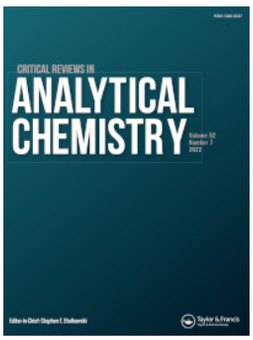

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A Comprehensive Review on Biopolymer Mediated Nanomaterial Composites and Their Applications in Electrochemical Sensors

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ABSTRACT

Biopolymers are an attractive green alternative to conventional polymers, owing to their excellent biocompatibility and biodegradability. However, their amorphous and nonconductive nature limits their potential as active biosensor material/substrate. To enhance their bio-analytical performance, biopolymers are combined with conductive materials to improve their physical and chemical characteristics. We review the main advances in the field of electrochemical biosensors, specifically the structure, approach, and application of biopolymers, as well as their conjugation with conductive nanoparticles, polymers and metal oxides in green-based noninvasive analytical biosensors. In addition, we reviewed signal measurement, substrate bio-functionality, biochemical reaction, sensitivity, and limit of detection (LOD) of different biopolymers on various transducers. To date, pectin biopolymer, when conjugated with either gold nanoparticles, polypyrrole, reduced graphene oxide, or multiwall carbon nanotubes forming nanocomposites on glass carbon electrode transducer, tends to give the best LOD, highest sensitivity and can detect multiple analytes/targets. This review will spur new possibilities for the use of biosensors for medical diagnostic tests.

KEYWORDS

Biopolymers; high-performance detection; nanosensors; sensing elements

Introduction

Electrochemical biosensors are simple devices that transform biochemical information produced from a redox reaction into an electrical signal.[1] They play an important role in detecting biomarkers and monitoring environmental pollutants by detecting various bio-analytes and compounds. Their ease of use, simplicity, high sensitivity, portability, low-cost, rapid response, and eco-friendliness have led to their widespread adoption.[2,3] The performance of biosensors depends on three main components, namely a bioreceptor, a transducer, and a signal processing system. A bioreceptor comprises of an immobilized biocomponent that can detect a specific analyte. Examples of biocomponents include antibodies, nucleic acids, enzymes, cells and biomarkers. The interaction between a bioreceptor and an analyte result in chemical changes such as the synthesis of a new chemical, heat release, electrons flow, and change in pH and mass. A transducer or a converter converts the biochemical changes due to the interaction between the analyte and the bioreceptor into an electrical signal. The electrical signal is subsequently amplified and processed as a digital display, a print-out, or as an optical change. The layering of probe material on a transducer increases the strength of the response signal in terms of its current, potential, or impedance. The greater the stacking, the higher the signal strength. Various electrochemical measurable techniques such as electrochemical impedance spectroscopy (EIS), differential pulse voltammetry (DPV), linear sweep voltammetry (LSV), cyclic voltammetry (CV), anodic stripping voltammetry (ASV), differential pulse stripping voltammetry (DPSV), differential pulse anodic stripping voltammetry (DPSAV), square wave anodic stripping voltammetry (SWASV) and square wave voltammetry (SWV) have been used to measure the interaction between analyte and target. When an analyte/target and electrode interact, there is a measurable change in current and potential of a biosensor, depending on the target/analyte concentration on the sensing surface of the electrode.

There are three types of electrodes used in electrochemical sensing, a working electrode, a counter or auxiliary electrode, and a reference electrode.[4] For reliable measurement, the stability of these electrodes is crucial, especially in terms of conductivity and chemical composition. The working or sensing electrode acts as a transducer

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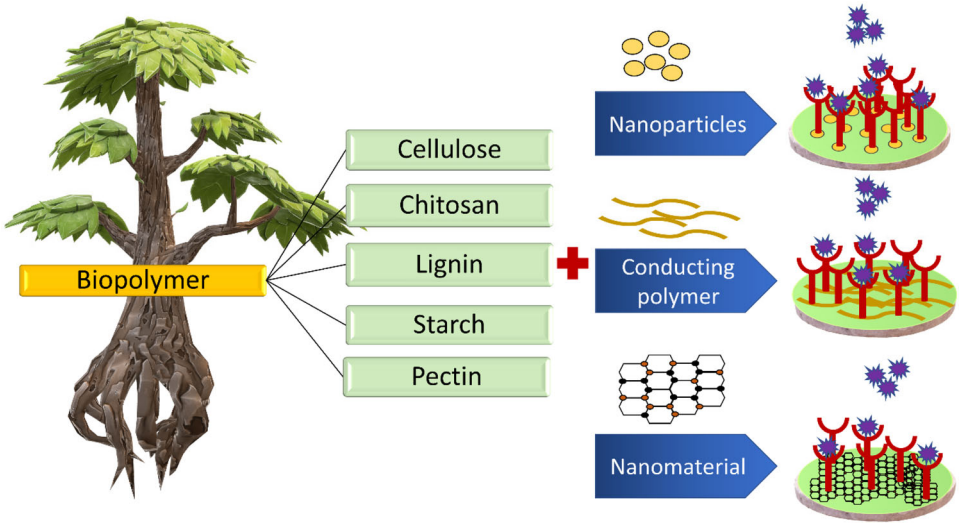

Figure 1. Schematic illustration of biopolymer conjugate with nanoparticles, conducting polymer, and nanomaterial in electrochemical sensors.

during the interaction of the bioreceptor and analyte/target, while the counter electrode measures the current flow to and from the sensing electrode and forms a connection path between the electrode surface and electrolyte solution. The reference electrode, commonly silver chloride, provides a stable potential when placed at a constant distance from the working electrode.[5] Electrochemical biosensors that function using a liquid medium are generally classified based on the type of measurement, as well as depending on the type of transducer (electrode) used, such as amperometric (current), potentiometric (potential), impedimetric (impedance) and conductometric (modifying conductive properties of a medium).[6–9]

Chemical modification of these electrodes can enhance its electrochemical sensing properties. The electrodes are usually modified with toxic non-biodegradable active materials such as carbon-derivatives and synthetic polymers. Recently, biopolymers have emerged as a promising environmentally friendly alternative to synthetic polymers as a polymer host in electrolytes. Biopolymers are polymers that are derived from living matter and can be grouped into three types, namely natural, synthetic, and microbial. Natural biopolymers are macromolecules that are extracted from natural sources, while synthetic biopolymers are derived from biological precursor materials, whereas microbial biopolymers are produced by organisms such as algae, bacteria, and fungi from carbon.[10] Common natural biopolymers are polysaccharides, polyester, and protein, which are found in plants and animals and are composed of numerous amino acids and nucleotides that form a large structure from linear chains that are bonded covalently.

Biopolymers are environmentally friendly, biocompatible, biodegradable, flexible, inexpensive, and form easily. Owing to their abundance and diverse structures, biopolymers have been extensively used in biomedical,[11] supercapacitors,[12] biosensors,[13] drug delivery, tissue engineering, and environment monitoring[14] applications. The most widely used biopolymers are polysaccharides such as cellulose, chitosan, lignin, starch, and pectin, as these biopolymers can be easily modified and functionalized owing to their diverse chemical composition, numerous reactive sites, and remarkable structural features.[15,16] The main functions of biopolymers in electrochemical sensors are for biochemical modification, to induce bio-functionality, conductivity, and biochemical reaction. However, biopolymers have poor solubility, high thermal degradability, high chemical degradability, and poor mechanical properties. Nevertheless, these limitations can be mitigated with conductive additives such as nanoparticles, conducting polymers, and metal oxides. These combinations are mostly environment friendly as compared with the non-biopolymer alternatives such as graphene or graphene oxide, which require lengthy processing time and hazardous chemicals.

The solubility properties of biopolymers are based on the strength of hydrogen bonds in intramolecular or intermolecular interactions. Generally, weak hydrogen bond interactions with amino groups facilitate the dissolution of biopolymers in common organic and diluted aqueous solvents. The existence of amino groups affects the pH of the solvent, changing the charge state and accountabilities of biopolymers. The ease of dissolving biopolymers in ordinary solvents makes its processing and chemical modification feasible. The biodegradability and solubility of biopolymers are principally attributed to their vulnerability to biomolecules such as enzymes, proteins, and body tissues. Therefore, modification of biopolymers with both inorganic and organic materials is required. For example, the electrical conduction of a biopolymer can be further enhanced with conductive materials and modifying its hydroxyl, carboxyl, and amino groups.[17–19] These modified biopolymer composites acquire useful properties from the added material while retaining the advantages of the biopolymers.[20] As for sensing applications, the immobilizing properties in biopolymers and their compatibility with bodily fluids make biopolymers an ideal biosensor candidate.

There is a growing interest in conjugating biopolymers such as cellulose, chitosan, lignin, starch, and pectin with supporting materials such as nanoparticles, conducting polymers, and metals for electrochemical sensors (Figure 1). To the best of our knowledge, there is no comparative study yet

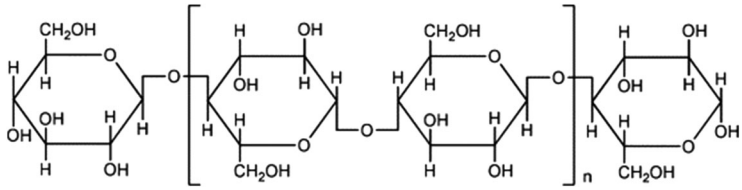

Figure 2. (a) Repeating unit of cellulose, (b) the crystalline and amorphous regions of cellulose chains. Reproduced with permission from Ref. [23]. Copyright 2015, Elsevier.

reported on biopolymers such as cellulose, chitosan, lignin, starch, and pectin composites in terms of signal measurement, substrate bio-functionality, biochemical reaction, sensitivity, and limit of detection. In this review, the applicability of biopolymers as a stabilizer and a reducing agent is reviewed, with emphasis on the synthesis, structure, and physical development of biosensors. Pectin biopolymer, when combined with gold nanoparticles, polypyrrole, reduced graphene oxide or multiwall carbon nanotubes on a glass carbon electrode transducer, tends to give the best limit of detection (LOD), highest sensitivity, and can detect multiple analytes/targets compared to other biopolymers considered. This review also summarizes the various types of biopolymer composites available and their applicability for medical diagnostic tests.

Biopolymer synthesis, structure, and physical properties

Biopolymers such as cellulose, chitosan, lignin, starch, and pectin have different chemical and physical properties, as well as structures. The oxygen-rich polysaccharide of cellulose and starch provides good mechanical strength and acts as a reducing agent, whereas chitosan, with its dual-skeleton structure, can maintain its original features even after alteration to its structure. Lignin is the only biopolymer that can form a polyaromatic structure via an acetylation process. Pectin, made of a sugar compound, has biodegradable stabilizer properties that can easily capture covalently bonded biomaterials. These biopolymers have unique properties, such as crystallization, high toughness, oxygen permeability, carbon content, and being a reducing and stabilizing agent. A detail description of these biopolymers is given below.

Cellulose

Cellulose is an abundant biopolymer and one of the most popular polysaccharides used in biosensors. It is an oxygen-rich polysaccharide composed of an anhydroglucose unit bonded by an oxygen linkage.[21] Cellulose is generally synthesized by plants, but it is also formed through bacterial interactions.[22] It is tough and fibrous, important in preventing plant cell walls from collapsing. Cellulose has the highest strength of all biopolymers, due to its chains that are organized in fibrils, which enables the formation of a bundle of polysaccharides cell wall. It has both a crystalline and an amorphous nature, as shown in Figure 2, which can be observed from its carbon atoms compositions. However, due to its poor electrical conductivity and extreme hydrophilicity, cellulose utilization in biosensor development is limited. Hence, the cellulose structure must be modified chemically and physically.

