected UA by developing an amperometric biosensor [97]. They electrodeposited the PB nanoparticles on screen-printed electrode (SCPE) followed by drop-casting of chitosan-graphene (Chi-Gr) cryogel-conjugate onto the SPCE. Finally, they immobilized uricase using Chi-NH_2 groups of Chi-Gr composite to form uricase/Chi-Gr cry/PbNPs/SCPE. This amperometric biosensor was designed for UA detection in clinical samples. The UA detection was based on the cyclic voltammetry that results in the production of hydrogen peroxide (H_2O_2) due to the oxidation of UA. Modified SPCE provided an effective platform for efficient electron kinetics during the UA investigation. LOD and linear range of this amperometric biosensor were 2.50 μM/L and 0.0025–0.40 mM/L, respectively. This biosensor exhibited an improved reproducibility, *i.e.*, 98.2%–102.5%, and the unique binding affinity of UA by exhibiting the Michaelis-Menten constant of 0.23 mM/L.

Desai et al. (2018) have also detected Cys C in urine samples by immobilizing multiwalled carbon nanotubes (MWCNTs) on SCPE. This biosensor exhibited 1583.49 μA/cm^2/μg sensitivity, 0.58 ng/L LOD, and 10 min of response time [98]. This developed biosensor can detect the trace-amount of the kidney biomarker (Cys C) in nanogram-level and exhibited very high sensitivity as compared to other biosensors. Furthermore, they used screen-printed electrode, which also provided a promising platform for the miniaturization of biosensing devices. However, this biosensor showed a poor working range, and the response period of this amperometric biosensor was longer (10 min) as compared to other biosensors. The biosensor integrated with enzyme NPs developed by Kumar et al. (2017) exhibited a wider working ranging of

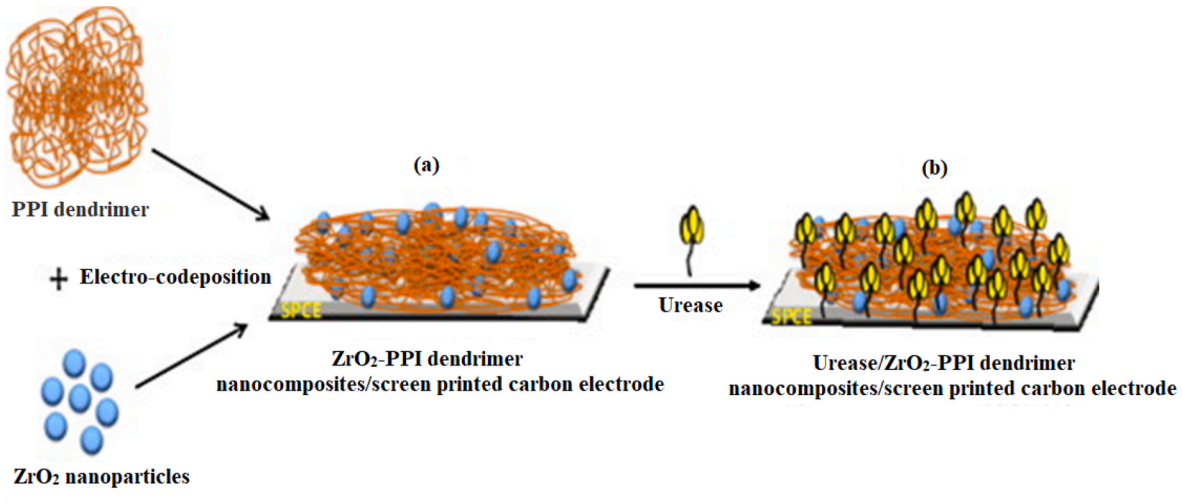

Fig. 4. Schematic diagram of (a) ZrO_2-PPI dendrimer/screen printed carbon electrode designing, and (b) urease immobilization by nanocomposite electrode of ZrO_2-PPI dendrimer [84] (Copyright @ 2014, with permission from Elsevier Inc.).

0.1–200 μM with a unique stability of 180 days and a quick response time of 2 s [46]. Therefore, these reports provide effective knowledge to scientific communities for the development of improved amperometric biosensors by using enzymatic NPs and their immobilization onto screen-printed electrode.

3.2.1.1.2. Immunosensors. Immunosensors work based on antigen (Ag) and antibody (Ab) interactions [99]. These analytical devices measure the specific analyte-antibody complex formation in the reaction system. According to the types of immune responses, these immunosensors may be classified based on their mechanisms: direct and indirect. Direct detection mechanisms involve the direct interaction between Ag and Ab, while indirect procedures require fluorescence to check the binding of Ag or Ab with analytes [53]. These devices involve the complex formation of a specific antigen or analyte, *i.e.*, kidney biomarkers (urea, uric acid, creatinine, *etc.*) with the specific antibodies immobilized onto the transducing element. The detection of a specific kidney biomarker generates an analytical signal in the form of alternating current peaks. These immunosensor devices have exhibited high affinity for a specific antigen or antibody of the investigated analyte. Ferreira et al. (2020) constructed an immunosensor for the investigation of the Cys C renal biomarker by immobilizing nanocomposite of polypyrrole and carbon nanotube onto an inter-digitated gold electrode (Fig. 5) [100]. The aforesaid biosensor exhibited a LOD of 28 ng/mL.

Recently, researchers have identified a novel biomarker, Lipocalin-2 or NGAL, for diagnosing the function of the kidney [11,12,62,101]. This biomarker is secreted by neutrophils as well as injured renal tubular epithelial cells. Neves and co-researchers (2020) reported the detection of NGAL in the urine of diseased individuals [62]. They reported that the aforesaid biosensor was sensitive, specific, and exhibited a 0.096 ng/mL LOD. The response time was 10 min, and the linearity range was 0.1–5.0 ng/mL. Thus, this biosensor is more sensitive as it can detect minute concentrations of the NGAL biomarker than the above-mentioned immunosensors. Though the linear range of the immunosensor developed by Lopes et al. (2019) was found to be better (10–100 ng/mL) than other immunosensors [102].

3.2.1.1.3. Potentiometric biosensors. This technique has been widely used for the investigation of kidney biomarkers and helps in the quick, efficient, and accurate diagnosis of kidney disorders [103].

