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Review paper

Next-generation electrochemical sensors and biosensors for paracetamol detection: emerging trends and future perspectives

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Abstract

Paracetamol (PCT), a widely used drug, is increasingly present in environmental and pharmaceutical samples, raising the need for monitoring and control. Electrochemical sensors (ES) and electrochemical biosensors (EBS) have proven to be promising analytical methods for PCT detection. This review aims to provide a comprehensive comparison of ES and EBS for PCT detection, highlighting advances in electrode modification strategies, signal amplification approaches and biological recognition elements. The reported limits of detection range from the picomolar level (≈10 pM in immunosensors) to the micromolar range, varying with material design and recognition element. Carbon-based and metal/metal oxide materials enhance sensitivity through improved electron transfer and catalytic activity. Enzymatic and antibody-based sensors provide higher selectivity. The drawbacks of enzymatic and non-enzymatic biosensors are low long-term stability, enzyme degradation, lack of interference testing in different sample matrices and lack of standardized protocols. Antibody- and DNA-based electrochemical platforms for PCT are under-analysed fields compared to nanomaterial-driven approaches. This review also identifies current challenges, the need for standardised protocols and key drawbacks of ES and EBS systems. Future perspectives for the development of hybrid, portable, miniaturized, and real-time monitoring systems are further outlined.

Keywords

Environmental monitoring; pharmaceutical pollutants; acetaminophen detection; electrochemical techniques; electrode surface modification

Introduction

Over the last decade, there has been a steep increase in the consumption of drugs to improve the quality and longevity of human life. The global market for these pharmaceuticals has experienced significant growth. In 2023, it is estimated that 1.6 trillion USD was spent on pharmaceutical products in 2025, an increase of 100 billion USD compared to the previous year. This market includes drugs consumed by humans and animals. Increased consumption of these drug products has led to a significant increase in the excretion of these pharmaceutical pollutants in water and wastewater systems. Wastewaters around the world contain various pollutants, among which the most concerning are persistent pharmaceutical pollutants (PPP), an emerging micropollutant. These PPPs are known to disrupt endocrine function in humans and animals, ultimately leading to hormonal imbalances. Excretion of these pharmaceuticals can occur due to improper metabolism in humans and animals, with excretion via urine or faeces [1,2].

Paracetamol (PCT) (also known as acetaminophen, $C_8H_9NO_2$) is a commonly used over-the-counter (OTC) drug that is used as a pain reliever or to reduce fever (antipyretic/analgesic) around the world for children and adults. The availability of PCT at a low price and being an OTC drug has inevitably led to its overconsumption. Owing to its extensive use, it is one of the most prevalent pharmaceuticals in the environment, present in various forms. Their prevalence in water systems has been calculated around the world [3]. It was seen that the wastewater treatment plants of France, the USA, and the UK had PCT concentrations of 11.3, 150 and 11.7 μg L^{-1} (0.0748, 0.992 and 0.0774 μM), respectively. Another study conducted in Kenya found PCT at concentrations of 107 μg L^{-1} (0.07 μM) in river water [4,5]. In Taiwan, river water and hospital wastewater were tested for PCT with concentrations of 15.7 and 75.5 μg L^{-1} (0.104 and 0.499 μM) [6].

Conventional treatment for PCT in water includes biodegradation, sedimentation, adsorption, membrane filtration, and photolysis, depending upon the concentration of the drugs in the water. Although many treatment methods are being implemented globally, the lack of proper regulation for the disposal of PCT makes it prevalent in various water bodies. Prolonged exposure to PCT causes adverse effects to humans and aquatic life, mainly disrupting the endocrine system, followed by the development of chronic liver diseases. The harmful effects of PCT in aquatic bodies have been extensively studied. A study conducted on PCT-exposed zebrafish helped us better understand the dangerous effects of PCT exposure in living organisms. Given the potential impact of pharmaceutical residues on the environment, even at concentrations as low as nanograms per litre, it is crucial to prioritise the development of new methods for their detection and measurement [7].

Conventional detection methods include chromatographic, photometric, chemiluminescent, and titrimetric techniques. These methods require trained professionals and large equipment to analyse contaminated samples, and do not provide quick, real-time results. To overcome these obstacles, the most commonly used innovative approach in the scientific literature for detecting PCT in water is the use of carbon-based electrochemical sensors (ES) or electrochemical biosensors (EBS). PCT is an electroactive compound, making it a viable option for a simple, quick, and accurate analysis of PCT in water samples. ES are analytical devices that electrically detect the occurrence of chemical reactions (redox reactions) at the electrode surface. Carbon-based ES is one of the most used methods for detecting pharmaceutical waste in water owing to its cost-effectiveness, wide potential range, and sensitivity. These carbon-based ES include materials like carbon nanotubes (CNT), graphene, graphene oxide (GO), graphene quantum dots (GQD), carbon quantum dots (CQD), and reduced graphene oxide (rGO). Other popular materials for ES of pharmaceutical compounds,

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metals, and metal oxide-based materials. EBS are a class of biosensors that use an electrochemical transducer and a biological material like enzymes, ligands, antigens, and sometimes tissues. EBS can not only give real-time results but also provide high selectivity and sensitivity [8-15].

Given that numerous studies have been conducted on the detection of PCT using ES and EBS, this review aims to provide a critical and comparative analysis of these two sensor categories, with a specific focus on sensitivity, selectivity, stability, interference tolerance, and real-sample applicability. The studies considered for this review include developments over the past decade. A special focus was placed on recent advancements that reveal emerging routes in material engineering and bio-recognition opportunities. The studies were selected based on sensor performance in electrochemical settings, real-life sample analysis and detailed discussion of the mechanism. Previous reviews have summarised electrochemical detection of pharmaceutical pollutants, many of which focus on multiple drugs or on material types, without critically comparing ES and EBS platforms specifically for PCT. Therefore, this work is an updated and focused analysis that integrates recent developments, highlights current limitations, and identifies research gaps for next-generation sensor design.

Paracetamol: an emerging persistent pharmaceutical pollutant

Fate of paracetamol

Paracetamol has become increasingly prevalent in water bodies due to its overconsumption and non-standardised disposal methods. The fate of PCT is shown in Figure 1. After being introduced into the environment, PCT demonstrates significant mobility and durability, especially in aquatic systems. It readily accumulates in water bodies without being significantly absorbed or slowed, resulting in potentially dangerous concentrations.

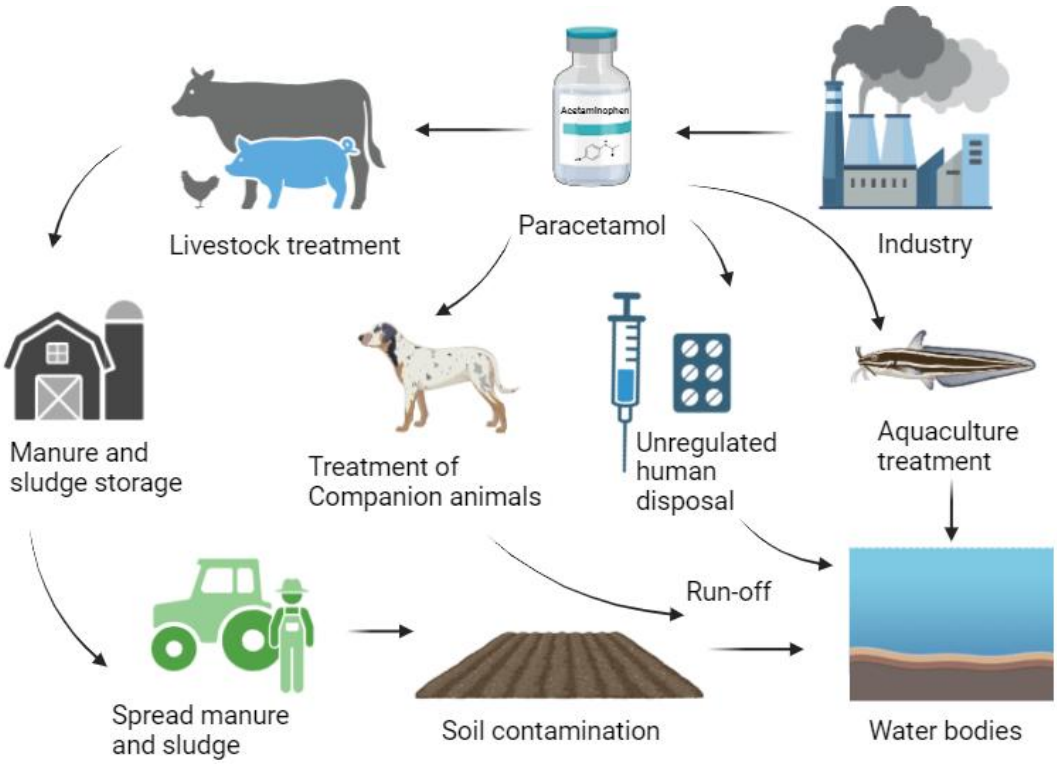

Figure 1. *Fate of paracetamol in the environment*

The continuous release of PCT and its byproducts poses ecological hazards that can disrupt aquatic ecosystems and affect species that are not the intended targets. Furthermore, the presence

of PCT in various environmental matrices, including drinking water sources, raises concerns about human exposure to this pollutant.