Cellulose can be modified to form porous surface cellulose nanofibers (CNFs), high absorption capacity cellulose nanocrystals (CNCs), and conductive carboxymethyl cellulose (CMC). CNFs are made of β-1,4 linked anhydro-D-Glucose unit and are excellent for biosensing applications, as it has a large surface area, porous structure, and abundant hydroxyl groups, which act as binding sites for analyte biomarkers. CNFs can be electrospun to maintain a width of 5 to 20 μm.[24] The porous surface of CNFs can be tailored by controlling parameters such as precursor ratio, voltage, solution viscosity, rotational drum speed, relative humidity, and distance between needle and drum during electrospinning. Acid hydrolysis is used to convert crystalline cellulose to CNCs. Hydrolyzed CNCs are non-cytotoxic, resistant to oxidative stress, highly biocompatible, and extensively used in biomedical industries and electronic applications.[25] Additionally, CNCs have a large aspect ratio, good mechanical properties, low thermal-expansion, and high biomolecule absorption capacity. CNCs can be easily modified through hydrolysis and oxidation to form carboxylated CNCs, which are rich in carboxyl and hydroxyl groups that bind nanoparticles firmly, owing to their strong ability to adsorb nanoparticles. Furthermore, both CNFs and CNCs have excellent polymer composite stability in water, owing to the electron rich properties of hydroxyl and sulfate ester groups on their surface. On the other hand, CMCs are composed of carboxymethyl groups ($-CH_2COO^-Na^+$) that are bound to the cellulose backbone that exchanges its sodium ions with various metal ions. It also has numerous -COOH and -OH functional groups in its polymer structure, which gives it hydrophilic properties and forms coordination bonds with metal ions. The conductivity of CMC as a polyelectrolyte makes it ideal for the detection of heavy metal ions.[26] All these nano-cellulosic materials, which are negatively charged, react with positively charged materials to form electrostatic interactions that enhance the mechanical properties and dispersibility of the biomaterials, which in turn improves the selectivity of biosensors.[27,28]

Chitosan

Chitosan is a biopolymer that forms via the deacetylation of chitin and has both an exoskeleton and endoskeleton structure.[29] Chitosan comprises linear polysaccharide chains consisting of D-glucosamine and N-acetyl-D-glucosamine bonded by glycosidic,[30,31] as shown in Figure 3. The

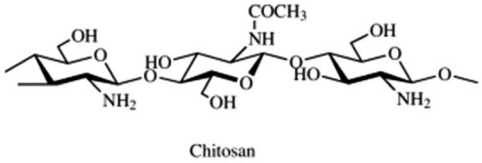

Figure 3. Structure of chitosan constituting co-polymer of glucosamine and acetyl-glucosamine. Reproduced with permission from Ref. [32]. Copyrights 2012, Elsevier.

structures of chitin and chitosan are markedly different, as observed by the acetamide and amine structures in chitin and chitosan respectively. The free amine groups in chitosan are active sites for chemical reactions, which is especially useful in modifying chitosan into composites. The amine group in chitosan is the reason for its widespread use in various applications such as the food industry, biomedical, biosensors, waste water treatment, and environmental monitoring.[33] The properties of chitosan depend on the degree of deacetylation (DDA) and molar mass.[34] Chitosan has an average DDA of 80%, whereas chitin has an average DDA below 50%. Chitosan can be categorized as chitosan I with low DDA and chitosan II with high DDA. The functionality of chitosan is mostly dependent on the pH of the solution. High DDA (>50%) enables chitosan to be dissolved in diluted acidic solutions. The amines in chitosan become positively charged between a pH of 3 and 4, but remain insoluble, as it is unable to attract hydrogen atoms from the solution to form a positively charged amine group.[35] The protonated amine group in acid solution attracts chitosan, which reacts with negatively charged biomolecules or structures. The glycosidic bond in chitosan is a type of covalent bond that joins a carbohydrate molecule to another functional group. The glycosidic bond in chitosan helps in the formation of chitosan film or membranes, which is an excellent biosensor surface immobilization matrix.[36] Structural or physical alteration of chitosan chemically does not change its original properties. It can retain it's nontoxic, biodegradable, biocompatible, and minimal immunogenic properties while reacting with additive organic/inorganic material because of the presence of hydroxyl and amine groups.[37] It can be re-shaped and re-sized into sol-gels, nanofibers, and nanoparticles. Since it is nonconductive, its electrical properties have to be enhanced by the addition of conductive material such as gold nanoparticles,[38] conducting polymer such as polypyrrole[39] and polyaniline,[40] as well as metal oxide such as manganese (IV) oxide.[41]

Lignin

Lignin is the second most abundant biopolymer after cellulose that can be extracted from wood, paper, and pulp. In lignocellulose, lignin is responsible for binding cellulose and hemicellulose. Lignocellulosic plants and animals (crustaceans) derived biomass is made up of 40–50% cellulose, hemicellulose composed of 15–30% polysaccharides, and aromatic polymer consisting of N-acetyl polysaccharides.[42] The strong hydrophobicity of lignin present in the secondary cell wall of lignocellulosic plants keeps the plant from

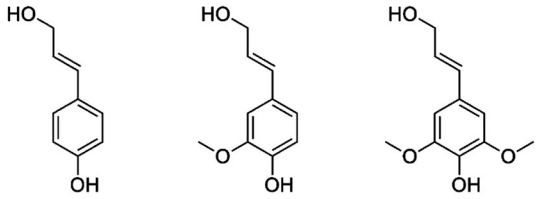

Figure 4. The three monolignols, the building block of lignin. Reprinted with permission from [44]. Copyright 2010, American Chemical Society.

collapsing and decaying, as lignin enhances the mechanical support and water transportation system through the xylem in the bark of a plant. Lignin has a three-dimensional amorphous network and it is a bio-renewable resource that generates aromatic biochemical.[43] Moreover, lignin is the only poly-aromatic structured biopolymer in plants that is composed of three types of phenyl-propane monomers, namely coniferyl alcohol, sinapyl alcohol and p-coumaryl alcohol, which forms the structured backbone of lignin, as shown in Figure 4. The reactivity, environmental impact, and degree of lignin branching are based on the proportions of these three types of monomers in lignin. The flexible monomers can be broken down into three phenolic sub-structures, namely guaiacyl (G), syringyl (S), and p-hydroxyphenyl (H) units. These sub-structures consist of numerous functional groups such as hydroxyls, carboxyls, carbonyls, and methoxyls that are widely utilized as active sites in electrochemical biosensing. The composition of many functional groups makes lignin a high-value functional material due to its high molecular weight, biocompatibility, and sensitivity to biomolecule interactions. Furthermore, the cross-linked flexible aromatic compound and polyphenolic characteristics of lignin can be modified chemically and physically with organic/inorganic material, making it ideal for the synthesis of a renewable bio-based sensing platform. Acetylation of aliphatic and phenolic alcohol enhances the functionality of lignin, by producing more hydrocarbons that interact with various classes of solvents. However, as lignin has a complex structure, an efficient and reliable hydrolysis method is required to break the bonds in lignin structure, improve its solubility and create a homogenous mixture.[45] Amorphous lignin has poor electrical conductivity, with a detection limit of 0.28×10^{-6} mol L^{-1} within concentrations ranging from 5×10^{-6} to 2×10^{-4} mol L^{-1}.[46] As such, lignin needs to be conjugated with other materials to increase its effectiveness as a biosensing material.

Starch

Starch is one of the largest carbohydrate polysaccharides composed of glucose monomers bonded in α^{-1}, 4-linkage and chain-shaped structure of amino acids (hydroxyl groups). The structure can be reshaped and resized to easily form composites.[47,48] It can be commonly found in the shape of spheres, platelets, and polygons with sizes ranging from 0.5 to 175 µm.[49] Raw starch is available as granules and hydrolysis of these granules can break it down into nanowires and nanoparticles with excellent electroactive

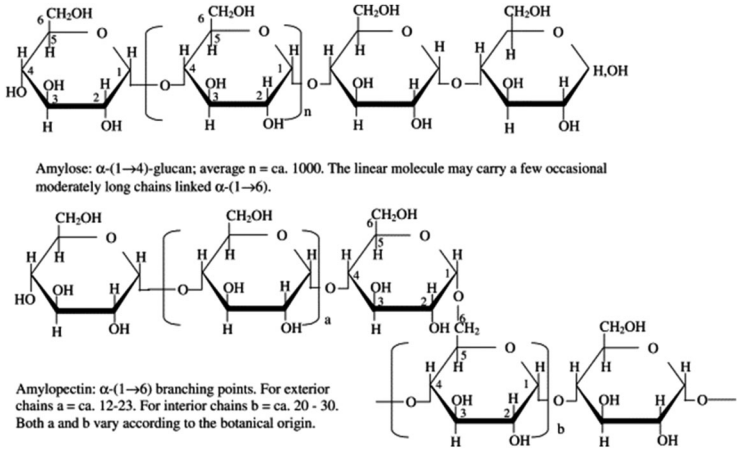

Figure 5. Structure of amylopectin and amylose in starch. Reused with permission from Ref. [50]. Copyright 2004, Elsevier.

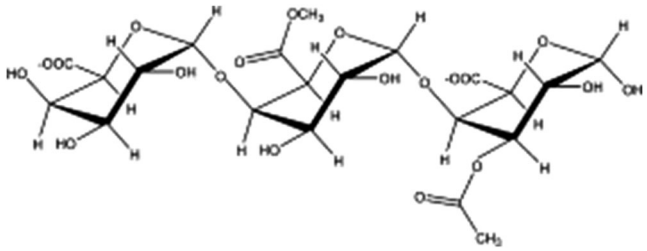

Figure 6. Chemical structure of pectin. Reproduced with permission from Ref. [56]. Copyright 2001, Elsevier.

properties. It can be classified as an amorphous (amylose) and crystalline (amylopectin) structures, as depicted in Figure 5. The insulated areas of starch are composed of amylose chains and amylopectin branching points, whereas the semi-crystalline areas of starch consist of amylopectin side chains with some of the amylose chains having crystalline structures as well.[51] Tatsumi et al.[52] investigated the kinetics of hydrolyzed starch by determining glucose levels from the glucoamylase deposition on various types of starch granules surface namely, rice, wheat, maize, cassava, sweet potato, and potato. The number of enzymes absorbed by each starch granule is influenced by the surface area, type, and crystalline structure of the starch granules. They concluded that the density of the crystalline structure of starch granules directly affects the amount of glucoamylase deposited on the surface of the starch granules. Additionally, starch also functions as a cheap reducing agent and a chiral template for one-dimensional structure formation. The large number of amyloses formed by the bonding with the D-glucose unit in starch can reduce the complex structure of starch doped with foreign molecules. Amylose is not active at room temperature and requires hydrothermal treatment for structural modification of amylose branches to form crystalline structures, so that it can be used as a template in the formation of hybrid nanoparticles and nanowires.[53] Heat treatment of amylose (starch) is a promising method to modify the structure in a simple, safe, and non-hazardous way. However, starch exhibits poor electrical conductivity, low proton mobility, high sensitivity to water and poor mechanical properties. In cold water, starch is somewhat susceptible to damage, and in warm water, it produces starch hydrogels. To enhance the conductance and improve its mechanical strength, starch is doped with conductive supporting material such as metal halides for immobilization of bioreceptor and target.[54]

Pectin

Pectin or polygalacturonic acid is a naturally occurring polysaccharide with hydrophilic properties that is suitable for stabilizing and immobilizing analytes on a sensing platform. Pectin is primarily found in plant primary cell walls and skins of citrus fruits. It has methyl ester of (1-4)α-D-galacturonic residues and rhamnogalacturonan that is partially attached to neutral sugars namely, D-galactose, L-arabinose, D-xylose, L-fucose, and D-mannose,[55] as shown in Figure 6. It has a linear anionic backbone with regions having no side chains known as “smooth regions” and regions with nonionic side chains known as “rough regions.” The high content of the sugar compound makes pectin an attractive biodegradable alternative stabilizer, as pectin can be used to trap covalently bonded enzymes and proteins on a sensing device. Pectin has abundant –OH and –COOH functional groups that can be modified into various structures, especially to form gels and films.[57] The easily modified pectin can be combined with various substances to improve the efficient transfer of analytes, as pectin has limited interfering electron chemical features.[58] The gelling features in negatively charged pectin form cross-linked pectin ‘egg box’ models, which involve the formation of junction zones through electrostatic and ionic bonding interactions, improving the sensitivity of biosensors.[59] Calcium cross-linked pectin (CCLP) is an example of ion cross-linked pectin network utilized as scaffolds for a stable hybrid material on a transducer through simple and rapid electrodeposition processes.[60] The free-moving calcium ions in calcium react with the active sites of the hydroxyl and carboxyl group of pectin, forming CCLP. It has maximum stability at pH 4, with degradation in terms of glycosidic linkage break down at low pH and high temperature. In an alkaline solution, pectin de-esterifies and degrades at room temperature.[61] As

pectin is an amorphous biopolymer, the addition of conductive materials is necessary to improve the stability and conductivity of pectin-based materials. The coupling of pectin with a carbon paste transducer is cost-effective for the determination of copper in biofuel, with a detection limit of 2.5×10^{-8} mol L^{-1} for a concentration range between 5.0×10^{-8} and 1.0×10^{-4} mol L^{-1}.[62] Pectin can stabilize enzymes and proteins employed in bioactive layers, for increased storage lifespan and reproducibility, as enzymes degrade at ambient temperature.[55]

Biopolymer with nanoparticles composites in electrochemical sensor

Nanoparticles refer to small particles that have diameters between 1 and 100 nanometers. The shape and size depend entirely on its physical and chemical properties, and the fabrication method. Nanoparticles functions as immobilizer, signal amplifier, mediators, electroactive substances, and probe detection in biosensing applications. In recent years, there has been wide interest in nanoparticles-based biosensors because their flexible immobilization platform stabilizes biomolecules, enhances electron transportation, increases sensitivity and selectivity due to wide surface area, improves surface free energy and exhibits quantum phenomena. As such, biopolymer-nanoparticles composites have been frequently used because of their increased surface area, good electrical conductivity, reduced response time, good integration, adhesion, optical, and catalytic properties. Commonly used nanoparticles in biopolymer-nanoparticles composites are silver, gold, carbon, copper, and oxides. However, these nanoparticles have certain drawbacks namely, poor stability, poor reusability, and poor particle distribution.[39,63] Conjugation of biopolymers and nanoparticles can overcome these limitations.

