Biosensors based on ZnO Nanostructures and their role in Health Diagnosis: A Review

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Abstract

Nanosensors are currently gaining immense attraction in industry due to high sensitivity and specificity. In order to detect and measure chemical and physical properties in nanoscale region the sensor and analyte should have maximum surface area of interaction. The large surface to volume ratio offered by nanostructures has increased the search of nanomaterials that are compatible with biological and ecological systems. Unique optical, piezoelectric, semiconducting and electrochemical properties of ZnO makes it a potential candidate to be a multifunctional biological sensing device. Moreover facile fabrication methods, easy availability of precursors, low cost, low temperature processing, no toxicity, biodegradability and biocompatibility has made ZnO nanomaterial a good choice to work on. This paper reviews the current analysis on ZnO biosensors, their types in medical diagnosis, transduction mechanism of detection and future scope of biosensors in medical diagnosis.

Keywords: Nanostructure, Biosensors, Bioreceptors, Analyte, Transduction, Electrochemical, Enzyme, Antibody

1. Introduction

Precise health monitoring and timely medical diagnosis has always been prioritised in medical care industry and so nanotechnology has been explored for our wellness. Nanotechnology have been used to reach out to difficult regions in body at nanoscale to detect the changes in body. Nanosensors is one of the application of nanotechnology, having at least one of the sensing dimensions of the nanosensors less than 100 nm. These sensors allow interaction at a molecule scale thus improving the sensitivity and detection level in 1 count parts per million [1]. Precise and timely detection of diseases, their diagnosis and assimilation of data is important for efficacy in monitoring health. This can be achieved by biological nanosensors (biosensors) by monitoring glucose, cholesterol, uric acid, urea levels in blood serum. It is capable of detecting CO_2 and ethanol vapours in breath and pathogens like bacteria, fungi, virus in air. A biosensor can directly sense these mentioned targets as well as transduce the signal directly into an electrical or optical measurable signal. In some cases, biological components (bioreceptors) like enzymes are integrated to a transducer (ZnO nanostructure) in order to produce an output electronic/optical signal [2]. When this electrical signal is processed (micro controlled), it can be trans received via internet technology to take instant appropriate action for immediate cure. This has paved the way for IoT based wearable diagnostic biosensors. They are going to be new age smart sensing technology in future to provide new healthcare opportunities to patients for detection, treatment and data analytics and instant cure action as shown in Fig 1. Also in this covid era biosensors can have application in environment monitoring to trace the propagation of viruses. This can help in prevention and spread of disease as biosensors have the potential to reveal the early onset of viral infection, inflammation in body and risks for diabetes or kidney malfunction.

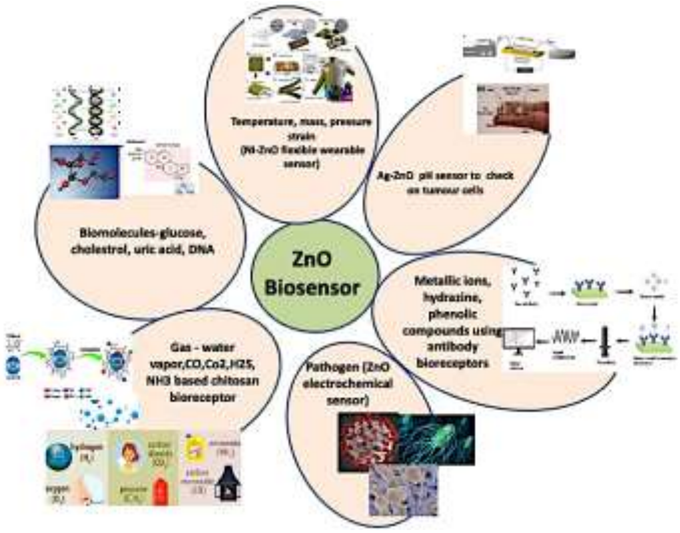

Fig 1. Medical diagnosis and health care with biosensors

2. Working Principle of a Biosensor

Biosensor system has the following components: (a) Analyte (b) Sensor (c) Transducer and (d) Signal processor as shown in Fig 2.

a. Analyte: They are the targets to be sensed. They can be in form of gas, liquid or solid-state and are as follows:
   - Gases like carbon dioxide & water vapours.
   - Biomolecules like glucose, cholesterol, uric acid, hormones, antibiotics, vitamins.
   - Proteins or nucleic acids like enzymes, DNA/RNA, cells.
   - Ions like metallic ions, Halides.
   - Organisms like viruses, bacteria, fungi.

