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ELECTROCHEMICAL BIOSENSORS FOR TRYPTOPHAN DETECTION: A MINIREVIEW

BIOSSENSORES ELETROQUÍMICOS PARA DETECÇÃO DE TRIPTOFANO: UMA MINI-REVISÃO

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ABSTRACT

Tryptophan (Trp) is an essential amino acid that plays a key role in several physiological processes. Its main breakdown route, known as the kynurenine pathway, produces bioactive metabolites that have been linked to the pathogenesis of many diseases — including cancer, neurodegenerative disorders like Alzheimer's and Parkinson's, and inflammatory conditions. That's why measuring Trp levels in biological fluids such as blood, urine, and cerebrospinal fluid has become an important parameter for early diagnosis, prognosis, and treatment monitoring. Among the available analytical techniques, electrochemical biosensors stand out because they offer high sensitivity, selectivity, fast response, low cost, and great potential for miniaturization — which makes them suitable for point-of-care testing. This minireview aims to summarize and discuss the most recent and significant advances in the development of electrochemical biosensors for Trp detection. We focus on the design and functionality of electrodes modified with innovative nanomaterials, including different carbon allotropes (graphene, carbon nanotubes, carbon dots), nanoparticles (metallic, magnetic, oxides), and conductive polymers. For each modification category, we discuss the electrocatalytic mechanisms, key characteristics, and analytical performance — highlighting parameters like detection limit, linear range, sensitivity, and selectivity. Finally, we explore practical applications of these sensing platforms in complex biological samples, address matrix-related challenges, and present future perspectives for the next generation of Trp biosensors

Keywords: Tryptophan; kynurenine pathway; electrochemical biosensors; modified electrodes.

RESUMO

O triptofano (Trp) é um aminoácido essencial que desempenha um

papel fundamental em diversos processos fisiológicos. Sua principal via de degradação, conhecida como via da quinurenina, produz metabólitos bioativos que têm sido associados à patogênese de muitas doenças — incluindo câncer, distúrbios neurodegenerativos como Alzheimer e Parkinson, e condições inflamatórias. Por isso, a medição dos níveis de Trp em fluidos biológicos como sangue, urina e líquido cefalorraquidiano tornou-se um parâmetro importante para o diagnóstico precoce, prognóstico e monitoramento do tratamento. Dentre as técnicas analíticas disponíveis, os biossensores eletroquímicos se destacam por oferecerem alta sensibilidade, seletividade, resposta rápida, baixo custo e grande potencial de miniaturização — o que os torna adequados para testes no local de atendimento. Esta minirrevisão tem como objetivo resumir e discutir os avanços mais recentes e significativos no desenvolvimento de biossensores eletroquímicos para a detecção de Trp. Nosso foco está no design e na funcionalidade de eletrodos modificados com nanomateriais inovadores, incluindo diferentes alótropos de carbono (grafeno, nanotubos de carbono, pontos quânticos de carbono), nanopartículas (metálicas, magnéticas, óxidos) e polímeros condutores. Para cada categoria de modificação, discutimos os mecanismos eletrocatalíticos, as principais características e o desempenho analítico — destacando parâmetros como limite de detecção, faixa linear, sensibilidade e seletividade. Por fim, exploramos aplicações práticas dessas plataformas de sensoriamento em amostras biológicas complexas, abordamos desafios relacionados à matriz e apresentamos perspectivas futuras para a próxima geração de biossensores de triptofano.

Palavras-chave: Triptofano; via da quinurenina; biossensores eletroquímicos; eletrodos modificados.

1. INTRODUCTION

Tryptophan is an essential amino acid, meaning our bodies can't produce it, so we have to get it from food. It's involved in several important physiological processes, including protein synthesis, serotonin production, and immune system modulation [1]. When Trp levels are altered, that has been associated with pathological conditions ranging from neurological disorders to inflammation and cancer [2]. So developing fast, accurate, and low-cost analytical methods for Trp detection is highly relevant for clinical diagnosis and therapeutic monitoring.

Conventional methods for Trp quantification, like high-performance liquid chromatography (HPLC) and mass spectrometry, are still considered the gold standard. HPLC separates mixture components with high resolution, allowing precise identification and quantification of Trp. Mass spectrometry, especially when coupled with HPLC (a technique known as LC-MS), offers even more specificity and sensitivity [2,3]. But here's the catch: these methods have significant limitations. They're expensive, require bulky and complex equipment, involve time-consuming sample preparation, have long analysis times, and need highly trained personnel. These disadvantages explain why alternative techniques like electrochemical biosensors are so attractive, particularly when speed, low cost, and portability are critical [3].