Biopolymer-silver nanoparticles (Ag NPs)

The porous polysaccharide chain in cellulose biopolymer helps in the deposition of nanoparticles. Liu et al.[64] added Ag NPs on porous and high absorption capacity carboxylated CNC, forming a high-density surface area for the hybridization of target DNA on glass carbon electrodes (GCE). The CNC/AgNPs composites have a 2.3×10^{-11} mol L^{-1} detection limit for a DNA concentration range of 1.0×10^{-11} to 1.0×10^{-7} mol L^{-1}. The CNC/Ag NPs were initially treated with sodium borohydride (NaBH4) to reduce the metallic cation, to avoid interruption during DNA detection. Apart from cellulose, chitosan and lignin react with Ag NPs because Ag NPs are stable, have wide spectral features, and are easy to modify. The addition of chitosan with Ag NPs improves the biocompatibility structure, nanoparticles aggregation, and adsorption characteristics. P. Tiwari et al.[65] developed a sensing probe from chitosan and Ag NPs to detect azidothymidine on screen printed graphite electrode (SPGE) and glassy carbon electrode (GCE). The biobased sensing probe has a better azidothymidine detection on SPGE transducer with a detection limit of 1 μM in buffer solution and 10 μM in biological samples (human plasma). Saratale et al.[45] synthesized a one-step method to embed silver Ag NPs in wheat straw lignin through the ultrasonication method. A crystal-filled structure of phenolic, hydroxyl and carboxylic group in lignin-Ag NPs composite was produced. The lignin-Ag NPs composite reduces toxic emissions to the environment and exhibits improved antimicrobial activity compared to metallic Ag NPs in detecting hydrogen peroxide. Tai et al.[66] reported on the use of oil palm lignin coupled on a laser-scribed graphene nanofiber electrode for the rapid detection of tuberculosis (TB) biomarker. This environmentally friendly and affordable sensing device with lignin-Ag NPs has excellent binding, high electrical conductivity, low cytotoxicity, and remarkable analytical performance. The lignin-Ag NPs form a string rigidly interconnected with single-strand DNA to detect TB biomarkers, with a detection limit of 10^{-15} M using electrochemical impedance spectroscopy (EIS). De Oliveira et al.[67] synthesized starch-Ag NPs utilizing a mixture of silver nitrate, soluble starch from potato, and sodium borohydride as a catalyst. They embedded starch-stabilized Ag NPs on silsesquioxane polymer to detect triiodide, as silver forms a strong bond with iodine. The protonated starch-Ag NPs bonded covalently to polycation silsesquioxane polymer, using a layer-by-layer method on a fluorine-doped tin oxide substrate.

Biopolymer-gold nanoparticles (Au NPs)

Dong et al.[68] used negatively charged gold nanoparticles (Au NPs) in developing a non-enzymatic glucose sensor composed of poly(diallyldimethylammonium chloride)–cellulose nanocrystal (PDDA–CNC)/Au NPs. The strong interaction of conductive gold nanoparticles on PDDA-CNC/CGE has a detection limit of 2.4 μM, a sensitivity of 62.8 μA mM^{-1} cm^{-2} for a linear concentration range from 0.004 mM to 6.5 mM. B. Batra et al.[69] developed an electrochemical amperometric sensor based on chitosan supported by carboxylated multiwalled carbon nanotube (cMWCNTs) and Au NPs on a gold electrode to detect glutamate. The strong electrostatic interactions of chitosan and cMWCNTs boosted the sensitivity and selectivity of a sensor by increasing the surface of the electrode and electron transfer (Figure 7). Satyanarayana et al.[70] used Au NPs, multiwall carbon nanotubes (MWCNTs), and chitosan composites to identify 5-fluorouracil. The superstructure morphology has excellent electrocatalytic behavior and a large surface area. L. Ding et al.[71] found that chitosan can be tuned into a bio-gel through a simple and green preparation method. They created Au NPs/Chitosan nanocomposite gel for immobilization of K562 leukemia cells, with a limit of detection of 8.71×10^2 cells Ml^{-1} at 10σ. Jodar et al.[72] fabricated a conductive film filling with reduced graphene oxide, Au NPs, and potato starch to identify estriol. Starch from potato has excellent film-forming characteristics and is chemically stable. Cyclic voltammetry (CV) reading showed that the conducting film has a high peak current of 0.64 V and a detection limit of 0.48 μmol L^{-1}, for a concentration range of 1.5 to 22 μmol L^{-1}. Devasenathipathy et al.[73] reported

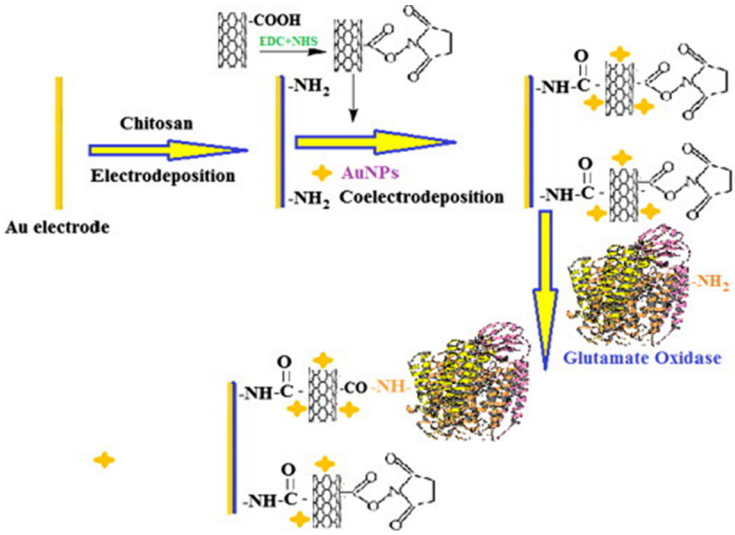

Figure 7. Schematic representation of chemical reaction involved in the fabrication of GluOx/cMWCNT/AuNP/CHIT/Au electrode. Reused with permission from Ref. [69]. Copyright 2013, Elsevier.

the use of CCLP as a stabilizer with Au NPs on MWCNTs to detect cysteine in food. The sensor exhibited a sensitivity of 0.46 μA μM^{-1}cm^{-2} and a detection limit of 19 nM, with a linear range from 0.1 to 1000 μM. A picomolar determination of amitrole based on CCLP stabilized Au NPs showed a detection limit of 36 pM in a concentration range of 100 pM to 1500 pM through square wave voltammetry (SWV) analysis.[60]

Biopolymer-carbon nanoparticles (CNPs)

Shahrokhian et al.[74] investigated the electro-analytical and uniform structure of CNFs and CNPs on GCE to detect anticonvulsant agents. CNFs have a large porous surface with an adhesive layer that prevents the CNPs from falling out of their surface. CNFs and CNPs have excellent specific interconnectivity and compact adherence bonding, with long-term stability of the sensing electrode surface, forming a linear response for clonazepam concentrations ranging from 0.1–10 μM and a detection limit of 0.08 μM. Carbon dots are distinctive nanoparticles, as it forms amine and carboxyl groups in their structure when the carbon dots are dissolved in citric acid, resulting in high permeability and good physiochemical properties. Sarkar et al.[75] fabricated carbon dots-based chitosan film as a sensing platform through microwave pyrolysis for a more reliable, conductive, thermally stable with high mechanical firmness biosensor, to detect vitamin D in food. Metallic and semiconducting nanoparticles were introduced on chitosan film to enhance the selectivity, sensitivity, and electrical conductivity of an electrochemical glucose sensor.[76] Positively charged chitosan was found to react with negatively charged composite metallic and semiconducting materials, forming a stable platform for immobilization of glucose oxidase, which prevents biomolecules from falling out and remaining in their folded state. Pectin extracted from musk melon peels was used to alter MWCNT through the solvent casting method to create a non-enzymatic sensing device to identify the creatinine biomarker, as shown in Figure 8. The pectin-MWCNT matrix has an excellent electron transfer tendency, large surface area, high diffusion coefficient, good rate of electron transfer constant, and quick respond time. The matrix could identify creatinine biomarker under normal conditions without the presence of enzymes.

Biopolymer-copper nanoparticles (Cu NPs)

Duran et al.[77] carried out thermal decomposition pyrolysis on CNFs, forming carbonized CNFs, to increase carbon element content by integration of Cu NPs on CNFs. The carbonized CNFs/CuNPs have more micropores, larger surface area, good electrical conductivity, and good mechanical stability. The synthesized CNFs/Cu NPs/paper-based carbon electrode detects glucose by glucose oxidase (probe), with a sensitivity of 460 ± 8 μA cm^{-2} mM^{-1} at linear response up to 3 mM. Wang et al.[78] developed a glucose and hydrogen peroxide dual function sensor on a matrix of chitosan modified covalently with copper (Cu) nanoparticles and carbon nanotube (CNT) on GCE. The presence of CNT on GCE can contribute significantly to the promotion of the electrochemical activity of the sensing electrode. This composite has a glucose detection limit of 0.02 mM for concentrations ranging from 0.05 to 12 mM. Recently, a simple sonochemical method was used to fabricate copper ferrite nanoparticles ($CuFe_2O_4$ NPs)/chitosan composites. The large surface area and anti-fouling matrix of copper ferrite nanoparticles make it a suitable candidate to be doped on chitosan, to determine the 8-hydroxyguanine marker. This composite does not require a reducing or stabilizing agent, as chitosan is inherently stable. The copper ferrite nanoparticles ($CuFe_2O_4$ NPs)/chitosan composite on a glassy carbon electrode electrochemical biosensor has a concentration limit of 8.6 nM and a broad linear range from 0.025 to 697 µM.[79] As for lignin, the coupling of lignin with copper oxide nanoparticles and the large surface area morphology of MWCNTs improves the electrocatalytic activity and sensitivity of biosensors. Lignin serves as a platform for identifying chlorogenic acid with numerous actives sites due to the functional

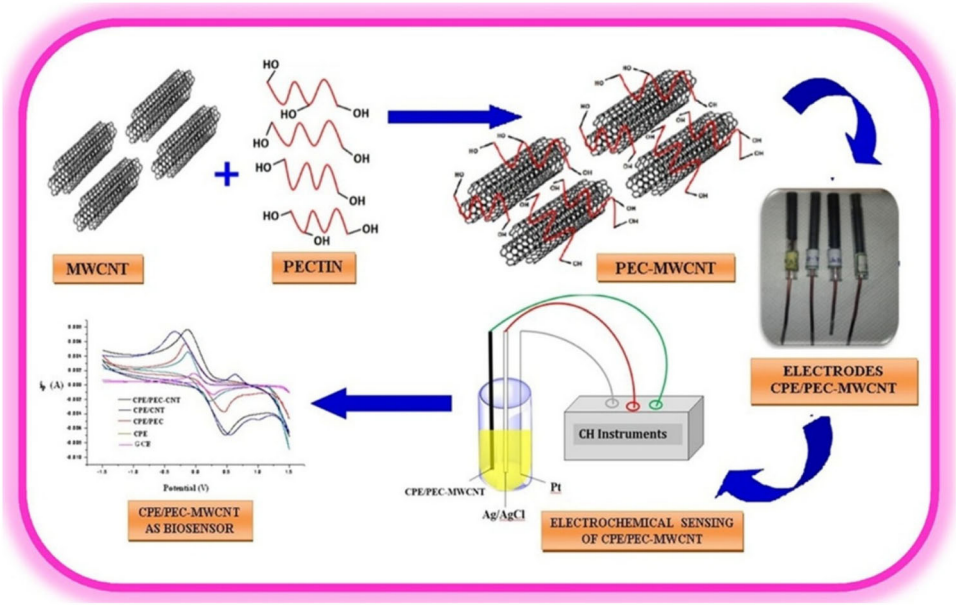

Figure 8. Schematic representation of preparation of CPE/PEC-MWCNT and its efficiency in electrochemical sensing of creatinine. Reused with permission from Ref. [76]. Copyright 2018, Elsevier.

groups present in lignin, which makes up the tubular nanocomposite strong π–π non-covalent bond, resulting in an efficient interaction between probe and chlorogenic acid. This significantly boosts the stability, as well as reproducibility, of the biosensor.[80] The amorphous lignin can be shaped and sized into nanoparticles with excellent rheological and physiochemical properties. The π–π bond in lignin nanoparticles enhances the electron and charge transfer and further strengthens the monooxygenase activity.[81] The combination of Cu NPs with pectin and graphene through electrodeposition to form graphene/pectin-Cu NPs was used for the detection of glucose and hydrogen peroxide. Pectin was used as a scaffold with graphene as hybrid material support. The Cu NPs conjugated pectin possesses stable, uniform, and physiochemical active properties, with a relative standard deviation of 2.54% for repeatability and 2.92% for reproducibility. Graphene facilitated the electrical conductivity of the hybrid material, with a sensitivity of 0.0457 μA μM^{-1} cm^{-2} and 0.391 μA μM^{-1} cm^{-2} for the detection of glucose and hydrogen peroxide.[82]

Biopolymer-dual nanoparticles

Ranjbar et al.[83] combined chemically synthesized Au NPs and CNPs on CNFs, forming a biosensor for the detection of *Staphylococcus aureus*. Au NPs were utilized to facilitate the binding of the thiolated aptamer (probe) on functionalized CNFs for porosity and electron transfer. E. Darvishi et al.[84] synthesized nontoxic and environmentally friendly nanoparticles using the *Calendula officinalis L* plant to produce Au NPs and Ag NPs. The green Au NPs and Ag NPs embedded on a cellulose quince seed mucilage platform were used to detect a biomarker for prostate cancer. They proved that a green biosensor was possible to develop, with a detection limit as low as 0.078 pg mL^{-1} with a biomarker concentration range from 0.1 pg mL^{-1} to 100 ng mL^{-1}.

