Food Spoilage: Detection of Biogenic Amines in Food Samples by Enzyme-based Electrochemical Biosensors

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Biogenic amines (BAs) are used as a quality indicator of food freshness that evaluates microbial action, which potentially affects human health and has become a major concern for consumers and health agencies around the world. Electrochemical biosensor technology, with its rapid tools and incredible potential, represents a major field that significantly impacts food quality control. This is a sensitive, green, and easily adaptable method that can detect BAs even at low concentrations. Numerous electrochemical biosensors with a combination of enzymes and nanomaterials are widely used in the fabrication of biosensors to increase their sensitivity. This article comprehensively reviews the basic concepts of biosensors, the mechanism and application of enzyme-based electrochemical biosensors, enzyme immobilization, and performance-enhancing biosensors. In addition, the use of enzyme-based electrochemical biosensors as a modifier for the detection of BAs in spoiled food is also discussed.

Key words: Biogenic amines (BAs); enzyme-based electrochemical biosensor; food spoilage; food safety; nanomaterials

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Food is an essential requirement that provides nutrition for human beings. It also serves as an excellent source of nutrients for microbes such as pathogens, bacteria, and viruses that may partially or even wholly deteriorate the quality of foods, especially during production, handling, processing, distribution, and consumption. In fact, this can happen anywhere in the supply chain, from producer to consumer. In general, bacteria can cause the transamination of aldehydes and ketones or decarboxylation of amino acids to form active biogenic amines (BAs) [1]. The common BAs related to food are spermine, spermidine, putrescine, cadaverine, agmatine, tyramine, tryptamine, and histamine. Table 1 shows several BAs that are generally found in food and their chemical properties. In particular, spermine, spermidine, putrescine, and cadaverine are extensively found in the human body [2]. In addition, consuming food contaminated with BAs causes adverse health effects with different symptoms [3,4]. Therefore, food safety is one of the major concerns among consumers, and requires continuous monitoring for toxicity. This is also in line with most of the health agencies around the world, such as the Food and Drug Administration (FDA), European Food Safety Authority (EFSA), and the World Health Organization (WHO). Besides, BAs in food have become an important parameter that may be used as a spoilage marker or an indicator of microbial activity in food [4], especially in the food industry and clinical analyses.

The demand for safer food has promoted more research into the quantification of BAs over the past few years. Chromatographic and spectrophotometric methods, such as high-performance liquid chromatography (HPLC) [3], gas-chromatography (GC) [5], ion-exchange chromatography (IEC) [6], cation exchange chromatography (CEC) [7] and thin-layer chromatography (TLC) [8], have been employed for this purpose. Conventional spectrophotometric detectors such as UV-visible optical absorbance or fluorescence cannot be used because of the absence of absorption bands in the region of the aliphatic BAs [9]. Fluorimetry, amperometry, and conductometry are alternative detection methods that have been employed more recently.

These methods provide better results than conventional methods, which are associated with several drawbacks including low sensitivity, poor precision, time-consuming procedures, and sophisticated instruments requiring high maintenance. Interestingly, electrochemical biosensors hold the top position for their high performance due to the possibility of a miniaturized, cost-effective and rapid screening test that could lead to the formation of lab-on-a-chip, *in-situ* testing with a low detection limit (LOD) and high selectivity [10]. There are a variety of biocomponents and bioreceptors such as organelles, nucleic acids, aptamers, tissues, and whole cells that are integrated into the analytical devices of biosensors.

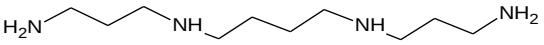
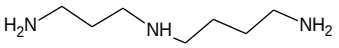
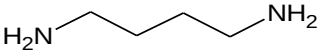
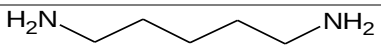
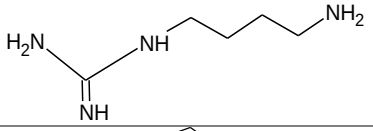
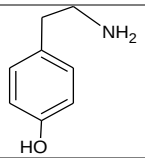
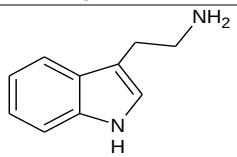
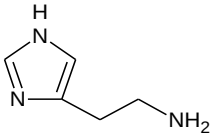
However, the involvement of enzymes in biosensors has attracted a lot of attention in electroanalysis [11]. Electrochemical enzyme biosensors, capable of having specific interactions with the analyte, usually produce an electrical signal which can be detected and measured. Further, electrochemical enzymatic biosensors have the potential to be launched in the food market to control the quality of food.