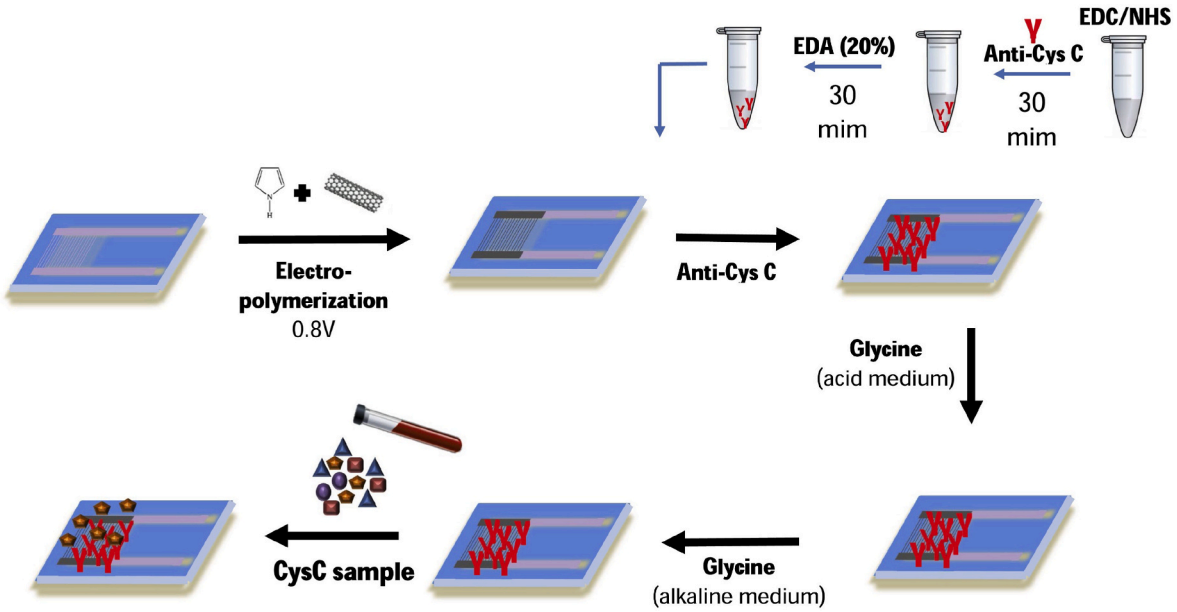

Fig. 5. Schematic representation of an immunosensor for CysC detection [100] (Copyright @ 2020, with permission from Elsevier B.V.).

Potentiometric biosensors detect specific analytes by estimating the potential variation among reference and working electrodes without current. The potential difference generated by a working electrode relies on the analyte concentration in the reaction system. Reference electrodes provide the required reference potential. This potential difference is employed to investigate the analyte concentration in a given sample. The basic constituents of a potentiometric biosensor are illustrated in Fig. 6.

Guilbault and Montalvo (1969) designed a potentiometric urea biosensor using the urease enzyme for the first time [104]. After that, a number of biosensors, including electrochemical as well as potentiometric were employed for the measurement of urea in the body fluids [105,106]. Various types of matrices, including latex polymers [107], conducting polymers like polypyrrole [83], metallic nanoparticles [108], metal oxides [109] have already been reported for their uses in the designing of potentiometric biosensors. Reverse iontophoresis integrated potentiometric biosensors have also been used for the blood analysis with the measurement of urea concentration [110]. Bonini et al. (2020) immobilized the urease enzyme onto graphene oxide and potentiometrically detected the urea in the plasma of a person suffering from chronic diseases [111]. Immobilized urease enzyme hydrolyzed the urea into CO_2 and NH_3. Consequently, the pH of the reaction buffer got elevated, and this increased pH was measured as an analytical signal. The response period of this potentiometric biosensor was 120 s, and the LOD was 19.5 μM. Jakhar and Pundir (2018) have also constructed a potentiometric biosensor for urea detection in real samples (Fig. 7) [41]. They employed nanoparticles of urease enzyme in conjugation with chitosan deposited onto nitrocellulose membrane. This entire conjugate was confined at the surface of the ammonium ion selective electrode. This biosensor was highly specific and sensitive for urea detection, exhibiting 1 μM/L LOD, 2–80 μM working range and 10 s response time. This potentiometric biosensor performed optimally at 40 °C and pH 5.5. This potentiometric biosensor has shown an elevated sensitivity and a shorter response period in comparison to other aforesaid potentiometric biosensors.

3.2.1.2. Optical biosensors for kidney biomarker detection. Optical biosensors are composed of optical fibres that help in the investigation of kidney biomarkers (analytes) by recording their absorption, colour, scattering of light, or fluorescence [112,113]. These biosensors are capable of detecting distinct types of analytes by measuring their characteristic absorption in the form of wavelength. Researchers have also reported the utility of this technique in *in vivo* applications for the detection of specific analytes. An optical device quantifies the investigating signal of the target analyte in several different ways, like fluorescence, phase shift, absorbance, reflectance, *etc*. Optical detection of any analyte involves the tagging of an aptamer sequence with a fluorescent component that emits fluorescence upon binding of a suitable analyte [65]. There are a number of reports available that demonstrate the uses of optical biosensors in kidney disease diagnosis [114,115]. The principle of measurement of the urea biomarker using an optical biosensor has been illustrated in Fig. 8.

Zhu and co-researchers (2020) synthesized single-mode coreless single-mode optical biosensor by immobilizing urease enzyme encapsulated with a zeolite imidazole framework for urea detection in the real samples [88]. The sensitivity and LOD of this optical biosensor were, respectively, 0.8 mM/RIU and 0.1 mM. Bleher and co-researchers (2012) optically detected Cys C in the kidney failure condition. This optical biosensor was integrated with reflectometric interference spectroscopy (RIS) [114]. Using RIS, binding signals require a low temperature. Therefore, the detection of biomolecular interactions occurring on the sensitive layer does not require a stringent temperature regulator. The augmented temperature of the sensitive layer increased the volume, which is compensated by lowering the refractive index. Label-free antigens and antibodies were immobilized on transducers. Specific immuno-interactions between Cys C and antibodies alter the refractive index that was employed for the quantification of Cys C concentration in serum. The working ranging and response time of this biosensor were 0.53–1.02 mg/L and 20 min, respectively. However, this biosensor prolonged the duration for measuring the analyte concentration in comparison to the optical system developed by Ref. [114]. Duan and co-researchers (2020) quantitatively detected the urea in the urine samples via the whispering gallery mode (WGM) [115]. This optical biosensor was based on nematic liquid crystal (LC) 4-cyano-4′-pentylbiphenyl (5CB) microdroplet. The 5CB micro droplet was doped with stearic acid that was acting as both an optical resonator as well as a sensing reactor (Fig. 9). Urease catalysis of urea generated hydroxide ions. After that, deprotonation along with self-aggregation of stearic acid resulted at the reaction mixture and LC interface. This occurrence elevated the pH of the sensing system, which led to the reconfiguration of the LC microdroplet. As a result, a measurable alteration in WGM spectra was observed that was associated with the urease enzyme-based configural shift of LC molecules. This alteration in the spectra of LC molecules was taken as an analytical signal for assessing the urea concentration in real sample. The sensitivity and LOD of the aforesaid optical biosensor were, respectively, 0.1 mM and 1.56 nm/pH. The response period of this optical biosensor was 4 min.