Biopolymer-oxides nanoparticles

Jagadish et al.[85] combined zinc oxide nanoparticles with starch through a wet chemical method to detect caffeine. Starch controls the shape and size of zinc oxide by preventing the growth and accumulation of nanoparticles. The zinc ion attaches to the hydroxyl group of starch in a warm solution, as the crystalline structure of starch breaks down in a warm solution. The zinc oxide nanoparticles-based glassy carbon electrode showed a detection limit of 0.038 μM for a concentration linear range of 2 to 100 μM. Using co-precipitation method, starch was combined with magnetic iron oxide nanoparticles to form a biosensor to detect folic acid (FA) using differential pulse stripping voltammetry (DPSV), with a detection limit of 2.8 and 48 nM.[86] Cassava starch has the potential as a basic functional polymer for biosensors. The combination of cassava starch with a conductive material such as iron (II, III) oxide forming nanoparticles doped on molecularly imprinted polymer (MIP) has been used to detect acetaminophen and caffeine. Cassava starch can be cross-linked with conductive foreign material in a sodium hydroxide solvent, forming a polymer material with basic functionality. These composite materials have a sensitivity of 0.5306 A/M for the detection of acetaminophen and 0.4314 A/M for the detection of caffeine, with a detection limit of 16 µM (acetaminophen) and 23 µM (caffeine).[87] Copper oxide nanoparticles enhance the electrochemical oxidation of glycerol through amperometric measurement. The copper oxide nanoparticles on MWCNT and pectin composite were used to detect glycerol in biodiesel, as pectin can attract copper ions in a solution. Pectin facilitates

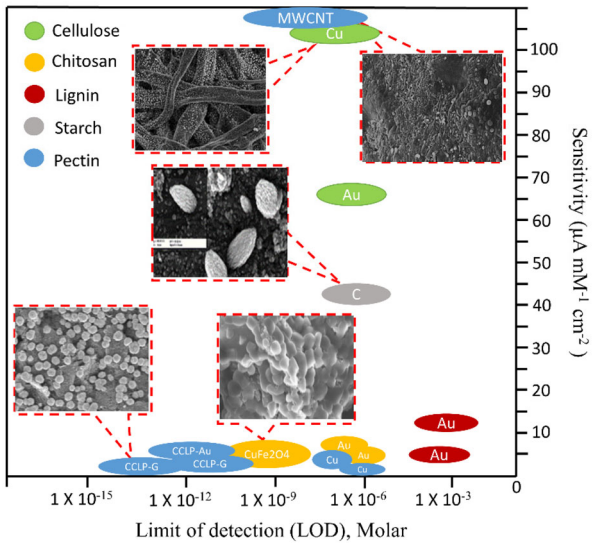

Figure 9. Comparison of different biopolymer-based nanoparticles. High-performance by sensitivity and limit of detection (LOD) in electrochemical sensor. Inserted images are reproduced with permission from Refs. [76, 77, 79, 82, 91]. Copyright 2018, 2016, 2020, 2015, Elsevier.

the dispersion of the MWCNT homogenously to produce repeatable results without the use of toxic chemicals such as dioxolane, dimethylformamide, and dimethyl sulfoxide.[88]

Biopolymer nanoparticles

Biopolymers can be reshaped and resized into nanoparticles. Tortolini et al.[89] developed kraft lignin (sulfur filled) and organosolv lignin (sulfur free) nanoparticles for electrochemical eco-friendly biosensing on a gold electrode. Chemical pulping and bioethanol production are two types of processes that are used to extract sulfur lignin and sulfur-free lignin. The bonding between kraft lignin nanoparticles with concanavalin A and glucose oxidase on gold electrode showed excellent electrochemical probe and target interaction compared to organosolv lignin nanoparticles composite. The kraft lignin nanoparticles and organosolv lignin nanoparticles showed a sensitivity of (13.74 ± 1.84) and (4.53 ± 0.467) μAmM^{-1} cm^2 respectively, which led to stable sensing devices, demonstrating that while lignin can augment the sensitivity of a biosensor, the analytical performances depend on the number of lignin composites layers on the gold electrode. The addition of nanoparticles in starch forming starch-nanoparticles composite significantly improves crystallization kinetics, the morphology of the hybrid structure, crystal formation, crystalline size, and overall mechanical and physical features of starch-nanoparticles composite.[90] Starch is extensively used as an alternative anchoring and stabilizing material in the formation of metal nanoparticles. The abundant network of glycoside bonds in starch acts as a stabilizer in a mixture solution to provide a surface passivation layer or protection, to avoid the accumulation of nanoparticles.[67] Furthermore, starch can be used as an alternative carbon nanomaterial for the development of a sensing device. Das et al.[91] used peeled potatoes as an alternative carbon source using pyrolysis and slow heating to obtain almond-shaped CNPs to detect sucrose. The unique properties of amylose and amylopectin in potatoes form conductive CNPs easily. The potato-based device is disposable and exhibits a sensitivity of $\sim 41.73725 \pm 0.01$ $\mu AM^{-1}cm^{-2}$, with a detection limit of 1 μmol/L through differential pulse voltammetry (DPV) and linear sweep voltammetry (LSV). The hydrothermal method at high temperature without a catalyst is another method to convert potato starch into a uniform and single carbon microsphere to detect Hg (II) ions.[92] Figure 9 shows the comparison of different biopolymer-based nanoparticles composites in an electrochemical sensor in terms of sensitivity and limit of detection (LOD). Table 1 summarizes biopolymers with nanoparticles composites electrochemical sensors.

Biopolymer with conducting or synthetic composite materials on electrochemical sensors

Conducting polymers are a special class of organic materials with the ability of overlapping polymer molecular orbitals caused by extended π-conjugation structures along the polymer backbone. The presence of cationic salts in conducting polymers modifies the physiochemical properties and reversible reaction, as it has an oxidized state and a reduced state. Conducting polymers have good compatibility, excellent electrical conductivity, chemical, and optical properties, which improve electron-transfer efficiency and processability, extensively boosting their popularity for biosensing applications. Synthetic polymers, on the other hand, have high carbon content, high biostability, and resistance to degradation due to stacking carbon-carbon backbone. Therefore, the coupling of biopolymers and conducting or synthetic polymers is one of the most promising techniques for the development of these sensors, due to their relative stability, low ionization potential, large surface area, redox conductivity, and optical features. As such, biopolymer-based conducting polymers have been widely used in biosensors, due to their significantly faster response time, having suitable features for interactions of biological elements and morphology metrics, resulting in immediate charge and discharge reactions. Biosensors that utilized biopolymer-based conducting or synthetic polymer are reviewed in the following section.

Biopolymer-polyaniline (PANI) composites

PANI is one of the most studied conducting polymers, especially its potential electrical properties and doping chemistry. It functions as an organic semiconductor with a semi-flexible polymer. PANI is made up of aniline molecules through an oxidation acidic chemical reaction. Several studies were conducted on PANI incorporating biopolymers, as PANI has weak mechanical properties, weak ability to dissolve and inability to disperse uniformly in organic solvents. The coupling of PANI and biopolymer through π-π bond forms intracellular matrices with high volume surface area for the interaction of probe and target, to improve the capturing and determination of a target. In-situ chemical

polymerization, bottom-up and top-bottom applications have been used to synthesize green-PANI/multiwalled carbon nanotubes/carboxymethyl cellulose (PANI/MWCNTs/CMC) composites. The numerous hydroxyl and carboxyl groups found in CMC allow protonated PANI to bind ionically with negatively charged CMC. Furthermore, the addition of MWCNT rich with benzenoid rings increases the conductivity of the composite material. These composite materials have a wide surface area per volume ratio, small pore diameter, and excellent dissolution in organic solvents. The PANI/MWCNTs/CMC/CPE electrochemical biosensor has a detection limit of ascorbic acid at 0.01 mM in 0.05 mM^{-5} mM direct range and high sensitivity of 100.63 $\mu AmM^{-1}cm^{-2}$, making PANI/MWCNTs/CMC composite materials suitable for the detection of clinical biomarkers.[93] Chitosan is also bonded with PANI, as chitosan has good mechanical strength, excellent film-forming capability, and relatively good hydrophobicity. The polycations of chitosan attract polyanions of other materials. A biopolymer bilayer using protonated chitosan bonded with negatively charged carboxymethylpullulan, doped on PANI was used as a transducer for the detection of urea.[94] The electrostatic force between the amine group of chitosan and carboxyl group of carboxymethylpullulan forms a mechanically excellent biopolymer with PANI, increasing electrical conductivity. Kushwaha et al.[95] added zinc oxide on PANI-grafted chitosan composite to detect urea with enhanced sensitivity, as zinc oxide increased the specific surface area and enhanced electron transfer. The sensitivity of the self-activating tertiary hybrid material urea biosensor was 187.5 $\mu V\ ppm^{-1}cm^{-2}$, with a detection limit of 29.84 ppm in the 20 ppm to 500 ppm range.

Gautam et al.[48] interconjugated biopolymer starch with conducting polymer PANI doped with carbon-filled MWCNTs forming PANI/MWCNTs/Starch nanocomposite. This nanocomposite exhibits remarkable electrical conductivity, as the functional groups found in these nanocomposites can disperse in organic and inorganic solvents easily with excellent biocompatibility properties. This PANI/MWCNTs/Starch nanocomposite was used to determine the presence of cholesterol in cow's milk. The covalently bonded starch with PANI and MWCNT improves binding sites, electrocatalytic performances, and transfer of electrons, which led to the oxidation of cholesterol. The nanocomposite has a high surface area and porous morphology that enhances the hybridization of bioreceptors on the PANI/MWCNTs/Starch platform. This cholesterol biosensor has a sensitivity of 800 $\mu AmM^{-1}cm^{-2}$, with a detection limit of 0.01 mM in the 0.032 to 5 mM range.[96] The addition of hemoglobin on the PANI/MWCNTs/Starch nanocomposite enables the detection of hydrogen peroxide and glucose by boosting the electrons charge transfer in terms of sensitivity and selectivity. The PANI/MWCNTs/Starch/HB nanocomposite biosensor is stable, with a sensitivity of 76.43 $\mu A/mM\ cm^2$ and a detection limit of 0.032 Mm.[97] Thakur et al.[58] used pectin on the surface of PANI to determine glucose in an amperometric biosensor. The pectin biopolymer was dispersed homogenously in hydrochloric acid and aniline mixture solution to avoid clumping. The pectin/PANI composite has high water dispersibility, excellent covalent bonding with glucose oxidase, porous morphological structure (due to the gelatinous structure of pectin coated around PANI) and good electrical conductivity, with pectin acting as a stabilizer and reducing agent. The efficiency of electron transfer during amperometric analysis improved, leading to a sensitivity of 79.49 $\mu A\ mM^{-1}cm^{-2}$ and a detection limit of 43.5 μM. The pectin-PANI composite has a sensitivity three times better than conventional PANI for glucose oxidase.

