A Review of Sensors and Biosensors Modified with Conducting Polymers and Molecularly Imprinted Polymers Used in Electrochemical Detection of Amino Acids: Phenylalanine, Tyrosine, and Tryptophan

Ancuța Dinu and Constantin Apetrei*

Department of Chemistry, Physics and Environment, Faculty of Sciences and Environment, “Dunărea de Jos” University of Galati, RO-800008 Galati, Romania; ancuta.dinu@ugal.ro
* Correspondence: apetreic@ugal.ro; Tel.: +40-727-580-914

Abstract: Recently, the studies on developing sensors and biosensors—with an obvious interdisciplinary character—have drawn the attention of many researchers specializing in various fundamental, but also complex domains such as chemistry, biochemistry, physics, biophysics, biology, bio-pharmacology, and bioengineering. Along these lines, the present paper is structured into three parts, and is aimed at synthesizing the most relevant studies on the construction and functioning of versatile devices, of electrochemical sensors and biosensors, respectively. The first part presents examples of the most representative scientific research focusing on the role and the importance of the phenylalanine, tyrosine, and tryptophan amino acids, selected depending on their chemical structure and their impact on the central nervous system. The second part is dedicated to presenting and exemplifying conductor polymers and molecularly imprinted polymers used as sensitive materials in achieving electrochemical sensors and biosensors. The last part of the review analyzes the sensors and biosensors developed so far to detect amino acids with the aid of conductor polymers and molecularly imprinted polymers from the point of view of the performances obtained, with emphasis on the detection methods, on the electrochemical reactions that take place upon detection, and on the electroanalytical performances. The present study was carried out with a view to highlighting, for the benefit of specialists in medicine and pharmacy, the possibility of achieving and purchasing efficient devices that might be used in the quality control of medicines, as well as in studying and monitoring diseases associated with these amino acids.

Keywords: sensor; biosensor; polymer conductor; molecularly imprinted polymer; amino acid; tyrosine; tryptophan; phenylalanine

1. Introduction

Prevention of various hereditary metabolic diseases, such as phenylketonuria (PKU), alkaptonuria, Parkinson’s disease, and orientation toward a ‘bio’ diet and a healthy lifestyle—removing the factors that lead to numerous disorders and forms of depression—represent the reasons why the present study was conducted. Amino acids (AAs), responsible for the equilibrium of the nervous system—especially phenylalanine (Phe), tyrosine (Tyr), and tryptophan (Trypt)—were analyzed with a view to detecting their lack or excess and to treating them accordingly, in due time.

Over the years, many scientific researchers have developed numerous methods through which these AAs can be detected rapidly and precisely, both in biological and in pharmaceutical products. From among these methods, mention must be made of the classical high-performance liquid chromatography (HPLC) [1–5], mass spectrometry [6–9], fluorimetry [10], colorimetry [7,11,12], chemiluminescence [13–15], Raman spectroscopy [16,17], UV-Vis spectroscopy [18], capillary electrophoresis [19–21], and atomic
force spectroscopy [22]. Moreover, versatile methods for detecting AAs have been developed and used: electrochemical ones based on sensors and biosensors, which use cyclic voltammetry (CV) [23–28] as a detection method, chronoamperometry (CA) [29], differential pulse voltammetry (DPV) [30–32], square wave voltammetry (SWV) [33–35], and linear sweep voltammetry (LSV) [36,37].

Modern challenges for scientific researchers, both in chemistry and in pharma-medicine, consist of designing sensors and biosensors with the aid of new polymers, since the latter can contribute to determining the quality of pharmaceutical products, especially during a pandemic, when new products (with various combinations of active substances) were introduced to the pharmaceutical market to address the new, severely acute coronavirus (SARS-CoV-2) [38]. Sensors and biosensors can contribute to detecting interest analytes like AAs very rapidly and exactly [24,39]. On the other hand, the selection of materials for the construction of sensors and biosensors is of crucial importance because it can lead to solving problems such as the rapid fouling of electrodes, the overlapping of the analytes redox potentials, etc. [40]. In the last five years, numerous research groups have made major contributions to the field of electroanalysis, as well as to the field of materials science, obtaining new classes of materials, such as novel polymers, which have allowed the possibility of a wide range of analytes detection [41]. The unique physical and chemical properties of CPs and MIPs, such as versatility, adaptability, sensitivity, and adjustable architecture, have led many researchers, including our group, to apply and use these new materials to develop novel chemically modified sensors and biosensors [42]. The polymers that were used in sensors were conductor polymers (CPs)—polypyrrole (PPy) [27,28,43,44], poly(3,4-ethylenedioxythiophene) (PEDOT) [45,46], polyalanine (PANI) [47], and polythiophene (PT)—and molecularly imprinted polymers (MIPs) [48,49].

Furthermore, ample studies, as well as reviews, were carried out on detection methods used to determine AAs [15,50–52]. The novelty of this review resides in synthesizing the studies carried out so far regarding the detection of the three AAs in human fluids, foods, and medicines, depending on the polymer used to produce sensors and biosensors, especially focusing on CPs and MIPs since they have demonstrated notable results, and since the synthesizing method is easy, having exceptional electric, thermic, and morphologic properties.

2. Phe-Tyr-Trypt. Properties and Importance for the Human Body

Out of the 11 amino acids essential for the human body and the nine amino acids non-essential for the human body, only three have been subjected to the present study—Phe, Trypt (essential amino acids), and Tyr (non-essential amino acid)—because of their structural similarities and the role these AAs play for the human body. Compared with other amino acids, Phe, Tyr, and Trypt are of particular importance to the central nervous system [53]. Their use as food supplements contributes to the treatment of neurovegetative disorders, disorders that can affect a number of cognitive functions, such as memory, learning, thinking, etc. [52]. These AAs are also essential components in the production of several bioactive compounds called neurotransmitters that act on the brain [6]. Thus, Phe is converted into Tyr in the human body, being substances with a hydrophobic group used in treating genetic disorders, PKU and in the biosynthesis of the main neurotransmitters (dopamine, epinephrine, and norepinephrine), while Trypt is the precursor of another important neurotransmitter (serotonin) responsible for treating insomnia and anxiety (as shown in Table 1).
Table 1. Chemical structure and physical-chemical properties of AAs: Phe, Tyr, and Trypt.

| Amino Acid     | Chemical Structure | Chemical Formula | Chemical and Physical Properties | References |
|----------------|--------------------|------------------|----------------------------------|------------|
| Phenylalanine  | ![Phenylalanine Structure](image) | C₉H₁₁NO₂ | Aromatic Non-polar Mₜ = 165.19 g/mol Hydrophobic substance | [54]        |
| Tyrosine       | ![Tyrosine Structure](image)   | C₉H₁₁NO₃ | Aromatic Non-Polar Mₜ = 181.19 g/mol Hydrophobic substance | [55]        |
| Tryptophan     | ![Tryptophan Structure](image) | C₁₁H₁₂N₂₂ | Aromatic Non-polar Mₜ = 204.22 g/mol Hydrophobic substance | [56]        |

One of the diseases frequently appearing in the population is depression; in this regard, a useful method could be the monitoring of the Phe, Tyr, and Trypt AAs, respectively [38]. This psychological affliction can manifest itself through various symptoms, such as concentration problems, insomnia, and sadness [57,58]. The causes of its emergence can reside in various sources: biological, genetic, environmental, and social-psychological factors [59]. Depending on the type of symptom and the nature of the cause, there are many types of depression, and each needs adequate treatment. To prevent and treat mild forms of depression (postpartum, seasonal, and premenstrual), the pharmaceutical market has developed a variety of medicinal supplements that contain the AAs focused on here—in various concentrations, as shown in Table 2.

Table 2. Pharmaceutical products that contain amino acids Phe, Tyr, and Trypt.

| Amino Acid     | Pharmaceutical Products           | Concentration/Capsule | Producer/Country          |
|----------------|-----------------------------------|-----------------------|---------------------------|
| Phenylalanine  | Amino 75                          | 75 mg                 | SOLGAR/USA ²              |
|                | L-Phenylalanine 500               | 500 mg                | SOLARAY/USA               |
|                | DLPA ¹ 500                        | 500 mg                | SOLGAR/USA                |
|                | Best D-Phenylalanine              | 500 mg                | DOCTOR’S BEST/USA         |
| Tyrosine       | L-Tyrosine 500                    | 500 mg                | SOLARAY/USA               |
|                | Tiroidin                          | 90 mg                 | PARAPHARM/ROMANIA         |
|                | Cebrium                           | 4.12 mg               | NEUROPHARMA/GERMANY       |
|                | Thyroid Caps                      | 100 mg                | SOLARAY/USA               |
| Tryptophan     | Sleep Optimizer                   | 150 mg                | SOLARAY/USA               |
|                | Cebrium                           | 0.2 mg                | NEUROPHARMA/GERMANY       |
|                | L-Tryptophan                      | 500 mg                | SOLARAY/USA               |
|                | Tonico Vita                       | 18 mg                 | TERAPIA/ROMANIA           |
|                | MaxiMag Women                     | 150 mg                | ZDROVIT/ROMANIA           |

¹ DLPA, DL Phenylalanine; ² USA, United Stated of America.

Phenylalanine, or (S)-2-Amino-3-phenylpropanoic acid, an essential AA and precursor of Tyr (Figure 1A), is assimilated by the human body through consuming foods like eggs, meat, fish, and milk, or through the administration of medicinal supplements in view of preventing Parkinson’s disease, depression, vitiligo, and attention deficit hyperactivity disorder (ADHD) [60–62]. Special attention should be paid to people who suffer from PKU, which is an inherited disorder caused by excessive accumulation of Phe in the human body [63]. Consequently, these people should avoid consumption of foods or supplements that contain the Phe AA, or they risk developing other disorders or diseases such as mental retardation, high blood pressure, or cerebrovascular accidents [64]. Today, there is a test for the detection of Phe, starting from birth, with sanguine serum: the Guthrie Test for the neonatal detection...
of PKU. It was created in 1963 by Robert Guthrie [65]. L-Phe, D-Phe, and DL-Phe are the three forms of this AA, namely the natural form, the synthetic form, and the form found in pharmaceutical products, respectively [66].

**Figure 1.** Biosynthesis of amino acids in the human body: (A) Phe adapted from [62]; (B) Tyr adapted from [67]; and (C) Trypt adapted from [68].

Tyr, or L-2-Amino-3-(4-hydroxyphenyl) propanoic acid, a non-essential AA by comparison with Phe and Trypt, is produced naturally in the human body, even from Phe, and through hydroxylation becomes the precursor of two important neurotransmitters of the central nervous system (SNC): adrenaline and noradrenaline—as shown in Figure 1B [67]. As in the case of the other AAs, the absence of Tyr in the human body can be compensated for by consuming various foods (nuts, oat, beans, meat, fish, and wheat) or pharmaceutical products—supplements that have the role of treating PKU and neurological disorders like depression, ADHD, Alzheimer’s disease, and mental retardation [61,69,70]. Tyrosinemia and phenylketonuria are diseases that can occur as a result of excess accumulation or an insufficient amount of Tyr in the body [63]. Thus, tyrosinemia is characterized by an abnormally high level in the blood or urine of Tyr. Phenylketonuria is a condition that
prevents tyrosine biosynthesis, in the sense that individuals who suffer from this condition cannot properly process Phe AA, as a result of which they cannot obtain the proper amount of Tyr [7].