[Electrochemical biosensors have become well-established as highly sensitive and selective analytical tools for detecting biomarkers, pathogens, and metabolites, with applications ranging from clinical diagnosis to environmental monitoring and food quality control.] In this context, they emerge as a viable alternative, combining the specificity of antibodies or aptamers with the sensitivity and portability of electrochemical techniques [4]. These devices allow

real-time detection, consume small sample volumes, and can be miniaturized for point-of-care (POC) applications [5].

Some of the strategies used in biosensor fabrication include functionalizing electrodes with nanomaterials to amplify signals and developing new bioreceptor immobilization methods [6]. Plus, integrating technologies like 3D printing and the Internet of Things (IoT) has expanded the use of these sensors for remote diagnostics and continuous monitoring [7].

Despite these advances, developing Trp-specific immunosensors still faces challenges. Interference from other molecules in complex biological matrices is a recurring problem, and improving device stability and reproducibility remains a goal [8]. So, this review aims to summarize recent advances in electrochemical immunosensors for Trp detection, discussing their working principles, electrode modification strategies, and applications in biological samples. We'll also address current challenges and future perspectives for optimizing these devices and implementing them in clinical and pharmaceutical analyses.

2. FUNDAMENTALS OF TRYPTOPHAN ELECTROCHEMICAL DETECTION

2.1. Tryptophan Oxidation Mechanism

The electrochemical oxidation of Trp has attracted considerable interest in recent literature, mainly because of its relevance in analytical, clinical, and industrial contexts. Trp, being an essential aromatic amino acid, has a highly electroactive indole ring that makes it susceptible to oxidation at relatively low potentials. This characteristic is widely exploited in developing electrochemical

sensors, whose effectiveness depends directly on understanding the redox mechanisms involved [9].

Trp oxidation occurs mainly on surfaces modified with nanocatalysts, such as gold nanoparticles (AuNPs), graphene, or conductive polymers. The process involves electron transfer from Trp's indole group to the electrode, generating reactive species like Trp quinone and its oxidized derivatives, as shown in Figure 1.

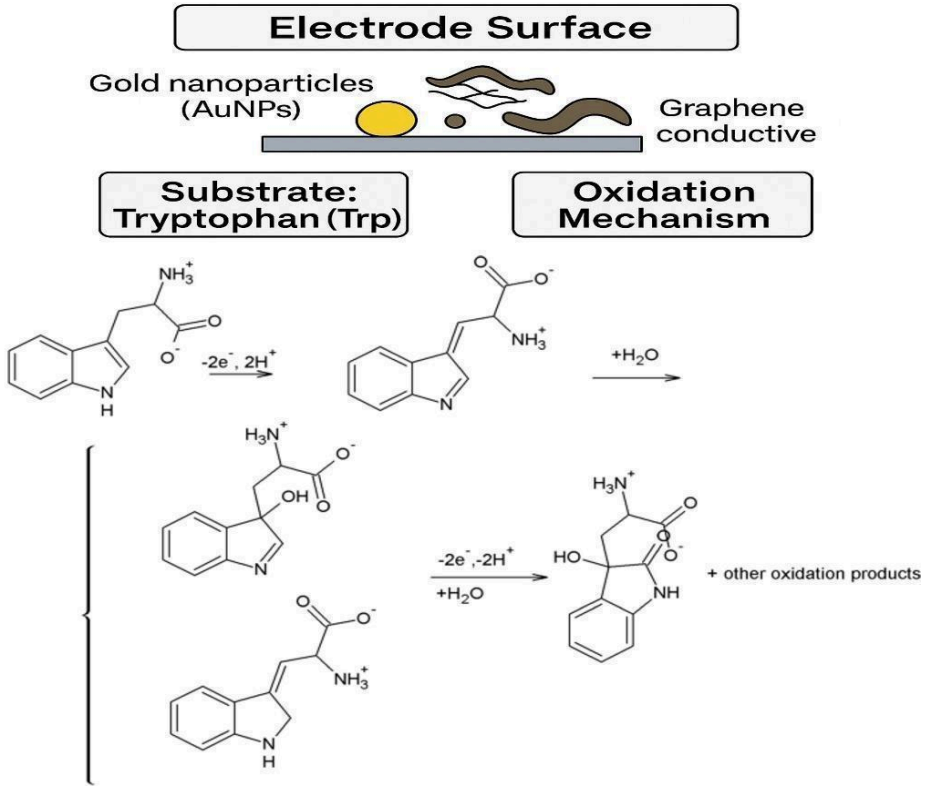

Figure 1: Tryptophan oxidation mechanism. Adapted from Nazarpour et al., 2020 [16].