Biopolymer-polypyrrole (PPy) composites

PPy is another type of conducting polymer that has a different polymer structure from PANI with simpler polymerization and substitution, good physiochemical properties, controllable polymer thickness, and excellent electrical conductivity. PPy is an organic polymer produced through oxidative polymerization of pyrrole with formula $H(C_4H_2NH)_nH$. A study conducted by Esmaeili et al.[27] found that the conjugation of polypyrrole-cellulose nanocrystal (PPy-CNC) increased the performance of the biosensor in detecting glucose using glucose oxidase bioreceptor such as PPy-CNC composite's unique physicochemical properties. The novel native structure of PPy-CNC/SPE composite has a sensitivity of 0.73 $\mu A{\cdot}mM^{-1}$ and a detection limit of (50 ± 10) μM, with concentrations ranging from 1.0 to 20 mM. PPy-CNC/SPE sensors exhibit excellent stability, retaining a DD of 95% after 17 days and a relative standard deviation (RSD) of 4.47% for repeatability. Recently, Uzunçar et al.[98] developed a biocompatible electrochemical biosensor for common interfering compounds on indium tin oxide coated glass electrodes. They synthesized PPy, carboxymethylcellulose (CMC) together with Prussian Blue nanoparticles (PBNPs) peroxidase to overcome the dispersibility limitation of PPy in solution and to enhance the electrical conduction of the PPy polymer chain. The CMC stabilizes the composite material and enhances the affinity for solutions such as water. The CMC-PPy-PBNPs/ITO sensor platform can detect hydrogen peroxide and glucose as well. The glucose sensing platform has a sensitivity of 456.8 $\mu A\ mM^{-1}cm^{-2}$ and a detection limit of 5.23 μM within a range of 20 to 1100 μM, while the hydrogen peroxide sensor platform had a sensitivity of 456.8 $\mu A\ mM^{-1}cm^{-2}$ and a detection limit of 0.59 μM in a rectilinear range of 5 and 470 μM. PPy nanotubes and gold nanoparticles strengthen the electrical conductivity, although the nanocomposite has poor reproducibility. The high structural mechanical strength of PPy conducting polymer and gold nanoparticles resisted the breaking of the bond, allowing for better reusability. Chitosan in PPy nanotubes and gold nanoparticles nanocomposite has excellent biocompatibility and eases the breaking of bonds, enabling the biosensor to regenerate by reverse surface modification reaction.[39] Chitosan–PPy–gold nanoparticles nanocomposite has better charge transportation efficiency and provides a proper platform for enzyme

Table 1. Literature on biopolymers-based nanoparticles composites in electrochemical sensor.

Biopolymer	Structure	Source	Electrode	Probe	Analyte	Technique	Linear range	Limit of detection	Sensitivity	Real sample	Ref
Cellulose	Nanocrystals		Ag/CNC/GCE	DNA	dsDNA	DPASV	1.0×10^{-11}–1.0×10^{-7} mol L^{-1}	2.3×10^{-11} mol L^{-1}			[64]
	Nanofiber		CNFs/CNPs/GCE		Clonazepam	LSV CV	0.1–10 μM	0.08 μM		Human serum	[74]
	Fibers		Cu NPs/cellulose fiber	Glucose oxidase	Glucose	CV	0–3 mM	5 μM	460 ± 8 μA cm^{-2} mM^{-1}	Beverages	[77]
	Nanocrystals	Wood Plup	Au/PDDA–CNC	Glucose oxidase	Glucose	CV	0.004 mM–6.5 mM	2.4 μM	62.8 μA mM^{-1} cm^{-2}		[68]
	Nanofiber		Au NPs/Cu NPs/CNF	Aptamer	Staphylococcus aureus	CV EIS	1.2×10^{1}–1.2×10^{8} CFU mL^{-1}	1 CFU mL^{-1}		Blood	[83]
	Quince seed mucilage	Quince seed mucilage	Quince seed mucilage/ GNPs/SNPs	Antibody	Prostatic specific antigen (PSA)	EIS	0.1 pg mL^{-1}–100 ng mL^{-1}	0.078 pg mL^{-1}		Human serum	[84]
Chitosan	Matrix		Cu/CHIT/CNT/GCE	Glucose oxidase	Glucose	EIS	0.05–12 mM	0.02 mM			[78]
	Film		GluOx/cMWCNT/AuNP/CHIT/ Au electrode	Glutamate oxidase	Glutamate	CV EIS	5–500 μM	1.6 μM	155 nA/μM/cm^2	Sera	[69]
	Gel		Au NPs/CHIT/GCE	K562 Leukemia Cells	Cells	CV EIS	1.34×10^{4}–1.34×10^{8} cells mL^{-1}	8.71×10^{2} cells mL^{-1}			[71]
	Film		Au NPs–CS/PB–CS/ Au electrode	β-glucanase	β-glucan	CV	6.25–93.75 μM	1.56 μM	100 nA μM^{-1} cm^{-2}	Red wine, Beijing Erguotou, Mianzhudaqu, Hericium, Oatmeal	[63]
	Nanocomposite		GNP-MWCNT-CHIT/GCE		5-fluorouracil	CV DPV	0.03–10 μM	20 nM		Urine	[70]
	Matrix		Ch@Ag NPs/SPGE	Ch@Ag NPs (probe)	Azidothymidine	CV	10 μM to 533 μM	1 μM		Human plasma	[65]
	Composite		BSA/Ab/CD-CH/ITO	Antibody (Ab-VD2)/bovine serum albumin (BSA)	Vitamin D	CV EIS	1–50 ng/mL	1.35 ng/mL	0.02 μA ng^{-1} mL		[75]
	Nanostructure		$CuFe_2O_4$/chitosan/GCE		8-hydroxyguanine	CV DPV	0.025–697.6 μM	8.60 nM	2.807 $\mu A \cdot \mu M^{-1} \cdot cm^{-2}$	Blood serum, Urine	[79]
Lignin	Nanostructure		LGN-MWCNT-CuONPs-GCE		Chlorogenic acid	CV DPV	5 μM–50 μM	0.0125 μM		Coffee	[80]
	Nanoparticles		LNPs/CATLIG/HRP–GO_X/GCE	Horseradish peroxidase and glucose oxidase	Glucose Chromogenic	CV	4.0 μM–16 μM	0.85 μM			[81]
	Nanoparticles	Oil palm	LSG-NF-AgNPs	DNA	Tuberculosis	EIS	1 fM–1 nM	1 fM			[66]
	Nanoparticles	Kraf lignin, organosolv lignin	Au/SAMCys/OLNPs/ConA/GOx and Au/KLNPs/ConA/GOx	Concanavalin A, Glucose oxidase	Glucose	CV EIS	0.33–2.5 mM, 0.15–2.5 mM	0.11 mM, 0.05 mM	(4.53 ± 0.467) and (13.74 ± 1.84) μA mM^{-1} cm^2		[89]
Starch	Almond-shape nanoparticles	Potato	CNA		Sucrose	CV DPV LSV	1–100 μM	1 μmol/L	$\sim 41.73725 \pm 0.01$ $\mu A \cdot M^{-1} \cdot cm^{-2}$	Fruit juices (Jack fruit, Mango, Pineapple)	[91]
	Film	Potato	rGO-GNPs-PS/GCE		Estriol hormone	CV	1.5–22 μmol L^{-1}	0.48 μmol L^{-1}		Tap water, river water, synthetic urine	[72]

(*continued*)

Table 1. Continued.

Biopolymer	Structure	Source	Electrode	Probe	Analyte	Technique	Linear range	Limit of detection	Sensitivity	Real sample	Ref
	Nanoparticles		ZnO-GCE		Caffeine	CV DPV	2–100 μM	0.038 μM		Beverages	[85]
	Nanoparticles		γ-Fe_2O_3 nanoparticles/GCE		Folic acid	DPSV	0.05–1 μM and 1–80 μM	2.8 nM and 48 nM		Pharmaceutical tablets	[86]
	Membrane	Cassava	GCE-M221-Fe_3O_4		Acetaminophen and caffein	DPV	50–2000 μM and 50–900 μM	16 and 23 μM	0.5306 A/M and 0.4314 A/M	Headache medicine	[87]
Pectin	Cross linked		CCLP-Au NPs/MWCNT/GCE		L-Cysteine	CV	0.1–1000 μM	19 nM	0.46 μA μM^{-1} cm^{-2}	Human blood serum	[73]
	Cross linked	Citrus peel	CCLP-GNPs/GCE		Amitrole	SWV	100–1500 pM 100–1500 nM	36 pM 20 nM	0.075 μA pM^{-1} cm^{-2}, 0.1 μA nM^{-1} cm^{-2}	Tap water, River water	[60]
	Scaffold	Citrus peel	Graphene/pectin-CuNPs		Glucose, Hydrogen Peroxide	CV	10–5.5 μM 1 μM–1 mM	2.1 μM 0.35 μM	0.0457 μA μM^{-1} cm^{-2}, 0.391 μA μM^{-1} cm^{-2}	Human serum, Contact lens cleaning solution	[82]
	Nanostructure		CuONP/Pectin(MWCNT)/GCE		Glycerol	CV	9×10^{-3}–1 mg L^{-1}	5.8×10^{-3} mg L^{-1}		Biodiesel	[88]
	Nanostructure	Musk melon peels	PEC-MWCNT/CPE		Creatinine	CV DPV	16 nM–3.3 μM	0.6 μM	3550 μA mM cm^{-2}	Urine	[76]

Ag, silver, CNC, cellulose nanocrystals, GCE, glass carbon electrode, CNF, cellulose nanofiber, CNPs, carbon nanoparticles, Au, gold, PDDA-CNC, poly(diallyldimethylammonium chloride)–cellulose nanocrystal, Au NP & GNPs, gold nanoparticles, SNPs & Ag NPs, silver nanoparticles, CHIT, CS, CH & Ch, chitosan, CNT, carbon nanotubes, GluOx, glucose oxidase, cMWCNT, carboxylated multiwall carbon nanotubes, PB, prussian blue, BSA, bovine serum albumin, Ab, antibody, CD, carbon dots, ITO, indium tin oxide, GOx, graphene oxide, $CuFe_2O_4$, copper ferrite nanoparticles, LGN, lignin nanocomposite, CuONPs, copper oxide nanoparticles, LNPs, lignin nanoparticles, CATLIG, cationic lignin, HRP, horseradish peroxidase, LSG-NF, laser scribed graphene nanoflower, OLNPs, organosolv nanoparticles, KLNPs, kraft lignin nanoparticles, CNA, carbon nano almond, PS, potato starch, ZnO, zinc oxide, γ-Fe_2O_3, maghemite, CCLP, calcium cross-linked pectin, SPGE, screen printed graphite electrode

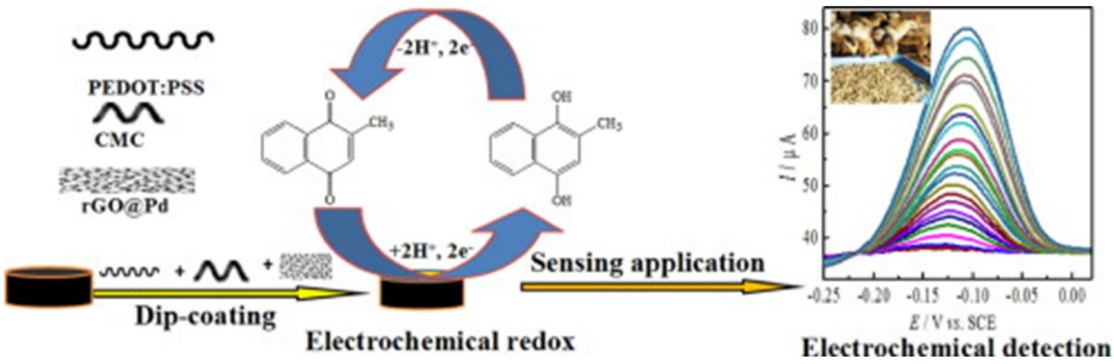

Figure 10. The fabrication procedure of PEDOT:PSS-CMC-rGO@Pd/GCE for the voltammetric determination of vitamin K3 in real samples. Reproduced with permission from Ref. [103]. Copyright 2016, Elsevier.

connectivity for the detection of xanthine, with a 0.25 μM detection limit in the 1 to 200 μM[99] range.