Trypt, or 2-amino-3-(1H-indol-3-yl) propionic acid, is also an essential AA that the human body uses to synthesize proteins; its intake is from external sources such as foods and pharmaceutical products. It has two important functions in the human body: on the one hand, it contributes to the biosynthesis of serotonin (Figure 1C), and on the other hand, it is involved in the biosynthesis of melatonin [68,71]. The values of Trypt sanguine concentration in the human body are situated within the following normal limits: between 10 and 40 millimoles/L—that is, between 2.05 and 5.15 mg/L [72]. In the case of values under the normal limit of Trypt, various forms of depression and insomnia are triggered, and in the case of values above the normal limit of Trypt, SNC disorders appear: manic-depressive psychosis with delirium, and schizophrenia [73,74].

Another aspect shared by the three AAs is the domain they are used in. Table 3 presents, for each domain, the uses of each AA studied here. The specialized literature mentions numerous studies focusing on the three AAs. For example, in 2020, Mahmoud Alagawany et al. published a review of the nutritional significance of AAs for raising birds and keeping them healthy, representing an alternative to therapy using antibiotics [75].

| Domain of Use | Phe Uses | Tyr Uses | Trypt Uses | References |
|--------------|----------|----------|------------|------------|
| Chemistry Medicinal | Depression, ADHD 1, Parkinson’s disease, chronic pain, osteoarthritis, rheumatoid arthritis, alcohol withdrawal symptoms, and vitiligo skin disease | Phenylketonuria, mental performance, alertness or memory, depression, or ADHD | Premenstrual dysphoric disorder syndrome, sleep problems (insomnia), anxiety, depression, and ADHD | [76–81] |
| Pharmacology Pharmacy | Is part of medicinal supplements under various forms: capsules, creams, vials, and syrups. | | | [26,28,82–86] |

1 ADHD, attention deficit hyperactivity disorder.

Another study on AAs (with special focus on Tyr) was carried out in 2021 by Félix Javier Jiménez-Jiménez et al. They outlined a meta-analysis of methods for determining the AAs involved in Parkinson’s disease, both in the sanguine serum and in the cerebrospinal fluid. In their conclusions, they mention that high concentrations of Tyr were found in the cerebrospinal liquid, and low concentrations of Tyr were found in the sanguine plasma [87]. Moreover, in 2020, Xiaoyang Jing et al. presented methods of AA codification. The authors mentioned five categories of methods: binary codification, codification of physical-chemical properties, codification based on evolution, codification based on structures, and codification of automatic learning. They concluded that, out of the five, codification based on evolution could obtain the best results [53]. The paper, signed by Paolo Tessari et al., presented the recommended daily doses of AAs, considering that they are the main regulators in the nutrition of an adult, being present in a wide variety of foods. The conclusion of this study highlighted the benefits of vegetable food product consumption, since necessary and important quantities of AAs are found in such products (as shown in Tables 4 and 5) [88].

In 2020, Fieke Terstappen et al. published a paper of interest in regards to studies evaluating whether prenatal supplementation with AAs can represent a promising method of growing a healthy fetus; it included studies on 22 people and 89 animals. In the authors’ reevaluation, analyses were centralized to identify oral supplementation with AAs, the most efficient from the standpoint of the dose administered being highlighted. It was therefore concluded that the AAs in the arginine family, or BCAA (branched chain AAs), normalize
the underdeveloped fetus, while the methyl-donating AAs normalize the excessive growth of the fetus [89].

In conclusion, AAs gained the title of the most important nutrients for the human body, representing “the elements which form our life” and offering the human body, alongside vitamins and minerals, the material needed to repair muscles, organs, or any other of its tissues.

Table 4. Recommended daily doses for a 70 kg male, and AAs in various foods: animal source foods. Reprinted with permission from [88].

| RDA | Egg 100 g | Milk 100 mL | Beef 100 g | Pig 100 g | Chicken 100 g | Sea Bass 100 g |
|-----|-----------|-------------|------------|-----------|---------------|---------------|
|     | Protein content (g) |            |            |            |               |               |
|     | 12.1       | 3.3         | 22         | 20.7      | 23.3          | 21.3          |

**Essential amino acids**

| RDA | Lysine | Histidine | Threonine | Cyst + Meth | Valine | Isoleucine | Leucine | Phenylalanine + Tyrosine | Tryptophan | Total EAAs (mg) |
|-----|--------|-----------|-----------|-------------|--------|------------|---------|----------------------------|------------|-----------------|
|     | 2100   | 700       | 1050      | 1050        | 1820   | 1400       | 2730    | 1750                       | 280        | 12,880          |
|     | 1001   | 322       | 674       | 740         | 896    | 741        | 748     | 1247                       | 228        | 6597            |
|     | 272    | 93        | 164       | 118         | 233    | 192        | 355     | 318                        | 50         | 1795            |
|     | 2002   | 849       | 898       | 871         | 1063   | 950        | 1892    | 1677                       | 246        | 10,448          |
|     | 1737   | 647       | 919       | 780         | 1243   | 1080       | 1624    | 1166                       | 183        | 9379            |
|     | 2246   | 937       | 1160      | 974         | 1384   | 1153       | 1955    | 1776                       | 273        | 11,858          |
|     | 2021   | 552       | 967       | 897         | 1044   | 914        | 1655    | 1531                       | 249        | 9830            |

1 RDA, Recommended daily doses.

Table 5. Recommended daily doses for a 70 kg male, and AAs in various foods: vegetable source foods. Reprinted with permission from [88].

| RDA | Soybeans 100 g | Beans 100 g | Peas 100 g | Wheat 100 g | Maize 100 g | Rice 100 g | Potato 100 g | Cauliflower 100 g | Quinoa 100 g |
|-----|----------------|-------------|------------|-------------|-------------|------------|--------------|-------------------|--------------|
|     | Protein content (g) |            |            |            |             |            |               |                   |              |
|     | 38.9           | 10.2        | 5.5        | 11          | 8.7         | 6.7        | 2.1          | 3.2               | 19.6         |

**Essential amino acids**

| RDA | Lysine | Histidine | Threonine | Cyst + Meth | Valine | Isoleucine | Leucine | Phenylalanine + Tyrosine | Tryptophan | Total EAAs (mg) |
|-----|--------|-----------|-----------|-------------|--------|------------|---------|----------------------------|------------|-----------------|
|     | 2100   | 700       | 1050      | 1050        | 1820   | 1400       | 2730    | 1750                       | 280        | 12,880          |
|     | 3047   | 1170      | 1843      | 1183        | 2176   | 2222       | 3689    | 3970                       | 618        | 19,918          |
|     | 714    | 303       | 428       | 238         | 616    | 556        | 885     | 963                        | 113        | 4816            |
|     | 348    | 85        | 310       | 238         | 226    | 201        | 342     | 345                        | 54         | 2006            |
|     | 239    | 228       | 310       | 95          | 452    | 403        | 741     | 855                        | 116        | 3798            |
|     | 258    | 251       | 334       | 307         | 472    | 350        | 1028    | 761                        | 61         | 3822            |
|     | 257    | 165       | 246       | 257         | 438    | 306        | 590     | 588                        | 84         | 2931            |
|     | 92     | 28        | 59        | 51          | 99     | 68         | 96      | 132                        | /          | 624             |
|     | 120    | 37        | 74        | 63          | 104    | 73         | 126     | 129                        | /          | 726             |
|     | 1025   | 478       | 849       | 565         | 961    | 808        | 1399    | 1542                       | 726        | 8353            |

1 RDA, Recommended daily doses.

3. CPs and MIPs Used to Determine Phe, Tyr, and Trypt

Known as macromolecular compounds, polymers may be found in almost all the materials that people use in everyday life. In essence, polymers are made up of several small molecules—called monomers—linked to form long strands [41]. Since they are
applied in numerous fields (science, industry, and technology), the importance of polymers has been emphasized in many published articles, the advantages of their use residing in thermal stability, processability, various optic and mechanic properties, and relatively inexpensive and easy manufacturing [40]. Naturally, therefore, these versatile compounds have been used to increase the rate, stability, and sensitivity of various devices with applicability in biomedicine and bioengineering [90]. Furthermore, more types of polymers have been identified in keeping with their chemical structure, molecular mass, origin, and strand topology (as shown in Figure 2) [91].

Figure 2. Types of polymers with various strand topologies: (a) linear polymer, (b) branched polymer, (c) graft polymer, and (d) reticulated polymer. Reprinted with permission from [91].

The new areas in which polymers play a significant role are represented by biochemistry, pharmacy, biomedicine, molecular biology, and biophysics [40]. For example, in the pharmaceutical field, a polymer could be used to precisely release the active substance in a medicine [92]. In recent years, polymers have been studied in fields of research that involve the manufacturing of sensors and biosensors, endowing them with properties such as increased conductivity, and improved kinetics of electron transfer and of electrocatalytic activity [93,94]. This is the reason why the present study highlights the importance of CPs and MIPs in achieving various versatile devices for the quantification of AAs in pharmaceutical products, foods, and biological fluids.

Thus, CPs, also known as “synthetic metals”, represent a new generation of polymers, electrochemical synthesis being the preferred method of obtaining them since it has the advantage of simplicity and the possibility of achieving polymeric films of various thicknesses and doping levels [95]. Following the discovery of CPs, Alan J. Heeger, Alan G. MacDiarmid, and Hideki Shirakawa received the Nobel Prize for Chemistry in 2000 [96]. The CPs most frequently encountered in scientific research are PPy [97–101], PANI [102–105], PEDOT [46,106–109], PT [110–113], and polyacetylene [114–116], the chemical structures of which are shown in Figure 3. This type of polymer is usually obtained by electrochemical polymerization, a process that takes place in a solution that includes the solvent, the polymerizable monomer, and the electrolyte. Electropolymerization can be performed through either potentiostatic, galvanostatic, or multi-sweep techniques [117].
This category of polymers has drawn the attention of many researchers, particularly because of their main property: electrical conductivity. This property of polymers is based on the presence of conjugated double bonds between carbon atoms along the polymer chain, and this bond can alternatively be single and double. Thus, a process of doping the polymer creates the conducting properties of the electrical charge [96]. Along these lines, the authors of the present paper carried out a study, published this year, that presents the manufacturing of a sensor to detect the L-Tyr AA in pharmaceutical products with the aid of the PPy conductor polymer and three doping agents: potassium hexacyanoferrate (II) (FeCN), sodium nitroprusside (NP), and sodium dodecyl sulphate (SDS). Two methods were used: chronoamperometry for the deposit on electrodes of the polymer doped with various anionic agents, and cyclical voltammetry for the electrochemical characterization of the sensors achieved. The devices obtained demonstrated good sensitivity and selectivity in detecting L-Tyr, having the following detection limits: $8.2 \times 10^{-8}$ M for PPy/FeCN-SPCE, $4.3 \times 10^{-7}$ M for PPy/NP-SPCE, and $3.51 \times 10^{-7}$ M for PPy/SDS-SPCE (as shown in Figure 4) [27].

![Response curves for different sensors](image)

**Figure 4.** Responses of sensors modified with PPy immersed in a 0.1 M KCl and $10^{-3}$ M L-Tyr la 0.1 V × s⁻¹ solution: (A) PPy/FeCN-SPCE, (B) PPy/NP-SPCE, and (C) PPy/SDS-SPCE [27].