The complexity of removing PCT contamination poses challenges for efforts to mitigate its environmental impact. Traditional methods of treating wastewater, such as chemical oxidation processes, are efficient but can generate additional pollutants and require expensive operations. Recent trends also include investigating environmentally friendly alternatives such as biodegradation. Microorganisms are essential for converting PCT into harmless substances through biotransformation. Ongoing research focuses on studying the metabolic pathways and enzymes involved in microbial degradation to develop treatment techniques that are both efficient and cost-effective. The persistent presence of PCT in the environment emphasises a need for sensitive and rapid monitoring techniques [16].

Natural degradation route of paracetamol

Wastewater containing pharmaceutical contaminants is remediated using an advanced oxidation process (AOP). The most used AOPs include the Fenton process, photo-Fenton process, TiO_2 photocatalysis, UV photocatalysis, and ozonation with H_2O_2 [17].

Detailed knowledge of the fate of PCT in the environment is very limited. Current accounts show that the efficiency for the removal of PCT varies from 70 to 99 %, depending upon the specific systems used in different countries [18,19]. In aquatic systems, PCT degrades by photolysis, biodegradation, and hydrolysis. These processes change in efficiency depending on environmental factors such as pH, temperature, light intensity, and microbial activity [3,4,16,20,21].

PCT degradation predominantly occurs via photolysis in sunlight-exposed waters. The drug absorbs light in the range of 245 to 310 nm, which causes bonds in the aromatic ring to break. The primary products formed by this cleavage is 1,4-benzoquinone and hydroquinone, which result from deacetylation and hydroxylation. Indirect photolysis transpires when dissolved organic matter and nitrate function as photosensitizers, generating reactive oxygen species, including hydroxyl radicals, singlet oxygen, and triplet excited states of dissolved organic matter. These radicals assault the aromatic ring and amide group of PCT, producing intermediates such as N-acetyl-p-benzoquinone imine and p-aminophenol. Photolysis efficiency is inhibited by water depth, as shallow waters allow greater light penetration, and by climate variations. Microorganisms in water can enzymatically degrade PCT via aerobic (e.g., *Pseudomonas spp*.) and anaerobic processes. In aerobic reactions, the bacteria use PCT as a source of carbon and nitrogen. Arylamine N-acetyltransferases and dioxygenases are some of the enzymes that break the aromatic ring, resulting in the formation of p-aminophenol and hydroquinone. Under anaerobic conditions, the PCT reaction forms p-aminophenol, which remains in the water because anaerobic reactions are slow. Studies on the pathway of PCT degradation in anaerobic conditions are limited. The efficiency of microorganism biodegradation is dependent on microbial variety and oxygen presence [3,21].

Another method of PCT degradation is through the process of hydrolysis. This is a pH-dependent method and primarily occurs in alkaline conditions where the pH is above 8. Here, the amide bond is broken down, which in turn forms p-aminophenol and acetic acid. In neutral waters, between 6 and 8 pH, hydrolysis occurs very rarely. Apart from the influence of pH, higher temperatures also accelerate the hydrolysis of PCT, resulting in similar byproducts. Other processes, such as adsorption and sedimentation, also affect the presence of PCT in water. The drug tends to adsorb onto sediments or organic matter present in water or by aquatic plants like Lemna minor. The efficiency of adsorption depends on the amount of carbon in the water; the higher the carbon content, the

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higher the PCT adsorption rate. Another factor that affects the efficiency is the surface area of the organic matter, since a higher surface area leads to increased adsorption [3]. The summary of the various degradation pathways is given in Figure 2.

Although PCT undergoes natural degradation through various processes, it remains abundant in water bodies. PCT has been found in surface waters worldwide, mostly in urban areas. All the above methods of degradation are dependent on various environmental factors. When over 145,000 metric tons of the drug are produced every year, a large amount of it enters the water bodies, making it essential to produce a real-time analysis device to prevent long-term contamination [22].

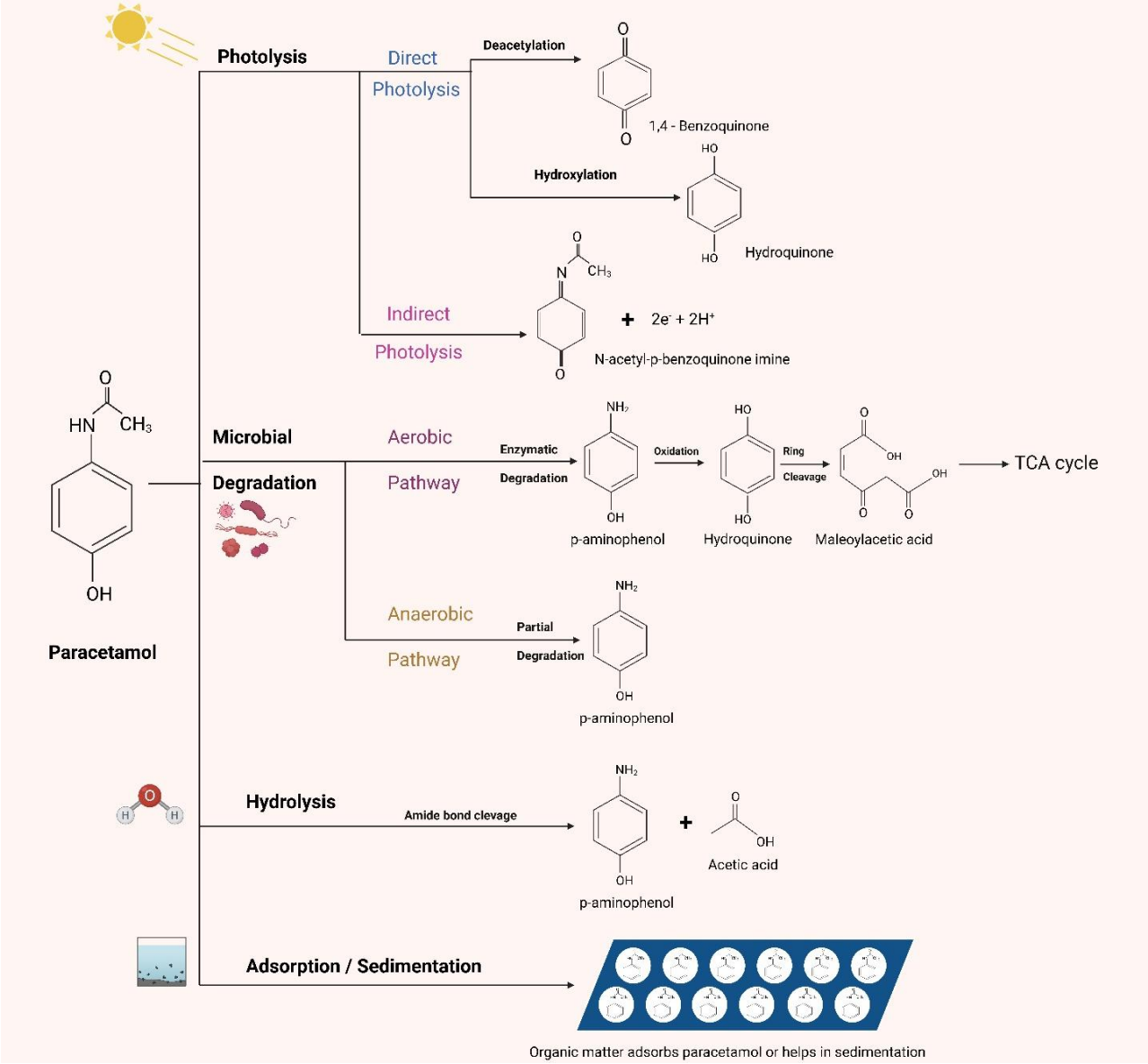

Figure 2. *Various degradation pathways of paracetamol*

Electrochemical sensors

Sensors convert physical or chemical stimuli into processable and measurable electrical signals. The physiochemical stimuli include heat, pressure, force, temperature, light, *etc*. These are then transformed into electrical signals like voltage, current, and frequency, which are processed and measured. This helps us to achieve a quantifiable response at the sensor interface. The two most important parts of sensors are the transducer (which converts physicochemical phenomena into electrical signals) and the recognition element (the material on the surface of modified electrodes).