Bulk PPy has slow electron transfer, which affects the sensitivity of a sensing surface. The addition of chitosan and metal oxide to conducting polymer forms a stable, conductive, large surface area, biocompatible, simple, reproducible, and selective composite film, which acts as an active material for biosensor development. The amphipathic nature of chitosan and PPy makes it a suitable coupled material for opto-chemical sensing. The PPy-chitosan-iron oxide nanoparticles on indium tin oxide (ITO) glass displayed an amperometric response with a limit of glucose identification of 234 μM in the 1 to 16 mM range.[100] Starch is a polysaccharide that can be used as a template or morphology-directing agent to form a one-dimensional conducting polymer. The formation of a one-dimensional conducting polymer is very challenging in terms of biomolecule degradation and optimization of biopolymer amino-acid growth. Uniform-sized PPy nanowires were synthesized by dissolving pyrrole in soluble starch, with the pyrrole monomers attracting starch molecules via hydrogen attachment formed between pyrrole and the hydroxyl group of starch.[47] Polymerization occurs along the chain of starch, which forms the PPy nanowires. The linear chain of amino acids in starch combines with functional groups as a template. The coupling of starch with conducting polymers has many applications, especially in electrochemical sensing. The combination of the contrasting properties of starch and conducting polymer has excellent synergic effects and allows simpler modification. Generally, almost all conducting polymers such as PPy and PANI possess bonding capabilities and electron charge transfer ability when foreign material is present. The combination of starch with a conducting polymer causes an electron exchange or the attraction of opposite ions, which changes the conductivity, physiochemical, and optical properties of the hybrid material. As pectin and PPy have similar nitrogen and oxygen atoms, they exhibit good mechanical strength and ease in forming amides in an aqueous ammonia mixture to form films. Arulraj et al.[101] added graphene in pectin/PPy composite as supporting material, to enhance conductivity and to provide a larger surface area to absorb mercury ions. The graphene/PPy/pectin composite has a detection limit of mercury ions as low as femtomolar, with a sensitivity of 28.64 $\mu A\ \mu M^{-1}$. Biopolymers such as pectin are rich in galacturonic acid and can act as a biopolymer electrolyte in biosensors, forming proton-conducting biopolymer electrolytes embedded with ammonium chloride and ammonium bromide. Notably, pectin-ammonium bromide electrolyte film has excellent optimized ionic conductivity and good electrical properties compared to pectin-ammonium chloride. This is because pectin-ammonium bromide has poor lattice energy and larger anionic size, as well as high dielectric constant and dielectric loss.[102]

Biopolymer-poly(3,4-ethylenedioxythiophene) (PEDOT) composites

Poly(3,4-ethylenedioxythiophene) (PEDOT) and poly(styrene sulfonate) (PSS) are two of the most important noble carbon conducting polymers that are chemically stable, environmentally friendly, conductive, have fewer network defects with the capability to dope as well as reverse its doping properties. A conductive, synergistic electrochemical sensor with excellent electron transfer was developed by integrating (PEDOT:PSS) composite conducting polymer with carboxymethyl cellulose (CMC) and reduced graphene oxide@palladium (rGO@Pd) for the detection of vitamin K_3 (VK_3) using voltametric analysis, as shown in Figure 10.[103] CMC can overcome the limitations of PEDOT:PSS in terms of substrate interface, brittle structure defects, and weak fixative force between PEDOT and PSS. It is capable of enhancing and strengthening the carbon structure of PEDOT:PSS composites and provides a stable and long-lasting sensing GCE. The synergistic composite electrode has a 1.4×10^{-8} M detection limit for a 4×10^{-7} to 9×10^{-5} M concentration range.

Xu et al. developed carboxylated cellulose nanocrystals (CNCC) through chemical treatment on microcrystalline cellulose and ammonium persulfate doped with Ag NPs on CNCC. The PEDOT conducting polymer was integrated with Ag NPs/CNCC substrate with excellent catalytic activity in detecting dopamine through an oxidation process. The PEDOT/Ag NPs/CNCC/GCE electrochemical sensor detected dopamine at a low detection limit of 17 nM in the range of 0.05 to 782 μM, and retained a 93.2% stability after 1 month with an RSD value of 5.8% for repeatability and 3.97% for reproducibility.[104] They also modified PEDOT/Fe3O4-CNCC with GCE using a similar oxidation-reduction

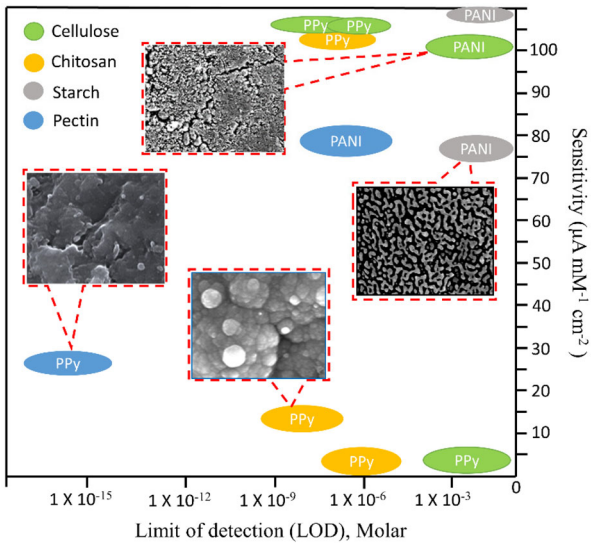

Figure 11. Comparison of different biopolymer-based polymers (conducting or synthetic) by sensitivity and limit of detection (LOD) in electrochemical sensor. Inserted images are reproduced with permission from Refs. [93, 97, 100, 101]. Copyright 2018, 2016, Elsevier.

method to produce CNCC from microcrystalline cellulose to detect nitrite in food. The addition of Fe3O4 increased the transfer of charged electrons of the composite transducer with a 0.1 μM detection limit for a nitrite concentration range of 0.5–2500 μM. The PEDOT/Fe3O4-CNCC/GCE sensor has an excellent synergistic effect with a 4.7% loss in stability in 2 weeks and a relative standard deviation (RSD) of 4.6% for repeatability and 3.7% for reproducibility.[105]

Biopolymer-polyacrylonitrile (PAN) composites

PAN is a type of synthetic semicrystalline resin from the polymerization of acrylonitrile. It has a linear formula of (C3H3N) and has been extensively used as a precursor in the electrospinning technique for use in biosensors because it is a petroleum-based polymer that has high resistance to chemicals and good membrane formation. However, the electrospinning heating process of PAN is time consuming and requires high operating costs. To overcome these drawbacks, biorefinery lignin is used as a replacement for PAN, as lignin has a 68% carbon content and can be electrospun easily.[106] Mustafov et al.[107] blended lignin and PAN, forming carbon-filled nanofibers through an electrospinning technique doped with conductive graphene to develop a highly activated platform on a screen-printed electrode to detect acetaminophen. The diameter of the composite nanofibers depends on the mass of lignin and the temperature of the carbonization process. They concluded that the large surface area of lignin/PAN/graphene is one of the factors that enhances the sensitivity of acetaminophen biosensors. It should be noted that the detection of a biopolymer and synthetic polymer electrochemical biosensor is related to detectable changes in the electrical properties of these materials, which is proportional to the concentration of a specific biological element. Apart from PAN, molecularly imprinted conducting polymers are used for the detection of condensed lignin molecules in pulping industries. Lignin can combine with a synthetic polymer to form functional groups.[108]

Biopolymer-polyurethanes composites

Poor solubility in organic solvents affecting the dissolution of lignin in a polymer matrix is one of the biggest challenges to forming lignin-polymer composites. Lignin's structure is easily modified as lignin contains oligometric and low-weight polymeric particles that can be separated into a liquidized mixture. The covalent binding of lignin (hydroxyl group) with polymer (isocyanate group) can be formed through condensation, as lignin has an OH group that forms polyurethanes.[43] While polyurethanes have good stability, they are not conductive. The combination of lignin-polymer with a conductive material using percolation is therefore necessary, especially when used as a conducting polymer. Kraft lignin polyurethane doped with MWCNT has excellent ion transfer properties, which makes it an excellent sensing platform candidate.[109] Gonçalves et al.[110] used polyurethane-kraft lignin with carbon nanotube composites as a potentiometric sensor to detect copper (II) ions, demonstrating that polyphenolic groups found in that composite material enhance the selectivity and sensitivity. A. Rudnitskaya et al.[111] formed polyurethanes by co-polymerization with tolylene 2,4-diisocyanate terminating poly(propylene glycol) using various types of lignin namely, kraft lignin, lignosulphate, and organosolv lignin to form polyurethanes embedded with MWCNT. The lignin-based polyurethanes/carbon nanotubes composites are highly conductive active material candidates for chromium (VI) determination, with a detection limit of 5.0×10^{-6} M within the range of 1×10^{-5} M to 1×10^{-2} M. Carbon nanotube boosts the electrical conductivity of substrate used as sensing platform on glass sensor whereas organosolv lignin and lignosulphate have a very sensitive sensing surface, especially in an acid mixture. The strong C-C structural bonding between carbon filled carbon nanotubes with numerous type functional groups of lignin make the sensor stable, rigid, and reproducible. Lignocellulose has more than two hydroxyl groups and can be passed down as polyols for organic polyurethane preparation. Lignocellulose has the tendency to escalate the electrochemical reactions by interacting with metal sulfides. Figure 11 shows the sensitivity and LOD of various biopolymer based conducting polymer and synthetic polymers composites electrochemical sensor. Table 2 shows electrochemical sensors based on biopolymers with conducting polymers composites.

Biopolymer with nanomaterial composite on electrochemical sensor

Biopolymers based on nanomaterials including metal oxides, graphene, molybdenum disulfide, and nanodiamonds are promising candidates for use in electrochemical biosensors. These nanomaterials have remarkable features namely,

Table 2. Literature on biopolymers-based polymers (conducting or synthetic) composites in electrochemical sensor.

Biopolymer	Structure	Source	Electrode	Probe	Analyte	Technique	Linear range	Limit of detection	Sensitivity	Real sample	Ref
Cellulose	Hydrogel		PANI/MWCNTs/CMC		Ascorbic acid	CV	0.05 mM–5 mM	0.01 mM	100.63 μA mM^{-1} cm^{-2}		[93]
	Nanocrystal		SPE/PPy/CNC/GluOx	Glucose oxidase	Glucose	DPV	1.0 to 20 mM	0.05 mM	0.73 $\mu A \cdot mM^{-1}$	Glucose solution	[27]
	Nanostructure		ITO/CMC-PPy-PB		Glucose, Hydrogen peroxide	CV	20–1100 μM, 5–470 μM	5.23 μM, 0.59 μM	456.8 $\mu A \cdot mM^{-1}$	Milk, Tap water	[98]
	Nanostructure		PEDOT:PSS-CMC-rGO@Pd/GCE		Vitamin K3	LSV EIS CV	4×10^{-7} to 9×10^{-5} M	1.4×10^{-8} M		Animal blood and feedstuff	[103]
	Nanocrystal		PEDOT/AgNPs/CNCC/GCE		Dopamine	CV EIS	0.05–782 μM	17 nM		Human urine	[104]
	Nanocrystal		PEDOT/Fe3O4-CNCC/GCE		Nitrite	DPV CV	0.5–2500 μM	0.1 μM		Pickles	[105]
Chitosan	Nanostructure		Urs/ZnO-en/CHIT-g-PANI/ITO		Urea	Potentiometric	20 ppm–500 ppm (0.3 mM–8.3 mM)	29.84 ppm	187.5 μV ppm^{-1} cm^{-2}	Human blood serum	[95]
	Nanotubes		Chi/PPy-NTs/Au-NPs/ITO	Glucose oxidase	Glucose	EIS CV	3–230 μM	3.10 μM	149 μA μM^{-1} mL		[39]
	Film		Chitosan/PPy/AuNPs/GCE		Xanthine	CV EIS	1–200 μM	0.25 μM	1.4 nA/μM	Meat	[99]
	Film		PPy-CS-Fe_3O_4 NP/ITO		Glucose	Amperometric	1–16 mM	234 μM	12 μA cm^{-2} mM^{-1}		[100]
Lignin	Membrane	Kraft pulping of eucalypt wood (Eucalyptus globulus)	Kraft lignin/MWCNTs		Copper (II) ions	Potentiometric					[110]
	Nanofiber		Lignin/PAN/GRP/SPE		Acetaminophen	EIS DPV					[107]
	Kraft lignin, Organosolv lignin	Kraft pulping of eucalyptus wood (E. globulus), spruce wood (P. abies)	Lignin-based polyurethanes/MWCNTs		Cr(VI)	Potentiometric	1×10^{-5} M–1×10^{-2} M	5.0×10^{-6} M	20 mV pX^{-1} (Kraft) and 21 mV pX^{-1} (Organosolv)		[111]
Starch	Nanostructure		PANI/MWCNTs/Starch/CPE		Cholesterol	CV EIS	0.032 to 5 mM	0.01 mM	800 μA mM^{-1} cm^{-2}	Cow milk	[96]
	Nanostructure		PANI/MWCNTs/Starch/HB/CPE, PANI/MWCNTs/Starch/HB/GluOx/CPE	Glucose oxidase	Hydrogen peroxide and glucose	CV EIS	0.1 mM^{-5} mM	0.032 mM	76.43 μA mM^{-1} cm^{-2}		[97]
Pectin	Nanoparticles		GluOx-PANI–Pec NPs/Pt	Glucose oxidase	Glucose	CV	0.06–4 mM	43.5 μM	79.49 μA mM^{-1} cm^{-2}	Human blood serum	[58]
	Film		PPy/Pct/GR/GCE		Mercuric ions	DPASV	2 μM–29 μM	4 fM	28.64 μA μM^{-1}	Tap water	[101]

PANI, polyaniline, SPE, screen printed electrode, CMC, carboxymethyl cellulose, PPy, polypyrrole, PEDOT, poly(3,4-ethylenedioxy thiophene), PSS, poly(styrene) sulfonate, Pd, palladium, CNCC, carboxylated cellulose nanocrystals, Fe_3O_4, iron (II, III) oxide, Urs, urease, CNC, cellulose nanocrystals, GCE, glass carbon electrode, Au NP, gold nanoparticles, Ag NPs, silver nanoparticles, CHIT, CS, & Chi, chitosan, GluOx, glucose oxidase, MWCNTs, multiwall carbon nanotubes, PB, prussian blue, ITO, indium tin oxide, rGO, reduced graphene oxide, ZnO, zinc oxide, CPE, carbon paste electrode, HB, hemoglobin, NTs, nanotubes, PAN, polyacrylonitrile, GRP & GR, graphene, Pec NPs, pectin nanoparticles, Pct, pectin, Pt, platinum.