On the other hand, other polymers involved in numerous studies are MIPs in monomer solutions with template molecules, reticulation agents, or solvents, this being a versatile preparation method that can frequently be used to configure various biomimetic receivers (as shown in Figures 5 and 6) [43,118]. Initially, these MIPs were synthesized by thermal heating, but because of the disadvantages of the long synthesis time and excess internal energy of the system, other methods for the synthesis of MIPs were developed,
such as photopolymerization, electropolymerization, ultrasound-assisted synthesis, and microwave-assisted synthesis [119].

![Diagram](image)

**Figure 5.** General method of preparation of MIPs. Adapted from [118].

![Diagram](image)

**Figure 6.** The general scheme for obtaining an MIP. Reprinted with permission from [120].

Generally, MIPs are stable, and resistant to various pH values and temperatures, but are also in various solvents [96]. Another advantage of MIPs is their relatively simple and inexpensive synthesis, which represents an alternative in using natural biological receivers [121]. Due to their affinity and selectivity, MIPs have proved to be adequate receivers for various organic and biological species such as enzymes and antibodies, and, in recent years, they have been used to manufacture electrochemical sensors and biosensors, a model for preparation being given in Figure 7 [42].

Regarding the AAs tackled in this present study, A. Nan et al. reported (in a paper published in 2000) the synthesis and characterization of hybrid magnetic nanostructures for the analysis of AAs: Phe, Tyr, Trypt, leucine, and serine—used to functionalize the pyrrole monomer, being linked through various types of hydrophobic linkers in the azoth atom of the pyrrole monomer [50]. The methods for the characterization of these nanostructures were FTIR spectroscopy, transmission electronic microscopy (TEM), and magnetic measurements. N-hydroxyl succinate was the precursor used to obtain the monomers of pyrrole functionalized with AA, as shown in Figure 8.
Figure 7. Typical manufacturing of MIP potentiometric sensors with polymeric membranes, through three processes: MIP incorporation (a), MIP covering (b), and MIP electropolymerized (c). Reprinted with permission from [42].

Figure 8. Reactions between N-hydroxy succinate and AAs. Adapted from [50].
Three stages were necessary to prepare these hybrid nanoparticles based on functionalized PPy: magnetic nanoparticle synthesis (MNS), synthesis of pyrroles functionalized with Trypt, leucine, phenylalanine, serine, and Tyr, and copolymerization of functionalized pyrroles in the presence of magnetite MNP [50]. Figure 9 shows the results obtained through FTIR in the process of preparing hybrid magnetic nanoparticles (MNP) based on functionalized polypyrrole. The results obtained demonstrate a high level of magnetic nanoparticle dispersibility, a uniform dimension, and a spherical shape, as shown in Figure 10. In conclusion, the authors proved the superparamagnetic behavior for the functionalized magnetic nanostructures based on functionalized PPy.

Figure 9. FTIR spectra of (a) tryptophan functionalized MNP-2, serine functionalized MNP-5, and (b) phenylalanine MNP-4 and tyrosine MNP-6. Reprinted with permission from [50].

Since the three AAs are found in biological fluids, implicitly in human blood serum and urine, it is extremely important to monitor their levels in the body, to measure their concentration by means of more sensitive and more selective devices such as sensors and biosensors.

4. Sensors and Biosensors Based on CPs and MIPs to Quantitatively Determine AAs (Phe, Tyr, and Trypt)

4.1. General Methods Used to Determine AAs

Many scientific articles, reviews, book chapters, and volumes about how to detect Phe, Tyr, and Trypt have been published so far. Each scientific paper describes unique methods of AA detection, which, as technology has advanced, highlighted advantages and
disadvantages. In compiling the data in Table 6, a series of method performance criteria were in view: precision, selectivity, accuracy, sensitivity, detection limit, cost, and duration, classified according to the intensity of each method.

**Table 6. Performance criteria of the methods developed for the detection of AAs.**

| Precision          | Selectivity | Accuracy | Detection limit | Cost and Duration |
|--------------------|-------------|----------|-----------------|-------------------|
| High               | Electrochemical methods based on achieving sensors and biosensors [15,37,49,92] |          |                 |                   |
| Medium             | Instrumental (electrical methods [122], optical methods [123], thermal methods [124], magnetic methods, and radiochemical methods [125]) |          |                 |                   |
| Low                | Chemical methods (volumetry, gravimetry, precipitation methods) [126] |          |                 |                   |

The disadvantages connected with electrochemical methods have stimulated researchers to improve the properties and performances of sensors and biosensors using, for the quantitative determination of AAs, Phe, Tyr, and Trypt, resorting to their modification, either with CPs doped with electroactive ions or with MIPs. Thus, researchers highlighted the unique properties of these devices: their optical, electrical, and mechanical properties, increased stability, high response rate, and increased sensitivity in the process of rapidly and precisely detecting AAs [127]. These analytical instruments were therefore found applicable in a large range of fields, including biotechnology and bio-pharma-medicine [93,94,121].

In short, the specific goal of this review resided in synthesizing the articles published so far in which CPs and MIPs were involved to develop electrochemical sensors and biosensors used to detect the three amino acids mentioned: Phe, Tyr, and Trypt.

**4.2. CPs and MIPs Involved in Developing Electrochemical Sensors to Detect AAs: Phe, Tyr, and Trypt**

Sensors and biosensors, high-interest instruments, are used in many research fields: medicine, pharmacy, industry, transport, environmental protection, and automation. Thus, in the future humanity will depend on many of these devices (with people who suffer from diabetes depending on glucometers—devices that detect the glycaemia levels in the body—constructed with the aid of a biosensor) [103,128]. Thus, the stage of selecting sensor construction/manufacturing materials is extremely important, as the materials can contribute to solving various problems related to analyte detection, such as the redox potential of molecules, the deterioration of electrode surfaces—leading to low reproducibility. To improve various properties—such as electrical conductivity, mechanical stability, and chemical surface—electrochemical sensors were achieved with the aid of a wide range of materials like CPs, applying the following electrochemical methods: potentiometry [66], conductometry [94], amperometry [103], and voltammetry [36,129]. This category of sensors is used especially in systems for monitoring the environment and health, in food quality control, and in the general scheme of the equipment used to electrochemically analyze an electrode, as illustrated in Figure 11 [130].

In 1959, chemist Jaroslav Heyrovsky received the Nobel prize for discovering the polarographic voltammetric method, which allowed the further development of other electroanalytical techniques such as CV, DPV, LSV, and SWV [129]. These methods showed a series of advantages through the years: simultaneous determination of more analytes, increased sensitivity with regard to detecting organic and inorganic species in various concentration ranges, the ability to work with a large range of temperatures, the capacity to determine kinetic parameters and to estimate unknown parameters, and rapid analysis [131,132]. Due to these advantages, this review has summarised, in Table 7, the notable studies developing sensors characterized through voltammetric methods and constructed based on CPs and MIPs to detect the three AAs.
Table 7. Performances of various electrochemical sensors based on CPs and MIPs to detect the Phe, Tyr, and Trypt AAs. A summary.

| AA 1 | CPs 2 | LOD 4 (M)/Sensitivity/Linear Range | MIPs 3 | LOD 4 (M)/Sensitivity/Linear Range |
|------|-------|-----------------------------------|--------|-----------------------------------|
|      | Electrode Architecture | Detection Technique | Electrode Architecture | Detection Technique |
|     | Sensor with Gum Arabic based polyurethane modification [133] | DPV 5 | Sensor with p-Toluene Sulfonic Acid Modified Pt Electrode [134] | DPV |
|     | PPy-β-CD/GCE (polypyrrole-β-cyclodextrin conjugate)/glassy carbon electrode [135] | CV 6, LSV 7 | MIP/TP3C-Trp (molecularly imprinted polymer/Thiophen-3-carbonyl tryptophan) [43] | SWV 8, CV |
|     | MIP-grafted ITO/EDMA/MBAA (electrode grafted with a molecularly imprinted polymer crosslinked via a combination of hydrophobic ethyleneglycol dimethacrylate and hydrophilic methylene bisacrylamide) [136] | CV | | |

Figure 11. Schematic illustration of the equipment used for analysis with an electrochemical sensor. Reprinted with permission from [130].
### Table 7. Cont.

| AA  | Electrode Architecture | Detection Technique | LOD (M)/Sensitivity/Linear Range | Electrode Architecture | Detection Technique | LOD (M)/Sensitivity/Linear Range |
|-----|------------------------|---------------------|---------------------------------|------------------------|---------------------|---------------------------------|
| Tyrosine | GC/CNT/PEDOT/NF/Crown (glassy carbon/multi-walled carbon nanotubes/poly(3-4-ethylene dioxythiophene/Nafion/Crown) [45] | CV | \(0.429 \times 10^{-9} / 963.1 \times 10^{-9} / 0.06-20 \times 10^{-9}\) | MIP/pTH/Au@ZIF-67 (molecularly imprinted polyaniline/polythionine/gold nanoparticles@zeolitic imidazolate framework-67 composite) [47] | DPV | \(7.9 \times 10^{-10} / 0.0005 \times 10^{-10} / 1 \times 10^{-8}-4 \times 10^{-6}\) |
| | EB-Ppy-BSA/GCE (Electron beam irradiated polypyrrole nanospheres embedded over bovine serum albumin) [137] | SWV | \(8.8 \times 10^{-9} / 1.04 \times 10^{-9} / 100 \times 10^{-9}-800 \times 10^{-6}\) | In situ copper oxide modified MIPPy (molecularly imprinted polypyrrole) coated GCE (glassy carbon electrode) [138] | LSV | \(4.0 \times 10^{-9} / 0.47 \times 10^{-9} / 1 \times 10^{-6}-1 \times 10^{-6} \text{ and } 2 \times 10^{-6}-8 \times 10^{-6}\) |
| | EB-Ppy/MGA (Electron Beam-modified Gum Acacia) [139] | CV, SWV | \(85 \times 10^{-9} / 18.944 \times 10^{-9} / 0.4-600 \times 10^{-6}\) | MIP-Ppy/AuE (molecularly imprinted polymer-polypyrrole/gold electrode) [140] | CV, SWV | \(2.5 \times 10^{-9} / 0.6567 \times 10^{-9} / 5.0 \times 10^{-9}-2.5 \times 10^{-8}\) |
| | CuNPs/p-TAOX/GCE (copper nanoparticles/poly(3-amino-5-mercapto-1,2,4-triazole)/glassy carbon electrode) [141] | DPV, CV | \(0.16 \times 10^{-6} / 8.2058 \times 10^{-6} / 4.0-144.0 \times 10^{-6}\) | Polypyrrole (OPPy)/Poly (p-aminobenzene sulfonic acid) modified glassy carbon electrode [142] | CV | \(1.2-4 \times 10^{-6}\) |
| **Tryptophan** | 3DCu(x)O-ZnO NPs/PPy/RGO A three-dimensional porous nanocomposite of reduced graphene oxide decorated with polypyrrole nanofibers and zinc oxide-copper oxide p-n junction heterostructures [143] | DPV, CV | \(0.016 \times 10^{-6} / 0.1345 \times 10^{-6} / 0.053-480 \times 10^{-6}\) | Nafion-MIP-MWCNTs@IL/GCE (Nafion-molecularly imprinted copolymer-ionic liquid (i.e., 1-butyl-3-methylimidazolium hexafluorophosphate) functionalized multi-walled carbon nanotubes/glassy carbon electrode) [49] | DPV, LSV | \(6 \times 10^{-9} / 5.09 \times 10^{-9} / 8 \times 10^{-9}-26 \times 10^{-6}\) |
According to Table 6, Funda Alişık et al. contributed to detecting AA L-Phe by preparing polyurethane sensors based on Arabic gum, modifying platinum electrodes using the electropolymerization technique. It was analyzed through DPV, showing increased sensitivity and reproducibility in detecting a wide range of L-Phe concentrations. The development of such a sensor was considered useful for selectively detecting PKU, the sensor being analyzed and validated by numerous techniques, such as FTIR, DTA, TGA, and SEM. The novelty of the research is represented by the polyurethane polymer, which gives the sensor good adhesion and a selective permeability. [134].