This article summarises the recent studies on the detection of BAs in food spoilage using enzyme-based electrochemical biosensors, and will begin with a section on the toxicology of BAs and the use of BAs as an indicator of food safety. The following section will discuss the mechanism and concept of how biosensors work with a few different types and groups. This includes enhancing the performance of biosensors. Additional nano-materials and mediators in increasing biosensor performance will also be briefly described.

1. Occurrence and Toxicology of Biogenic Amines in Food

The formation of biogenic amines (BAs) is influenced by various factors that are divided into three groups: (i) raw materials, such as pH, ion strength, and composition; (ii) microorganisms, including *Micrococcaceae, Pseudomo-nadaceae,* and lactic acid bacteria, which are attributed to decarboxylase activity; and (iii) storage and processing conditions such as freshness, curing, modified atmo-spheres, fermentation and refrigeration [12,13]. BAs are suitable for the detection of food spoilage because they are hard, thermostable, and difficult to destroy, even after they have undergone subsequent processing such as pasteurization and cooking. Thus, BAs will still be present in the final product.

Table 1. Structure and chemical properties of common biogenic amines.

Classification	Abbreviation	Molecular formula[a]	Structure formula	pK	Molecular weight[a]
Aliphatic	Spm	$C_{10}H_{26}N_4$		pK_1=11.5, pK_2=10.9, Pk_3=9.7, Pk_4=8.9	202.3
	Spmd	$C_7H_{19}N_3$		pK_1=9.5, pK_2=10.8, Pk_3=11.6	145.3
	Put	$C_4H_{12}N_2$		pK_1=10.8 pK_2=9.4	88.2
	Cad	$C_5H_{14}N_2$		pK_1=11.0 pK_2=9.9	202.2
	Agm	$C_5H_{14}N_4$		pK=12.5	130.2
Aromatic	Tyr	$C_8H_{11}NO$		pK=9.6	137.2
	Tyrp	$C_{10}H_{12}N_2$		pK=10.2	160.2
Heterocyclic	His	$C_5H_{10}N_3$		pK_1=9.8 pK_2=6.0	111.1

[a] Table 1 references from a website (https://pubchem.ncbi.nlm.nih.gov/), Agm: agmatine, C: carbon, Cad: cadaverine, H: hydrogen, His: histamine, N: nitrogen, pKa: the logarithmic scale of the acid dissociation constant, Put: putrescine, Spm: spermine,
Spmd: spermidine, Tyr: tyramine, Tyrp: tryptamin

Instead of being nitrogen sources, BAs also act as precursors and are responsible for forming various compounds in organisms such as hormones, nucleic acids, alkaloids, and proteins. Moreover, BAs also form during intake of nutrition, body temperature regulation, and alteration in the blood pressure of the organism. As a highlight, polyamide is required in every bodily process, including metabolism and growth [14].

As potential precursors for the formation of carcinogenic N-nitroso compounds, spermidine, and putrescine can also produce the carcinogenic compound N-nitrosopyrrolidine, especially in foods that contain lipids with a high water content, such as ham and bacon. Putrescine, cadaverine, spermidine, and tyramine are important BAs and may play the role of free radical quenchers. For instance, spermine can regenerate tocopherol from the tocopheroxyl radical through hydrogenic donors from the amino group. The antioxidant capacity of tyramine is directly proportional to its concentration and it is regarded as a very good antioxidant. Free radical inhibition depends on the amino and hydroxyl groups. The radical binds lipids into lipid complexes and peroxide radicals [15]. Some BAs also alter taste and flavour in the fruit development process of plants, like putrescine, spermine, and spermidine which affect numerous physiological processes such as cell division and flowering.

The concentrations of some BAs, such as putrescine, cadaverine, and tyramine, increase during the storage and processing of meat. However, the concentration of these compounds would increase during microbial fermentation or food spoilage, while spermine and spermidine decrease or remain constant along with the spoilage. Therefore, a quality index has been proposed for the hygiene conditions of raw food and manufacturing practices [4,16]. In addition, the capability of BAs are influenced by other compounds, which cause a difficulty in determining the exact toxic threshold of BAs in food samples. This could be due to the specific efficiency of the detoxifying mechanisms in different individuals.