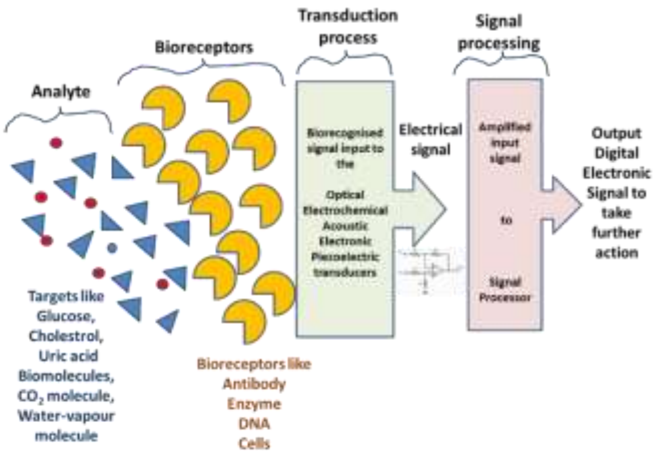

Fig 2. Schematic illustration of components of Biosensors

b. Sensors : They are molecules or elements that recognize the analytes. Here the bioreceptors have high affinity for the specific targets. They act as biorecognising molecules. Bioreceptors bind to the targets, interact and bring biochemical changes. It acts as sensing part of the biosensor and aid in quantifying target.

c. Signal transduction: Transducers are devices that use optical, electrochemical, piezoelectric, pyroelectric, electronic input signals and convert the recognition events into electrical signals. ZnO nanostructures have the unique capability to provide conversion of these input signal into electrical signal. The output signal is amplified for further processing and assimilation of data.

d. Signal processor: Computers are required to process information content in amplified transduced signals into actionable data.

Biosenser works on the principle of biorecognition of elements and signal transduction as shown in Fig. 3. A biological derived material called bioreceptor (like enzyme) is molecular recognition element. It is placed close to the transducer (ZnO nanostructure). The analyte to be tested links to the bioreceptor and induces biochemical changes in it. This change is transduced into electrical signal by the various transduction mechanism mentioned in the block diagram of Fig 4.

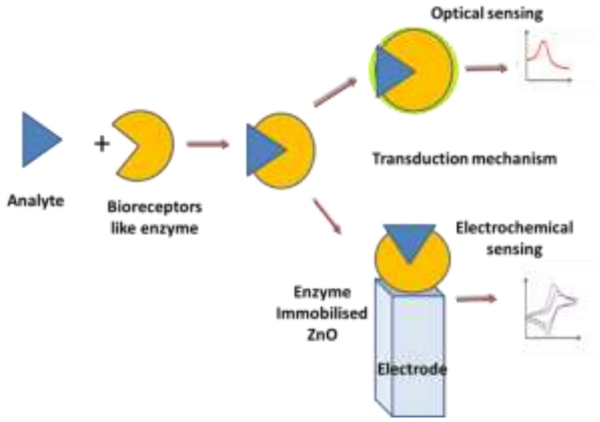

Fig 3. Principle of Biosensors working

3. Classification of Biosensors

ZnO nanostructures can be explored as multi-sensing sensors owing to its vibrant properties. Fig 4 show various types of biosensors classified on the basis of transducing method employed. The unique properties help in transducing signals to measurable and quantifying signals that can be stored and processed using signal processor.

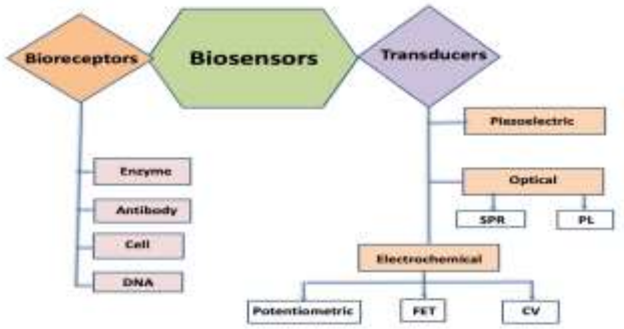

Fig 4. Classification of Biosensors

a. Transducers

Piezoelectric Biosensors: ZnO has unique property of exhibiting piezoelectric behaviour having piezoelectric coefficient around 12.4 pCN^{-1}. ZnO nanostructures act as nanomechanical transducer. The principle of this method is the measurement of the resonance frequency as described by Fumio Narita et al [3] and is shown in Fig. 5. The resonant frequency of ZnO nanostructure changes with and without the bioreceptors. In absence of target the frequency of signal is higher than target bounded bioreceptor on ZnO piezoelectric NPs. There is also decrease in amplitude of signal after binding of target with transducer. The output is plotted and analysed. The variation in frequency and amplitude is linearly proportional to concentration of target. Another advantage of this property is that it is used in self powered wearable biosensing devices required for integrating with IoT and allow ease in miniaturisation [4]. Luo et al [5] developed a lab on chip biodetection system using acoustic wave as a single actuation mechanism for biosensing using piezoelectric ZnO film.