Considering the various sensing routes achieved to date, sensors are categorized into electrochemical, optical, thermal, calorimetric, gas, and other types. For this review, we focus on principles and techniques of widely used electrochemical sensors [23].

Working principle of electrochemical sensors

The main working principle of ES is the transfer of electrons at the electrode/electrolyte interface. This results from redox reactions on the electrode surface. These reactions take place in an electrochemical cell. This concept of electrochemistry enables a system that permits the exchange of electrical and chemical energy and is used in various fields, including energy storage technologies such as supercapacitors and solar cells, hydrogen production, and environmental remediation. When examining an electron redox reaction, the reduced species ($\underline{r_n}$) and the oxidized species (o^{n+1}) participate as described in Equation (1):

$$r_n \rightleftharpoons o^{(n+1)} + e^- \quad (1)$$

Upon applying a potential (*E*), the equilibrium of this reaction is disrupted, driving the reaction in both directions. Specifically, the reduced form (r) is oxidized to the oxidized form (o), and simultaneously, *o* is reduced back to *r*. This dynamic exchange generates an electron flow, producing a measurable current. The measured current (*i*) is directly proportional to the quantitative changes in the electrolyte used. This current is described by Equation (2):

$$i = nAFJ \quad (2)$$

where *i* / A is the current, *n* is the number of electrons transferred, F = 96,485 C mol^{-1} is the Faraday constant, *A* / m^2 is the electrode area and *J* / mol m^{-2} s^{-1} is the molar flux of the electroactive species to the electrode surface. Equation (2) is fundamental for ES because the measured current is directly proportional to the flux of the electroactive species at the electrode surface. Under diffusion-controlled conditions, the molar flux is governed by Fick's first law and is proportional to the concentration gradient between the bulk solution and the electrode surface. Therefore, the current is directly related to the analyte concentration in solution, as variations in analyte concentration produce proportional changes in current response. Flux is very important in an ES, as it occurs when an analyte present in the bulk electrolyte moves toward the electrode surface. This facilitates electron transfer between the analyte and the surface of the working electrode. The movement of analyte through the bulk electrolyte solution towards the electrode surface is called mass transfer. However, in ES, mass transfer occurs at a slower rate than electron transfer. Hence, if an electroactive species in the analyte reaches the reaction, it is reduced, making mass transfer the rate-limiting step. Mass transfer can occur in three ways: diffusion (analyte moves down a concentration gradient), convection (analyte movement by mechanical forces or temperature), and migration (charge analyte movement in an electric field) [24,25].

ES can be further classified based on the electrical parameter that is measured. In amperometric sensors, the potential is held constant and the resulting current is measured as a function of time. Under diffusion-controlled conditions, the current is directly proportional to the analyte concentration. In voltammetric sensors, the potential is varied under controlled conditions, and the resulting current-potential relationship is recorded. The peak current obtained in techniques such as cyclic voltammetry or differential pulse voltammetry is proportional to analyte concentration and provides both qualitative and quantitative information. Potentiometric sensors measure the potential difference between a working and reference electrode under negligible current conditions. The measured potential follows the Nernst equation and is logarithmically related to

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analyte concentration rather than being directly proportional to flux. For redox-active compounds such as PCT, amperometric and voltammetric techniques are most commonly used [24].

ES are analytical devices that quantify chemical reactions through electrochemical processes. They usually consist of a sensing element (the electrode), a transducer (which converts chemical reactions into measurable electrical signals), and a signal processing system. In pharmaceutical pollutant detection, the electrodes are often modified using various materials and methods. For this review, to conduct a comparative analysis of the selectivity of ES and EBS towards PCT, we will consider the most commonly used electrode modifiers. They are carbon-based ES and metals and metal oxides-based ES. The general schematic principle of ES is given in Figure 3.

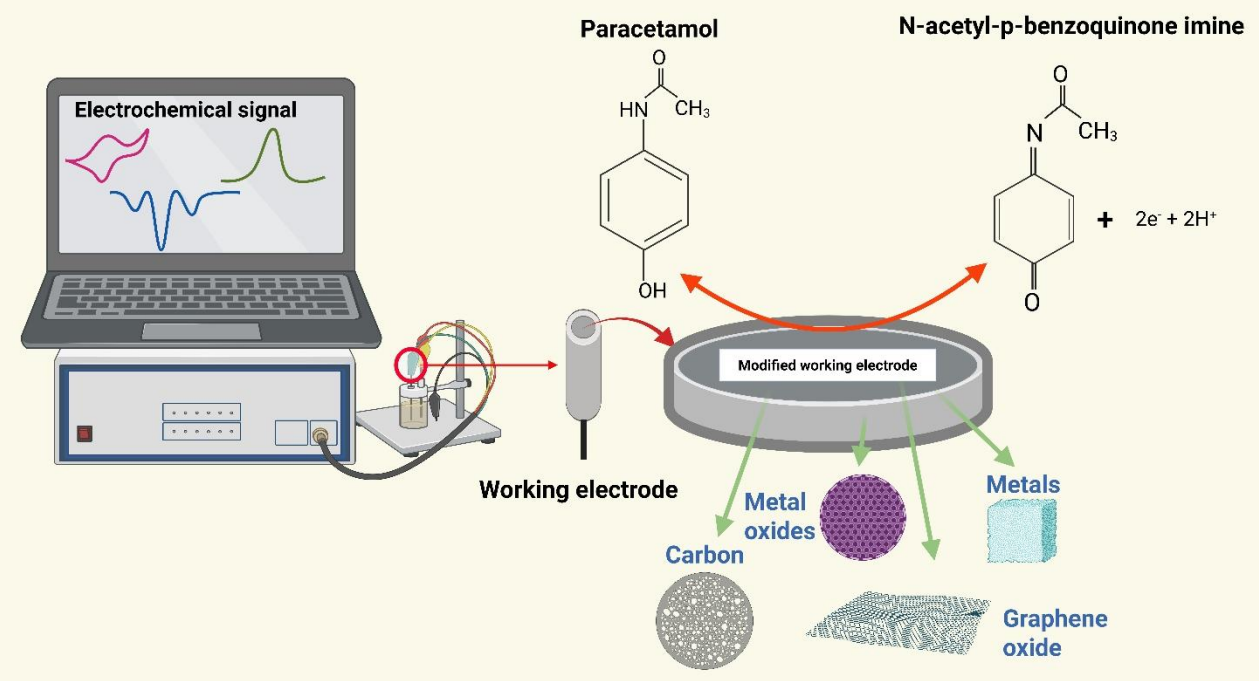

Figure 3. *Structure of an electrochemical sensor for paracetamol detection*

Carbon-based electrochemical sensors

Due to the growing interest in electrochemical sensors for PCT detection, carbon-based materials have garnered significant attention as electrode-modifying materials. CNTs, graphene, and their analogues are widely used due to their ease of synthesis, abundant availability, biocompatibility, and cost-effectiveness. CNTs have been widely investigated for use in electroanalytical devices due to their excellent physicochemical properties, high conductivity, and large surface area. A study [12] was performed using a CNT composite with zinc oxide nanoparticles (NPs) for the detection of PCT, diclofenac, and orphenadrine. The electrode proved to have superior detection towards PCT at 2 µM. The primary sensing mechanism involved interactions between the CNT and O-H/N-H groups, forming hydrogen and π-π interactions with the aromatic rings of the PCT, leading to increased adsorption of the compound on the electrode surface. This occurs during the simultaneous oxidation of PCT to NAPQI, resulting from the transfer of two electrons coupled with two protons. In this study, an anti-interference test was performed in the presence of anions, cations, excipients, surfactant, organic acids, amino acids, and other organic compounds. It was also seen that the optimal potential window of PCT detection was between 0.2 to 0.5 V *vs.* Ag/AgCl. The potential windows of the other interfering compounds were not presented.