2. Indicators and Application for Food Safety

Biogenic amines (BAs) are found in various food products, especially dairy products, seafood, meat, vegetables, fermented products, and even beverages. BAs present in foods consist of amino acids or proteins in free form that have a higher likelihood of microbial or biochemical activity. Some adverse effects caused by the consumption of foods with a high level of BAs include respiratory discomfort, hot flushes, nausea, palpitations, cold sweats, headaches, red rashes, and low or even high blood pressure. The presence of certain compounds such as alcohol and acetaldehyde in the body also affects the behaviour of BAs, which increases our sensitivity toward them [17]. Thus, the Chemical Quality Index (CQI) was introduced [18] for fish and seafood, and it is based on the following equation:

$$CQI = \frac{cHIM + cPUT + cCAD}{1 + cSPD + cSPM},$$

where SPD: spermidine, SPM: spermine, HIM: histamine, PUT: putrescine, CAD: cadaverine, and c: concentration [mg kg^{-1}].

Spoilage of food or freshness parameters can be evaluated by amine content, where tyramine should be in the Biogenic Amine Index (BAI). This is because BAs are related to meat spoilage, as the amount of tyramine will increase during meat storage. However, BAs are not always an accurate signal of micro-biological quality, even at low concentrations. Not all spoilage or starter micro-organisms can decarboxylate free amino acids. Even within the same species, not all microbial strains develop the same decarboxylating capacity [19]. Therefore, establishing a BAI that predicts quality for products of a complex matrix is still challenging even though this knowledge has been used in the proposed BAI since 1982.

The toxicological level of BAs has been challenging to establish until now. The maximum acceptable level for tyramine in foods is 100–800 mg/kg, while for histamine it is 50–100 mg/kg [20]. Health conditions and the quality of food products indirectly impact the estimation of their levels. A quality ratio has been suggested for the index [21]: BAI <5 mg/kg indicating good quality fresh meat, between 5 and 20 mg/kg for acceptable meat.

Table 2. Limits for BAs in meats.

Biogenic amines	Good quality	Acceptable	Initial spoilage	Spoiled	Ref.
Put + cad + his + tyr	<5 mg/kg	5 – 20 mg/kg	20 – 50 mg/kg	>50 mg/kg	[21] [25]
His	-	10 mg	00 mg	1000 mg	[26]
His	-	8 – 40 mg	40 – 100 mg	>100 mg	[25][27]

Tyr: Tyramine, Cad: Cadaverine, His: Histamine, Put: Putrescine

Note that signs of initial spoilage are between 20 and 50 mg/kg for low-quality meat and >50 mg/kg for spoiled meat, as interpreted in Table 2. Studies have proven that BA indexes are highly acceptable in fresh meat, meat products, and heat-treated products but less acceptable in fermented products [22]. However, the nature of the product, whether it is fresh, canned, modified atmosphere, or fermented, is usually of concern because the presence of BAs as a quality index also depends on numerous factors. According to a previous report [23], a maximum of 750–900 mg/kg of BAs (putrescine, tyramine, cadaverine, and histamine) was established as safe to consume. In such cases, the EU Commission Regulation (EC 2073/2005) that examines BAs levels in foods and beverages was implemented [24].

Owing to the inherent toxicity of BAs to human health, the determination of tyramine has great importance in the food industry and clinical analysis. Thus, biosensor technology represents a field with rapid tools and incredible potential that significantly impacts food quality control. Numerous biosensors with different biological elements and nanomaterials are being extensively developed and will be discussed in the next section of this article.

3. Working Principles of an Enzyme-based Electrochemical Biosensor

Electrochemical biosensors are the most extensively used sensors in the food industry. They are highly efficient, green and user-friendly devices that have been used in recent years for day-to-day applications [28] in food sample analysis [29]. Three necessary components in electrochemical enzymatic bio-sensors are usually biological recognition elements or bioreceptors, a transducer, and signal processing as end sources, as shown in Figure 1. In the case of enzymatic biosensors, enzymes are used to recognize specific targets in analytes that are also called bioreceptors [30]. The enzymes are immobilized to the material with a specific immobilization method that will be further explained in Section 4. The immobilization method maintains the enzyme's features without denaturing it within the support matrix-like nanomaterials [31].