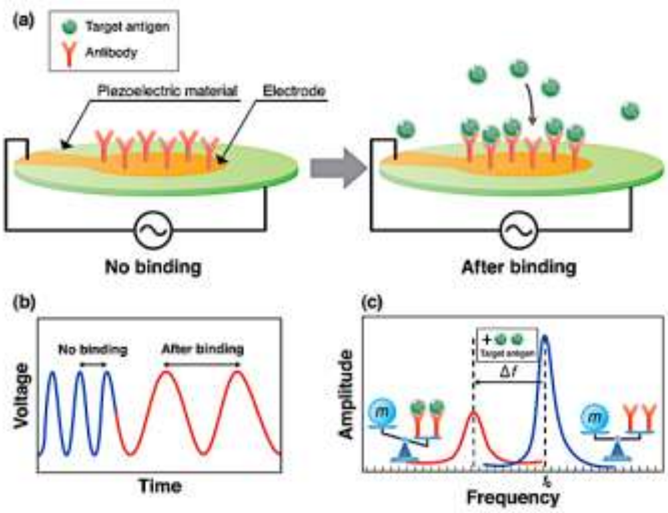

Fig.5 Basic working principle of Piezoelectric Biosensor [3]

Optical Transducer: Optical biosensors consist of biorecognition elements (enzymes, antibodies, aptamers, whole cells) which is amalgated into an ZnO NPs transducer structure. An optical biosensor generates signals, that are in proportion to the analyte's concentration. The process of transduction effectuates a modification in the absorption of the optical biosensor, due to chemical changes initiated by the biorecognition elements as shown in Fig 6. The most common technique used optical-based ZnO NPs biosensors are fluorescence and surface plasmon resonance. These methods are quiet expensive and take lot of time. However they are most selective and sensitive to targets. The main advantage is that it allows contactless measurement with the sample. The optical biosensor is estimated to witness a CAGR of 6.9% till 2030 [6]. Photoluminescence technique is also used as it is simpler but is less selective to targets. As shown in Fig 6. surface of biosensor is exposed to optical signal from the source. The light interaction brings changes in functionalised transducers and photoluminescence at 390nm in uv region is exhibited . The change in intensity with comparison to unfunctionalised ZnO NPs is plotted and analysed. The output signal linearly varies with analyte concentration. Rodrigues et al. [7] discussed that ZnO nanostructures is a transducer element and can be used as PL-based biosensors.