Trp is electroactive and preferentially oxidizes at the indole group at potentials between +0.6 V and +0.9 V (vs. Ag/AgCl). Recent studies show that this mechanism is influenced by pH, applied potential, and electrolyte composition. At neutral pH, for example, oxidation occurs around +0.6 V (vs. Ag/AgCl), with intermediate formation of free radicals that get stabilized by modifications on the electrode surface. When Trp is conjugated to antibodies or aptamers, its oxidation is modulated upon target binding, which changes the

electrochemical current proportionally to the analyte concentration [10,11].

Many studies have highlighted the use of nanocomposites to amplify signals, metal oxides (e.g., ZnO) and carbon quantum dots, for instance, which reduce oxidation potential and increase sensor stability [9-13].

Modifying carbon electrodes with conductive or functionalized compounds significantly improves Trp detection sensitivity, especially in complex matrices. This happens because these materials increase the active surface area and facilitate electron transfer between the analyte and the electrode. This improvement is crucial for real-sample applications, where interferents can compromise selectivity [9,11].

Martins and colleagues investigated Trp's electrochemical behavior using cyclic voltammetry and amperometry. Voltammetry reveals characteristic oxidation peaks associated with the indole ring, allowing observation of the reaction's reversibility and kinetics. Amperometry, on the other hand, offers better sensitivity for real-time quantification. The choice of technique depends on the analytical goal, and both help elucidate the oxidation mechanism [12].

According to Silva et al., pH is a key factor in this process. Trp's electrochemical behavior is highly dependent on the medium, since the reaction involves proton transfer coupled with electron transfer. Under optimized pH conditions, a shift in oxidation potentials is observed, revealing better catalytic efficiency and selectivity when nanomaterials are used as electrode modifiers [13,14].

In a more theoretical approach, Khan et al. proposed a computational model correlating Trp's structural variations with its electrochemical response. The orientation of the indole ring and its interactions with functional groups on modified electrodes significantly influence the oxidation potential. These findings not only help predict Trp's electrochemical behavior but also guide the rational design of new materials for optimized sensors [13].

Zhang and colleagues proposed an innovative paradigm: detecting Trp using enzymes immobilized on electrode surfaces. The presence of biocatalysts alters the reaction pathway, facilitating analyte oxidation through enzymatic processes coupled with electron transfer. Enzyme immobilization not only lowers the required oxidation potential but also provides high selectivity, something essential in environments with multiple interfering compounds [10].

So, it's clear that Trp oxidation is a multifactorial process, influenced by physicochemical variables of the environment, the analyte's molecular structure, and the characteristics of electrocatalytic materials. The integration of experimental data and theoretical modeling has helped clarify this mechanism and enabled the development of increasingly sensitive, selective, and applicable devices across different sectors of science and industry [12,13].

2.2. Challenges In Biological Fluids

Biomarkers present in biological fluids have wide applications in diagnosis, prognosis, and therapeutic response monitoring, playing a central role in personalized medicine. Currently, most routinely used biomarkers are measured in blood, cerebrospinal fluid (CSF), or urine.

According to Nasimi et al., when selecting an appropriate biomarker, several criteria should be considered: availability, ease of collection, composition, proximity to the disease site, and patient discomfort. In this context, urine has emerged as a promising biomarker source, providing information about both the urological tract and systemic conditions. Produced by the kidneys through glomerular filtration of plasma, urine contains metabolic waste products, and under normal kidney function, only low-molecular-weight markers are effectively filtered and detected [15].

Studies with modified electrodes have demonstrated the ability to detect concentrations of these amino acids in biological matrices through recovery experiments. However, not all modifications worked well for simultaneous Trp measurements, which highlights the importance of carefully selecting materials for electrochemical modification. Reduced graphene oxide (rGO) is a promising material due to its excellent electronic conductivity and large surface area. To further enhance sensitivity, gold nanoparticles (AuNPs) are often incorporated because of their remarkable catalytic and conductive properties. The rGO/AuNPs nanocomposite is easy to synthesize and shows high potential for multiple electrochemical sensor applications [16].

Nasimi et al. reported the only known study that measured Trp directly in clinical samples without prior sensor modification. They obtained a detection limit of 1.13 µmol/L for Trp in human urine samples and observed an inverse correlation between prostate cancer (PCa) severity and the sum of the electrochemical signals of these amino acids. These findings suggest Trp could be a diagnostic and prognostic biomarker for PCa [15].