Tatiana V. Shishkanova et al. used the β-cyclodextrin pyrrole polymer in preparing the sensor used to molecularly recognize Phe enantiomers. In this case, the electrochemical method used was LSV, in the 0.1–0.75 $\times 10^{-6}$ M ($n = 3$) concentration range, manifesting higher sensitivity for the D-Phe enantiomer as compared to the L-Phe one. This study was based on the characterization, deposition, and recognition of the properties of the modified CP (pyrrole-β-cyclodextrin conjugate)-modified sensor [135].

Yu-fang Hu et al. developed an electrochemical sensor in whose fabrication CP PANI was involved, the electrochemical behavior of the sensor being studied through CV and DPV methods in view of using it to determine L-Phe in human serum samples. The sensor demonstrated excellent stability, sensitivity, selectivity, recuperation, and reproducibility. The research developed a new electrochemical printing technique using a PANI-coated electrode, a stable conductive polymer with high electrocatalytic ability [102]. Other researchers developed sensors to detect L-Phe through the molecular imprinting technique. Along these lines, Funda Alişık et al. obtained, for the 20 sensors prepared, a stable reproducibility percentage of 97.67%, with an RSD value of 2.33%, thus demonstrating that the sensor prepared from p-toluene sulphonic acid (PTSA) polymeric films had high stability, repeatability, and selectivity for L-Phe [134]. Nihal Ermiş et al. used the Thiophen-3-carbonyl tryptophan (TP3C-Trp) monomer, developing electrochemical sensors characterized through CV, drawing a parallel between non-imprinted sensors (NIP) and imprinted ones (MIP) to selectively and sensitively determine L-Phe. The linearity range obtained was wide, $1.0 \times 10^{-8}$–$1.0 \times 10^{-7}$ M, and proved to be useful in detecting L-Phe in egg whites and chicken samples. By electropolymerizing the polymer, the authors with the help of TP3C-Trp developed a new sensor for Phe detection [43]. Another sensor prepared through the molecular imprinting technique belongs to Yasuo Yoshimi and Noriyuki Ishii, who discovered enantioselective sensitivity to Phe in water solution through the cyclic voltametric method, at the same time using a mixture of reticular hydrophobic (hydrophobic ethylene glycol dimethacrylate) and hydrophilic (hydrophilic

| AA  | CPs  | MIPs  | LOD (M)/Sensitivity/Linear Range | LOD (M)/Sensitivity/Linear Range |
|-----|------|-------|----------------------------------|----------------------------------|
| L-Phe | PPy/FeCN/SPCE (polypyrrole/potassium hexacyanoferrate (II))/carbon screen-printed electrode) [28] | CV | 1.05 $\times 10^{-7}$ / 0.87268 $\times 10^{-7}$ / 3.3 $\times 10^{-7}$ / $-1.06 \times 10^{-5}$ | CV | 1.0 $\times 10^{-9}$ / 35.8632 $\times 10^{-6}$, 1.1142 $\times 10^{-6}$, 0.16352 $\times 10^{-6}$ / 2.0 $\times 10^{-9}$ / $-0.2 \times 10^{-6}$, 0.2 $\times 10^{-6}$ / $-10 \times 10^{-6}$ and $100 \times 10^{-6}$ |

1 AA, amino acid; 2 CPs, conductive polymers; 3 MIPs, molecularly imprinted polymers; 4 LOD, limit of detection; 5 DPV, differential pulsat voltammetry; 6 CV, cyclic voltammetry; 7 LSV, linear sweet voltammetry; 8 SWV, square wave voltammetry.
methylene bisacrylamide) agents, which demonstrated improvement of sensor sensitivity. The concentration range used was $3-5 \times 10^{-6}$ M, demonstrating the utility of MIP for molecular recognition in biomimetic sensors. The development of such an anilide-printed poly (ethylene glycol dimethacrylate (EDMA) co-methacrylic acid (MAA))-based electrode was intended to demonstrate the possibility of chiral-selective detection of Phe using MIPs, using a crosslinked monomer combination [136].

To determine Tyr, the CPs most frequently involved in developing electrochemical sensors were PEDOT and PPy. Thus, F. Nada et al. carried out a study in which sensors were tested on real samples of biological fluids to determine four analytes: norepinephrine, paracetamol, Tyr, and ascorbic acid. Each component that contributed to sensor preparation had unique characteristics that conferred the devices a remarkable electro-catalytic activity. CP PEDOT was used to endow the sensor with increased electrical conductivity and stability [45]. The linear range obtained for detecting Tyr was $0.06-20 \times 10^{-6}$, and the detection limit was low; it was therefore considered that this device would be attractive and useful in the medical field. The novelty of the study is underlined by the advantages of the PEDOT, multi-walled carbon nanotubes, Nafion, and crown that it gives to the new sensor prepared by electrochemical polymerization. In the papers published by Nathiya Dhananjayan et al. (2019) [139] and Ramya, R. et al. (2018) [137], PPy was used as CP in fabricating sensors for the ultrasensitive detection of Tyr. Both articles demonstrated that the PPy polymer contributed considerably to improving the properties of sensors through increased stability, conductivity, sensitivity, and better biocompatibility. In the first case, the sensor was applied to determine the concentration of Tyr in human urine samples, chicken meat, and cow’s milk; in the second case, it was applied to tea and chicken meat samples. In a study by Nathiya Dhananjayan et al., a sensor was developed based on a biopolymer, namely modified gum acacia, encapsulated with electron-beam-irradiated polypyrrole nanospheres, and in the Ramya study, R. et al. applied a new synthesis of electron-beam-irradiated polypyrrole modified with sheets over bovine serum albumin. [137,139].

Furthermore, sensors prepared through the molecular imprinting technique are present in this case also. For example, Bangjie Chen et al., obtained a linearity range of $1 \times 10^{-8}$ M to $4 \times 10^{-6}$ M for determining Tyr. A carbon electrode was molecularly imprinted with a polyaniline/polystyrene/gold nanoparticle@zeolitic imidazolate framework-67 composite, and analyzed with a cyclical voltammetric method on human serum samples, with satisfactory results: 98.8%. The materials used in the molecular imprinting were selected because of their large surfaces, high porosity, and biocompatibility [47]. In the case of the study carried out by Nihar Ermiş et al., the molecular imprinting was achieved with PPy films on a gold electrode, with excellent results obtained on the human plasma samples used to detect Tyr, demonstrating good reproducibility and repeatability [140]. On human urine samples, Varghese Saumya et al. applied the MIPPy/GCE sensor, prepared and analyzed on site through an electrochemical method, which had the advantage of increased simplicity and sensitivity. The concentration range used for Tyr was $1 \times 10^{-8}$ to $8 \times 10^{-6}$ M, and the sensor was applied to detect tyrosine in human urine samples [138].

To identify and quantify tryptophan with sensors based on conductor polymers and molecularly imprinted polymers, a series of studies were carried out, with applicability on the following types of real samples: human urine [141], biological fluids [143,144], and pharmaceutical products [28,49]. In Figure 12 is presented the detection principle of a voltammetric sensor based on polypyrrole doped with ferrocyanide ion.

The studies demonstrated the increased performance of the devices achieved, mainly due to using CP or to the diversity of the molecular imprinting materials.

All the benefits of the conducting polymers demonstrate their ability to integrate into micro/nano devices in order to detect or monitor different bioanalytes. The various types of conducting polymers make it possible to couple them with various biological and/or chemical species to obtain high performance characteristics, such as improved sensitivity and selectivity. The progress observed is closely related to the selection of the
type of polymers, the processing technologies that aim to integrate CPs on the surface of (bio)sensors with wide applications in various applicative fields [93].

Thus, we found in the literature that one of the major challenges in the development of an electrochemical (bio)sensor based on CP is represented by the immobilization of the transducer on the electrode surface in order to achieve a good transduction of the signal [145]. As a result, the mechanical properties of CP films and the effects of thickness and microstructures on them, and breaking behaviour in the presence of thermal and mechanical factors, should be taken into account when a CP is selected [146].

4.3. CPs and MIPs Involved in Developing Electrochemical Biosensors to Detect AAs: Phe, Tyr, Trypt

As mentioned by the authors of the research described in this section, the application of CPs for the design of MIPs and the various possibilities for the immobilization of biological recognition elements, such as enzymes, antibodies, or proteins, are important advantages of biosensors based on CPs, finding applicability in many directions of research [147]. So, the challenge in the principle of the selection of conducting polymers used in the manufacture of biosensors is closely related to the method of production, the enzyme used, and the analytes to be detected [148]. The polymer matrix provides a suitable environment for the immobilization of the enzyme, while maintaining its long-term activity, especially in electrochemical measurements [149].

If the sensor is an analytical instrument that translates physical and chemical data into measurable signals, biosensors play the same role, but are based on a combination of a biological recognition compound and a physical translator—the recognition element being either an enzyme, an antibody, or a microorganism—which renders it more sensitive for detecting the substance analyzed. Immobilization methods of biomolecules include covalent binding, crosslinking, entrapment, adsorption, and affinity. All the methods have advantages and disadvantages, but one of the most important aspects to be taken into account is the maintaining of the bioactivity of the biomolecules [150].

The typical scheme of a biosensor is presented in Figure 13 [151].

Therefore, a biosensor is a device designed to obtain a digital electronic signal proportional to the concentration of a chemical compound in the presence of an interfering species. Their difference from the sensors is even written with the prefix “bio”, precisely because of their biofunctionality, respectively biocatalysis and molecular recognition, and this aspect led to a typical biosensor architecture represented by two types of components: the biological component, and the transducer component [152].

Biosensors are applied to a variety of samples: biological fluids, food samples, medicine samples, cellular cultures, or environment samples [153]. Their sensitivity is higher in comparison with sensors because of the biological recognition compound [127]. In this section also, the criteria for scientific paper selection were represented by the use of CPs and MIPs, AA (Phe, Tyr, Trypt) detection, and the use of voltametric methods.

Thus, in 2018, C.S. Pundir et al. compiled a review on the determination of the D and L enantiomers of amino acids with the aid of biosensors. They mentioned the optimum functioning parameters used to detect AAs: the 5.3–9.5 pH interval, the 25–45 °C temperature interval, the 0.0008–8000 × 10^{-6} M AA concentration interval, the 0.02–1250 × 10^{-6} M
detection limit, and the −0.05–0.45 V work potential between 2 s and 900 s. AAs were detected in fruit juices, beverages, urine, and blood serum, the biosensors showing a 200 times repeatability during an interval of between 7 and 120 days [127]. Moreover, Table 8 presents other studies in which biosensors with CPs and MIPs were achieved to detect AAs through voltametric methods.