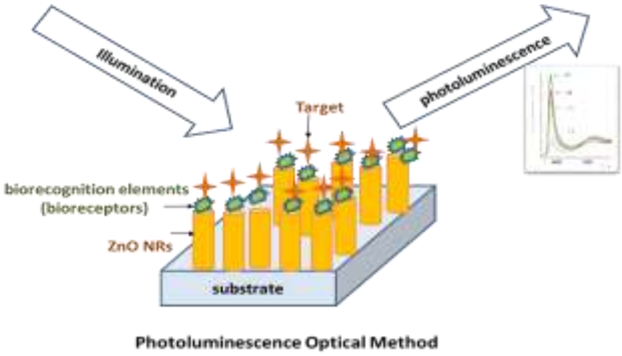

Fig. 6 Schematic illustration of Optical transduction technique

Electrochemical transducer are based on electrical conduction through the electrodes dipped in the solution. There is a working electrode which is ZnO nanostructure transducer. The bioreceptors (enzyme, antibody, cell or DNA) are placed in close proximity to ZnO nanostructures. This is called functionalized ZnO biosensor which then develops affinity to the analyte. When analyte links to bioreceptor, physical and chemical changes occur at the working electrode and as a result electrode develops potential. The potential difference between the reference and the working electrodes is measured. The output electrical signal is amplified and processed further. The electrochemical sensors produce electrical signal proportional to the analyte concentration. They are based on generating electrical signals by detecting changes occurring at ZnO electrode's surface due to redox reaction. Based on the analyte and transducer there is exchange of electrons between the electrode and a solution. Analytes like glucose, cholesterol, uric acid, dopamine, L-cysteine, can all be discriminated with ZnO-based electrochemical biosensors. The electrochemical biosensors delivers benefits such as low cost, rapidity, high sensitivity, simplicity, wide range and good selectivity. Thus electrochemical biosensor accounts for the largest market revenue 55.9% in 2021 and dominates, owing to its sensitivity, reproducibility, and ease of maintenance [6]. Though there is always a scope and work to overcome its limitation of relatively shorter lifetime, difficulty in revealing failure mode. Cyclic voltammetry and potentiometry are two common methods used in electrochemical technique [8] as shown in Fig 7.

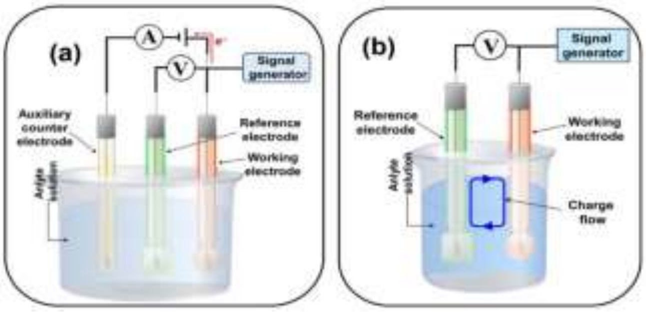

Fig. 7 a) Cyclicvoltameric/Amperiometric b) Potentiometric technique [8]

In Cyclic Voltammetry, applied potential is varied across the electrodes to detect the analyte and current is measured at output. They offer high sensitivity and allow simultaneous detection of multiple analytes. ChOx (cholesterol oxidase) was placed on the ZnO thin films to produce cholesterol sensor by Singh et al. [9]. ChOx/ZnO/Au bioelectrode of sensor detected cholesterol in 25–400 mg/dl range using cyclic voltametric (CV) transduction measurement.

In Potentiometric method ZnO nanostructures are used as nano electrode and another metallic electrode is used as reference. Potential at the ZnO nanoelectrode is developed due to analyte chemical interaction with target. Potentiometric biosensors measure the voltage across the electrodes due to analyte and bioreceptor interaction.

FET biosensors: ZnO nanomaterials are being employed to produce ultrasensitive, miniaturised FET biosensors by allowing lab on chip integration of both sensor and measurement systems. The advantage of FET based transducer is that they produce amplified signal based on interaction between the analyte and FET surface resulting in high sensitivity. FET consists of Drain and Source made of highly conducting Gold metal. The active channel made of ZnO NRs layer is deposited on the Si/SiO_2 semiconductor substrate and is functionalized with bioreceptors. Such bioreceptors capture the required analyte. This activity of binding is called conjugation. This results in charge production and causes gating effect on the semiconductor. The gating effect produces electric field and the current between source and drain. Greater the current produced , higher will be the response of the FET and higher will be its sensitivity. The change in current due to biomolecule conjugation is measured and provided as the sensitivity. FET based ZnO NRs glucose sensor was fabricated by Zhu et al [10] exhibiting high performance. The ZnO NRs were fabricated hydrothermally.

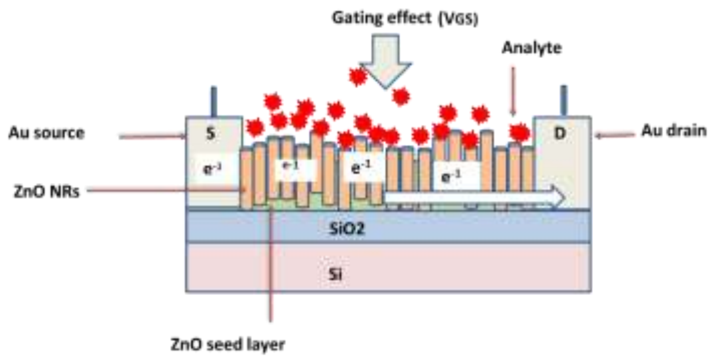

Fig.8 Schematic of FET based ZnO NRs biosensor

The sensitivity produced by sensor is 1.6 $mA\mu M^{-1}cm^{2}$ with a detection limit of 1.0 µM glucose concentration. As shown in Fig. 8 the ZnO-FET biosensor, channel of ZnO nanorods are grown on Si/SiO2 substrate [11]. Bioreceptors are placed on top of the ZnO nanorods. There is change in conductance of the channel when the analyte interacts with the bioreceptors which is called gating effect. The free electrons gets path to move from Ag metal source electrode to the drain electrode via channel to produce drain current. This brings FET into conduction state. This structure offers reduction in size, cost and complexity. They offer high sensitivity as they generate high signal for very low analyte concentration. The response time exhibited is also very low, in ms. Their main advantage is that they are portable and compatible for allowing integration on-chip. Though there is much scope of improvement in signal to noise ratio and lowering the detection limit to bring these devices in industry.