Despite the limited amount of data obtained directly from biological samples, electrochemical sensors offer a promising alternative, they're portable, easy to operate, fast, capable of on-site detection, and provide adequate sensitivity without needing centralized laboratories [16].

3. ELECTRODE MATERIALS FOR TRYPTOPHAN DETECTION

3.1. Carbon-based Electrodes

Carbon-based modified electrodes have been widely used for electrochemical Trp detection. Among the most common are glassy carbon electrodes (GCEs), carbon paste electrodes (CPEs), and carbon nanotubes (CNTs) [17]. The use of carbon paste electrodes was first described by Ralph N. Adams in 1958, marking their introduction into electrochemical applications. Since then, these electrodes have gained popularity due to their simplicity of preparation and versatility. However, unmodified CPEs have some limitations, low sensitivity and high detection limits, which led to the introduction of nanomaterials to increase the electroactive area and improve analytical response [18].

In the study by Abebe et al., a voltammetric method for Trp determination was investigated using a carbon paste electrode modified with graphitic carbon nitride (g-C_3N_4). The modification aimed to improve the electrode's sensitivity and selectivity toward the analyte. The results showed that the modified electrode had a linear detection range of 0.1–120 µM and a detection limit of 0.085 µM. Kinetic parameters revealed a charge transfer coefficient of 0.28, a rate constant of 1.9×10^4 $M^{-1}s^{-1}$, and a diffusion coefficient of 3.2×10^{-5} cm^2s^{-1}. Practical applicability was evaluated by analyzing milk

samples, yielding recovery rates of 98% – 105.2%, highlighting its potential for real matrices [19].

Graphene, on the other hand, has high electrical conductivity, efficient electron transfer, and low cost. It's frequently used for electrochemical applications like sensitive and selective detection of dopamine, rutin, and Trp [20]. A recent study by Mehmandoust et al. presented the development of a voltammetric electrochemical sensor based on functionalized carbon nanotubes for Trp detection in milk samples. A GCE was modified with functionalized multi-walled carbon nanotubes (F-MWCNTs), resulting in a significant increase in anodic peak current for Trp compared to the unmodified GCE. The sensor's response showed a linear range of 0.01–0.7 μM, with a detection limit of 3.63 nM. The sensor also worked well in real milk samples [21].

3.2. Nanoparticles-modified Electrodes

In recent years, electrochemical Trp detection using nanoparticle-modified electrodes has been widely studied, because nanosized materials offer superior electrocatalytic properties like larger surface area, better electrical conductivity, and enhanced redox reaction kinetics, making them ideal for electrochemical sensor applications [16,17,19,20].

Arvinte et al. developed an electrochemical sensor based on electrodes modified with Cu-Zn-Co trimetallic nanoparticles. These nanoparticles were synthesized by direct electrodeposition on carbon electrodes, resulting in an improved electrochemical response for Trp oxidation. The sensor showed a linear range of 5 –

230 µM and a detection limit of 1.1 µM, demonstrating high sensitivity and selectivity in real samples like milk [22].

Furthermore, He et al. reported the fabrication of a GCE modified with a nanocomposite of copper(I) oxide (Cu_2O) and electrochemically reduced graphene oxide (ERGO). This sensor exhibited excellent electrocatalytic activity toward Trp, with a linear range of 0.02 – 20 µM and a detection limit of 0.01 µM. The combination of Cu_2O with ERGO provided an effective platform for sensitive and rapid analyte detection [20].

These studies highlight the effectiveness of nanoparticle-modified electrodes for electrochemical Trp detection, offering promising solutions for both clinical analysis and food quality control

3.3. Conductive Polymers And Molecular Imprinting

The use of polymers in electrochemical detection has become a recurring theme in the literature, mainly due to their low cost, good chemical stability, and ease of direct synthesis on various substrates. Among the most effective approaches in this field, electrode modification with conductive polymers stands out because of the variety of functional groups they offer [24]. Several studies have demonstrated successful application of conductive polymer-modified electrodes for detecting amino acids like Trp [15,20,25].

In one of these studies, a GCE modified with a composite film of poly(L-methionine) and graphene (PLME/GR/GCE) was used for Trp determination, achieving satisfactory results in terms of sensitivity and selectivity [26].

Another relevant strategy involves molecularly imprinted polymers (MIPs), known for their high selectivity and specific affinity for target molecules. Although MIPs offer clear advantages in selectivity, their low electrical conductivity still limits analytical sensitivity. To overcome this, many researchers have combined MIPs with other conductive materials, like metallic nanoparticles, to expand binding sites and improve sensor performance [25].