3.2.1.3. Colorimetric biosensors for kidney biomarker detection. Colorimetric biosensors analyze the samples to detect the amount of coloured compounds [116]. These devices sense the target analyte by altering its colour, which is then compared with the reference colour that can be visually monitored. Researchers have constructed various colorimetric biosensors for the investigation of kidney biomarkers. Wang and co-researchers (2020) demonstrated UA detection in serum and urine samples using polypyrrole (PPy) layered polyoxometalates (POM) conjugated with helical metal organic frameworks (MOFs) [90]. The conjugation of PPy-integrated POMs with MOFs showed unique stability and peroxidase-like activity. Therefore, the synergistic effect of Ag_5PMo_{12} coated with PPy, catalysed the oxidation of 3,3′,5,5′-tetramethylbenzidine (TMB) and converted it into oxidized green TMB in the occurrence of H_2O_2. This green TMB was further transformed into

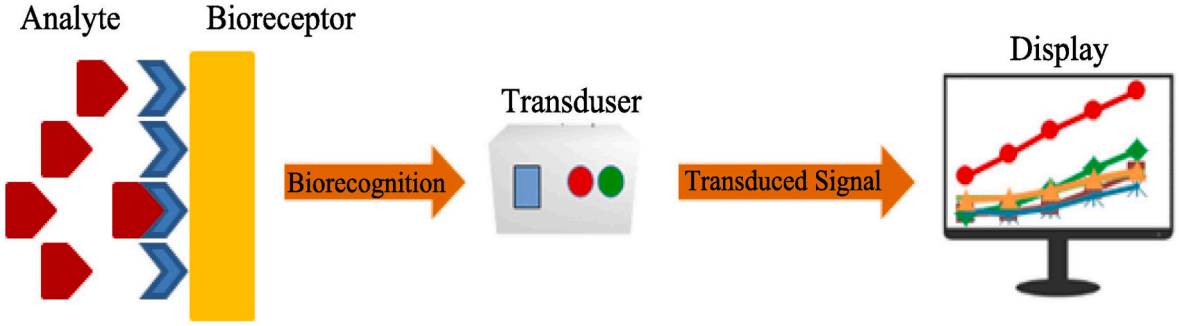

Fig. 6. Basic constituents of a typical potentiometric biosensor [103].. (Copyright @ 2021, with permission from Elsevier B.V.)

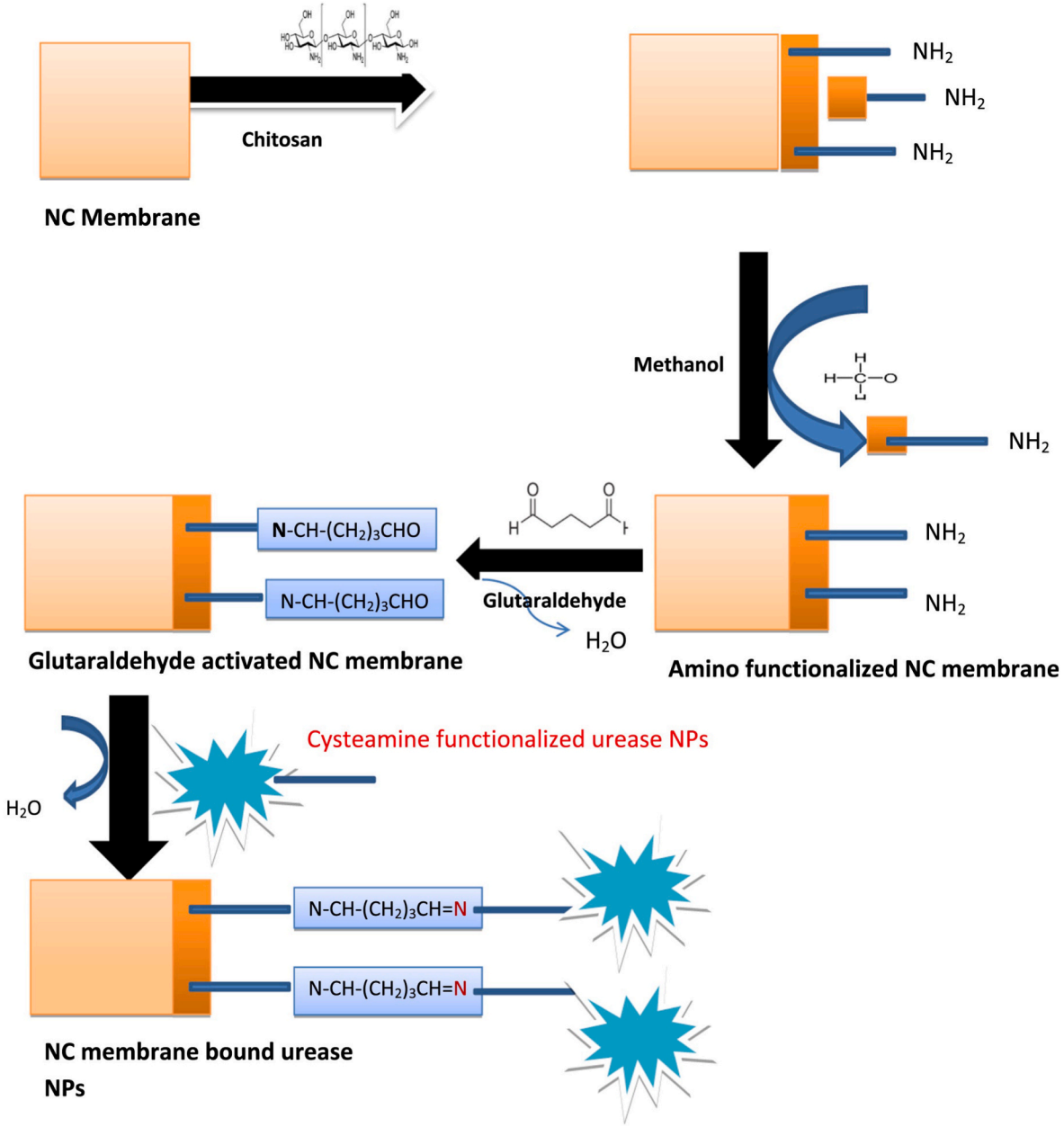

Fig. 7. Schematic illustration of potentiometric biosensor for the detection of urea [41] (Copyright @ 2017, with permission from Elsevier B.V.).