Commonly, biological recognition elements (also called sensing elements) such as antibodies, bacteriophages, enzymes, microorganisms, nucleic acids, and proteins are used as modifiers in biosensors. These modifiers consist of a sensing layer that plays a key role in the sensitivity and selectivity of the device [32]. The sensing elements with an electronic component will generate a measurable signal on the device or probe. According to their operating principles, transducers are broadly categorized as electro- chemical, optical, thermal, electronic (mass), and gravimetric (magnetic) transducers. Among these transducers, the electro-chemical type is the most commonly used in the literature, probably because the first developed bio-sensor was an enzymatic electrochemical biosensor [33]. Figure 2 shows the different types of biological recognition and transducers in biosensors. The transducer is a component that converts one form of energy into another, which then converts the bioreceptor readings into a measurable signal, also known as signalization. Electrochemical sensor measurement of the output signal involves current, conductivity, resistance, and potential.

The output signal may be displayed in various forms such as numerical, image, graphic, or tabular, depending on the end-user's requirements. An electrolyte solution is involved as a medium of electron movement in which the electrodes are immersed. The electrochemical biosensor employs three types of electrodes: a working electrode (WE), a reference electrode (RE), and a counter electrode (CE). The detection capacity of the biosensor can be affected by the electrode surface materials, dimensions, and modifications [34].

Potential energy is applied between RE and WE during the electrochemical reaction, and the resulting current is measured between WE and CE [33]. The electrical energy generated from chemical reactions will facilitate the detection of specific biomolecules in the electrochemical cell, which operates by reacting with the analyte of interest to produce an electrical signal. For example, the signals for oxidation and reduction of the analyte or enzyme-substrate are measured currents proportional to the substrate concentration [35] generated in amperometry.

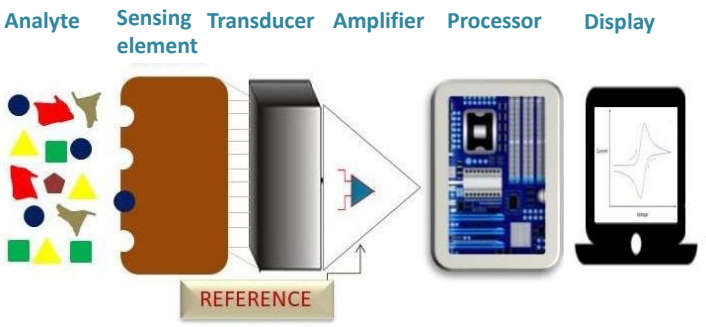


Figure 1. Schematic diagram of the biosensor working principles.

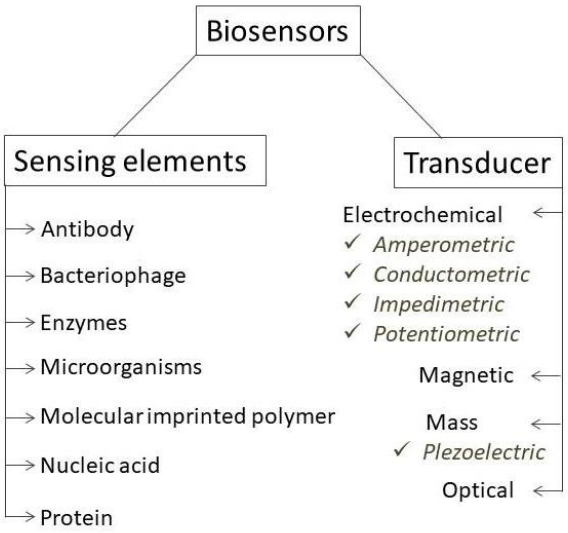


Figure 2. The different types of sensing elements and transducers in biosensors.

4. Modification of Electrode with Enzyme for Food Analysis

Based on the literature, the field of enzyme-based electrochemical biosensors for food analysis has increased significantly in the last two decades [36] due to the use of biogenic amines (BAs) as an indicator of food spoilage and their ability to impact human health and food quality. This goal of the food industry can be achieved by the application of electrochemical biosensors for the detection of chemical and biological contaminants in foods. Table 3 summarises the previous work on the determination of BAs in food samples using an enzyme-based electrochemical biosensor. Oxidases are mainly used for developing enzyme-based biosensors that can determine the existence of BAs in food formed by decarboxylation of amino acids [37].

Peroxidase and dehydrogenase are also common enzymes employed for substrate detection. In contrast, the compounds for detection include hydrogen peroxide (H_2O_2) and nicotinamide adenine dinucleotide in a reduced form (NADH) [38]. Similarly, tyramine detection in dairy products and fermented drinks as indicators of freshness is done with biosensors based on tyrosinase [39], in sauerkraut [40], pickled and smoked fish samples [41]. Lysine oxidase enzymes are used to detect L-lysine, a crucial tool in food quality control [42].