Among the promising structures used in this context, ZIF-67 (zeolitic imidazolate framework-67) stands out for its large surface area and excellent biocompatibility. In a recent study, a GCE modified with a hybrid compound containing polyalanine, polythionine, gold nanoparticles, and an MIP on the ZIF-67 structure (MIP/pTH/Au@ZIF-67) was developed for selective tyrosine detection. The sensor showed excellent performance, with high selectivity, stability, and reproducibility [25].

The advancement in electrochemical biosensing has been significantly driven by the development of highly selective immunosensors for Trp. These devices leverage the specific binding affinity of antibodies or antibody mimetics to capture target molecules, offering exceptional specificity even in complex matrices like biological fluids.

A prominent strategy in this field involves conductive polymers and MIPs. As highlighted by Dinu and Apetrei [17], these materials are key for creating selective recognition interfaces for amino acids. Conductive polymers, like polyaniline or polypyrrole, serve dual functions: they facilitate efficient electron transfer and can be easily functionalized to immobilize biological recognition elements. MIPs, often called "artificial antibodies," offer a robust and cost-effective

alternative. They're synthesized to create tailor-made cavities with high affinity for Trp, giving these sensors remarkable selectivity and resistance to harsh environments, crucial for practical applications in biological fluids like serum, urine, or CSF.

Expanding further on the sensor landscape, Khan et al. provided a comprehensive comparative analysis of optical and electrochemical sensing platforms for Trp and related biomolecules like melatonin. Their work critically discusses the inherent advantages of electrochemical methods, superior sensitivity, lower detection limits, and miniaturization potential, while also addressing ongoing challenges like minimizing non-specific binding in complex samples and improving long-term stability and reproducibility. Their perspective reinforces a clear trend in the literature: the convergence of innovative nanomaterials (graphene, carbon nanotubes, metallic nanoparticles) with advanced molecular recognition techniques (MIPs, enzymes, aptamers) is the main driver behind the new generation of more efficient, sensitive, and reliable sensors. This synergistic effect not only enhances the electrochemical response but also significantly improves selectivity toward Trp, enabling effective discrimination from structurally similar compounds [27].

In summary, the field of electrochemical immunosensing for Trp is evolving rapidly through strategic electrode functionalization with nanomaterials, innovative application of MIPs as synthetic recognition elements, and continuous refinement of detection platforms and transducer design. This multidisciplinary approach has driven the creation of analytical devices that are not only accurate and fast but also increasingly viable for point-of-care testing. The growing body of research in high-impact journals

demonstrates the maturing potential of these technologies for transformative applications in clinical diagnostics (e.g., monitoring neurodegenerative disease biomarkers), pharmacology (drug development and pharmacokinetic studies), and environmental analysis.

To better compare the different types of electrodes used for Trp detection, we prepared Table 1, which includes analytical parameters to address questions about electrochemical biosensor fabrication.

Table 1: Electrochemical sensors for Tryptophan detection.

Active Material	Matrix	Linear Range	LOD	References
Carbon nanotube-modified electrode	Pharmaceutical and physiological samples	0.1 - 100 µM	0.02 µM	[3]
Polythiophene	Amino acid mixtures and pharmaceutical formulations	1.0×10^{-7} to 1.0×10^{-5} M	50 nM	[4]
Graphene-modified electrode	Clinical samples (blood serum)	0.001 - 1000 µM	0.39 nM	[5]
Trimetallic nanoparticles (CuZnCo)	Pharmaceutical supplements and biological samples	1-25µM and 25-80 µM (dual range)	0.33 µM	[6]
Cu_2O nanoparticles-coated	Human urine samples	0.01 - 100 µM	2.7 nM	[7]

reduced graphene oxide nanocomposite				
Graphene-modified electrode	Buffer solutions (mechanistic study)	25 - 300 μM	7.4 μM	[9]
Graphene-modified electrode	Cancer cells (metastasis competence)	0.01 - 10.0 μM	3.0 nM	[10]
$CuSn(OH)_6$ microspheres decorated on reduced graphene oxide	Milk and urine samples	0.005 - 124.6 μM	1.6 nM	[11]
Carbon nanotube-modified electrode	Human serum and urine	10 - 200 μM	0.12 μM	[12]
Cerium oxide nanoparticles loaded on reduced graphene oxide (rGO)	Pharmaceutical samples	0.05 - 200 μM	19 nM	[13]
rGO/Gold nanoparticles nanocomposite modified screen-printed electrodes	Dietary supplement samples	0.0019 - 10.0 μM	0.57 nM	[16]
Graphitic carbon nitride ($g\text{-}C_3N_4$) modified	Milk and pharmaceutical samples	5 - 100 μM	1.49 μM	[19]

carbon paste electrodes				
Polyvinylpyrrolidone functionalized Graphene	Urine and serum samples	0.1 - 120 µM	26 nM)	[20]
Carbon nanotube-based sensor	Milk and dairy products	0.05 - 10 µM	8 nM	[21]
Aptamer-based sensor	Human urine	1 - 100 µM	110 nM	[28]