colourless in the presence of UA, which means UA inhibited the oxidation of TMB. This colorimetric biosensor has shown a wider linear range in-between 1–50 μM and 0.47 μM LOD. In clinical samples, the analytical recoveries of this biosensor were 95% and 106.1%, respectively. Furthermore, Ciou and co-researchers (2020) revealed the creatinine measurement in urine [117]. They colorimetrically detected the creatinine in the urine of a diseased person by coating of 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) radical cations ($ABTS^{\cdot+}$) on an FTO electrode modified with chitosan. During colorimetric reactions, $ABTS^{\cdot+}$ decolorized and reduced to ABTS in the presence of creatinine and negatively charged components of urine. The sensitivity of this colorimetric biosensor was 27.3 μA/cm^2/mM and an 11 μM LOD was also measured. The response time was approximately 60 s. Evans et al. (1968) measured the concentration of urea in the saliva using dipstick strips, although this method was not so reliable [59]. Alev-Tuzuner et al. (2019) designed a urea testing strip using hydrogel, pH-indicator paper, and urease enzyme [118]. Polyethyleneglycol was used for hydrogel formation. They used the above-mentioned testing strip for the onsite investigation of urea in both urine and saliva samples. Exposure of the urea solution to the testing strip reacted with the immobilized urease enzyme. Enzymatic catalysis resulted in the urea hydrolysis into NH_3 and CO_2 and thereby, increased the pH of the reaction system. A colour analyzer was used to detect an alteration in colour when the urea concentration increased from yellow to green-blue, which was easily evident with the naked eye and compared with the standard colour of the urea sample. The urea concentrations in the real samples were estimated by a spectrophotometric diacetyl-monoxi-methiosemicar bazide approach. The response period of the urea detection was 1 min, and the LODs for naked eyes and the colour analyzer were 20 mg/mL and 3.41 mg/mL, correspondingly. The working range of this colorimetric biosensor was 20–200 mg/dL, which exhibited good storage stability for about 30 days when stored in a deep freezer.

Zusfahair and co-researchers (2019) reported the urea detection in the real samples by depositing urease enzymes on chitosan in the form of cryogel [119]. The cryogel formation was carried out by an ionic gelation procedure to absorb the urease. During colorimetric analysis,

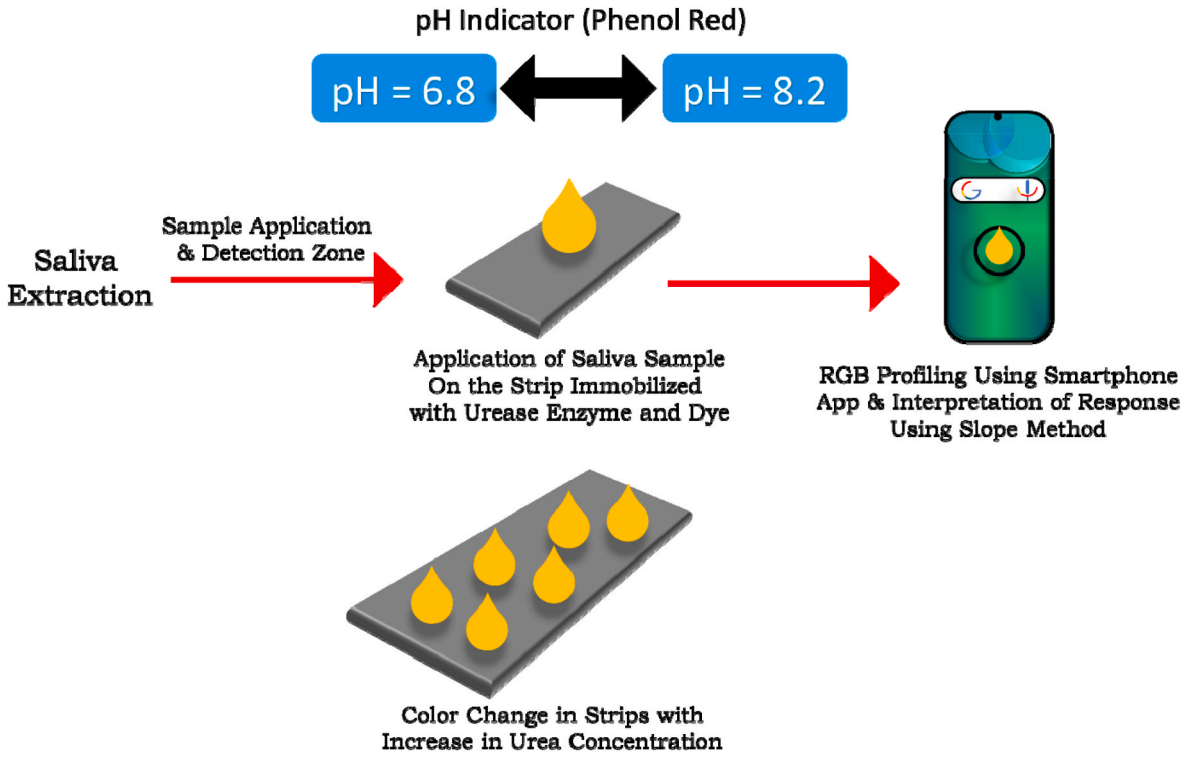

Fig. 8. Diagrammatic illustration of an optical biosensor for urea detection.