A portable device for the screening of histamine in fish samples has been successfully developed, and the biosensor involved was fabricated from the redox mediator hexacyanoferrate (III) and diamine oxidase (DAO) enzyme by cross-linking on a screen-printed carbon electrode (SPCE), in only 30 minutes. The economical miniaturized biosensor was achieved by chronoamperometry (+ 0.2V, 120 s) with a LOD value of 0.97 mg L^{-1} which maintained 87.7% of its initial signal after 35 days, indicating good stability [43]. Novel chitosan/coconut fibre/zinc oxide nanoparticles (CS/CF/nZnO) as a hybrid support were co-immobilized to generate a poly-amine sensing strip. Two enzymes, polyamine oxidase (PAO) and diamine oxidase (DAO), were used for spermine, spermidine, and putrescine determination, respectively. The biosensor provided great linearity of 5.0 mM with a low LOD of 0.01 mM [44]. Nanoparticles involving ZnO, annexed on a CS/CF matrix, were successfully developed to handle enzyme immobilization, enhancing biosensor performance and providing more interfacial space to load enzymes. Recently, Kacar et al. [45] developed a selective modifier from Prussian blue (PB) and indium tin oxide nanoparticles (ITONPs). Further modification was done with DAO and monoamine oxidase (MAO) enzymes on SPCE for detection of histamine, putrescine, and cadaverine in cheese samples. The fabricated biosensor DAO/ITONP/PB/SPCE gave the highest response of 6.0×10^{-6} to 6.9×10^{-4} M with a sensitivity of 1.84 μA mM, and the MAO/ITONP/PB/SPCE biosensor showed the most sensitivity towards cadaverine. ITONP is used as a nanoparticle modifier that enhances electrochemical working properties with low capacitive current and stable substrate adhesion. These features allow it to serve as an enhancement material in biosensor applications [46,47,48].

5. Enzyme Immobilization Mechanism

The immobilization of enzymes can be defined as the confinement of enzyme molecules on/within the matrix over the surface of the electrode while maintaining their enzyme character without denaturing. There are many advantages of enzyme immobilization, especially for commercial applications, as it allows easy separation of enzymes from the reaction mixture, is convenient to handle, economical, and can be reused [49]. Moreover, the purpose of enzyme immobilization is to develop a robust biocatalyst capable of working

under harsh operating conditions and is non-native with an extended lifetime [50]. Recently, a variety of immobilization procedures have been developed for immobilizing enzymes on a solid surface. Figure 3 illustrates different enzyme immobilization methods, such as adsorption, covalent bonding, cross-linking, encapsulation, and entrapment, where E: enzymes. M: matrix, L: link cross, CB: covalent bond.

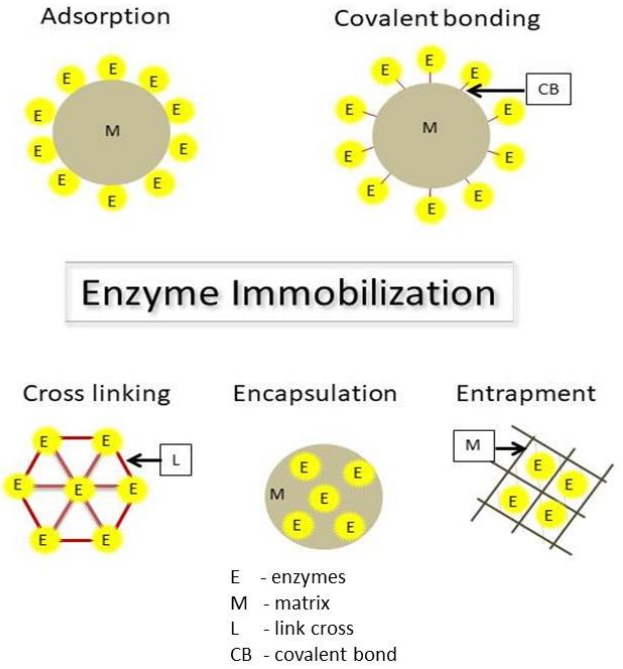


Figure 3. Various methods of enzyme immobilization.

Table 3. Previous reports on the detection of biogenic amines in food samples using an enzymatic electrochemical biosensor.