What stands out from Table 1 is that most recent sensors use nanomaterials to push detection limits down to nanomolar or even picomolar levels, as seen with Sridevi et al. (0.39 nM) and Nazarpour et al. (0.57 nM), while maintaining wide linear dynamic ranges. Importantly, these sensors have been validated in real-world matrices like urine, serum, milk, and even cancer cells, not just buffer solutions. The main application areas are clinical diagnostics and biomedical research, followed by pharmaceutical quality control and food product testing. This collective progress highlights the significant potential of electrochemical sensors as rapid, sensitive, and cost-effective tools for Trp monitoring across diverse fields.

4. BIORECOGNITION STRATEGIES

In recent years, researchers have invested in using antibodies and aptamers as biological recognition elements to improve electrochemical sensors for Trp detection. These approaches exploit the high affinity and specificity of these molecules, allowing the creation of more sensitive and selective devices [28,29].

Accurate detection of Trp in biological fluids like plasma has become increasingly essential for diagnosing metabolic disorders and monitoring patient therapy. One of the most promising approaches has been the use of nanocomposites combining gold nanoparticles (AuNPs) with graphene. These materials offer several advantages, high electrical conductivity, large surface area, and excellent biocompatibility, all crucial for building high-performance electrochemical sensors [30].

In the study by He et al., sensor sensitivity was optimized after graphene was modified with polyvinylpyrrolidone (PVP), resulting in a platform with excellent reproducibility and long-term stability. The sensor detected Trp with high accuracy, maintaining performance even under variable pH conditions and in complex biological samples [20].

Aptamers have gained prominence as promising molecular recognition elements in electrochemical sensors. Composed of single-stranded DNA or RNA sequences, these ligands are obtained through the SELEX (Systematic Evolution of Ligands by Exponential Enrichment) process, which allows selection of molecules with high specificity and affinity for a given target [27].

Compared to antibodies, aptamers offer several advantages: they're chemically synthesized, more stable under different environmental conditions, less immunogenic, and allow structural modifications easily and at lower cost. These characteristics make them ideal for biosensors, especially those aimed at rapid, accurate analysis of biologically relevant compounds like Trp [22,23].

A recent representative example was developed by Idili et al., who built an electrochemical sensor capable of detecting Trp in synthetic urine samples. In this system, the aptamer was functionalized with a redox marker, methylene blue, whose signal current varied with the aptamer's conformation upon binding to the analyte. The proposal demonstrated high selectivity and sensitivity at micromolar levels, without needing additional reagents [29].

Furthermore, recent studies have shown that incorporating aptamers into conductive nanomaterials, like graphene and gold nanoparticles, can enhance electrochemical responses, expand the sensor's active surface area, and improve electron transfer [26]. These advances not only confirm the value of aptamers as recognition elements but also pave the way for developing portable, low-cost analytical devices for clinical and environmental applications.

4.1. Clinical Applications

Recent research has highlighted the role of Trp metabolism in the pathophysiology of neurodegenerative diseases like Alzheimer's. Although total Trp levels in cerebrospinal fluid (CSF) don't show marked differences between Alzheimer's patients and healthy individuals, evidence indicates significant activation of the kynurenine pathway in these patients.

This pathway, responsible for the main route of Trp degradation in the central nervous system, leads to the formation of neuroactive metabolites like kynurenic acid (KYNA), whose levels are elevated in the CSF of patients with early and moderate-stage disease. This elevation suggests a chronic inflammatory response, with potential effects on excitotoxicity and cognitive function, underscoring the

importance of monitoring these metabolites as clinical indicators [30,31].

Furthermore, studies have shown correlations between intermediate products of the Trp pathway and classical Alzheimer's biomarkers like total tau protein (T-tau) and phosphorylated tau (P-tau). Specifically, the ratio of 3-hydroxykynurenine to kynurenine (3-HK/KYN) is positively associated with CSF tau levels, suggesting a link between neuroinflammation driven by this metabolic pathway and the progression of tau pathology [31]. These findings suggest that monitoring Trp metabolism, particularly using sensitive analytical platforms applied to CSF, could be a promising approach for early diagnosis and disease monitoring in Alzheimer's.