b. Bioreceptors

Enzyme bioreceptor: Enzymes are proteins which catalyse specific reactions. It acts as recognising element for the biological analyte. It is binded on to the surface of transducer. Enzyme based biosensor work by recognising the analyte by sensing the changes in proton concentration (H^+) or change in heat absorption/release or even light emission/absorption. Advantages of the enzymatic biosensors are that it allows continuous real-time monitoring and also offers high catalytic activity, high specificity and low response time.

Protein bioreceptor: Diphenylalanine (FF) peptide is used as biomolecule recognizing element. It is placed closed to the ZnO nanostructure transducers. It has affinity to trypsin. Trypsin is an enzyme used in digestion process. Levels of trypsin in urine can be measured by biosensors. In order to detect trypsin, diphenylalanine (FF) peptide is immobilized ZnO nanoparticle surface. The trypsin weakens the bond of peptide-bounded ZnO. This results into change in PL spectra ZnO. Nandini Swaminathan et al [12] performed the detection measurements using FF-ZnO hybrid nanostructure.

Aptamers Bioreceptors: These are artificial nucleic acid sequences of DNA or RNA. They can be synthetically produced as single-stranded nucleic acids which can be used to recognise the target molecules and interact with them. They can be easily produced and have longer shelf life. They play important role in medical diagnosis by detecting thrombin, coagulation factor. Thrombin converts fibrinogen to fibrin, which forms a clot in combination with platelets. Aptamers are also used in detecting riboflavin. Aptamers are the next generation bio-receptors in lieu of antibodies as they can bind to the target more specifically.

4. ZnO Based Biosensor Applications in Monitoring Health

Medical diagnosis involves rigorous series of sample testing and analysis. Traditional employed testing methods in centralized clinical laboratories have expensive equipment. They are required for sample processing and analysis in localised firms and centres. Trained laboratory personnel are required and large measuring time makes it costly and a time burden on patients . With advent of bio sensors in health care medical diagnosis has become easy and convenient. It offers inexpensive and easy-to-use devices in regions which are difficult to reach for testing, for clinical use or environment. As ZnO have high ionic strength and pH stability [13], they can be utilized with biological fluids. Bioreceptors like enzymes, nucleic acids, antibodies are immobilized on to surface of transducer (ZnO). Bioreceptors are sensitive to glucose, uric acid, cholestrol, gases, pathognes and thus are indispensable in diagnosis. This is called immobilization of bioreceptor on to the surface of transducer. The transduction material play important role in biosensor and has to be selected and designed for biosensor devices.

Popular Biosensors

a. Sugar Monitoring: One in ten persons suffers from diabetes mellitus. Statistics in Fig.9 shows that in 2021 the global glucose biosensor market had revenue of US$10.20 billion and is expected to reach US$ 20.1 billion by 2030. The demand for simple, stress-free, and time-saving tests have driven the

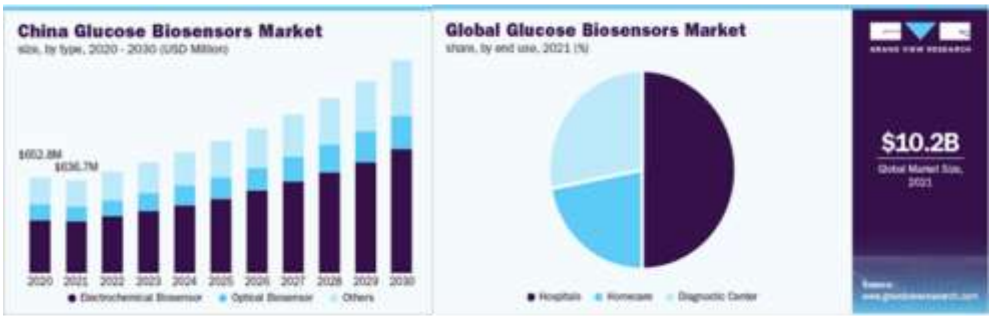

Fig. 9 Projected global glucose biosensor market growth from 2020-2030 [6]

market for glucose biosensors to new heights. It allows real time monitoring and helps in taking correct cures. Early diagnosis and correct cures and medication will help in maintaining healthy body. Measurement of blood glucose level on real time basis in controlling of diabetes mellitus can be done by glucose biosensors, using glucose oxidase (GOx) as the enzyme. Fig.10 shows glucose biosensor fabricated by using glucose oxidase on to the ZnO nanostructures Enzyme Glucose oxidase (GOx) offers strong affinity to glucose molecule[14].