Enzyme	Working electrode	Immobilization	Potential	Biogenic amines	Food samples	Linear range	LOD	References
DAO **MAO** **PUO**	HRP/Os mediator/GWE	PEGDGE	-50 mV -50 mV -50 mV	Cad Put Spm His Trp Tyr Pea	Pork and fish samples	0.01 – 0.5 mM	5 µM 0.4 µM 5 µM	[51]
PSAO	CPE modified MDO	Nafion	+400 mV	Put Cad	Fish sauce	24 - 67 µg/mL 30 - 88 µg/mL	8 µg/mL 10 µg/mL	[52]
MIPs	PPy-SG/ HA-MWCNTs	-	+0.7 V	Trp	Cheese and Beverage	9.0×10^{-8} – 7.0×10^{-5} mol/L	7.4×10^{-8} mol/L	[53]
PSAO	SPCE	Membrane NAFION	+400 mV	Cad Put Tyr His	Chicken meat	1 - 50 µM 1 - 50 µM 10 - 300 µM 10 - 300 µM	0.3 µM 0.3 µM 3.0 µM 3.0 µM	[54]
Tyro	PO4-Ppy/Pt	Cross-linking	-0.25 V	Tyr	Salted sauerkraut	$4 - 80 \times 10^{-6}$ M	5.7×10^{-7} M	[40]
Tyro	SPCE	SWCNT-COOH Cross-linking with GA	-0.20 V	Tyr	Smoked fish sample	5 - 180 µM	0.6 µM	[41]

Tyro	TYR/TiO_2/CMK-3 modified with PDDA	PDDA/Nafion	200 mV	Tyr	Fish	6 – 130 µM	1.5 µM	[55]
-	GCE	-	0.78 V	Tyr	Variety	4.7 - 54.5 x 10^{-8} M	0.8 x 10^{-9} M	[56]
HMD **PUO**	HMD/TTF/SPCEs PUO/TTF/SPE	Cross-linking with GA and BSA	+130 mV +300 mV	His Put	Food samples	8.1 ± 0.7 µM 10 ± 0.6 µM	8 - 60 µM 10 - 200 µM	[57]
DAO	nPt/GPH/chitosan/SPCE	Surface adsorption	+0.4 V	His	Freshwater fish	0. 1 - 300 µM	2.54 x 10^{-8} M	[58]
HMD **PUO**	Dual-TTF/SPCEs	Cross-linking	+130 mV	His Put	Variety	10 - 200 µM	8.1 ± 0.7 µM 10 ± 0.6 µM	[57]
Tyro	MPAA/CGL	EDC-NHS	+0.0 V	Tyr	Wine samples	10.0 - 60.0 µmol/L	3.16 µmol/L	[59]
DAO	SPCE	Cross-linking GA and BSA	-0.3 V	His	Fish	1 & 75 mg L^{-1}	0.5 mg L^{-1}	[60]
PO **DAO**	Glass support with membrane	-	-	Put	Beef, pork, chicken, turkey and fish meat	1 - 2 mg/L 1 - 2 mg/L	0.8 mg/L 1.3 mg/L	[61]
PPO	GCE	Cross-linking with GA	-0.1 V	Tyr	Cheese	5.8 x 10^{-7} – 1.6 x 10^{-5} M	4.85 x 10^{-8} M	[20]
PAO	CHIT/zeolites-AuNPs modified	Adsorption and cross-linking	+0.2 V	Spmd	Fish	0.2 - 200 µM	0.1 µM	[62]
PAO **DOA**	CS/CF/nZnO/PAO/DAO strip	Co-mobilization with GA	-	Spm Spmd	Fruits and vegetables	0.01 - 5.0 mM	0.01 mM	[44]
-	Cu-Pt electrode	-	+200 mV	His	Saury fish	1 - 750 µM	0.33 µM	[63]
PAO	Glass capillary HMDE	-	-1.0 V	Spm	Cow and sheep's milk	4.99 x 10^{-8} – 7.98 x 10^{-7} M	0.7 x 10^{-8} M	[64]
DAO	LSG-nCu-CNC/DAO LSG-Cu-MFC/DAO	Cross-linking	+500 V	His	Fish	50 - 1.6 mM	7.7 ± 2.8 µM 11.6 ± 2.6 µM	[65]
-	AuNP-PANSA modified Au electrode	-	+0.6 V	Tyr	Dairy products and fermented drinks	0. 8 - 80 µM	0.04 µM	[66]
DAO	SPCE	Cross-linking with GA and BSA	-0.3 V	His	Fish	1 - 75 mg/L	0.94 mg/L	[60]
MOA **DOA**	PB/ITONP/SPCE	Casting nafion	-0.15 V	His Cad	Cheese	6.0 x 10^{-6}– 6.9 x 10^{-4} M	1.84 µAmM^{-1}	[45]
DAO **MAO**	RU/CS/TiO_2/c-MWCNT	EDC-NHS	-0.30 V	His	Fish sample	9.9 x 10^{-} –1.1 x 10^{-3} M 5.6 x 10^{-5}–1.1 x 10^{-3} M	-	[67]
DAO	SPCE	Cross-linking	+0.2 V	His	Fish	-	0.97 mgL^{-1}	[43]
Tyro	MPAA/CGL	EDC-NHS	+1.27 V	Tyr	Wine	-	3.16 µmol L	[59]