Table 8. Performances of biosensors with CPs and MIPs to detect Phe, Tyr, and Trypt.

| AA       | Electrode Architecture                        | Detection Technique | LOD (M)/Sensitivity/Linear Range                      | Electrode Architecture                        | Detection Technique | LOD (M)/Sensitivity/Linear Range |
|----------|-----------------------------------------------|---------------------|------------------------------------------------------|-----------------------------------------------|---------------------|----------------------------------|
| Phenylalanine | L-AAOD-polytyramine electrode (L-amino acid oxidase) [154] | CV                  | 0.07 × 10⁻⁶ / 0.07–3 × 10⁻³                           | MIP/acid (poly(AN-co-AA)/QCN crystal nanobalance electrode imprinted polyacrylonitrile and acrylic) [155] |                      | 45 mgL⁻¹ / 0.5839 Hz/mgL⁻¹ / 50–500 mgL⁻¹ |
| Phe      | L-Phe-IPDA-CdS-CdSe-Zn/Ti PEC (L-Phe-imprinted polydopamine-coated Zn/CdS/CdSe/heterojunction) [147] | CV, CA ¹            | 0.9 × 10⁻⁹ / 0.005–2.5 and 2.5–130 × 10⁻⁶           |                                               |                      |                                  |
| Tyrosine | Polythreonine-modified graphite-carbon nanotube paste electrode [148] | CV, DPV             | 2.9 × 10⁻⁷ / 9.92 × 10⁻⁷ / 2 × 10⁻⁸ to 2.5 × 10⁻⁸ to 3 × 10⁻⁷ to 1.2 × 10⁻⁴ | MIP-OECTs (molecularly imprinted polymer-organic electrochemical transistors) [149] |                      | 30 × 10⁻⁹ / 14.5 and 12.5 / 300 × 10⁻⁹ to 10 × 10⁻⁶ |

Figure 13. Main elements of a biosensor. Reprinted with permission from [151].
Table 8. Cont.

| AA          | Electrode Architecture | Detection Technique | LOD (M)/Sensitivity/Linear Range | Electrode Architecture | Detection Technique | LOD (M)/Sensitivity/Linear Range |
|-------------|------------------------|---------------------|---------------------------------|------------------------|---------------------|----------------------------------|
| Tyrosine    | L/D-DHCNT@PPy@AuNPs @L/D-Cys (left-/right-handed double helix carbon nanotubes/Polypyrrole@Au nanoparticles nanocomposites/L/D-cysteine) [156] | DPV                 | 1.88 \times 10^{-1} L-Tyr and 5.72 \times 10^{-1} D-Tyr/−0.004 |
|             |                        |                     |                                 |                        |                     |                                  |
|             | D-CNT@PPy@Pt NPs@beta-CD (polypyrrole-coated chiral carbon nanotubes with Pt nanoparticles and beta-cyclodextrin) [157] | CV                  | 0.107 \times 10^{-9}/3–30 \times 10^{-6} |
| Tryptophan  | PT-Ag/L-Try/GCE (polythiophene with silver dendrites composite/L-Tryptophan/glassy carbon electrode) [110] | CV, SWV             | 20 \times 10^{-9}/200 \times 10^{-3}–400 \times 10^{-3} |
|             |                        |                     |                                 |                        |                     |                                  |
|             | D-CNT@PPy@Pt NPs@beta-CD (polypyrrole-coated chiral carbon nanotubes with Pt nanoparticles and beta-cyclodextrin) [157] | CV                  | 0.133 \times 10^{-9}/19.6–196 \times 10^{-6} |
|             |                        |                     |                                 |                        |                     |                                  |
|             | L/D-DHCNT@PPy@AuNPs @L/D-Cys (left/right-handed double helix carbon nanotubes/Polypyrrole@Au nanoparticles [156] | DPV                 | 0.012 L-Trp% and 0.14 D-Trp% and 0.659 and 0.02 |

1 CA, chronoamperometry.

The detection principle of the MIP-based sensors could be mainly impedimetric, voltammetric, or amperometric. In Figure 14 is presented the detection process of the Trypt with a MIP-based sensor.
Figure 14. The procedure for the development of the MIP/acetylene black paste electrode and the principle of Trypt detection [159].

Biosensor studies in which CPs and MIPs were involved, developed to determine the three AAs, are less numerous than the studies on electrochemical sensors. Thus, for the Phe AA, quartz crystal electrodes molecularly imprinted with copolymer, polyacrylonitrile, and acrylic acid were used. Their analysis was carried out in parallel with a series of non-molecularly imprinted copolymer electrodes, emphasizing higher sensitivity in the case of the poly(AN-co-AA)-modified biosensor, (0.5839 Hz/mgL$^{-1}$), as compared to the non-imprinted one, $-0.2724$ Hz/mgL$^{-1}$, and reproducibility (RSD) was 1.84%. Biosensor selectivity was demonstrated by simultaneous testing of analytes: Phe, dopamine (DA), ascorbic acid (AscA), vanillylmandelic acid (VMA), uric acid (UA), Trypt, and Tyr. This study was conducted by Ablolreza Mirmohseni et al. in 2008, stating that the developed biosensor could be successfully applied to human serum samples [155]. The novelty of the research is in the use of poly (AN-co-AA) polymer to detect the level of Phe in different solutions, compared to a study done prior to this research, in which the polymer was applied for the racemic separation of Phe [160].

A representative study for the chiral recognition of L/D-Tyr and L/D-Trypt with biosensors was signed by Lijun Zhang et al. They proposed a model of electrodes modified with MIP films and organic electrochemical transistors (OECTs). Selectivity toward the L-Trp, D-Trp, L-Tyr, and D-Tyr enantiomers was 11.6, 3.5, and 14.5, respectively, $2.6 \times 10^{-6}$ M,
the MIP films bringing a remarkable contribution to obtaining these values [156]. The study’s authors present a new approach to the quantitative recognition of Tyr and Trypt enantiomers, constructing a biosensitive chiral electrochemical system in which the synergistic and complementary effect of L-DHCNT/L-Cys and D-DHCNT/D was analyzed (left-/right-handed double helix carbon nanotubes @ Polypyrrole @ Au nanoparticles @ L/D-Cysteine) on this system, influencing the potential and intensity of the signal. The study presents a new approach to the quantitative recognition of Tyr and Trypt enantiomers, constructing a biosensitive chiral electrochemical system in which the synergy and complementary effects of L-DHCNT/L-Cys and D-DHCNT/D-Cys were analyzed (left-/right-handed double helix carbon nanotubes @ Polypyrrole @ Au nanoparticles @ L/D-Cysteine) on this system, influencing the potential and intensity of the signal. The research carried out in view of obtaining portable, sensitive, and precise devices is in constant development and regards multiple areas of interest (medicine, pharmacy, chemistry, biochemistry, and the food industry). In connection with determining the Phe, Tyr, and Trypt AAs in various real samples (medicines, foods, and biological samples), the emphasis lies on the use of a new generation of materials such as CPs and MIPs because of their excellent properties.

As mentioned in the literature, the application of CPs for the design of MIPs and the various possibilities of immobilization of biological recognition elements, such as enzymes, antibodies or proteins, are important advantages of biosensors based on CPs, giving them applicability in many fields of research [161].

The principle for the selection of conducting polymers used in the development of biosensors is closely related to the method of fabrication, the enzyme, or other biological recognition elements used and the analytes to be detected [162]. For instance, the polymer matrix provides a suitable environment for immobilizing the enzyme, which maintains its long-term activity, especially in the electrochemical measurements [163].

5. Conclusions and Future Developments

This critical analysis synthesizes and describes the main sensors and biosensors achieved with the aid of various relatively new polymer classes, namely CP and MIP—which have remarkable sensitive properties: electrical conductivity, increased stability, and biocompatibility. The molecular imprinting technique is based on manufacturing synthetic receivers with the capability of recognizing a certain analyte, and with electrochemical or optical detection. CPs are mainly used to develop voltametric and potentiometric sensors. Due to the high level of interest in the field, the study concentrates especially on the detection of three AAs (Phe, Tyr, and Trypt), as humanity is inflicted with various forms of depression caused by the lack or the excess of these AAs—afflictions that are increasingly more difficult to manage. In conclusion, the sensitive and precise quantification of AAs to evaluate the quality and authenticity of pharmaceutical products, beverages, and foods, alongside their physiological and nutritional importance, has stirred interest in many researchers. Furthermore, attention was paid to developing versatile systems for analyzing and rapidly detecting AAs, and the electroanalytical methods employed demonstrated efficiency, precision, and low costs.

Future research developments are oriented toward achieving, improving, and marketing these kinds of sensitive devices—useful not only for each individual, but for the European Medicines Agency also—in controlling the quality of various products with amino acid content. In regards to the technical challenges, they are mainly related to developing functionalized polymers that have the possibility to selectively interact with the target amino acid. This new type of polymer can be useful both for molecularly imprinted polymers—polymers that represent the sensitive material—and for polymers that represent the support for biological element immobilisation, such as enzymes, nucleic acids, or antibodies. Achieving functionalized nanocomposite polymers—carbon nanomaterials—is another method that can be applied and lead to increasing the selectivity of sensitive devices.
The detection performance can also be improved by using new techniques that are more rapid and more sensitive, such as ultra-fast cyclical voltammetry, or through combining the detection techniques—as is the case with the spectroelectrochemical technique, which combines voltammetric techniques with UV-Vis or Raman spectroscopy. Accessing and applying information from various fields can prove useful in the process of detection and quantification.

Author Contributions: Conceptualization, C.A. and A.D.; methodology, C.A.; Writing—Original draft preparation, A.D.; Writing—Review and editing, C.A.; supervision, C.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were waived for this study, due to the character of the publication that is based on reviewing recent literature.

Informed Consent Statement: Not applicable.