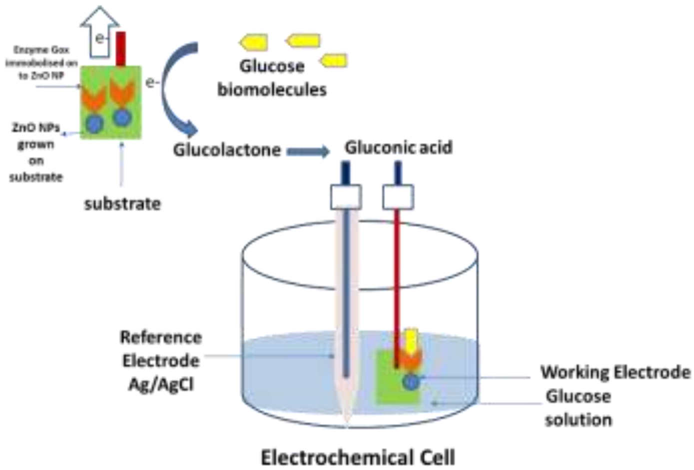

Fig. 10 Schematic diagram for measuring glucose by ZnO:GOx biosensor

It offers short response time of around 10s. At the working electrode GOx chemically interacts with glucose molecule to form gluconic acid and hydrogen peroxide (H_2O_2) as a byproduct. H_2O_2 breaks into H_2O and $2e^{-1}$. The free electrons are produced that participate in conduction.

$$\text{Glucose} + O_2 + H_2O \xrightarrow[\text{Glucose Oxidase}]{GOx} \text{Gluconic acid} + H_2O_2$$

As a result current is produced from hydrogen peroxide oxidation which is proportional to glucose concentration. Apart from blood, glucose is present in sweat too. The new technology advancement has led to self-powered non-invasive wearable piezo-biosensing unit matrix of enzyme/ZnO nanoarrays [15]. It provides sweat analysis on real time basis. The electronic-skin can detect urea, uric acid and glucose in the sweat. This biosensing process needs no battery. It provides continuous monitoring of the athlete while running. The biosensor analyses the sweat present on the skin. Data can be collected and assessed online too via internet technology. This is mark of new age devices which are part of internet of medical things.

b. **Cholesterol Monitoring:** Due to fast food eating habits and sedentary lifestyle there have been surge of high cholesterol cases in young people. If left uncontrolled it can lead to severe diseases hypertension, myocardial infarction, and arteriosclerosis and can be life threatening. So to keep a regular check of cholesterol, biosensors have been developed for fast measurement. Singh et al. [9] fabricated cholesterol sensor using ChOx (cholesterol oxidase) and ZnO thin films. Cyclic voltametric (CV) transduction measurement with ChOx/ZnO/Au bioelectrode detected cholesterol in 25–400 mg/dl range. Umar et al. fabricated ChOx -ZnO NPs biosensor. Electrochemical technique was used to detect the cholesterol. The linear range reported was 1–500.0 nM and a limit of detection was reported to be 0.37 - 0.02 nM. Khan et al. [16] fabricated nano ZnO–CHIT hybrid nanocomposite film on substrate of ITO glass. The ZnO NPs were uniformly spread in CHIT. The film was functionalised with ChOx. LOD of 5mg/dl and device linearity range 5–300mg/dl was declared. Recently Ahmad et al.[17] reported high performance biosensor based on ZnO nanotubes developed on Si/Ag electrodes. The fabricated cholesterol biosensors exhibited high sensitivity of 79.40 $\mu A/mM/cm^2$, wide linear range 1.0 μM to 13.0 mM, small response time of ~ 2 s and very low detection limit of 0.5 nM.

c. **Uric acid monitoring:** The kidney and intestinal tract excrete unwanted uric acid. In case of malfunction of kidney there is abnormal level of uric acid in body. This can cause hypertension, cardiovascular diseases, neurological disorders, arthritis and insulin resistance. Uric acid needs to be monitored in patients in real time basis for instant cure and correct medication. Here we present few glimpse of ZnO based uric acid biosensors. Ahmad et al. [18] fabricated uric acid biosensor. The ZnO nanorods immobilised the Uricase enzyme. LOD of 5 nM and wide-linear range of 0.01–4.56 mM has been documented. RGO/ZnO nanorod composite was fabricated by Fu et al. [19]. They reported LOD of 0.312 μM and linear detection was in range 1 to 800 μM.