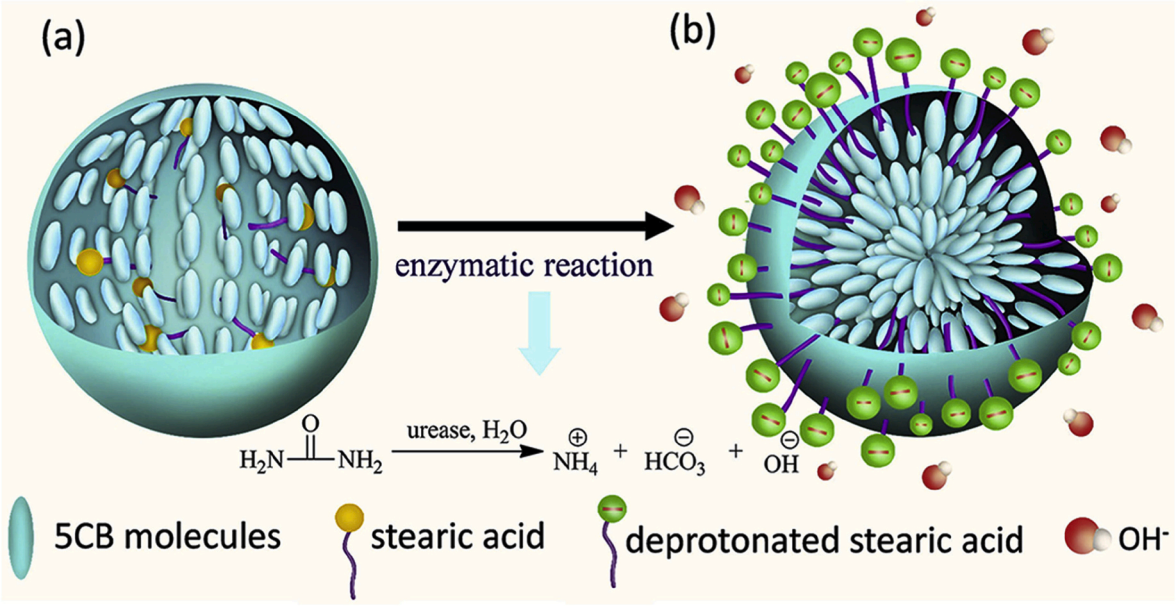

Fig. 9. Schematic representation of the structural transition of stearic acid-doped 4-cyano-4′-pentylbiphenyl (5CB) microdroplet from planar anchoring (a) to homeotropic anchoring (b) [115] (Copyright @ 2019, with permission from Elsevier B.V.).

cryogel urease catalysed the urea hydrolysis to form Co^{2-} and NH^{4+} ions. BTB indicator was incorporated that changed the colour. The altered colour of the sample was measured using a spectrophotometer. The analytical potential of the above-mentioned colorimetric biosensor was found to be good, showing 0.018 mM LOD, 0.9 mM linearity, and a 15 min response time. Sivasankaran and co-researchers (2018) reported a simple and less expensive colorimetric sensor-based creatinine determination procedure for both serum and urine samples, where the colorimetric sensor probe was based on the copper nanoparticles (CuNPs) stabilized by L-cysteine [120]. They also reported that these L-cysteine stabilized CuNPs demonstrated a sensitive as well as selective interaction with creatinine. In this work, a colorimetric biosensor has been designed by employing this interaction based on the reduction in localized surface plasmon resonance intensity as examined by means of a UV–visible spectrophotometer. The designed colorimetric biosensor demonstrated a linear dynamic ranging of 5.33×10^{-6} M to 3.33×10^{-7} M. The sensitivity for the detection of creatinine was as low down as 4.54×10^{-10} M. The colour change in the analysis of creatinine was

found to be by reason of the aggregation of L-cysteine stabilized CuNPs contained by the tested samples (Fig. 10). Therefore, a L-cysteine stabilized CuNPs-based colorimetric biosensor can successfully be employed for fast and on-site creatinine analyses of in both urine and serum samples.

3.2.1.4. POC devices for the detection of kidney biomarkers. Existing conventional diagnostic techniques used in kidney biomarker detection have many drawbacks, such as being time-consuming, non-portable, costly, complicated, and invasive. To overcome these issues, researchers have designed novel analytical devices, *i.e.*, POC devices, for the clinical assessment of kidney biomarkers [121]. These POC devices are cost-effective, quick, simple, use a tiny drop of sample and reagents, permit on-site detection, and are simple to transport [53,54,122]. Developing POC devices has been miniaturized by integrating potentiometric and amperometric biosensing techniques. This is due to their cost-effectiveness, simplicity, and improved analytical performances (sensitivity, specificity, reproducibility, quick response time, and accuracy) [53,123]. POC devices can also be designed by using optical or colorimetric biosensors. Although these biosensors are simple in fabrication and user friendly, these sensing techniques require expensive instrumentation setup and produce pseudo-results; therefore, they are