Ag: argentum, AgCl: argentum chloride, AuNPs: gold nanoparticles, BSA: bovine serum albumin, Cad: cadaverine, CGL: carbon graphite lead, CHIT: chitosan, CS/CF:/nZnO: chitosan/coconut fiber/zinc oxide nanoparticle, Cu-Pt: copper platinum, DAO: diamine oxidase, EDC-NHS: 1-ethyl-3-(dimethylaminopropyl) carbodiimide hydrochloride (EDC) and hydroxy succinimide (NHS), GA: glutaraldehyde, GCE: glass carbon electrode, GWE: graphite working electrode, HA-MWCNTs: hyaluronic acid-multiwalled carbon nanotubes, His: histamine, HMD: histamine dehydrogenase, HMDE: hanging mercury drop electrode, HRP: horseradish, ITONP/SPCE: indium tin oxide nanoparticles/Screen-printed carbon electrode, LSG-nCu-CNC: laser scribed graphene-nano copper-nanocrystalline cellulose hydrogel, MDO: manganese dioxide, MFC: microfabricated cellulose, MIPs: molecularly imprinted polymers, MPAA: 4-mercaptophenylacetic acid, MPAA: mercaptophenylacetic acid, PANSA: 8-anilino-1-napthalene sulphonic acid, PAO: polyamine oxidase, PB: prussian blue, PDDA: polycationic polymer poly(diallyl dimethylammonium chloride), PEA: phenylethylamine, PEGDGE: poly(ethylene glycol) diglycidyl ether, PO: putrescine oxidase, PPO: polyphenol oxidase, PPy-SG: polypyrrole-sulfonated graphene, PSAO: pea seedling amine oxidase, PUO: putrescine oxidase, Put: putrescine, RU/CS/TiO_2/c-MWCNT: hexaammineruthenium (III) chloride/chitosan/carboxylated multiwalled carbon nanotubes, SPCEs: screen-printed carbon electrode, SPE: screen printed electrode, Spm: spermine, Spmd: spermidine, TAO: tyramine oxidase, TiO^2/CMK-3: titania dioxide sol/ multi-walled carbon nanotubes or mesoporous carbon CMK-3-type , Trpt: tryptamine, TTF: tetrathiafulvalene, Ty: tyrosinase, Tyr: tyramine, Tyro: tyrosinase.

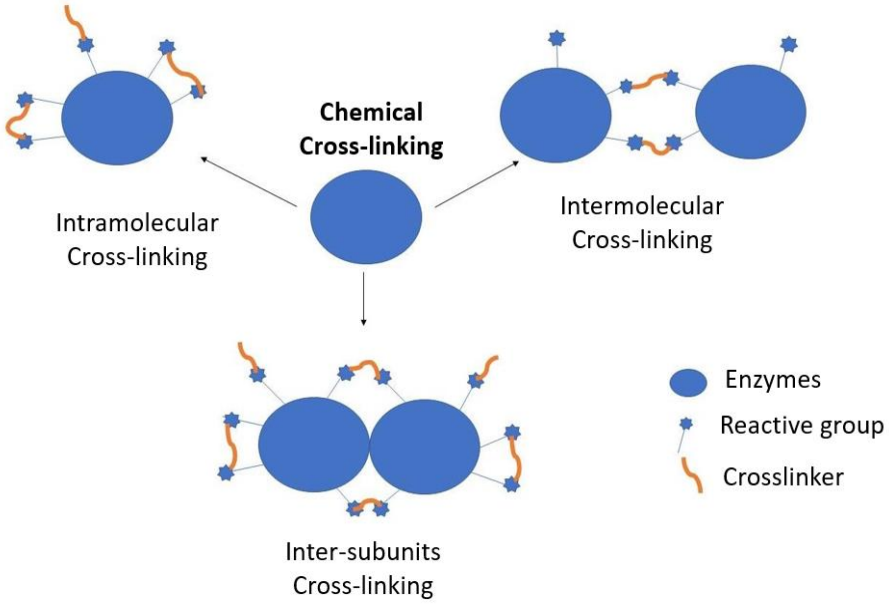


Figure 4. Different types of bond formation via cross-linking and modification of enzymes.