Acknowledgments: The contribution of author A.D. was supported by the ANTREPRENORDOC project, in the framework of the Human Resources Development Operational Programme 2014–2020, financed from the European Social Fund under Contract Number 36355/23.05.2019 HRD OP/380/6/13—SMIS Code: 123847. All individuals included in this section have consented to the acknowledgement.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Neurauter, G.; Scholl-Bürgi, S.; Haara, A.; Geisler, S.; Mayersbach, P.; Schennach, H.; Fuchs, D. Simultaneous measurement of phenylalanine and tyrosine by high performance liquid chromatography (HPLC) with fluorescence detection. *Clin. Biochem.* 2013, 46, 1848–1851. [CrossRef] [PubMed]

2. Zhong, Y.-F.; Bao, G.-M.; Xia, Y.-F.; Peng, X.-X.; Peng, J.-F.; He, J.-X.; Lin, S.; Zeng, L.; Fan, Q.; Xiao, W.; et al. Recyclable europium functionalized metal-organic fluorescent probe for detection of tryptophan in biological fluids and food products. *Anal. Chim. Acta* 2021, 1180, 338897. [CrossRef] [PubMed]

3. Bech-Andersen, S. Determination of Tryptophan with HPLC after Alkaline Hydrolysis in Autoclave using α-methyl-tryptophan as Internal Standard. *Acta Agric. Scand.* 1991, 41, 305–309. [CrossRef]

4. Boulet, L.; Faure, P.; Flore, P.; Montérelmal, J.; Ducros, V. Simultaneous determination of tryptophan and 8 metabolites in human plasma by liquid chromatography/tandem mass spectrometry. *J. Chromatogr. B* 2017, 1054, 36–43. [CrossRef] [PubMed]

5. Whiley, L.; Nye, L.C.; Grant, I.; Andreas, N.J.; Chappell, K.E.; Sarafian, M.H.; Misra, R.; Plumb, R.S.; Lewis, M.R.; Nicholson, J.K.; et al. Ultra-high-Performance Liquid Chromatography Tandem Mass Spectrometry with Electrospray Ionization Quantification of Tryptophan Metabolites and Markers of Gut Health in Serum and Plasma—Application to Clinical and Epidemiology Cohorts. *Anal. Chem.* 2019, 91, 5207–5216. [CrossRef]

6. Chen, S.; Fu, Y.; Bian, X.; Zhao, M.; Zuo, Y.; Ge, Y.; Xiao, Y.; Xiao, J.; Li, N.; Wu, J.-L. Investigation and dynamic profiling of oligopeptides, free amino acids and derivatives during Pu-erh tea fermentation by ultra-high performance liquid chromatography tandem mass spectrometry. *Food Chem.* 2021, 371, 131776. [CrossRef]

7. De Silva, V.; Oldham, C.D.; May, S.W. L-Phenylalanine concentration in blood of phenylketonuria patients: A modified enzyme colorimetric assay compared with amino acid analysis, tandem mass spectrometry, and HPLC methods. *Clin. Chem. Lab. Med.* 2010, 48, 1271–1279. [CrossRef]

8. Kawana, S.; Nakagawa, K.; Hasegawa, Y.; Yamaguchi, S. Simple and rapid analytical method for detection of amino acids in blood using blood spot on filter paper, fast-GC/MS and isotope dilution technique. *J. Chromatogr. B* 2010, 878, 3113–3118. [CrossRef]

9. Orhan, H.; Vermeulen, N.P.; Tump, C.; Zappey, H.; Meerman, J.H. Simultaneous determination of tyrosine, phenylalanine and deoxyguanosine oxidation products by liquid chromatography–tandem mass spectrometry as non-invasive biomarkers for oxidative damage. *J. Chromatogr. B* 2004, 799, 245–254. [CrossRef]

10. Rigobello-Masini, M.; MasiniJ, C. Sequential Injection Chromatography for Fluorimetric Determination of Intracellular Amino Acids in Marine Microalgae. In *Advanced Structural Safety Studies*; Springer: Singapore, 2012; Volume 828, pp. 305–315.

11. Shokrollah, A.; Refahi, M. Development of Cloud Point Extraction-Scanometry, for the Preconcentration and Determination of Colorless Species: Application for the Determination of Phenylalanine. *Quim. Nova* 2019, 42, 36–41. [CrossRef]

12. Fan, Y.; Liu, J.-H.; Lu, H.-T.; Zhang, Q. Electrochemistry and voltammetric determination of L-tryptophan and L-tyrosine using a glassy carbon electrode modified with a Nafion/TiO2-graphene composite film. *Mikrochim. Acta* 2011, 173, 241–247. [CrossRef]

13. Kamruzzaman, M.; Alam, A.-M.; Kim, K.M.; Lee, S.H.; Kim, Y.H.; Kim, G.-M.; Dang, T.D. Microfluidic chip based chemiluminescence detection of L-phenylalanine in pharmaceutical and soft drinks. *Food Chem.* 2012, 135, 57–62. [CrossRef]
14. Li, S.; Xing, M.; Wang, H.; Zhang, L.; Zhong, Y.; Chen, L. Determination of tryptophan and tyrosine by chemiluminescence based on a luminol–N-bromosuccinimide–ZnS quantum dots system. RSC Adv. 2015, 5, 59286–59291. [CrossRef]

15. Dinu, A.; Apetrei, C. A review on electrochemical sensors and biosensors used in Phenylalanine Electroanalysis. Sensors 2020, 20, 2496. [CrossRef]

16. Da Silva, K.P.; Puk, M.; Pizani, P.; Filho, J.M.; Melo, F.; Freire, P. Raman spectroscopy of l-phenylalanine nitric acid submitted to high pressure. Vib. Spectrosc. 2016, 85, 97–103. [CrossRef]

17. Sereda, V.; Balbovsy, N.M.; Vasudev, M.C.; Naik, R.R.; Ledney, I.K. Polarized raman spectroscopy for determining the orientation of di-d-phenylalanine molecules in a nanotube. J. Raman Spectrosc. 2016, 47, 1056–1062. [CrossRef]

18. Li, Q.Q.; Duan, J.; Wu, L.J.; Huang, Y.; Tang, G.; Min, S.G. Sucrose as chiral selector for determining enantiomeric composition of phenylalanine by UV–vis spectroscopy and chemometrics. Chin. Chem. Lett. 2012, 23, 1055–1058. [CrossRef]

19. Dailey, C.A.; Garnier, N.; Rubakhin, S.S.; Sweedler, J.V. Automated method for analysis of tryptophan and tyrosine metabolites using capillary electrophoresis with native fluorescence detection. Anal. Bioanal. Chem. 2013, 405, 2451–2459. [CrossRef]

20. Hawkins, G.; Zipkin, I.; Marshall, L. Determination of Uric Acid, Tyrosine, Tryptophan, and Protein in whole Human Parotid Saliva by Ultraviolet Absorption Spectrophotometry. J. Dent. Res. 1963, 42, 1015–1022. [CrossRef]

21. Zhao, M.; Zhou, M.-F.; Feng, H.; Cong, X.-X.; Wang, X.-L. Determination of Tryptophan, Glutathione, and Uric Acid in Human Whole Blood Extract by Capillary Electrophoresis with a One-Step Electrochemically Reduced Graphene Oxide Modified Microelectrode. Chromatographia 2016, 79, 911–918. [CrossRef]

22. Moscetti, I.; Cannistraro, S.; Bizzarri, A.R. Probing direct interaction of oncomiR-21-3p with the tumor suppressor p53 by fluorescence, FRET and atomic force spectroscopy. Arch. Biochem. Biophys. 2019, 365, 31–40. [CrossRef] [PubMed]

23. Hashkavavy, A.B.; Raoof, J.B.; Park, K.S. Sensitive Electrochemical Detection of Tryptophan Using a Hemin/G-Quadruplex Aptasensor. Chemosensors 2020, 8, 100. [CrossRef]

24. D’Souza, E.S.; Manjunatha, J.G.; Chenthatti, R.; Tigari, G.; Ravishankar, D.K. Rapid Electrochemical Monitoring of Tyrosine by Poly (Riboflavin) Modified Carbon Nanotube Paste Electrode as a Sensitive Sensor and its Applications in Pharmaceutical Samples. Biosensor Res. Appl. Chem. 2021, 11, 14661–14672. [CrossRef]

25. Zhang, J.-L. Electrochemical Determination of Tyrosine and Nitrite Using CS/CMWNTs/GCE-modified Electrode. Int. J. Electrochem. Sci. 2018, 13, 3527–3534. [CrossRef]

26. Dinu, A.; Apetrei, C. Voltammetric Determination of Phenylalanine Using Chemically Modified Screen-Printed Based Sensors. Chemosensors 2020, 8, 113. [CrossRef]

27. Dinu, A.; Apetrei, C. Development of Polypyrrole Modified Screen-Printed Carbon Electrode Based Sensors for Determination of L-Tyrosine in Pharmaceutical Products. Int. J. Mol. Sci. 2021, 22, 7528. [CrossRef] [PubMed]

28. Dinu, A.; Apetrei, C. Development of a Novel Sensor Based on Polypyrrole Doped with Potassium Hexacyanoferrate (II) for Detection of L-Tryptophan in Pharmaceuticals. Inventions 2021, 6, 56. [CrossRef]

29. Wang, Y.; Xiong, C.; Qu, H.; Chen, W.; Ma, A.; Zheng, L. Highly sensitive real-time detection of tyrosine based on organic electrochemical transistors with poly-(diallyldimethylammonium chloride), gold nanoparticles and multi-walled carbon nanotubes. J. Electroanal. Chem. 2017, 799, 321–326. [CrossRef]

30. Tiğ, G.A. Development of electrochemical sensor for detection of ascorbic acid, dopamine, uric acid and l-tryptophan based on Ag nanoparticles and poly(l-arginine)-graphene oxide composite. J. Electroanal. Chem. 2017, 807, 19–28. [CrossRef]

31. Yıldız, C.; Bayraktepe, D.E.; Yayan, Z. Electrochemical low-level detection of l-tryptophan in human urine samples: Use of pencil graphite leads as electrodes for a fast and cost-effective voltammetric method. Montash. Chem. 2020, 151, 871–879. [CrossRef]

32. Kavitha, C.; Bramhaiah, K.; John, N.S. Low-cost electrochemical detection of L-tryosine using an rGO–Cu modified pencil graphite electrode and its surface orientation on a Ag electrode using an ex situ spectroelectrochemical method. RSC Adv. 2020, 10, 22871–22880. [CrossRef]

33. He, Q.; Tian, Y.; Wu, Y.; Liu, J.; Li, G.; Deng, P.; Chen, D. Electrochemical Sensor for Rapid and Sensitive Detection of Tryptophan by a Cu2O Nanoparticles-Coated Reduced Graphene Oxide Nanocomposite. Biomolecules 2019, 9, 176. [CrossRef] [PubMed]

34. Ensafi, A.A.; Hajian, R. Determination of tryptophan and histidine by adsorptive cathodic stripping voltammetry using H-point standard addition method. Anal. Chim. Acta 2006, 580, 236–243. [CrossRef]

35. Kerman, K.; Kraatz, H.-B. Electrochemical detection of protein tyrosine kinase-catalysed phosphorylation using gold nanoparticles. Biosens. Bioelectron. 2009, 24, 1484–1489. [CrossRef]

36. Feng, J.; Deng, P.; Xiao, J.; Li, J.; Tian, Y.; Wu, Y.; Liu, J.; Li, G.; He, Q. New voltammetric method for determination of tyrosine in foodstuffs using an oxygen-functionalized multi-walled carbon nanotubes modified acetylene black paste electrode. J. Food Compos. Anal. 2020, 96, 103708. [CrossRef]

37. Liu, M.; Lao, J.; Wang, H.; Xu, Z.; Li, J.; Wen, L.; Yin, Z.; Luo, C.; Peng, H. Electrochemical Determination of Tyrosine Using Graphene and Gold Nanoparticles Composite Modified Glassy Carbon Electrode. Russ. J. Electrochem. 2021, 57, 41–50. [CrossRef]

38. Liguori, C.; Pierantozzi, M.; Spanetta, M.; Sarmati, L.; Cesta, N.; Iannetta, M.; Ora, J.; Mina, G.G.; Puxeddu, E.; Balbi, O.; et al. Depressive and anxiety symptoms in patients with SARS-CoV2 infection. J. Affect. Disord. 2020, 278, 339–340. [CrossRef]

39. Varmira, K.; Mohammad, G.; Mahmoudi, M.; Khodarahmi, R.; Rashidi, K.; Hedayati, M.; Goicoechea, H.C.; Jalalvand, A.R. Fabrication of a novel enzymatic electrochemical biosensor for determination of tyrosine in some food samples. Talanta 2018, 183, 1–10. [CrossRef]