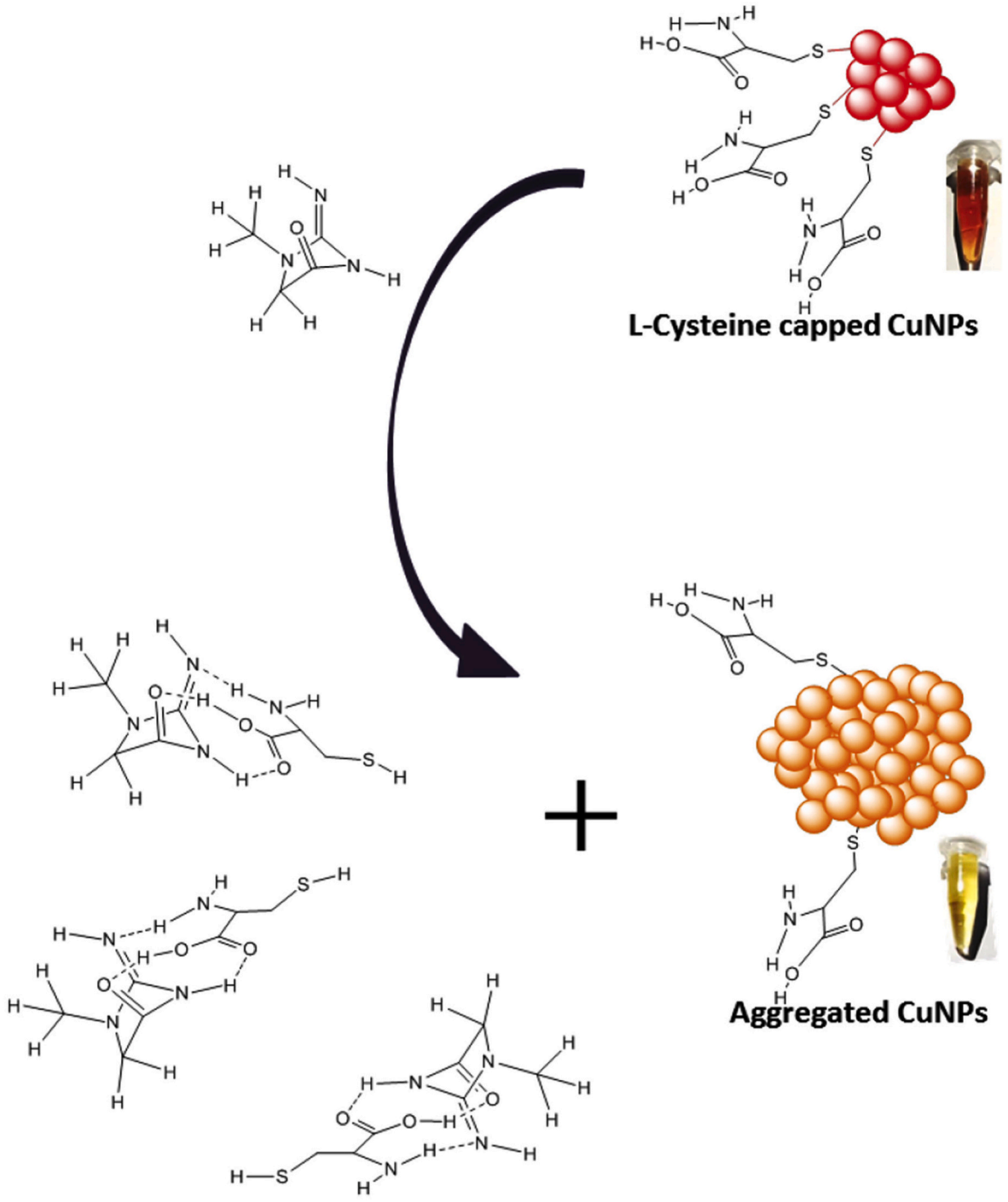

Fig. 10. The proposed mechanism for aggregation of L-cysteine stabilized CuNPs and the scheme of the L-cysteine stabilized CuNPs aggregation induced mechanism of sensing [120] (Copyright @ 2017, with permission from Elsevier Inc.).

less reliable. The analytical performance of biosensing devices also depends on the substrate-type employed for the immobilization of the recognition element. For instance, POC devices in combination with electrochemical biosensors fabricated by using SPCE have shown extraordinary analytical performance during the sensing of a specific analyte. Therefore, such POC devices can be easily disposed of and showed flexibility in the designing in contrast to traditionally used electrodes like gold, pencil graphite, and several others [124]. Furthermore, the use of SPCE increases the possibility of commercializing the monitoring of POC devices. Hence, SPCE-based biosensing devices have been employed in diverse research areas including supercapacitors, batteries, cosmetics, and in several medical applications like the detection of botulinum biowarfare agents [125] and kidney biomarker detection [53].

Fu and co-researchers (2021) have reported the designing of a smartphone powdered photochemical dongle for the investigation of creatinine in the blood of patients suffering from chronic diseases [126]. The aforesaid dongle system was a portable reflectance spectral analyzer that was comprised of an enzymatic photochemical testing strip. Moreover, Wang and Chatrathi (2003) have demonstrated the design of a lab-on-chip for the evaluation of four distinct kidney biomarkers, *viz.*, creatine, creatinine, UA, and *p*-aminohippuric acid in the urine [127]. In a research, Soni and co-researchers (2018) designed smartphone integrated biosensor for the urea detection in the saliva of individuals with renal disorders [54]. The LOD of the above-mentioned biosensor was 10.4 mg/dL, wide working range of 10–1000 mg/dL and a 20-sec response time. This biosensor has shown a better working range and a lower response time as compared to the other aforesaid POC sensing devices. Recently, Li and co-researchers (2020) designed a mobile healthcare system consisting of a lateral flow pad conjugated with nanoparticles of mesoporous PB in the form of synthetic nanoenzymes and software for the onsite UA detection in the blood sample [128]. The working range and storage stability of this POC device were 1.5–8.5 mg/dL and 14 days, respectively. The response time for UA determination by this POC device was 10 min. However, the POC device designed by Li and co-researchers (2020) demonstrated the lowest LOD in comparison to the other discussed POC devices [128]. Therefore, these studies facilitate the basic information to the researchers for the future design of highly advanced POC devices [129]. Table 2 depicts a comparison of different analytical parameters of distinct kinds of biosensors for the diagnosis of kidney disorders.

3.2.2. Optoelectronic technology for biosensor applications

Optical and electronic components are combined in biosensors using optoelectronic technologies in order to detect, measure, and analyze biological molecules or biochemical reactions. With the use of these technologies, measurements can be made precisely and sensitively by interacting light with biological materials. Several essential elements and ideas in optoelectronic technology for biosensors are light sources, optical detectors, waveguides, biosensing elements and transduction mechanisms etc. The electronic signals produced by the optoelectronic biosensor are processed and analysed using electronic circuits and software. The target analytes can be measured and recognised using this analysis. Optoelectronic biosensors provide a number of benefits, including high sensitivity, specificity, quick detection and the capacity to carry out tests in real-time or very close to it. The applications of optoelectronic technology for biosensor includes biomarker detection for illnesses, glucose monitoring, and DNA analysis are all examples of medical diagnostics. Apart from this environmental monitoring can be done by finding toxins and pollutants in the water, soil, and air. The applications of optoelectronic technology biosensor in drug discovery includes in High-Throughput Screening and in pharmacokinetics studies. The biomedical research applications are employed in Cellular Studies and Label-Free Assays. The other applications include the rapid testing, infectious disease detection, remote sensing, biological and chemical threat detection, neurotransmitter detection and data integration [132–134].

The direct insertion or installation of sensors into the body to measure various parameters or identify particular biomolecules is referred to as an invasive procedure in optoelectronic technology for biosensors. These intrusive biosensors are especially useful in clinical settings when precise and instant monitoring is necessary. Some important type or applications of invasive optoelectronic biosensors include Fiber Optic Biosensors, Fluorescence-based Sensors, Optical Coherence Tomography (OCT), Optical Fibers for Drug Delivery, Implantable Optical Sensors for Chemicals and Biomarkers and Intravitreal Sensors. Invasive optoelectronic biosensors are crucial tools for critical care, surgery, and numerous biomedical studies. However, they also highlight the dangers of implantation, including as tissue damage or infections [135–137]. Optoelectronic technology non-invasive techniques for biosensors enable the monitoring and detection of numerous parameters or biomolecules without the requirement for direct body entry or penetration. These non-invasive biosensors are commonly used in diagnosis, research and critical care. The type or biomedical applications includes pulse oximetry, photoplythysmography (PPG), multispectral imaging, Infrared imaging, functional Near Infrared Spectroscopy, breath analysis and infrared thermography etc [138–140].

The comparative analysis of invasive and non-invasive techniques suggested that, as they directly access body fluids or tissues, invasive procedures typically provide greater accuracy and precision and non-invasive techniques could be less accurate but are less invasive. Secondly, infections, tissue damage and patient pain are all possible side effects of invasive methods but patients typically feel safer and more at ease using non-invasive procedures. Continuous monitoring frequently needed in invasive procedures, whereas intermittent or routine assessments are best handled by non-invasive approaches. The application-based difference in both the technique suggested that when great accuracy and ongoing monitoring are essential, such as in intensive care units, invasive procedures are appropriate. For routine monitoring, screening, and early detection non-invasive techniques are desirable [141–143].

Depending on the clinical situation, several biomarkers may be chosen, but some of the most significant and necessary biomarkers for assessing kidney health are summarized in Fig. 11.