Another study used CNT-modified methyl orange for the simultaneous detection of PCT, folic acid, and diclofenac, which are all commonly used drugs [10]. Here, the primary mechanism of

sensing was claimed to be electrochemical oxidation of PCT into NAPQI. Cyclic voltammetry studies were performed to assess the effect of interfering compounds on the materials' sensitivity and selectivity. Three distinctive peaks across varying potential windows (the PCT oxidation window was 0.1 to 0.5 V vs. SCE), indicating the successful detection of all three compounds. Superior sensing ability was seen in PCT detection with a limit of detection of 38 nM.

Graphene was used to modify a bare glassy carbon electrode for the detection of PCT in [11]. The sensing mechanism was primarily dependent on the quasi-reversible redox reaction of PCT in the presence of graphene, its superior ability to form π-π interactions, and its increased adsorptive capacity. The graphene sheets on the glassy carbon electrode (GCE) interact with the redox-active species. The π-conjugation of graphene can enhance the adsorption of product molecules. Both paracetamol and its oxidized form, NAPQI, can interact with the graphene surface. However, NAPQI may exhibit stronger interactions because it can form π-π stacking with the sp2-bonded carbon atoms of graphene, thereby improving adsorption. The detection mechanism involves quantifying changes in the electrode current due to redox reactions at the electrode surface. The graphene-modified GCE effectively detects the presence of paracetamol by monitoring its redox behaviour, specifically the formation and reduction of NAPQI, which is the oxidized product of paracetamol. Thus, although the primary identification is of paracetamol, the graphene electrode also engages with and identifies the oxidized byproduct, NAPQI, as a result of the electrochemical reaction occurring at the electrode's surface. The increased adsorption and interaction of NAPQI with the graphene surface indicate that the electrode is highly responsive to the oxidized product, resulting in enhanced stability and amplified detection signals. The interference studies were done in the presence of dopamine and ascorbic acid. It was seen that the potential windows of PCT and dopamine were postulated to be very close to each other, as the PCT peak was observed between 0.1 to 0.35 V *vs.* Ag/AgCl and the dopamine peak was seen between 0.35 to 0.45 V *vs.* Ag/AgCl. Here, the PCT limit of detection was 32 nM [11].

Another study used GO to modify the electrode for PCT detection [13]. As seen in previous studies, the primary mechanism of detection is the catalytic behaviour of GO in the oxidation of PCT to form NAPQI. A survey of interfering compounds was not carried out, but the CV studies showed an oxidation peak between the potential window 0.2-0.4 V *vs.* Ag/AgCl. The limit of detection was found to be 48.69 nM.

A GO/Pd composite material was used for PCT detection in [26]. The material showed superior sensitivity to PCT (>10 seconds) owing to the prominent oxidation and reduction peaks observed in the CV, reflecting the quasi-reversible nature of NAPQI. The interference studies were done in the presence of ascorbic acid, dopamine, uric acid, other organic compounds, and inorganic ions. A comprehensive CV analysis in the presence of interfering compounds was not provided.

MoS_2-TiO_2/rGO was another material used and the interference studies were done in the presence of ascorbic acid, dopamine, uric acid, and some other ions. Three distinctive peaks were seen for PCT, dopamine, and ascorbic acid at varying potential windows from 0.1 to 0.6 V *vs.* Ag/AgCl. The peaks for uric acid and the ions were not observed in this window. The limit of detection was seen as low as 0.1 µM of PCT [27,28]. Over the past 5 years, advanced sensing interfaces for detection have been focusing on modifying the carbon material to improve adhesion, decrease signal drift and incorporate more stable and selective surface functional groups. Electrochemically reduced graphene oxide (ERGO) modified covalently with phenyl diazonium salts shifts our focus from conductivity enhancement to interfacial stabilisation. Owing to the covalent bonding, the material is chemically bonded to the electrode surface, overcoming the problem of film leaching, signal drifts and enhancing long-

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term reproducibility. A low LOD of 18.2 nM (0.0182 µM) was obtained, and the study has provided significant insights into the importance of material adhesion to the surface. Ionic-liquid (IL) functionalised graphene CNT composite with AuPd nanoparticles demonstrated the importance of structural and chemical integration [29]. The use of IL promoted stability and ionic conductivity, and also, it reduced the aggregation of CNT, which is commonly observed. The AuPd bimetallic nanoparticles improved biocompatibility and adsorptive properties towards organic molecules. The research achieved an extremely low LOD of 0.05 µM in an electrochemical setup and 1.12 µM in urine samples. The synthesis of carbon-based materials has recently been focusing on the use of sustainable precursor materials. A study showed the use of ground coffee powder to synthesise carbon quantum dots (CQDs), which were then doped with CuO NPs and graphene [30]. Beyond surface adsorption, selectivity engineering has also been a point of focus when employing carbon-based electrochemical sensors. A recent study showed the use of porphyrin-tetrathiafulvalene covalent organic frameworks (COFs) with reduced graphene oxide (rGO). A synergistic effect was observed, which promotes the formation of uniform porosity, redox-active frameworks and carbon scaffolds. Unlike traditional graphene sensors that rely on the π-π adsorption mechanism, incorporating COF into GO provides well-defined pore channels and tailored functional sites, enabling more selective recognition of PCT and improved resistance to interference. More analysis on antifouling behaviour, reproducibility and film uniformity needs to be carried out. The CQDs serve to conduct ions, enhance catalytic activity and align with developing new materials with the principles of the circular economy. Such strategies represent a conceptual shift from performance-driven material synthesis to the development of sustainable materials for sensor engineering. The most significant drawback of using biomass is the issue of reproducibility due to non-standardised synthesis routes [31].

The changes over the past years have shown a growing field of materials science focused on interface-engineered carbon structures. Existing reviews on paracetamol and pharmaceutical electrochemical sensing are primarily focused on summarizing material trends and analytical performances. These reviews predate the recent surge in sustainable carbon production. As research pivots to enhance the sustainability, electronic conductivity, catalytic nature, and matrix compatibility of sensor materials, the present section adds value by critically examining how new sensor designs address persistent challenges.

Metal and metal oxide-based electrochemical sensors

Metals and metal oxides are effective for detecting PCT due to their elevated catalytic activity, which enhances electron transfer and facilitates the oxidation and reduction of acetaminophen. They possess elevated surface area-to-volume ratios, which increase the number of active sites accessible to PCT, thereby enhancing sensitivity. Their distinctive electronic characteristics facilitate efficient transfer of charges, a vital requirement for precise and swift detection. Moreover, these materials exhibit chemical stability and corrosion resistance, rendering them dependable and long-lasting for sensor applications. The ability to adjust the properties of metal and metal oxide nanostructures makes it possible to tailor them to meet specific detection needs, thereby enhancing performance. A study used nickel oxide for the detection of 4-acetaminophen, achieving an extremely low LOD of 0.23 mM [9]. The material is highly cost-effective and is said to have pristine electrochemical and physical characteristics. They investigated the oxidation of PCT at the electrode surface, where the faradaic current served as the analytical signal. The interference studies (DPV) were carried out in the presence of 2 mM of inorganic and organic compounds (0.1 mM ascorbic

acid, 0.1 mM uric acid and 400 nM dopamine) while keeping paracetamol concentration constant at 2 mM. A single peak was obtained, which was attributed to the oxidation of paracetamol.