40. Kane-Maguire, L.A.P.; Wallace, G.G. Chiral conducting polymers. Chem. Soc. Rev. 2010, 39, 2545–2576. [CrossRef]
41. Namazi, H. Polymers in our daily life. *BioImpacts* 2017, 7, 73–74. [CrossRef]
42. Wang, J.; Liang, R.; Qin, W. Molecularly imprinted polymer-based potentiometric sensors. *TrAC Trends Anal. Chem.* 2020, 130, 115980. [CrossRef]
43. Ermis, N.; Uzun, L.; Denizli, A. Preparation of molecularly imprinted electrochemical sensor for L-phenylalanine detection and its application. *J. Electroanal. Chem.* 2017, 807, 244–252. [CrossRef]
44. Roy, S.; Nagabooshanam, S.; Wadhwa, S.; Chauhan, N.; Mathur, A.; Khan, S.A.; Davis, J. Ultra-sensitive detection of L-tyrosine using molecularly imprinted electrochemical sensor towards diabetic foot ulcer detection. *Electrochem. Commun.* 2020, 117, 106782. [CrossRef]
45. Atta, N.E.; Ahmed, Y.M.; Galal, A. Layered-designed composite sensor based on crown ether/Nafion®/polymer/carbon nanotubes for determination of norepinephrine, paracetamol, tyrosine and ascorbic acid in biological fluids. *J. Electroanal. Chem.* 2018, 828, 11–23. [CrossRef]
46. Duan, S.; Wang, W.; Yu, C.; Liu, M.; Yu, L. Development of Electrochemical Sensor for Detection of L-Tryptophan Based on Exfoliated Graphene/PEDOT:PSS. *Nano 2019*, 14, 1950058. [CrossRef]
47. Chena, B.; Zhang, A.; Lina, L.; Chenb, H.; Zhaoa, M. Au nanoparticles @metal organic framework/polythionine loaded with molecularly imprinted polymer sensor: A systematic review, characterization, and electrochemical detection of tyrosine. *J. Electroanal. Chem.* 2020, 863, 114052. [CrossRef]
48. Rahman, M.; Lopa, N.S.; Kim, K.; Lee, J.-J. Selective detection of L-tyrosine in the presence of ascorbic acid, dopamine, and uric acid at poly(thionine)-modified glassy carbon electrode. *J. Electroanal. Chem.* 2015, 754, 87–93. [CrossRef]
49. Xia, Y.; Zhao, F.; Zeng, B. A molecularly imprinted copolymer based electrochemical sensor for the highly sensitive detection of L-Tryptophan. *Talanta* 2019, 206, 120245. [CrossRef]
50. Nan, A.; Bunge, A.; Turcu, R. Hybride magnetic nanostructure based on amino acids functionalized polypyrrole. *AIP Conf. Proc.* 2015, 1700, 060007. [CrossRef]
51. Kisa, P.T.; Erkmen, S.E.; Bahceci, H.; Gulten, Z.A.; Aydogan, A.; Pekuz, O.K.K.; Inel, T.Y.; Uysal, S.; Arslan, N. Efficacy of Phenylalanine- and Tyrosine-Restricted Diet in Alkaptonuria Patients on Nitisinone Treatment: Case Series and Review of Literature. *Ann. Nutr. Metab.* 2021, 78, 48–60. [CrossRef]
52. Domä, K.; Singh, U.; Boullosa, D.; Connor, J.D. The effect of branched-chain amino acid on muscle damage markers and performance following strenuous exercise: A systematic review and meta-analysis. *Appl. Physiol. Nutr. Metab.* 2021, 46, 1303–1313. [CrossRef] [PubMed]
53. Jing, X.; Dong, Q.; Hong, D.; Lu, R. Amino Acid Encoding Methods for Protein Sequences: A Comprehensive Review and Assessment. *IEEE/ACM Trans. Comput. Biol. Bioinform.* 2019, 17, 1918–1931. [CrossRef] [PubMed]
54. Lieberman, M.; Marks, A.D. *Marks’ Basic Medical Biochemistry: A Clinical Approach*; Lippincott Williams & Wilkins: IUBMB: Philadelphia, PA, USA, 2009; ISBN 0-7817-7022-X. [CrossRef]
55. Litwack, G. *Human Biochemistry*; Academic Press: Los Angeles, CA, USA, 2018. [CrossRef]
56. Sadok, I.; Tyszczuk-Rotko, K.; Mroczka, R.; Staniszewska, M. Simultaneous voltammetric analysis of tryptophan and kynurenine in culture medium from human cancer cells. *Talanta* 2019, 209, 120574. [CrossRef] [PubMed]
57. Shaw, K.A.; Turner, J.; Del Mar, C. Tryptophan and 5-Hydroxytryptophan for depression. *Cochrane Database Syst. Rev.* 2002, 1, CD003198. [CrossRef]
58. Hudson, C.; Hudson, S.; MacKenzie, J. Protein-source tryptophan as an efficacious treatment for social anxiety disorder: A pilot studyThis article is one of a selection of papers published in this special issue (part 1 of 2) on the Safety and Efficacy of Natural Health Products. *Can. J. Physiol. Pharmacol.* 2007, 85, 928–932. [CrossRef]
59. Schneider-Helmert, D.; Spinweber, C. Evaluation of l-tryptophan for treatment of insomnia: A review. *Psychopharmacology* 1986, 89, 1–7. [CrossRef]
60. Zheng, F.; Zhou, J.; Wang, C.E.; Hu, W.; Krischek, B. There may be no significant increase of cerebrospinal fluid tyrosine levels in patients with Parkinson’s disease. *Eur. J. Neurol.* 2020, 28, e15–e16. [CrossRef]
61. Mette, C.; Zimmermann, M.; Grabemann, M.; Abdel-Hamid, M.; Uekermann, J.; Biskup, C.S.; Wiltfang, J.; Zepf, F.D.; Kis, B. The impact of acute tryptophan depletion on attentional performance in adult patients with ADHD. *Acta Psychiatr. Scand.* 2013, 128, 124–132. [CrossRef]
62. Prabhu, P.R.; Hudson, A.O. Identification and Partial Characterization of an L-Tyrosine Aminotransferase (TAT) fromArabidopsis thaliana. *Biochem. Res. Int.* 2010, 2010, 549572. [CrossRef]
63. Bross, R.; Ball, R.O.; Clarke, J.T.R.; Pencharz, P.B. Tyrosine requirements in children with classical PKU determined by indicator amino acid oxidation. *Am. J. Physiol. Metab.* 2000, 278, E195–E201. [CrossRef]
64. Harding, C.O.; Winn, S.R.; Gibson, K.M.; Arning, E.; Bottiglieri, T.; Gropper, M. Pharmacologic inhibition of L-tyrosine degradation ameliorates cerebral dopamine deficiency in murine phenylketonuria (PKU). *J. Inherit. Metab. Dis.* 2014, 37, 735–743. [CrossRef] [PubMed]
65. Idili, A.; Parolo, C.; Ortega, G.; Plaxco, K.W. Calibration-Free Measurement of Phenylalanine Levels in the Blood Using an Electrochemical Aptamer-Based Sensor Suitable for Point-of-Care Applications. *ACS Sensors* 2019, 4, 3227–3233. [CrossRef] [PubMed]
66. Bangaleh, Z.; Sadeghi, H.B.; Ebrahim, S.A.; Najafizadeh, P. A New Potentiometric Sensor for Determination and Screening Phenylalanine in Blood Serum Based on Molecularily Imprinted Polymer. *Iran. J. Pharm. Res. IJPR* 2019, 18, 61–71. [PubMed]
67. Shen, Y.-P.; Niu, F.-X.; Yan, Z.-B.; Fong, L.S.; Huang, Y.-B.; Liu, J.-Z. Recent Advances in Metabolically Engineered Microorganisms for the Production of Aromatic Chemicals Derived From Aromatic Amino Acids. Front. Bioeng. Biotechnol. 2020, 8, 407. [CrossRef] [PubMed]

68. Kagan, J.; Sharon, I.; Bejà, O.; Kuhn, J.C. The tryptophan pathway genes of the Sargasso Sea metagenome: New operon structures and the prevalence of non-operand organization. Genome Biol. 2008, 9, R20. [CrossRef]

69. Storå, D.; Vrecko, K.; Birkmayer, J.; Reibnegger, G. Monoaminergic neurotransmitters, their precursors and metabolites in brains of Alzheimer patients. Neurosci. Lett. 1996, 203, 29–32. [CrossRef]

70. Shi, D.; Li, Z.; Li, Y.; Jiang, Q. Variables associated with self-reported anxiety and depression symptoms in patients with chronic myeloid leukemia receiving tyrosine kinase inhibitor therapy. Leuk. Lymphoma 2020, 62, 640–648. [CrossRef]

71. Eroglu, I.; Eroglu, B.; Güven, G.S. Altered tryptophan absorption and metabolism could underlie long-term symptoms in survivors of coronavirus disease 2019 (COVID-19). Nutrition 2021, 90, 111308. [CrossRef]

72. Schopman, S.M.E.; Bosman, R.C.; Muntingh, A.D.T.; van Balkom, A.J.L.M.; Bateelaan, N.M. Effects of tryptophan depletion on anxiety, a systematic review. Transl. Psychiatry 2021, 11, 118. [CrossRef]

73. Negut, C.C.; Staden, R.I.S.-V. Review—Recent Trends in Supramolecular Recognition of Dopamine, Tyrosine, and Tryptophan. J. Electrochem. Soc. 2021, 168, 067517. [CrossRef]

74. Parker, G.; Brothie, H. Mood effects of the amino acids tryptophan and tyrosine. Acta Psychiatr. Scand. 2011, 124, 417–426. [CrossRef] [PubMed]

75. Alagawany, M.; ElNesr, S.S.; Farag, M.R.; Tiwari, R.; Yatoo, M.I.; Karthik, K.; Michalak, I.; Dhama, K. Nutritional significance of amino acids, vitamins and minerals as nutraceuticals in poultry production and health—A comprehensive review. Vet. Q. 2020, 41, 1–29. [CrossRef] [PubMed]

76. King, J.M.; Muthian, G.; Mackey, V.; Smith, M.; Charlton, C. L-Dihydroxyphenylalanine modulates the steady-state expression of mouse striatal tyrosine hydroxylase, aromatic L-amino acid decarboxylase, dopamine and its metabolites in an MPTP mouse model of Parkinson’s disease. Life Sci. 2011, 89, 638–643. [CrossRef] [PubMed]

77. Moja, E.; Lucini, V.; Benedetti, F.; Lucca, A. Decrease in plasma phenylalanine and tyrosine after phenylalanine-tyrosine free amino acid solutions in man. Life Sci. 1996, 58, 2389–2395. [CrossRef]

78. Reiner, C.; Nicholson, G.J.; Nagel, U.; Schurig, V. Evaluation of enantioselective gas chromatography for the determination of minute deviations from racemic composition of α-amino acids with emphasis on tyrosine: Accuracy and precision of the method. Chirality 2007, 19, 401–414. [CrossRef]

79. Biskup, C.S.; Helmbold, K.; Baummann, D.; Klasen, M.; Gaber, T.J.; Bubener-Busch, S.; Königschulte, W.; Fink, G.R.; Zepf, F.D. Resting state default mode network connectivity in children and adolescents with ADHD after acute tryptophan depletion. Acta Psychiatr. Scand. 2016, 134, 161–171. [CrossRef]