3.2.2.1. Future prospects. Screening of the concentration of kidney biomarkers in body fluids is vital for the healthy life of humans. Abnormal levels of emerging biomarkers such as urea, UA, NGAL, Kim, creatine, etc., have caused acute and chronic kidney disorders. Therefore, it is pertinent to detect the abnormal concentration of kidney biomarkers in the acute stage to prevent the severity of the disease by giving timely treatment. Though, biosensors have provided a promising platform for the diagnosis of kidney diseases. However, this technology is still in the zygotic phase. It has some gaps that must be filled in order to improve various parameters, including bio-consistency, cell-signalling systems, accuracy, and affordability. Therefore, future research should be oriented towards the construction of disposable biosensing devices that should be economical, fast, and capable of investigating a number of kidney biomarkers simultaneously. DNA microtechnology should be combined with the biosensors for the simultaneous detection of kidney biomarkers. The synthesis of novel nanomaterials like nanowires of biological origin has opened promising applications in the development of novel bioelectronic systems as well as in biosensor technology. The design of biocatalytic nanostructures by means of dip-pen nanolithography can also be used for the detection of kidney biomarkers in clinical samples. Moreover, the preparation of distinct nanotools by using physiological constituents as a model can open wide opportunities in upcoming nanointegrated technologies. The miniaturization of biosensors employed in renal biomarker investigations and their further development into wearable sensors can improve the existing diagnostic techniques that are beneficial for human health. It is

Table 2
Comparison of parameters of some of recent biosensors for the detection of kidney biomarkers.

Name of biosensor	Enzyme/nanomaterials used	Type of electrode/substrate for immobilization	Limit of detection (LOD)	Sensitivity	Response time	Target biomarker detected	Name of diseases	Advantages	Reference
Amperometric	Uricase/carbon nanotube/ carboxymethyl cellulose	Gold electrode	2.8 μM	233 μA/mM/cm^2	–	Uric acid detection in serum and urine	Kidney disease, renal dysfunction, hyperuricaemia, gout/arthritis, pneumonia, leukaemia, and Lesch-Nyhan syndrome	Sensitive and specific	[94]
	Creatininase/creatine, sarcosine oxidase	Au electrode	0.1 μM	–	2 s	Creatinine detection in sera of kidney and muscular ailments	Renal failure, glomerulonephritis, urinary tract obstruction, diabetic nephropathy, preeclampsia, muscular dystrophy and myasthenia	Showed quick response, better consistency and sensitive	[95]
	Palladium nanoparticles/ polypyrrole/reduced graphene oxide	Glassy carbon electrode	4.7×10^{-8} M	–	–	UA	Kidney disease, organic acidemia Lesch-Nyhan syndrome, and gout	Catalytic activity, high selectivity, andexcellent reproducibility	[130]
	Papain	Screen printed multiwalled carbon nanotube	0.58 ng/L	1583.49 μA/ cm/μg	10 min	Cystatin C in urine	Chronic kidney diseases	Specificity, sensitivity and user friendly	[98]
	Uricase/cryogel platform of graphene-incorporated chitosan/Prussian blue layer	Screen printed electrode	2.5 μM/L	–	–	Detection of UA in serum samples	Gout and renal diseases	Simple, selective and sensitive	[97]
	Zirconia-polypropylene imine dendrimer	Screen printed carbon electrode	0.01 mM	3.89 μA/ mM/cm^2	4 s	Urea detection in real samples	Urinary tract obstruction, renal failure, burns, dehydration, hepatic failure, cachexia, nephritic syndrome and gastrointestinal bleeding	Simple, stable, rapid and sensitive	[84]
Immunosensors	Polypyrrole/carbon nanotube nanoyhybrid film	Interdigitated electrode was designed by two gold fingers by electropolymerization of nanohybrid film to obtain a supercapacitor	28 ng/mL	0.93°/ng/ mL	–	Cystatin C in serum samples	Renal failure	Exhibited high sensitivity, selectivity and rapid	[85]
	Gold nanoparticles/ antibodies	Screen-printed electrode	6 ng/mL	6.4 μA ng/ mL/cm^2	–	Detection of cystatin C in serum samples	Chronic kidney diseases	Fast, sensitive and cost-effective	[102]
	Graphene oxide-ferrocene nanofilm	Gold electrode	0.03 ng/mL	–	15 min	Detection of cystatin C in serum samples	Kidney failure	Reproducible, simple, specific and sensitive	[89]
Potentiometric	Urease/graphene oxide/4-amino benzoic acid	–	19.5 μM	92.1 μV/μM	120 s	Investigation of urea concentration in plasma of dialyzed patients	Chronic kidney diseases	Effective and sensitive	[111]
	Urease	Chitosan activated nitrocellulose (NC) membrane	1 μM/L	23 mV/ decade	10 s	Urea detection in serum samples of kidney patients	Renal failure, urinary tract obstruction, shock and stress, pregnancy, augmented protein catabolism, congestive heart failure, malnutrition, dehydration, and bleeding in digestive tract. burns,	High selectivity, broader working range, low LOD, good reproducibility and high storage stability	[41]

(*continued on next page*)

Table 2 (*continued*)

Name of biosensor	Enzyme/nanomaterials used	Type of electrode/substrate for immobilization	Limit of detection (LOD)	Sensitivity	Response time	Target biomarker detected	Name of diseases	Advantages	Reference
Colorimetric	Polypyrrole coated polyoxometalate-encapsulated fourfold helical MOFs	–	0.627 μM towards ascorbic acid and 0.07 μM towards H_2O_2	–	–	UA detection in clinical samples	Diagnosis of gout, arthritis, urolithasis and Lysch Nyhans ysndrome	Simple, reliable and economic	[131]
	2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) radical cations/chitosan film	FTO substrate	11.0 μM	27.3 $\mu A/cm^2/mM$	<60 s	Detection of creatinine in urine samples	Kidney and cardiovascular diseases	Simple, accurate, sensitive	[117]
	Urease	Chitosan cryogel beads	0.018 mM	–	15 min	Detection of urea	Kidney diseases	Selective, sensitive, simple and reproducible	[119]
	Urease	Urea test strip employing polyethylene glycol based hydrogel and pH-indicator paper	20 mg/dL	–	1 min	Detection of urea	Detection of urea in saliva and urine samples	Rapid, accurate and simple	[118]
Optical	Urease enzyme encapsulated in zeolitic imidazolate framework	Single-mode coreless single-mode optical fiber	0.1.mM	0.8 mM/ Refractive Index Unit	30 min	–	Urea in blood and urine samples	High sensitivity, selectivity, fast and marker independent	[88]
	Urease	Single stearic acid-doped 5CB microdroplet	0.1 mM	–	5–17 min	Kidney impairment, hepatic failure, liver cirrhosis, and toxic hepatitis decelerate urea metabolism	Detection of urea in urine samples	real-time, quantitative and sensitive	[115]
Point of care (POC) devices mobile healthcare (mHealth) system	Mesoporous Prussian blue nanoparticles	Paper-based lateral flow pad (LFP),	30 μL	–	10 min	Detection of UA in blood	Hyperuricaemia in gout, UA stones, chronic kidney diseases, cardiovascular diseases, *etc*.	Enzyme-free LFP high convenient, selectivity, sensitivity and stability	[128]
Smartphone based handheld optical biosensor	Urease enzyme	Filter paper based strip	10.4 mg/dL	−0.005 average pixels/sec/ mg/dL	20 s	Detection of urea in saliva	Chronic kidney diseases, heart failure, hypovolemic shock, bleeding in gastrointestinal tract, glomerulonephritis and cardiovascular disease	Cost-effective, sensitive, specific and better reproducibility	[54]
Smartphone-powered photochemical dongle	Creatinase	Enzymatically photochemical test strip	200 μmol/L	–	–	Quantification of creatinine in blood	Chronic kidney diseases	Reliable, accurate, sensitive and specific	[126]