The kynurenine pathway (KP) has gained prominence in oncology research due to its crucial role in tumor progression and modulation of the antitumor immune response. Recent studies, like that by León-Letelier et al., show that metabolic alterations in this pathway are associated with vulnerabilities in several cancer types [30], paving the way for new therapeutic strategies (Figure 2).

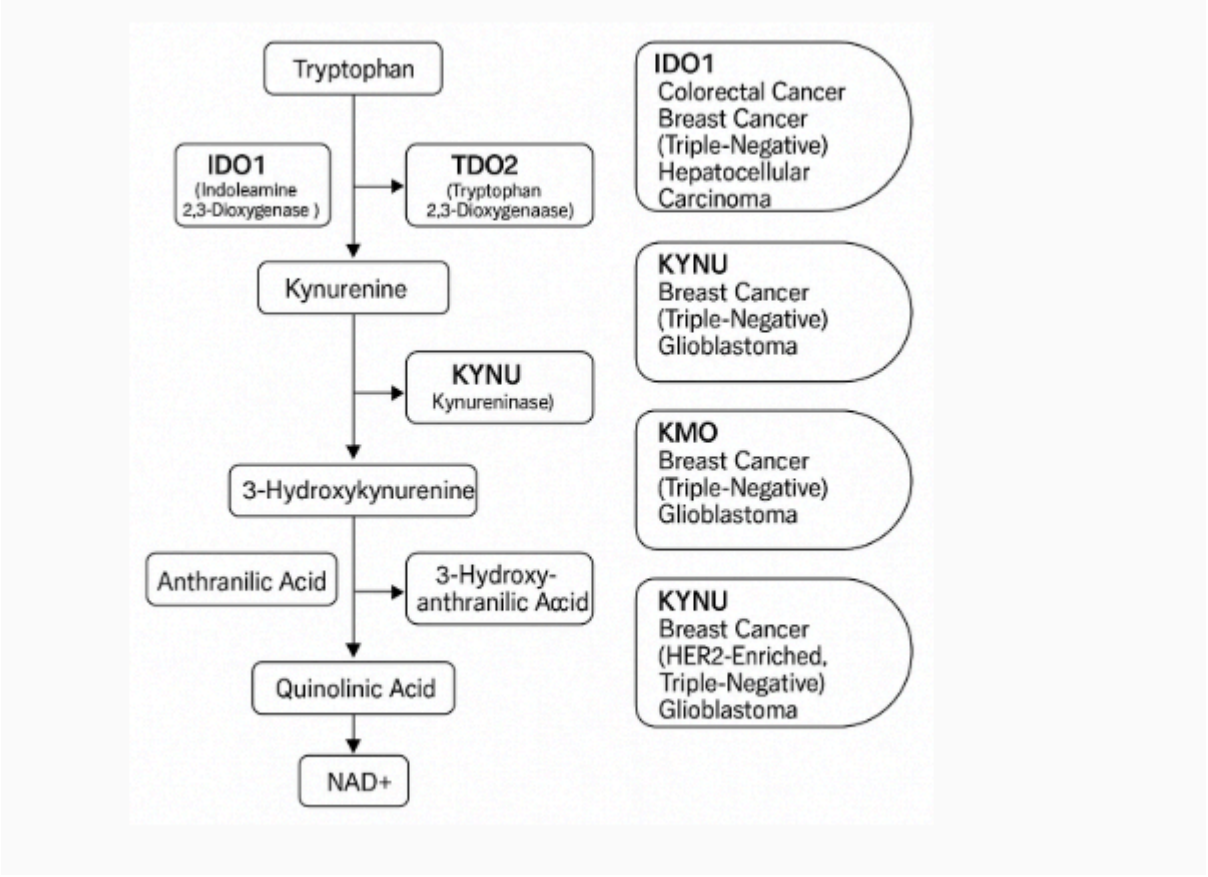

Figure 2: Kynurenine pathway in oncology.

The pathway is initiated by indoleamine 2,3-dioxygenase 1 (IDO1), which catalyzes the conversion of Trp to N-formylkynurenine. Overexpression of IDO1 in tumors is associated with immune suppression, facilitating tumor evasion. Its paralog, IDO2, also participates in this process, and evidence suggests its expression may be co-regulated with IDO1, enhancing the immunosuppressive effect. In addition to these enzymes, tryptophan 2,3-dioxygenase (TDO2), although more active in the liver, is frequently found in tumors. Its activity leads to kynurenine production, which activates the aryl hydrocarbon receptor (AhR), promoting tumor progression and immune resistance [22,30,31].