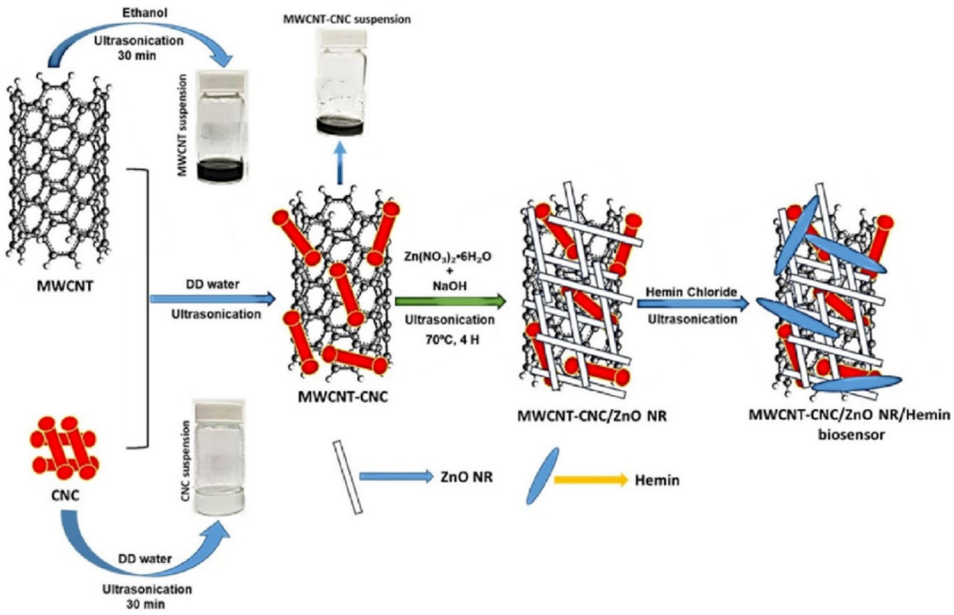

Figure 12. Pictorial depiction for the solution based sonochemical synthesis of ZnO and MWCNT-CNC/ZnO NR composite and fabrication of the MWCNT-CNC/ZnO NR/hemin biosensor. Reused with permission from Ref. [112]. Copyright 2020, Elsevier.

comparable sizes with biological molecules and unique mechanical, electrical, thermal, and multifunctional properties. Any analyte interaction on the biopolymer-nanomaterials will result in a significant change in the electrical properties as well.

Biopolymer-metal oxides

There are abundant metal oxides, but only certain oxides have been widely used in electrochemical biosensors such as zinc, iron, manganese, and copper. The conductivity and crystalline morphology structure of metal oxides induces electron mobility on a stable surface with easy bonding biopolymer. Metal oxides are synthesized mainly through the hydrothermal and sol-gel methods. Covalent bonding of metal oxides with biopolymer helps to overcome its hydrophobic drawback. Palanisamy et al.[112] developed cellulose nanocrystals biopolymer and hexagonal nanorods of ZnO conjugation deposited on MWCNT through sonochemical and ultrasonication for ultrasensitive electrochemical detection of hydrogen peroxide (H_2O_2), as shown in Figure 12. The substrate platform interacts to form iron protoporphyrin instead of an enzyme, for better analytical reaction through cyclic voltammetry. The detection limit of this novel substrate on screen-printed carbon electrode (SPCE) is 4.0 nM at concentrations up to 4183.3 µM.

Iron oxide/nanocellulose crystalline composite deposited on a screen-printed carbon electrode was used to detect *Mycobacterium tuberculosis* (TB).[113] This iron oxide/nanocellulose composite has low discernment at 7.96×10^{-13} M for concentrations in the 1.0×10^{-6} to 1.0×10^{-12} M range. Khalilzadeh et al.[114] developed a magnetic iron oxide@cellulose nanocrystals with copper using a plant extract (Petasites hybridus leaf) as a stabilizing and reducing agent for copper to detect venlafaxine. The sensor has a detection limit of 0.01 μM for venlafaxine with concentrations range between 0.05 to 600 μM. Chen at el.[41] developed a layer-by-layer deposition of manganese oxide in the form of nanoflakes with chitosan, with these materials interacting strongly due to opposite charges formed in them. Manganese oxide and chitosan improve physical and chemical properties, which enhances the oxidation of hydrogen peroxide with a sensitivity of 0.038 A M^{-1} $cm^{-}2$, as chitosan is used as a polyelectrolyte consisting of positively charged ions that facilitates layer-by-layer modification. Electrostatic interaction when combining chitosan with nickel ferrite and copper oxide is significant in biosensing applications. Chitosan has remarkable biocompatibility and the ability to form films, with nickel ferrite having excellent stability in catalytic chemical interactions to bond with chitosan. Copper oxide can enhance the electron transfer efficiency, as it is a monoxide medium. These nanocomposite substances result in high sensitivity of 0.043 μA/(mg/L cm^{-2}), with a detection limit of 313 mg/L.[115] Yazhini et al.[116] developed a hetro-metal oxides nanohybrid composite on pectin as a scaffold that has efficient shuttling of electrons for sensing applications, as the nanohybrids acquire synergistic effect due to the attachment of hetro-metal oxides nanohybrid to the pectin by –OH binding. The blending of copper oxide and iron oxide was made through co-precipitation method and ultrasonication, grown on a pectin matrix extracted from musk melon peels. The hetro-metal oxides nanohybrid composited has good electrocatalytic reactions as copper oxide and iron oxide are biocompatible, have easily modifiable structure, and have a highly charged surface. Liu et al.[117] developed pectin-derived carbon with cobalt (II, III) oxide to form a hollow nanosphere surface morphology that overcomes the major problems of cobalt (II, III) oxide in terms of high temperature and low response, with pectin acting as a soft template. The hollow nanostructure improves the transportation of electrons which directly effects the analytical performance in detecting hydrogen peroxide. Pectin derived

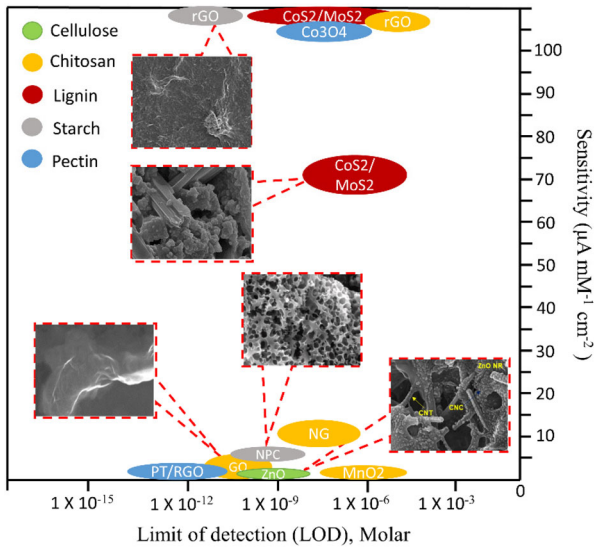

Figure 13. Comparison of different biopolymer-based nanomaterials composites by sensitivity and limit of detection (LOD) in electrochemical sensor. Reproduced with permission from Refs. [112, 119, 123, 124, 127]. Copyright 2020, 2019, 2018, 2021, 2017, Elsevier.

carbon with cobalt (II, III) oxide biosensor has a sensitivity of 405.8 μA·mM·cm^{-2} and a detection limit of 0.30 μM.

Biopolymer-graphene

Graphene is a single layer of carbon atoms, strongly bound in hexagonal honeycomb lattice. It has an allotrope of carbon in the form of a plane of sp^2 bonded atoms with a molecular bond length of 0.142 nm. Its derivatives such as reduced graphene, graphene oxide, and nitrogen-dopped graphene oxide have the best electrical conductivity of any material. Even though graphene is a nonmetal, it has a good specific surface area, extraordinary electronic properties, fast electron transport abilities, and ultra-flexibility. It is an excellent conductor with biopolymer owing to its large surface area and good film assembly, making the combination of graphene and especially chitosan an important substrate. A layer-by-layer method fabrication of a glucose biological sensor[118] resulted in the accumulation of biorecognition such as glucose oxidase on chitosan, by conjugating nitrogen embedded graphene on chitosan with a sensitivity of 10.5 μA cm^{-}2 mM^{-}1 and a detection limit of 64 μM. Adumitrăchioaie et al.[119] developed an electrochemical sensor based on chitosan and graphene oxide for the detection of serotonin. Graphene's carboxylic group interacts with antibodies covalently, while chitosan stabilized the nanocomposite deposited on an electrode during the sensing of serotonin concentrations, with a detection limit of 3.2 nM in the range of 10 nM to 100 µM. Similarly, the covalently bonded nanocomposite of graphene and chitosan structure can be modified into film and nanoribbons by blending for glucose, guanine, adenine, thymine, and cytosine determination.[120,121] R. Krishna et al.[122] synthesized reduced graphene oxide/nickel nanoparticles (rGo-Ni NPs) deposited onto glassy carbon electrode as a hybrid nanocomposite film of chitosan and glucose oxidase. The developed glucose sensor showed a sensitivity up to 129 μA cm^{-2} Mm^{-1} at a low operating potential. Starch is also capable of forming a film, as it has two carbohydrate units that have different structures and roles, amylose and amylopectin. Amylose forms a film when it attaches to water, forming hydrogen bonds with water and further reducing water affinity to form a matrix. Orzari et al.[123] developed a highly conductive film using manioc starch and reduced graphene oxide for phenolic compound detection. The functional groups in Manioc starch form π–π bonds with reduced graphene oxide to enhance the functionality of the film and electrical conductivity. Graphene disperses easily in polymers which increases the surface area and the interactive sensing surface. This film sensor can detect dopamine and catechol with a detection limit of 0.07 and 0.04 μmol L^{-1}, respectively through CV analysis. Starch can also be extracted from seeds such as *Artocarpus heterophyllus* to create a nitrogen bonded porous carbon material with high magnetic strength, indestructible carbon-nitrogen bond, a large surface area and porous surface morphology, which facilitates the transfer of electrons sensing interface. The nitrogen bonded porous carbon material exhibits excellent electrochemical stability, reproducibility, sensitivity (4.64 µA µM^{-1} cm^{-2}), and a low detection limit (2.74 nM) in detecting dopamine. The interactions of starch-based nitrogen bonded porous carbon materials with dopamine were stronger at −0.64 eV compared to oxygen-filled sheets.[124] Apart from metal oxides, graphene oxide has been widely used as a conductive substrate. However, the charged ions diffusion in graphene is limited due to the nonreversible aggregation or accumulation of hydrophobic sheets attached by van der Waals interaction in graphene. The conjugation of graphene oxides with pectin in an electrochemical sensor is necessary due to the presence of functional groups, with graphene oxide interfacial adhesion of pectin. Graphene oxide sheets exhibit good functionality, with smaller substrates forming a large surface area, enhancing the electrons transportation with low resistance ions compared to bulk graphene. Pectin and reduced graphene oxide was coupled to form a nanocomposite to detect dopamine and paracetamol, with a detection limit of 1.5 and 1.8 nM respectively through linear sweep voltammetry (LSV) techniques.[125]

Biopolymer-molybdenum disulfide (MoS_2)

Wang et al.[126] used molybdenum disulfide (MoS_2) for electrical conductivity in a cellulose-based substrate, as cellulose has poor conductivity. MoS_2 is derived from a transition metal, where molybdenum is placed in group 6, whereas chalcogen is from group 16 in the periodic table. MoS_2 layered semiconductor with a band gap of 1.2 eV can resists oxidation at temperatures of up to 85 °C. Cellulose from a straw can be modified structurally to a carbon nanotube structure using TEMPO-mediated oxidation. The TEMPO-oxidized straw cellulose underwent the hydrothermal method with a MoS_2 precursor to allow MoS_2 to grow at the edges of the TEMPO-oxidized straw cellulose (TOSC) surface. The TOSC substrate was subsequently used to detect

Table 3. Literature on biopolymer-based nanomaterials composites in electrochemical sensor.