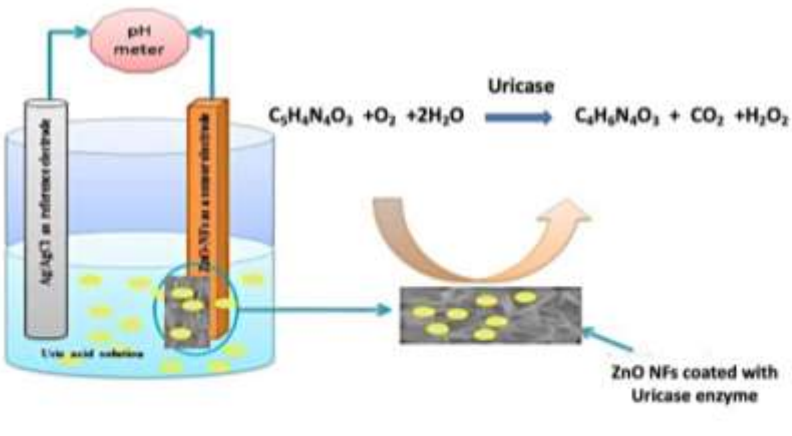

Fig 11 Schematic diagram for measuring uric acid by ZnO:Uricase biosensor [20]

Fig. 11 shows uric acid biosensor produced from ZnO nanoflakes by Ali et al. [20]. Uricase enzyme and Nafion is poured on ZnO NFs. The Uricase enzyme interacts with Uric acid and oxidizes it to allantoin ($C_4H_6N_4O_3$), hydrogen peroxide and carbon dioxide. 2D ZnO nanoflakes or nanosheets have larger surface area in comparison to 1D nanostructures, resulting in more enzyme sitting area on it and thus allowing more electron generation and their transport at the electrode and bioreceptor contact. Nanoporous ZnO films were fabricated by Mozaffari et al. using RF magnetron sputtering method [21]. Due to nanoporous structure there are cavities inside the film. This enlarges the surface area for the enzyme to get loaded on it. As a result the enzyme get strongly bound to films and allows sensors to proffer reasonably high sensitivity. Having wide linear detection range of 0.83 to 23.24 mM and a limit of detection of about 0.40 mM. Zhang et al . fabricated uric acid biosensors [22]. ZnO NRs were grown on carbon electrodes. The ZnO nanorods surface area aids quick transfer of the electron to the electrode due to interaction between uricase and uric acid. The electrochemical transduction measurements displayed a response that is linear for the concentration range 5μ to 1m mol L^{-1} with a LOD of 2μmol L^{-1}. Latest development in biosensor is generation of amplified signal from the FET transduction technique. Liu et al. fabricated bio-FET device using single ZnO nanowire [23]. Two hydrogen atoms are produced when uric acid reacts with uricase and that changes the surface potential and results in the conductance of the biosensor. The sensor displayed ultralow detection limit of 1 pM. This makes the device of superb performance. Also linearity for detection was wide from 1 pM to 0.5 mM concentration of uric acid. The advantage of FET based sensor was that it exhibited shorter response time in ms than other uric acid biosensor. Recently flexible self-powered implantable electronic skin was fabricated by Yang et al. for uric acid detection. Here uricase enzyme is immobilized on ZnO NWs [24-26]. It is based on piezo-enzymatic reaction on ZnO nanowire. The piezoelectric output impulse depends on analyte concentration. The biosensor do not require external electric supply. It is useful for in situ body fluids-analysis for patients suffering from chronic diseases. They show good electronic compatibility, flexibility and have high sensitivity, selectivity and are cost effective. However there are few challenges like skin irritability, repeatability, fresh sample requirement.

All the above-described glucose, cholesterol and uric acid biosensors based on ZnO nanostructures functionalized with bioreceptors have been summarized in the given Table 1 showing their linearity range and limit of detection (LOD).