80. Boros, F.A.; Vécsei, L. Tryptophan 2,3-dioxygenase, a novel therapeutic target for Parkinson’s disease. Expert Opin. Ther. Targets 2021, 25, 877–888. [CrossRef]

81. Zhai, G.; Sun, X.; Randell, E.W.; Liu, M.; Wang, N.; Tolstykh, I.; Rahman, P.; Torner, J.; Lewis, C.E.; Nevitt, M.C.; et al. Phenylalanine & Tyrosine Amino acids Coated Weight excipients for amorphization and dissolution enhancement of carvedilol. Int. J. Pharm. 2018, 547, 353–362. [CrossRef] [PubMed]

82. Pešić, N.; Dapčević, A.; Ivković, B.; Kachrimanis, K.; Mitrić, M.; Ibrić, S.; Medarević, D. Potential application of low molecular weight chitosan amidotriazolatoborane(3) complexes to activate the procaspase-3 activation in human breast cancer cell line, MDA-MB-231. J.是他ウク西 Illness 2021, 11, 112839. [CrossRef] [PubMed]

83. Moreno, L.S.S.; Junior, H.V.N.; da Silva, A.R.; Nascimento, F.B.S.A.D.; da Silva, C.R.; Neto, J.B.D.A.; Cavalcanti, B.C.; de Moraes, M.O.; Pinazo, A.; Pacheco, C.; Vivaldo-Lima, E. Polymers and polymer types. In Nutrients for the Production of Aromatic Chemicals Derived From Aromatic Amino Acids. Front. Bioeng. Biotechnol. 2020, 8, 407. [CrossRef] [PubMed]

84. Nosrati, H.; Hamzhehi, H.; Afroogh, S.; Ashahi, S.F.; Attari, E.; Manjili, H.K. Phenyl alanine & Tyrosine Amino acids Coated Magnetic Nanoparticles: Preparation and Toxicity study. Drug Res. 2018, 69, 277–283. [CrossRef]

85. Demeester, J.; Bracke, M.; Vochten, R.; Lauwers, A. Differential Spectrophotometric Determination of Tyrosine and Tryptophan in Pharmaceutical Amino Acid Solutions. J. Pharm. Sci. 1978, 67, 729–730. [CrossRef]

86. Unger, N.; Ferraro, A.; Holzgrabe, U. Investigation of tryptophan-related yellowing in parenteral amino acid solution: Development of a stability-indicating method and assessment of degradation products in pharmaceutical formulations. J. Pharm. Biomed. Anal. 2020, 177, 112839. [CrossRef] [PubMed]

87. Jiménez-Jímenez, F.J.; Alonso-Navarro, H.; García-Martin, E.; Agúndez, J.A. Cerebrospinal and blood levels of amino acids as potential biomarkers for Parkinson’s disease: Review and meta-analysis. Eur. J. Neurol. 2020, 27, 2336–2347. [CrossRef] [PubMed]

88. Tessari, P.; Lante, A.; Mosca, G. Essential amino acids master: Regularists of nutrition and environmental footprint? Sci. Rep. 2016, 6, 26074. [CrossRef] [PubMed]

89. Terstappen, F.; Tol, A.J.C.; Gremmels, H.; Wever, K.E.; Pauw, N.D.; Joles, J.A.; Van Der Beek, E.M.; Lely, A.T. Prenatal Amino Acid Supplementation to Improve Fetal Growth: A Systematic Review and Meta-Analysis. Transl. Psychiatry 2021, 11, 112017. [CrossRef]

90. Ravichandran, R.; Sundararajan, S.; Venugopal, J.R.; Mukherjee, S.; Ramakrishna, S. Applications of conducting polymers and their issues in biomedical engineering. J. R. Soc. Interface 2010, 7, S559–S579. [CrossRef] [PubMed]

91. Saldivar-Guerra, E.; Vivaldo-Lima, E. Polymers and polymer types. In Handbook of Polymer Synthesis, Characterization and Processing; Saldivar-Guerra, E., Vivaldo-Lima, E., Eds.; John Wiley and Sons: Hoboken, NJ, USA, 2013; Chapter 1.
92. Wadhwa, R.; Lagenaur, C.F.; Cui, X.T. Electrochemically controlled release of dexamethasone from conducting polymer polypropylene coated electrode. J. Control. Release 2006, 110, 531–541. [CrossRef]
93. Nambar, S.; Yeow, J.T. Conductive polymer-based sensors for biomedical applications. Biosens. Bioelectron. 2011, 26, 1825–1832. [CrossRef]
94. Apetrei, I.M.; Apetrei, C. Application of voltammetric e-tongue for the detection of ammonia and putrescine in beef products. Talanta 2011, 84, 305–313. [CrossRef] [PubMed]
95. Arslan, F.; Beskan, U. An amperometric biosensor for glucose detection from glucose oxidase immobilized in polyaniline-polyvinylsulfonate-potassium ferricyanide film. Artif. Cells, Nanomedicine, Biotechnol. 2013, 41, 284–288. [CrossRef]
96. Siddig, A.; Ansari, M.O.; Mohammad, A.; Mohammad, F.; El-Desoky, G.E. Synergistic Effect of Polyaniline Modified Silica Gel for Highly Efficient Separation of Non Resolvable Amino Acids. Int. J. Polym. Mater. 2013, 63, 277–281. [CrossRef]
97. Liu, Y.; Zhang, Z.; Zhang, H.; Luo, L.; Yao, S. Electrochemical determination of L-phenylalanine at polyaniline modified carbon electrode based on β-cyclodextrin incorporated carbon nanotube composite material and imprinted sol–gel film. Talanta 2011, 84, 305–313. [CrossRef] [PubMed]
98. Dong, L.-Q.; Hu, D.-F.; Duan, X.-M.; Wang, Z.-P.; Zhu, X.-F.; Sun, H.; Zhang, Y.-S.; Xu, J.-K. Synthesis and characterization of D-/L-methionine grafted PEDOT derivatives with excellent electrochromic performances. J. Environ. Chem. Eng. 2014, 2, 35597–35608. [CrossRef] [PubMed]
99. Moral-Vico, J.; Carretero, N.; Pérez, E.; Suñol, C.; Lichtenstein, M.; Casañ-Pastor, N. Dynamic electrodeposition of aminoacid-PEDOT substrates: Conducting polymer bilayers as electrodes in neural systems. Electrochim. Acta 2013, 111, 250–260. [CrossRef]
145. Wang, X.-S.; Tang, H.-P.; Li, X.-D.; Hua, X. Investigations on the Mechanical Properties of Conducting Polymer Coating-Substrate Structures and Their Influencing Factors. *Int. J. Mol. Sci.* 2009, 10, 5257–5284. [CrossRef]

146. Liu, C. Recent Developments in Polymer MEMS. *Adv. Mater.* 2007, 19, 3783–3790. [CrossRef]

147. Dashtian, K.; Hajati, S.; Ghaedi, M. L-phenylalanine-imprinted polydopamine-coated CdS/CdSe n-n type II heterojunction as an ultrasensitive photoelectrochemical biosensor for the PKU monitoring. *Biosens. Bioelectron.* 2020, 165, 112346. [CrossRef]

148. Raril, C.; Manjunatha, J.G.; Ravishankar, D.K.; Fattepur, S.; Siddaraju, G.; Nanjundaswamy, L. Validated Electrochemical Method for Simultaneous Resolution of Tyrosine, Uric Acid, and Ascorbic Acid at Polymer Modified Nano-Composite Paste Electrode. *Surf. Eng. Appl. Electrochem.* 2020, 56, 415–426. [CrossRef]

149. Zhang, L.; Wang, G.; Xiong, C.; Zheng, L.; He, J.-B.; Ding, Y.; Lu, H.; Zhang, G.; Cho, K.; Qiu, L. Chirality detection of amino acid enantiomers by organic electrochemical transistor. *Biosens. Bioelectron.* 2018, 105, 121–128. [CrossRef]

150. Asal, M.; Özen, O.; Şahinler, M.; Baysal, H.T.; Polatolu, I. An overview of biomolecules, immobilization methods and support materials of biosensors. *Sens. Rev.* 2019, 39, 377–386. [CrossRef]

151. Grieshaber, D.; MacKenzie, R.; Vörös, J.; Reimhult, E. Electrochemical —Sensor Principles and Architectures. *Sensors* 2008, 8, 1400–1458. [CrossRef]

152. Muguruma, H. Biosensors: Enzyme Immobilization Chemistry. In *Encyclopedia of Interfacial Chemistry*; Wandelt, K., Ed.; Elsevier: Oxford, UK, 2018; pp. 64–71. [CrossRef]

153. Narayan, R.J. Medical Biosensors for Point of Care (POC) Applications; Narayan, R., Ed.; Woodhead Publishing: Tokyo, Japan, 2016; ISBN 0-08-100078-2. [CrossRef]

154. Cooper, J.C.; Schuber, F. A biosensor for L-amino acids using polytyramine for enzyme immobilization. *Electroanalysis* 1994, 6, 957–961. [CrossRef]

155. Mirmohseni, A.; Shojaei, M.; Farbodi, M. Application of a quartz crystal nanobalance to the molecularly imprinted recognition of phenylalanine in solution. *Biotechnol. Bioprocess Eng.* 2008, 13, 592–597. [CrossRef]

156. Zhang, Q.; Fu, M.; Lu, H.; Fan, X.; Wang, H.; Zhang, Y.; Wang, H. Novel potential and current type chiral amino acids biosensor based on L/D-handed double helix carbon nanotubes@polypyrrole@Au nanoparticles@L/D-cysteine. *Sensors Actuators B Chem.* 2019, 296, 126667. [CrossRef]

157. Ning, G.; Wang, H.; Fu, M.; Liu, J.; Sun, Y.; Lu, H.; Fan, X.; Zhang, Y.; Wang, H. Dual Signals Electrochemical Biosensor for Point-of-care Testing of Amino Acids Enantiomers. *Electroanalysis* 2021. [CrossRef]

158. Prabakaran, K.; Jandas, P.; Luo, J.; Fu, C.; Wei, Q. Molecularly imprinted poly(methacrylic acid) based QCM biosensor for selective determination of L-tryptophan. *Colloids Surf. A: Physicochem. Eng. Asp.* 2020, 611, 125859. [CrossRef]

159. Tian, Y.; Deng, P.; Wu, Y.; Ding, Z.; Li, G.; Liu, J.; He, Q. A Simple and Efficient Molecularly Imprinted Electro-chemical Sensor for the Selective Determination of Tryptophan. *Biomolecules* 2019, 9, 294. [CrossRef]

160. Park, J.K.; Khan, H.; Lee, J.W. Preparation of phenylalanine imprinted polymer by the sol–gel transition method. *Enzym. Microb. Technol.* 2004, 35, 688–693. [CrossRef]

161. Ramanavicius, S.; Ramanavicius, A. Conducting Polymers in the Design of Biosensors and Biofuel Cells. *Polymers* 2021, 13, 49. [CrossRef]

162. Gerard, M. Application of conducting polymers to biosensors. *Biosens. Bioelectron.* 2002, 17, 345–359. [CrossRef]

163. Wang, X.; Uchiyam, S. Polymers for Biosensors Construction. In *State of the Art in Biosensors—General Aspects*; Rinken, T., Ed.; InTech: London, UK, 2013; ISBN 978-953-51-1004-0.