Another research group used a titanium oxide sol composite for the detection of PCT and ciproflaxin (CPX) [15]. They achieved an even lower LOD value of 0.210 µM than seen before for PCT. The electrochemical behaviour of CPX and PCT was studied using a modified graphite electrode sensor. For CPX, an anodic peak appeared between 250 and 450 mV *vs.* Ag/AgCl and a cathodic peak between -100 and 100 mV *vs.* Ag/AgCl, with the oxidation involving the nitrogen atom in the piperazine ring. PA showed two oxidation peaks at 300 to 500 mV *vs.* Ag/AgCl and 600 to 800 mV *vs.* Ag/AgCl, with the first step forming a radical that eventually produces NAPQI, explaining the smaller initial signal. The sensor could detect both ciprofloxacin and PCT simultaneously, with ciprofloxacin peaks at 300 to 400 mV *vs.* Ag/AgCl and PCT at 600 to 800 mV *vs*. Ag/AgCl, despite some signal overlap. Higher concentrations of PCT enhanced CPX signals beyond expected levels, suggesting the use of the standard addition method to mitigate interference. The interference studies were done in the presence of inorganic compounds along with amoxicillin and sulfamethoxazole. The study examined the sensor's selectivity for ciprofloxacin and PCT in the presence of various inorganic ions and other antibiotics, specifically amoxicillin and sulfamethoxazole, to ensure accurate determination in complex matrices such as environmental waters. Inorganic ions at a 15-fold excess had minimal impact on ciprofloxacin but increased the paracetamol signal by 14 %, indicating additive interference. At a 50-fold excess, significant signal increases of 31 % for ciprofloxacin and 35 % for paracetamol were observed. Amoxicillin at twice the concentration of the analytes did not significantly affect ciprofloxacin or paracetamol, but at 20 µM, it decreased the paracetamol signal by 18 % without affecting ciprofloxacin. Sulfamethoxazole at both lower and equal concentrations increased the ciprofloxacin signal by about 30 % but did not significantly affect paracetamol. These findings suggest that while the sensor can effectively differentiate ciprofloxacin and paracetamol, careful calibration strategies, such as integrated or generalized calibration, are necessary to account for potential interferences and ensure accurate analysis [15].

Another study used bismuth oxide with oxynitrate heterostructures for the detection of PCT [32]. As bismuth is available in many oxide phases and is easily produced via thermal routes, it serves as an excellent electrocatalyst, thereby facilitating the rapid oxidation of PCT. The oxidation peak of paracetamol was seen between 0.3 and 0.8 V *vs*. Ag/AgCl. The LOD was around 4.2 µM. No interference studies were performed.

A metal-organic framework was prepared from nickel and copper for the detection of PCT [33]. The LOD was found to be 5 µM. Metal-catecholates (M-CATs), a type of conductive metal-organic framework (MOF), exhibit good electrical conductivity, attributed to their unique structure, in which oxygen atoms in HHTP ligands form hydrogen bonds with axial water ligands, enabling charge delocalization. M-CATs can form two accumulation modes: a two-dimensional layered framework with hexagonal holes and a honeycomb structure, allowing charge delocalization in the 2D plane, and one-dimensional structures along the c axis through hydrogen bonding. Their porous structure facilitates efficient analyte diffusion, while the high conductivity ensures effective electrochemical sensing. PCT molecules interact with M-CATs, and upon oxidation, generate measurable signals due to M-CATs' conductivity and charge delocalization. The interference studies were done in the presence of inorganic ions, dopamine, and ascorbic acid. Here, it was observed in the DPV analysis that PCT and ascorbic acid produced a singular peak between 0.2 and 0.8 V *vs.* Ag/AgCl when ascorbic acid was at a concentration of 200 µM and PCT was at 40 µM [33]. Screen-printed carbon electrodes (SPCEs) with metal oxides Sm_2O_3 nanorods have also been proposed as a portable sensor. Unlike conventional GCE,

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SPCE enables miniaturization and on-site testing possibilities [34]. This study focused on creating a multi-analyte sensing platform in which results could be compromised by increased risks of signal overlap and misinterpretation when used in complex testing matrices. Over the past 5 years, metal and metal oxide-based electrochemical sensors for paracetamol detection have been moving towards using the benefits of dopant engineering strategies. A study reported Fe/Co co-doped ZnO grafted onto CNT, where, after systematic dopant optimization (1, 5 and 10 %), it was revealed that 1 % Fe/Co-ZnO@CNT achieved the lowest LOD (45 nM) and enhanced electron-transfer kinetics [35]. This approach to dopant ratio optimization focused on altering the traditional zinc oxide structure to increase the number of redox-active sites, thereby enhancing the material's catalytic activity. The integration of CNTs further increases structural stability. This study shows how next-generation metal oxide sensors are being designed by precise modification of material composition and hybridization with conductive carbon supports, moving beyond previous routes that relied on simple oxide nanoparticle loading.

Alongside material modifications, there has been a growing need for sensors with enhanced stability, possibility for large-scale production, and real-sample validation. This need has been researched by a study that demonstrated ruthenium NP-modified screen-printed electrodes (SPEs) for simultaneous dopamine and paracetamol detection, achieving an LOD of 0.17 µM (SWV) and successful application in pharmaceutical preparations and human serum with good recoveries [36]. Similarly, other studies validated metal-based (neodymium-doped indium and ruthenium oxide) sensing performance using commercially available tablets as their testing samples and reporting recovery rates of 98 to 100 % [37]. Furthermore, redox-active metal-organic charge-transfer systems such as copper-tetracyanoquinodimethan focussed on improving interference tolerance and signal retention (>95 % over extended periods). Collectively, these studies signal a shift toward portable sensors, including disposable screen-printed formats and commercial reproducible architectures [38].

Many reviews have focused on nanomaterial enhancements without discussing portability or disposability. The current review contributes by clearly connecting material innovation to platform scalability by critically analysing how portable electrodes influence selectivity and validation requirements. Related discussions appear in earlier literature, but the rapid evolution of SPCE-integrated nanocomposites over the last five years warrants a broader, more contemporary reassessment, which this manuscript seeks to provide through updated coverage and a deployment-oriented analytical framework.

Electrochemical biosensors

Electrochemical biosensors (EBS) combine a biological recognition element with an electro-chemical transducer to selectively detect the presence of biochemical pollutants in samples. EBS consists of a biological recognition element (enzymatic or non-enzymatic), a transducer (electrode), and a signal processing system. In this review, we will concentrate on the most used enzymatic and non-enzymatic recognition elements. The general schematic principle of EBS is given in Figure 4.

Enzymatic electrochemical biosensors

Electrochemical tools have proved to be a new, rapid, sensitive, selective, and user-friendly method for the detection of various biological pollutants. In particular, for PCT detection, the enzyme polyphenol oxidase (PPO) has played a major role in modifying electrodes for better selectivity towards PCT. This class of enzymes has garnered much attention owing to their abundance and low cost. Thus, research was conducted using a derived PPO from the Jenipapo fruit [39].