Other key enzymes include kynureninase (KYNU), which converts kynurenine to anthranilic acid. Its overexpression in cancers like lung and breast cancer is associated with remodeling of the tumor microenvironment and inhibition of immune response. Kynurenine 3-monooxygenase (KMO), which catalyzes the conversion of

kynurenine to 3-hydroxykynurenine, contributes to aggressive tumor cell characteristics like increased migration and invasion [30,31].

Advances in understanding KP have revealed opportunities for pharmacological interventions. IDO1 inhibitors, like epacadostat, have been developed to restore immune response, but clinical results have been inconsistent, indicating the need for combination therapies. TDO2 is also a promising target, as its inhibition can reduce kynurenine levels and improve immunosurveillance. Furthermore, modulation of KYNU and KMO can alter the profile of immunomodulatory metabolites in the tumor microenvironment, offering new strategies for cancer treatment [29,30].

The kynurenine pathway plays a complex role in cancer biology, influencing both disease progression and immune system response. Therapeutic exploitation of this pathway requires an integrated approach that considers the interactions between its metabolites and tumor escape mechanisms. Future research should focus on developing more effective inhibitors and combining them with other treatment modalities to maximize clinical benefits [31].

5. CHALLENGES AND FUTURE PERSPECTIVES

Electrochemical detection of tyrosine and Trp is feasible at clinically relevant concentrations, making it a rapid and reliable method for disease diagnosis. However, several obstacles need to be overcome before this technique can be widely adopted. One of the main challenges is the low reactivity of specific amino acids on conventional electrodes. Tyrosine and Trp exhibit well-defined oxidation peaks, but their oxidation potentials are very close, making identification more difficult in biological samples [26,27].

Cheng et al. developed an electrode (Au/CA/GCE) capable of detecting tyrosine even in the presence of Trp, thanks to the combination of gold nanoparticle conductivity with the abundance of electroactive groups in the CA film. On the other hand, Govindasamy et al. used an electrode modified with $SrTiO_3$@RGO, which allowed selective identification of Trp among other molecules like dopamine and uric acid, possibly due to the high surface area of the material and π-π interactions between reduced graphene oxide (RGO) and the composite [6,25].

Another difficulty is discriminating between enantiomers (D and L forms) of these amino acids, since their electrochemical properties are identical on conventional electrodes. Stochastic sensors have shown promise in this regard, allowing direct analysis of blood samples without pretreatment. Furthermore, techniques like ultrafast voltammetry, when combined with spectroscopy (UV-Vis or Raman), can improve sensitivity and provide more robust diagnostic data [27,28].

Despite advances, more research is needed to improve the accuracy and sensitivity of amino acid detection. Electrochemical sensors are particularly appealing because of their rapid response, low cost, and suitability for point-of-care analysis with minimal sample preparation. Overcoming current challenges could make this technology an indispensable tool in clinical diagnostics.

6. CONCLUSIONS

In recent years, research on electrochemical immunosensors for Trp detection has shown remarkable advances, especially in the development of new materials and detection strategies. The studies

analyzed show that carbon electrodes, particularly screen-printed ones, when combined with nanomaterials like gold and graphene, have become the preferred base for these sensors due to their versatility and good analytical performance.

Three main approaches stood out in the reviewed studies: first, the use of specific antibodies or molecularly imprinted polymers (MIPs) for selective Trp recognition; second, the addition of metal nanoparticles to enhance the electrical signal; and third, the application of modern electrochemical techniques like differential pulse voltammetry (DPV). These methods have shown the ability to detect extremely low concentrations of the amino acid, in the nanomolar range, even in complex samples.

However, some obstacles still need to be overcome. Sensor stability during prolonged use and the complexity of manufacturing processes remain critical points that limit practical application. Furthermore, few studies have tested these devices on real patient samples, with most evaluations conducted under controlled laboratory conditions.

From a future perspective, recent research points to promising directions. Combining different molecular recognition elements, such as aptamers, with nanostructured materials seems particularly interesting. Another path under development is integrating these sensors with microfluidic systems and using computational algorithms for data processing, which could lead to smarter, more autonomous devices.

Thus, through this research, we can infer that although electrochemical immunosensors for Trp have made important

strides between 2020 and 2025, becoming fast and sensitive alternatives to traditional methods, heir full potential still depends on advances in key areas. The coming years should focus on more comprehensive clinical trials, cost reduction, and standardization of production processes to enable large-scale adoption

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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