ZnO nanostructure	**Analyte**	**Bioreceptor**	**Tranducing technique**	**Linear range**	**LOD**	**Ref**
ZnO nanocombs	Glucose	GOx	Amperometric	0.1-5mM	0.02 mM	[27]
ZnO nanonails	Glucose	GOx	Electrochemical	0.1-7.1mM	5 µM	[28]
ZnO hollow nanospheres	Glucose	GOx	Potentiometric	$5.0*10^{-3}$ –13.15 mM	1.0 µM.	[29]
ZnO nanostructures	Glucose	GOx	PL	10mM- 130 mM	10 mM	[30]
ZnOnanorod/Auhybrid nanocomposites	Glucose	GOx	Amperometic	0.1–33.0 µM	10 nM	[31]

ZnO modified gold disc	Glucose	GOx	SPR	50–250μ g/ml	-	[32]
NiO doped ZnO	Glucose	GOx	Amperometic	0.5–8 mM	2.50 μM	[33]
ZnO nanowire	Glucose	GOx	Electrochemical	1.0mM–0.76 mM	0.7 mM	[34]
graphite nanosheets and ZnO NPs	Glucose	GOx	Electrochemical	0.3–4.5 mM	0.07 mM	[35]
ZnO quantum dots	Uric acid	Uricase	Electrochemical	1 to 10 mM	4mM	[36]
ZnO nanowire-based FET	Uric acid	Uricase	FET	1 pM to 0.5 mM.	-	[37]
ZnO nanorods	Uric acid	Uricase	Amperometric	$5.0\times10^{-6}$to 1.0×10^{-3} mol L^{-1}	2.0×10^{-6} mol L^{-1}	[38]
ZnO nanosheets	Uric acid	Uricase	Electrochemical	0.5 μM to 1500 μM	0.5 μM	[39]
Nanofilm	Uric acid	Uricase	Potentiometric	2 mg/dl to 10 mg/dl	7.14 μM	[40]
ZnO nanorods	Uric acid	Uricase	Electrochemical	0.01–4.56 mM	5 nM	[41]
ZnO nanorods	Cholestrol	ChOx	Potentiometric	10−6 M to 10−2 M	-	[42]
Au/ZnO/MWCNTs Biosensor	Cholestrol	ChOx	Electrochemical	0.1-100 μM	0.1 μM	[43]
ZnO thin films/ Au	Cholestrol	ChOx	Cyclic voltammetric	25–400 mg/ dl	2.1mM	[44]
ZnO thin films/ ITO	Cholestrol	ChOx	Electrochemical	5–400 mg/dl	0.5 mg/dl	[45]
ZnO/Au/prism [100]	Cholestrol	ChOx	SPR	0.12-10.23 mM	-	[46]

Table 1. Various glucose, cholesterol and uric acid biosensors based on ZnO nanostructures using different transduction technique

5. Conclusion

ZnO nanostructures have semiconducting properties as well as potential biosensing capability. This can be utilised in fabricating smaller, faster, cost effective devices which are compatible with semiconductor technology for biomedical field. It can be achieved by integration of sensing technology nanostructures with biomolecules. Thus ZnO based nanomaterials NDs, NWs, NRs having brilliant characteristics of semiconducting, optical, piezoelectric, catalytic, physio-chemical are a good choice to be employed as nano biosensors. Glucose is well established biosensors in the medical diagnostic industry. Lab on chip micro detection system based on ZnO will bring a revolution in medical diagnostic, treating diseases and promoting good health by offering high sensitivity, low cost and miniaturization. Selfpowered, wearable diagnostic biosensors have been fabricated to detect various illnesses like diabetes, heart diseases. They are based on piezoelectric property of ZnO. Immense scope of research work exist in bringing these devices to market. There is demand of more multifunctional wearable biosensors for real time montoring and continuous research and innovations are required in fabrication of these devices.

ZnO nanostructures immense potential in fabricating ZnO based biosensors is reviewed. The principle and mechanism of biosensors in health diagnostics and good human health is elaborated. We have reviewed types of biosensors, their mechanism of operation based on receptors and transduction process. The research progress of glucose, cholesterol and uric acid has been studied and it is found that glucose-ZnO based biosensors have been commercially most extensively used. It exhibited high sensitivity and responsivity, owing to its semiconducting properties via FET based biosensing technique. Non-invasive method for uric acid and glucose detection from sweat samples using wearable biosensors has been introduced in the industry. More research is required to improve the repeatability and sensitivity of these biosensors. Harnessing piezoelectric property of ZnO, will allow self-powered wearable, cost effective, miniature, real time monitoring biosensor and will open door for more devices to be innovated and explored for medical diagnostics.

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