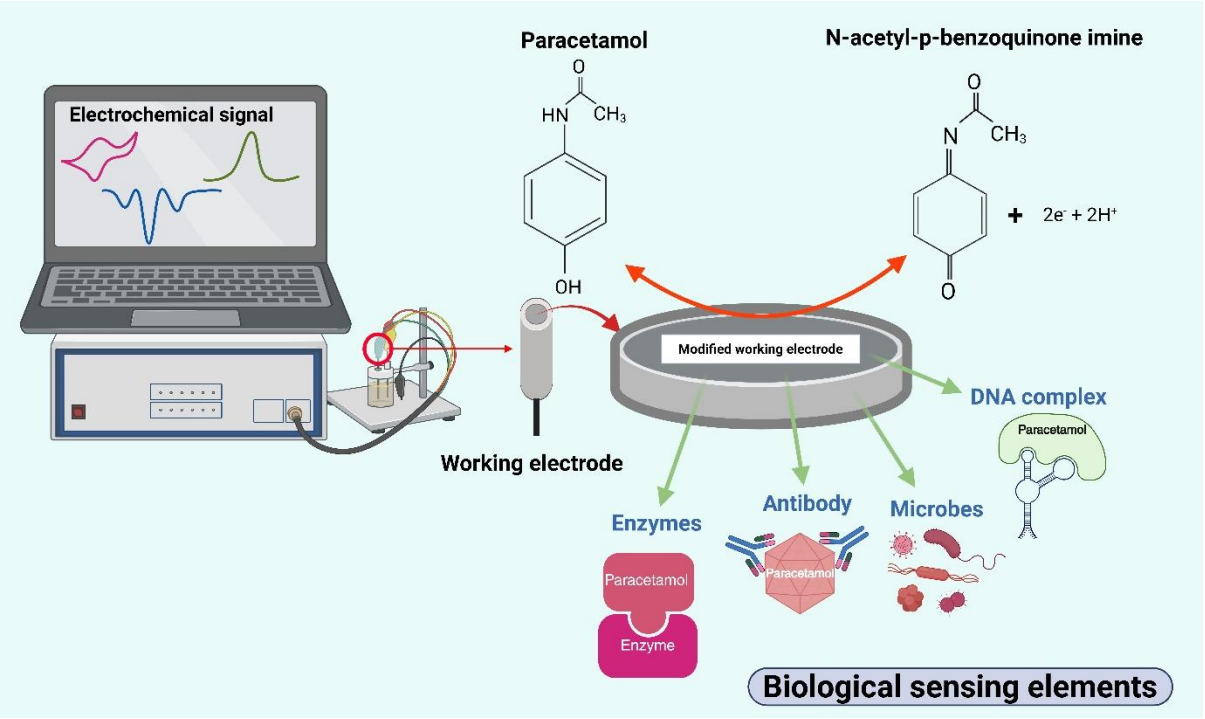

***Figure 4**. Structure of an electrochemical biosensor for paracetamol detection*

Enzymes are inherently catalysts, and here, PPO enhances the oxidation of paracetamol. PPO exhibits catalytic activity in the detection of phenolic compounds such as PCT. PPO enhances paracetamol detection by catalysing its oxidation to quinone intermediates. These quinone intermediates are electrochemically active and can be readily reduced during the cathodic scan of differential pulse voltammetry (DPV), thereby enhancing the faradaic signal. This enzymatic conversion and subsequent electrochemical reduction significantly amplify the detectable signal, thereby improving the sensitivity and accuracy of paracetamol detection in the biosensor. The cathodic peaks were obtained within a potential window from 0 to 0.4 V *vs.* Ag/AgCl. Here, the limit of detection was found to be 5 µM µg L^{-1} for PCT. In another study carried out by the same group, a PPO-based EBS for PCT detection was synthesized [40]. The PPO was derived from *Solanum lycocarpum* (commonly known as wolf apple). In that study, a detailed explanation of the exact chemical reaction between the PPO enzyme and PCT was not obtained. The cathodic peaks were seen between 0.1 and 0.4 V *vs.* Ag/AgCl. No interference studies were performed. The limit of detection was found to be 30 µM.

Similarly, another study shows the use of a PPO-derived banana with a hydrogen and carbon paste for the detection of PCT [8]. After a comparative analysis between hydrogel carbon paste only, and banana hydrogel carbon paste composite, it was seen that the electrode with the banana-derived PPO showed a better response between the potentials of 0.3 to 0.7 V *vs.* Ag/AgCl. The detection limit was found to be 1.6 µM. An interference study was done in the presence of lactose, fructose, ascorbic acid, and urea. It was concluded that the interfering compounds had no significant effect on the detection of paracetamol. The CV/DPV studies for these interfering compounds were not graphically represented. Another study used PPO from S*olanum melongena* (commonly known as eggplant) [41]. The limit of detection was found to be 5 µM. The main mechanism of detection with PPO is its ability to oxidise drugs to their quinone forms. For PCT, the first oxidation step forms the byproduct NAPQI (a quinone). The PPO catalyses the monophenolic compounds into diphenolic compounds and later into their quinone-based byproducts. Hence, here the faradaic cathodic

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current gives the quantity of the oxidised species. The cathodic peaks were observed between the potential windows of 0.1 to 0.3 V *vs*. Ag/AgCl. An interference study was not performed.

A study combined the use of multi-walled CNTs and laccase enzyme, immobilized using glutaraldehyde, for the detection of PCT [42]. The laccase enzyme is also naturally abundant; it belongs to a group of enzymes called oxidoreductases. It has been noted for its reductive capacity of phenolic compounds. The use of the laccase enzyme greatly enhanced the sensor's sensitivity, showing both cathodic and anodic peaks. The interference studies were done using ascorbic acid and uric acid. There was no significant change in current in the presence of the interfering compounds. The CV/DPV analysis, which shows the presence or absence of peaks of the interfering compounds, was not provided. The LOD was 7 µM using the laccase enzyme.

Recent advances in enzymatic electrochemical biosensors have increasingly focused on brainstorming ways to enhance enzyme immobilization and stability and overcome drawbacks like denaturation, leaching, and signal shift. One study highlights the importance of nanostructured conductive supports in preserving enzyme conformation and enhancing electron transfer efficiency [43]. Similarly, another study demonstrates that nanomaterial-assisted immobilization can significantly improve enzyme stability and catalytic activity by optimizing the experimental environments at the electrode interface [44]. Another study emphasizes optimized enzyme - electrode coupling routes that enhance reproducibility and signal amplification [45]. These recent studies show a transition from simple plant-extract-based PPO systems toward more consciously designed enzyme-nanoparticle hybrid platforms that utilize immobilization chemistry and structural stabilization. Enzymatic biosensors offer enhanced selectivity, but the number of studies on enzymatic electrochemical detection of paracetamol is low compared to the rapidly increasing research in nanomaterial-based non-enzymatic sensors. This trend likely reflects ongoing challenges related to enzyme stability, storage requirements, batch variability, and limited operational lifetime.

Non-enzymatic electrochemical biosensors

Non-enzymatic EBS depend on biological elements such as antigens, antibodies, or DNA as their recognition elements. Here, the mechanism of PCT detection does not entirely rely on the oxidation of PCT to NAPQI, but rather on forming a “click chemistry” reaction between the PCT in samples and the recognition element. One particular study used a hapten (a mimetic molecule of the pollutant of interest) and a specific antibody that binds specifically to PCT [46]. This approach entails the electro-polymerization of juglone (JUG), an electroactive molecule containing an azide group, on a surface. Subsequently, click chemistry is employed to functionalize the surface by attaching a mimic of the desired molecule (hapten), namely PCT, that has been modified with an alkynyl group. This process results in the formation of an altered surface on which the hapten (JUG-PCT) is fixed. An antibody called anti-PCT is introduced. It can bind either to the immobilized hapten or to free PCT in solution, resulting in a competitive balance. The PCT concentration is detected using square-wave voltammetry (SWV), which measures the change in current caused by steric hindrance resulting from antibody binding to the immobilized hapten. The use of non-covalent, non-denaturing methods for immobilizing antibodies ensures high binding efficiency to antigens. The primary benefits of this approach include adaptability, which enables the effortless replacement of the hapten for various pollutants without requiring individual synthesis for each one, as well as its effectiveness and sensitivity, resulting in high binding efficiency to antigens and the detection of pollutants with great sensitivity. The anodic peak was observed between 0.1 and 0.8 V *vs.* SCE and the limit of detection was found to be 10 pM. An increase in current was observed during PCT

binding to the modified electrode surface. As this mechanism does not depend on PCT oxidation, the side oxidation of other compounds is completely eliminated. The described methodology is optimal for PCT detection due to its high selectivity and sensitivity, demonstrated by its specific response to PCT even in the presence of structurally similar compounds (AHPP) and common additives (BPA, aspirin). The use of electropolymerized juglone functionalized with APAP mimics and the non-covalent, non-denaturing immobilization of anti-APAP antibodies ensures high antigen-binding efficiency and reproducibility. The competitive binding mechanism and SWV allow precise measurement of APAP concentrations.