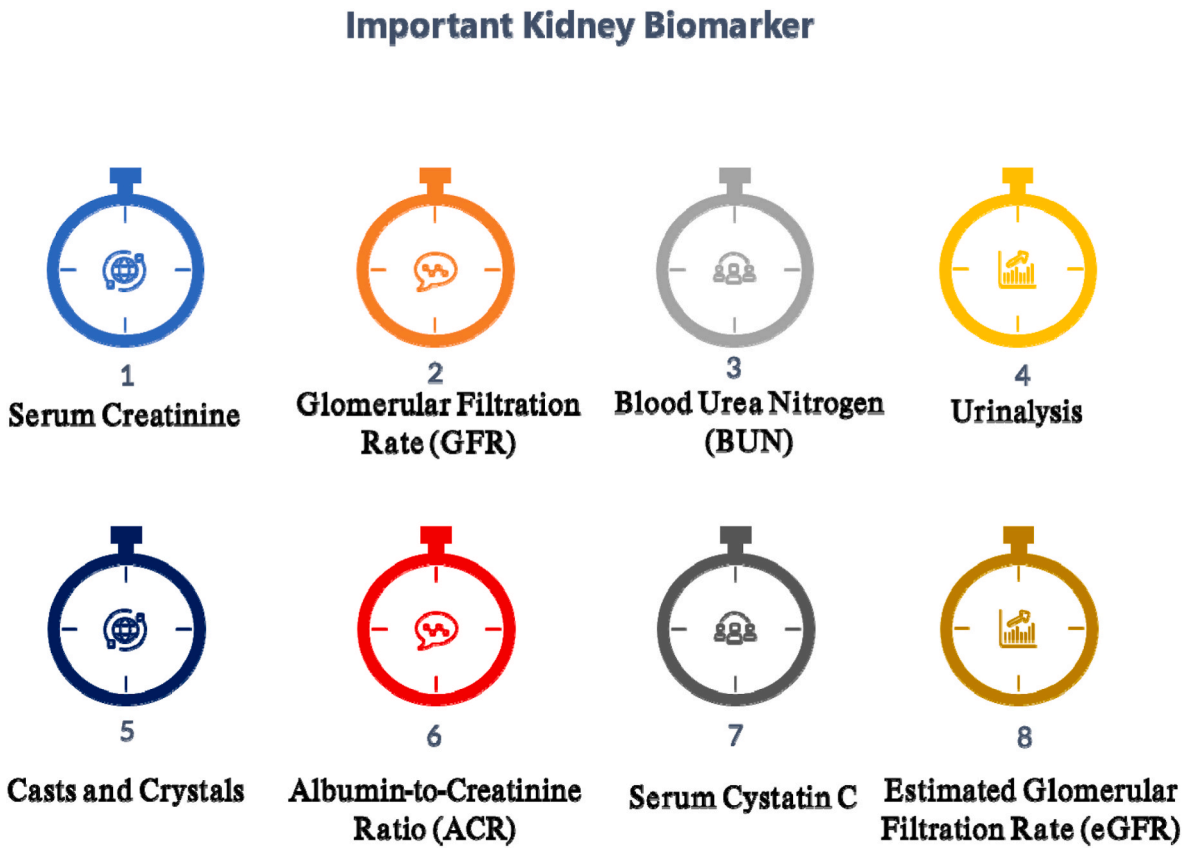

Fig. 11. Some effective biomarkers used for kidney diseases.

requisite to fabricate biosensors based on nanomaterials for the simultaneous investigation of distinct types of kidney biomarkers in clinical samples. Automated investigation of kidney biomarkers in hospitals and pharmaceutical industries is urgently needed. Scientific efforts are also needed in improving the analytical performance, consistency, and simple fabrication procedures of POC devices that can be used at the bedside of patients.

4. Conclusion

In this review article, we have highlighted the significance of biosensing technology for monitoring different kidney biomarkers like UA, Creatine, UA NGAL, KIM, urea, etc. in the real samples. Though, in the literature, researchers have reported distinct types of biosensors in the diagnosis of several kidney related disorders. However, electrochemical biosensors, particularly amperometric and potentiometric biosensors have attracted more attention. This is due to their unique efficiency, facile approach, rapidity, better analytical performance, reliability, and ease in miniaturization. Biosensors have been used for the investigation of kidney biomarkers in different clinical samples like saliva, urine, blood, and sweat samples. Among various kidney biomarkers, the impact of urea in kidney-related ailments has been found to be more profound, as samples for urea can be easily extracted from sweat, urine, and blood. Scientific communities have given more emphasis to the development of miniaturized devices for the investigation of emerging kidney biomarkers because these devices have offered many benefits like on-site patient care, being fast, cost-effective, portable, automated, and having improved sensitivity, specificity, reproducibility, and accuracy. Therefore, future research should be focused on the designing of novel nanomaterials-based biosensing technology for the kidney disease/disorder diagnosis in the acute stage by monitoring the concentration of kidney biomarkers in real samples. This is essential for proper and timely treatment of the patient to avoid the severity of kidney related disorders.

Declaration of AI

Authors are declared that no AI tool is used.

Declaration of competing interest

All the authors of this paper declare no conflict of interest.

Acknowledgement

Dr. Neelam thankfully acknowledges the UGC-Dr. D.S. Kothari Post-Doctoral Fellowship (Ref. No. F.4-2/2006 (BSR)/BL/18–19/0107) for the financial assistance.

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