Biopolymer	Structure	Source	Electrode	Probe	Analyte	Technique	Linear range	Limit of detection	Sensitivity	Real sample	Ref
Cellulose	Nanofiber	Straw pulp	TOSC-MoS_2/GCE		Nitrite	CV	6–3140 μM, 3140–4200 μM	2.0 μM		Drinking water, River water	[126]
	Nanocrystals	Cotton linters	MWCNT-CNC/ZnO NR/He/SPCE		Hydrogen Peroxide	CV	0.01–4183.3 μM	0.004 μM	0.134 μA μM^{-1}	Milk (low-fat)	[112]
	Nanocrystals	Plant extract (Petasites hybridus leaf)	Fe_3O_4@CNC/Cu/GSPE		Venlafaxine	CV DPV	0.05–600.0 μM	0.01 μM		Urine, Water, Pharmaceutical formulation	[114]
	Nanocrystalline		MPA-Fe_3O_4/NCC/CTAB/SPCE		Mycobacterium tuberculosis	DPV	1.0×10^{-6}–1.0×10^{-12} M	7.96×10^{-13} M		Sputums of patients (TB positive)	[113]
Chitosan	Film		PEI/MnO_2/(Chitosan/MnO_2)$_2$/ITO		Hydrogen peroxide	CV	2.5×10^{-6} to 1.05×10^{-3} M	2 μM	0.038 A M^{-1} cm^{-2}		[41]
	Film		Chit+(NG + GluOx)/PSS−/chit+(NG + GluOx)/AuQC	Glucose oxidase	Glucose	CV EIS	0.2–1.8 mM	64 μM	10.5 μA cm^{-2} mM^{-1}		[118]
	Film		ChOx/$NiFe_2O_4$/CuO/FeO-CH/ITO		Cholesterol	CV DPV EIS	50–5000 mg/L	313 mg/L	0.043 μA/(mg/L cm^{-2})	Human Serum	[115]
	Film		SPE/GO-chitosan/anti-serotonin Ab	Anti-serotonin Ab	Serotonin	DPV	0.01 μM–100 μM	3.2 nM	0.05 μA/μM	Human serum, Saliva, Artificial tears, Urine	[119]
	Film		GONRs-CH/GCE		Guanine, Adenine, Thymine and Cytosine	CV EIS	0.013–256 μM, 0.11–172 μM, 6.0–855 μM, 3.5–342 μM	0.0018 μM, 0.023 μM, 1.330 μM, 0.640 μM		Single nucleotides, dsDNA	[121]
	Film		rGO-Ni/Chitosan/GOx/GCE	Glucose oxidase	Glucose	CV EIS	0.025–1 mM	390 μM	129 μA·cm^{-2}·mM^{-1}		[122]
Lignin	Nanofiber	Paper pulp	N-LC/CoS_2-MoS_2/GCE		Ascorbic acid (AA), Dopamine (DA), Nitrite	CV EIS	9.9–6582 μM, 0.99–261.7 μM, 0.5–5160 μM	3.0 μM, 0.25 μM, 0.20 μM	4941.8 μA μM^{-1} cm^{-2}, 73.3 μA μM^{-1} cm^{-2}, 5732.9 μA μM^{-1} cm^{-2}	Human Urine	[127]
Starch	Nanostructure	Potato	Tyr-ND-PS/GCE	Tyrosinase	Catechol	DPV CV	5.0×10^{-6}–7.4×10^{-4} mol L^{-1}	3.9×10^{-7} mol L^{-1}		Tap water, River water	[128]
	Nanostructure	Manioc	ND-MS/GCE		Diquat	SWV	5.0×10^{-7} to 4.6×10^{-5} mol L^{-1}	1.1×10^{-7} mol L^{-1}		River water, Drinking water	[129]
	Film	Manioc	ND-MS/GCE		Tetracycline	DPV	5–180 μmol L^{-1}	2.0 μmol L^{-1}		Water, Wells water	[130]
	Film	Manioc (Manihot species)	rGO-MS/GCE		Dopamine, Catechol	CV	0.5–200 μmol L^{-1}, 0.5–74 μmol L^{-1}	0.07 μmol L^{-1}, 0.04 μmol L^{-1}	2913 μA (μmol L^{-1})$^{-1}$ cm^{-2}	Water, Synthetic urine	[123]
	Nanostructure	Artocarpus heterophyllus seeds	NPC/GCE		Dopamine	EIS CV DPV	30–90 μM, 200–400 μM	2.74 nM	4.64 μA μM^{-1} cm^{-2}	Human serum, Urine	[124]
Pectin	Hydrogel		PT/rGO/GCE		Dopamine, Paracetamol	CV LSV	0.003–90.206 μM, 0.003–91.04 μM	1.5 nM, 1.8 nM	5.71 μA μM^{-1}cm^{-2}, 3.896 μA μM^{-1}cm^{-2}	Human serum, Pharmaceutical	[125]
	Nanoparticles		hs-S300-Co3O4/C-GCE		Hydrogen Peroxide	Amperometric	0.90 μM–5.98 mM	0.30 μM	405.8 μA·mM·cm^{-2}	Tap water, River water	[117]

SPE, screen printed electrode, CNC, cellulose nanocrystals, GCE, glass carbon electrode, GluOx, glucose oxidase, MWCNTs, multiwall carbon nanotubes, rGO, reduced graphene oxide, ZnO NR, zinc oxide nanoribbon, TOSC, TEMPO-oxidized straw cellulose, MoS_2, molybdenum disulfide, He, hemin, Cu, copper, MPA, mercaptopropionic acid, CTAB, cetyl trimethyl ammonium bromide, PEI, polyethylenimine, rGO, reduced graphene oxide, Ni, nickel, MnO_2, manganese (IV) oxide, NG, nitrogen doped graphene, ITO, indium tin oxide, PSS, poly(styrene sulfonate), AuQC, gold quartz crystal, ChOx, cholesterol oxidase, $NiFe_2O_4$, nickel ferrite, CuO, copper oxide, FeO, iron oxide, CH, chitosan, GONRs, graphene oxide nanoribbons, N-LC, nitrogen doped lignocellulose, CoS2, cobalt sulfide, Tyr, tyrosinase, ND, nanodiamond, PS, potato starch, MS, manioc starch, NPC, nitrogen porous carbon, PT, pectin, Co3o4, cobalt (II, III) oxide.

nitrite. The composite substrate has an efficient signal transfer as cellulose nanofiber has a larger surface area and semi-crystallinity, whereas MoS_2 is a semi-conducting metal with graphene-like structure. This combination of materials enhances the detection of nitrite, with a detection limit of 2.0 μM in wide linear ranges of 6.0–3140 and 3140–4200 μM. Zhang et al.[127] found that cobalt disulfide (CoS_2) and MoS_2 incapacitated with nitrogen-doped lignocellulose improved the efficiency of electron transportation during ascorbic acid, dopamine, and nitrite identification on glass carbon electrode with a sensitivity of 4941.8 μA μM^{-1} for ascorbic acid, 73.3 μA μM^{-1} for dopamine and 5732.9 μA μM^{-1} for nitrite.

Biopolymer-nanodiamonds

Starch is an alternative biopolymer for carbon synthesis. Starch from potatoes and tapioca has unique properties to convert into carbon, especially when a high thermal process is applied, with an increased solubility. The concentration of starch in a metal mixture solution determines the electrochemical performance of a sensor. Starch, in particular potato starch, has good chemical stability, is easy to modify, inexpensive, can be found abundantly, in nature and is biocompatible. Camargo et al.[128] developed a toxic-free potato starch coupled with nanodiamonds for catechol detection. The conductive synergistic matrix forms a remarkably large surface area that eases the deposition of tyrosinase (enzyme) to detect catechol with a detection limit of 3.9×10^{-7} mol L^{-1} with a linear range from 5.0×10^{-6} to 7.4×10^{-4} mol L^{-1} through differential pulse voltammetry (DPV) measurements. N.A. Zambianco et al.[129] developed nanodiamond nanoparticles conjugated with manioc starch to detect herbicide diquat (DQ) in environmental samples. The composite material is structurally stable, and has good analytical performance with efficient electron transfer, with a detection limit of 1.1×10^{-7} mol L^{-1} from a linear range of 5.0×10^{-7} to 4.6×10^{-5} mol L^{-1}. Fernandes-Junior et al.[130] found that nanodiamonds improved electrochemical surface area and strengthen the manioc starch film polymeric mechanical nanocomposite structure for the detection of tetracycline. Figure 13 shows various biopolymer-based metal composites electrochemical sensors of their sensitivity and LOD. Table 3 summarizes biopolymers with metal composite electrochemical sensors.

Conclusions and future perspectives

Significant progress has been made in recent years on biopolymers for electrochemical sensors, especially on the structural composition of cellulose, chitosan, lignin, starch, and pectin conjugated with nanoparticles, polymers, and nanomaterials. Biopolymers are mainly for biochemical modification in electrochemical sensors, enhancing their bio-functionality, electron transfer, conductivity and biochemical reaction. In summary, cellulose, with its large and porous structure, forms numerous actives sites for bioreceptors to capture analytes (target), increasing its sensitivity. Chitosan, is the most promising substrate for enzyme immobilization due to its biocompatibility and multiple functional groups. It has free amino acids in its structure, which improves its solubility and active sites. It can be altered easily while retaining its original properties, and it can interact with bioactive molecules such as antibodies and enzymes. Meanwhile, lignin can be modified into functionalized lignin through simple chemical modifications as a biosensor substrate. Alteration in its aliphatic and phenolic alcohol through acetylation creates hydrocarbons that can be easily attached to any solvents and compounds. Starch's biggest advantage is having a reducing agent. As such, no additive such as formic acid or oxalic acid is needed in the fabrication of a hybrid material. Pectin on the other hand, has a stabilizer that traps covalently bonded enzymes and proteins. Conjugating biopolymers with conductive nanomaterials like nanoparticles, conducting polymers and metal oxides forming conducive composite substrates enhance the analytical performances of the biosensor. Pectin biopolymer tends to give the best LOD for nanoparticles (CCLP/Au NPs),[60] polymers (Pectin/PPy)[101] and nanomaterials (Pectin/rGO)[125] composites biosensors. In all three composites considered, pectin biopolymer has the lowest LOD (better than picomolar) compared to other biopolymer composites. Unfortunately, pectin biopolymer composites do not have the best surface sensitivity due to their hydrophobic characteristics, swelling under acidic condition, and fragile surface. Composites that display the best LOD have borderline sensitivity reading. The biosensor with the highest sensitivity to date is those with the combination of Pectin/MWCNT,[76] Starch/PANI,[96] and Lignin/CoS2/MoS_2.[127] Pectin/rGO/GCE[125] and Lignin/CoS2/MoS_2/GCE[127] biosensors can detect multiple analytes, although there are huge differences in LODs. Biopolymers increase the number of active sites, allowing more bioreceptors to be captured on a composite material. Indeed, these biopolymers have proven their efficiency in bonding through cross-linking, covalent, electrostatic and entrapment processes, with bioreceptor to detect targets. Conductive additive materials have been used to enhance the conductivity of the biopolymers, with biopolymers serving as a stabilizing, reducing, and absorbent agent for rapid response. Additionally, the production cost is reduced when using biopolymers instead of expensive engineered polymers. An ideal biosensor would be one that can detect multiple analytes in the lowest analyte concentration, highest sensitivity and highest selectivity. Deciding the right composite in a biosensor is challenging, with the choice depending on the analyte, sensitivity, and selectivity required. Future work should look at the development of a multi-analyte biosensor that is highly sensitive and selective, made from composites that are biodegradable and based on environmentally friendly technology. Additionally, the performance of carrageenan, alginates and pullulan composites should be compared with reviewed biopolymers for electrochemical biosensors.

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