Multi-walled CNTs and copper with chitosan were synthesised for the detection of PCT, achieving a detection limit of 0.02 µM [14]. Chitosan is a polymer made up of d-glucosamine and N-acetyl-d-glucosamine, glucosamine consisting of multiple amino and hydroxyl groups that are necessary for excellent adsorptive ability towards organic substances. They are also highly biocompatible and have low toxicity. Here, the detection mechanism was primarily oxidation due to the presence of carbon-based and metal materials. The potential window between which the anodic peak was observed is between 0.3 and 0.6 V *vs.* SCE. The interference studies were performed in the presence of ascorbic acid and dopamine. The highest peak was observed for dopamine (between 0.0 and 0.2 V vs. SCE) in the DPV analysis, although PCT detection was not significantly hindered, as the PCT peak remained apparent between 0.2 and 0.4 V *vs.* SCE.

Although non-enzymatic biosensors that use antibodies or DNA as recognition elements offer excellent selectivity, relatively few studies have focused on the electrochemical detection of paracetamol using these biological components. Compared with the rapidly growing research on nanomaterial-based catalytic sensors, antibody- and DNA-based platforms for paracetamol have not advanced at the same pace. This may be due to the small molecular size of paracetamol, which requires the design of haptens and competitive binding systems, making fabrication more complex. In addition, issues such as antibody stability, storage conditions, and reproducibility may limit large-scale development.

Comparative analysis of electrochemical sensors and electrochemical biosensors

A comparative analysis based on the abundant scientific research for both sensors is available in Table 1.

Although detection limits and linear ranges have improved significantly, the overall performance of ES for PCT detection depends on achieving a balance between sensitivity, selectivity, and stability.

Carbon-based ES are the most prevalent in recent research because of their stability, ease of modification, and compatibility with hybrid nanocomposites. Their improved performance is primarily due to enhanced electron transfer and surface engineering and does not focus on changes in detection chemistry. This makes them well-suited for environmental and pharmaceutical applications. Metal and metal oxide systems have strong catalytic activity and tuneable electronic properties.

Their efficiency, however, depends on surface uniformity when reproduced on larger scales. Advantages of highly sensitive ES must be balanced with synthesis complexity and durability. EBS introduces biological specificity. Enzymatic systems offer catalytic amplification but are restricted by stability and storage complications. Antibody-based systems provide excellent selectivity and sensitivity; however, their application to PCT remains limited, due to the complex nature of competitive binding chemistry for small molecules. Although biological recognition improves selectivity, it also causes challenges with immobilisation and long-term use.

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Table 1. *A comparative analysis of electrochemical sensor and biosensor characteristics*

Property	Electrochemical sensor	Biosensor
Principle of operation	Detects pollutants through electrochemical reactions	Utilizes biological components to detect target analytes.
Key components	Working electrode, reference electrode, counter electrode	Bioreceptor, transducer, signal processor
Sensitivity	High sensitivity for trace pollutant detection.	High sensitivity enables accurate detection
Selectivity	Can be selective	Specific binding enhances selectivity
Response time	Provides rapid response with real-time monitoring	Rapid detection facilitates timely intervention
Portability	Compact and portable for on-site monitoring	Portable design allows for versatile applications
Versatility	Suitable for various environmental settings	Adaptable to different sample types and matrices
Interference Resistance	Resistant to interference from other substances	Minimizes interference for reliable detection
Cost-effectiveness	Affordable solution for widespread monitoring	Cost-effective option for environmental monitoring
Application range	Applicable in water bodies, industrial sites, *etc*.	Used in diverse fields, including healthcare and food safety
Factor	Electrochemical sensors	Biosensors
Bioreceptor specificity	Nil	Bioreceptors provide specificity through selective binding
Electrode surface modification	Surface modifications enhance selectivity by promoting specific interactions with target analytes.	Surface functionalization, coating, immobilization, and nanomaterial incorporation
Signal processing techniques	Signal processing algorithms can differentiate between target and non-target signals, improving selectivity	Signal processing enhances selectivity by analyzing biological interactions
Detection mechanism	Relies on electrochemical reactions at the electrode surface, which can be tailored for specific analytes through electrode modification or selective membrane incorporation	Utilizes biological components such as enzymes or antibodies, which exhibit inherent selectivity for their target analytes through specific binding interactions
Environmental conditions	Operating conditions such as pH, temperature, and ionic strength can affect selectivity by influencing electrochemical reactions	Environmental conditions impact bioreceptor interactions and overall biosensor performance.

Summary

A quantitative comparison of ES and EBS for PCT detection, summarized in Table 2, shows significant variation in analytical performance depending on the material used and the recognition element.

Carbon-based ES showed excellent sensitivity, while their LODs vary from picomolar levels to nanomolar levels (10.2 to 50 nM, which is 0.0102 to 0.050 µM) for TTCOF/rGO, IL-3D graphene-CNT-AuPd, and rGO-phenyldiazonium. They mostly have the operating linear range of (0.0125 to 1433 µM). Their wide linear range allowed the sensors to be used in environmental and pharmaceutical environments. Metal and metal oxide ES achieved LODs ranging from 0.045 to 4.2 µM as seen with dopant-modified Co-ZnO-CNT nanocomposite. These sensors exhibited a narrower linear range (micromolar) compared with carbon-based systems. On the other hand, enzymatic EBS exhibited a linear range of operation in the micromolar range (0.2 to 30 µM), which could be due to drawbacks in enzyme stability and catalytic efficiency.

Table 2. *Recent trends in electrochemical detection of paracetamol in real samples*

ES/EBS	Recognition element	Linear range, µM	Sample matrix	LOD, µM	Potential window, V	Interference study	Ref.
Carbon-based ES	CNT/ZnO NPs	0.018 to 0.000005	Commercial tablets, tap/drinking water, sweat, saliva, human serum and urine	0.002	0.2-0.5 *vs.* Ag/AgCl	Performed in presence on anions, cations, *etc*	[13]
	CNT/methyl orange	2 to 50	Commercial tablets	0.038	0.1 to 0.5 *vs.* SCE	Performed in presence on ascorbic acid, *etc*	[10]
	Graphene/GCE	0.1 to 20	Commercial tablets, human plasma	0.032	0.1 to 0.35 *vs.* Ag/AgCl	Performed in presence on dopamine, ascorbic acid	[11]
	GO/Pd composite	0.05 to 1.0	Commercial tablets	0.0487	0.2 to 0.4 *vs.* Ag/AgCl	No	[26]
	IL-3D graphene CNT-AuPd NP	200 to 800	Commercial tablets, urine sample	0.050	0.2 to 0.6 *vs.* Ag/AgCl	Performed in presence of dopamine, epinephrine, catechin, uric acid	[29]
	rGO-phenyldiazonium salts	0.10 to 0.80	Commercial tablets	0.018	0.2 to 0.5 *vs.* Ag/AgCl	Performed in presence of talc, SiO_2, Mg.S, starch, PH101	[28]
	TTCOF/rGO	0.05 to 100	Commercial tablets	0.010	0.2 to 0.4 *vs.* Ag/AgCl	Performed in presence of uric acid, thymine, nitro-phenol, hydroquinone, benzene, ascorbic acid	[30]
	Cu_2O_3-CCQDs/GNRs	0.0125 to 1433.26	River water, tap water	0.016	0.2 to 0.5 *vs.* Ag/AgCl	Performed in the pre-sence of NO_2, urea, metals, uric acid and ascorbic acid	[31]
Metal/metal oxide ES	NiO NPs	7.5 to 3000	Commercial tablets	0.23	Not specified	Performed in presence on ascorbic acid, *etc*	[9]
	TiO_2 sol-gel composite	1 to 10	Commercial tablets, waste water	0.210	0.3 to 0.8 *vs.* Ag/AgCl	Performed in presence on antibiotics, ions	[15]
	Bi_2O_3 oxynitrate heterostructures	Not specified	Commercial tablets	4.2	0.3 to 0.8 *vs.* Ag/AgCl	No	[32]
	Sm_2O_3-CNT	2.6 to 2511	Commercial tablets, urine sample, human plasma	0.097	0.2 to 0.5 *vs.* Ag/AgCl	Yes	[34]
	Fe-Co-ZnO-CNT NP	0.69 to 3.47	Commercial tablets	0.045	0.3 to 0.6 *vs.* Ag/AgCl	Performed in presence on ascorbic acid, uric acid, *etc.*	[35]
	SP-Ru NP	1 to 400	Commercial tablets	0.17	0.1 to 0.3 *vs.* Ag/AgCl	Performed in presence on ascorbic acid, uric acid	[36]
Enzymatic EBS	PPO (Jenipapo fruit)	50 to 300	Commercial tablets	5.0	0 to 0.4 *vs.* Ag/AgCl	No	[39]
	PPO (Solanum lycocarpum)	10 to 310	Commercial tablets	30.0	0.1 to 0.4 *vs.* Ag/AgCl	No	[40]
	Laccase/MWCNT	10 to 320	Commercial tablets	7.0	Not specified	Performed in presence on ascorbic acid, uric acid	[42]
	Laccase based-MoS_2	132 to 395	Commercial tablets, groundwater sample	0.2	Not specified	No	[43]
Non-enzymatic EBS	Antibody-hapten (Click chemistry)	0.000001 to 0.00005	Commercial tablets	0.00001	0.1 to 0.8 *vs.* SCE	Performed in presence on BPA, aspirin	[46]
	Chitosan/ /MWCNT/Cu	0.1 to 200	Commercial tablets	0.02	0.3 to 0.6 *vs.* SCE	Performed in presence on dopamine, ascorbic acid	[14]

NP: nanoparticles; IL: ionic liquid; rGO: reduced graphene oxide; TTCOF: phorphirin tetrathiafulvalene covalent organic framework; CCQDs: coffee ground derived carbon quantum dots; GNRs: graphene nanoribbons; PPO: polyphenol oxidase

When focusing on environmental concentrations of PCT, it is present at ng L^{-1} to µg L^{-1} concentrations in surface and waste waters. Sensors with nanomolar detection limits are more favourable for environmental monitoring. Many studies have reported low LOD, but only hybrid nanomaterial systems have achieved commercially relevant ranges for environmental samples. Interference studies are commonly performed in the presence of ascorbic acid, uric acid and dopamine; however, a standard

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protocol and stability analysis remain under-explored. Interference from electroactive compounds remains a critical drawback in both sensors. Many studies exclude interference or selectivity data, making it hard to draw conclusions on the efficiency of these materials for real-life applications.

Overall, carbon-based hybrid nanocomposites offer the most feasible performance, combining low detection limits, wide linear ranges, and successful validation in real matrices, including river water, wastewater, urine, and pharmaceutical samples. Metal and metal oxide systems provide good catalytic activity but have higher LODs, while enzymatic biosensors have high selectivity but are limited by stability and sensitivity. Antibody-based systems demonstrate exceptional sensitivity but remain underdeveloped in recent literature. Despite significant progress, challenges remain in improving long-term stability, interference resistance, reproducibility, and environmental applicability. Future research should prioritise standardised performance evaluation, improved stability, and the development of portable, real-time detection systems to enable practical environmental and pharmaceutical monitoring of paracetamol.

Industrial applications and future opportunities in electrochemical sensing for paracetamol detection

ES and EBS have shown promising potential for industrial and environmental monitoring of paracetamol owing to their advantageous properties like rapid and real-time monitoring. An ES was synthesised recently using functionalized multi-walled carbon nanotubes (MWCNTs) loaded onto an indium tin oxide (ITO) electrode. It demonstrated effective paracetamol detection, with 0.0194 µM [47]. EBS can also be employed in the pharmaceutical industry for quality control purposes. These biosensors offer high specificity towards paracetamol. In contrast to ES, they have high specificity and accurate quantification in complex matrices. Pharmaceutical residues have been detected in various water bodies worldwide, raising concerns about their potential entry into the food chain. The food and beverage industry also benefits from the application of ES technology. They help monitor potential contamination by pharmaceutical compounds such as paracetamol. Research has shown that marine mussels exposed to paracetamol had accelerated degeneration of their follicles and gametes. This could impact their survival and, consequently, the ecosystems they inhabit [48].

Emerging approaches like paper-based microfluidic systems, SPE and portable sensing devices show promising opportunities towards point-of-care applications. As illustrated in Figure 5, the

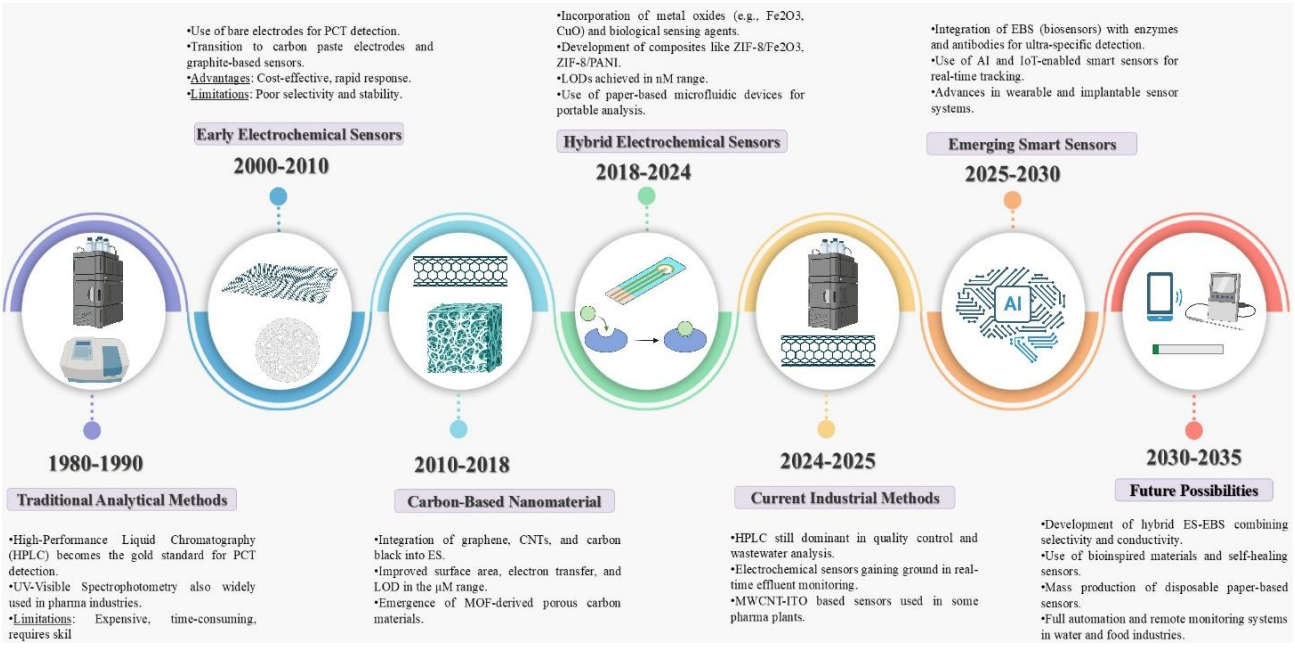

***Figure 5**. Evolution of PCT sensing techniques and prospects*

evolution of PCT sensing technologies has progressed from traditional analytical methods using expensive lab equipment to advanced hybrid nanomaterial and biosensor techniques, with future research emphasising integration of AI-assisted monitoring systems, improved portability, sensitivity and selectivity. Advancements in these fields will persistently enhance the functionalities of PCT sensors, overcoming existing constraints and facilitating improved environmental monitoring and pharmaceutical analysis [49,50].

Conclusion

This review provides a systematic and up-to-date comparative analysis of electrochemical ES EBS for paracetamol detection, focusing on recent advances in nanomaterial engineering, hybrid composite design, and biological recognition strategies. Carbon-based hybrid nanocomposites currently demonstrate the best analytical performance, owing to their low detection limits, wide linear ranges, and successful application in real matrices. Metal and metal oxide systems offer strong catalytic enhancement but require improved reproducibility and long-term stability. Enzymatic and antibody-based biosensors offer enhanced PCT specificity; however, their practical use across diverse sample matrices is limited by stability, cost, and a lack of recent development. Despite significant improvements in sensitivity, this work identifies the drawbacks caused by stability, interference control, and real-world possibilities and discusses future research directions. Future progress will depend on combining nanomaterial platforms with selective biological recognition elements, improving stability engineering, and advancing portable and real-time sensing technologies to enable reliable environmental and pharmaceutical monitoring of paracetamol.

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