5.1. Adsorption

Adsorption is physical immobilization. It is known as the most straightforward and conventional method, where enzymes become physically adsorbed by weak forces, including hydrogen bonding, Van der Waals forces, ionic and hydrophobic interactions, as well being as a salt linkage for enzyme stabilization onto the inert support [68]. In the adsorption method, there is no formation of a permanent bond between the carrier and the enzyme. Therefore, this method is inexpensive, straightforward, has no pore diffusion limit, no reagents are needed for the minimum step of activation and it is unreactive against enzymes compared to chemical methods. However, the interaction between enzymes and matrices is frequently found to be too weak. Hence, it causes the desorption of enzymes from a carrier and is thus less efficient [20].

5.2. Cross-Linking

This method is also called co-polymerization, whereby no support or matrix is needed. Maintaining the functional property and structure of the enzyme during immobilization is one of the major roles a cross-linking agent plays. Cross-linking agents are usually able to dissolve in aqueous solvents and form stable bonds of inter-and intra-subunit covalent bonds [69]. The most prominent agents that are used as bifunctional cross-linkers are glutaraldehyde (GA) [68] and diazonium salt [31]. In addition, as shown in Figure 4, intramolecular, intermolecular, or inter-subunit bonds between amino acid residues of proteins can be formed using a reagent that commonly contains two or more reactive functional groups from the chemical cross-linking of different groups on the enzyme surface [57, 58].

5.3. Covalent Bonding

Covalent bonding is one method of immobilization that is widely used. It is a comparatively simple method because it can produce a strong linkage between the enzyme and the support without causing desorption problems. In addition, the formation of various functional groups are possible, allowing a wide range of applications. Possible carrier materials include the terminal amino group of enzymes, phenyl ring of tyrosine, carboxyl group, hydroxyl group of serine and threonine, and thiol group of cysteine. These functional groups allow the formation of covalent bonds with their support or carrier. However, chemical modifications could lead to enzyme denaturation, a possible drawback [59, 60].

5.4. Entrapment

The entrapment immobilization method involves a porous, tight, and strong matrix to avoid leakage of the biocatalyst so that enzymes are physically trapped inside it. The enzymes are not directly attached to the support that gets permeable enough for the product and substrate to diffuse into or out of the reaction medium. Instead, covalent or noncovalent bonds are involved in stabilizing the enzymes in the matrix. Examples of commonly used matrices are cellulose triacetate, gelatine, agar, and many more. Nanostructures like electrospun nanofibers and pristine materials are examples of entrapment support. Their wide-ranging applications have revolutionized the world of enzyme immobilization, usually in the field of biofuels, fine chemistry, biomedicine and biosensors [61,62]. Thus, the method is fast, effective and simple, and the enzymes are protected from losing their activity and support. However, there are a few drawbacks related to

pore size problems, which may lead to enzyme leakage and contamination, which seem to be inapplicable to industrial processes.

5.5. Encapsulation

In the encapsulation method, enzymes are enclosed in a membrane capsule made up of semi-permeable membranes to support the enzymes. The support materials most commonly used in this type of enzyme immobilization include polyester, alginate polylysine and polyacrylamide [33]. In a previous study, alginate gelatine calcium hybrid carriers were used as an efficient encapsulation matrix, which provided increased mechanical stability against enzyme leakage [76]. This method allowed large quantities of enzymes to be immobilized, while the efficiency of the method depended on the stability performance of enzymes within the capsule. However, only small substrate molecules could cross the membrane due to the limited size of the pores, which was a technical challenge.

6. Enhancing the Performance of Enzymatic Biosensors

6.1 Nanomaterials/Nanoparticles

Enzyme immobilization on matrices often requires suitable environmental conditions to overcome the drawbacks, such as being easily inactivated in practical applications [77] and difficult to reuse [78]. The immobilization of enzymes in/on functionalized nanomaterials is expected to resolve these problems. Nanomaterials with better surface functionalization also offer ultrasensitive, selective electrode surfaces and better dispersibility for electrochemical detection [79]. For example, a novel amperometric biosensor was developed for tyramine detection in smoked fish samples, where carboxyl functionalized single-wall carbon nanotubes (SWCNT-COOH) were successfully used as a biocompatible matrix for immobilization of tyrosinase [41]. Due to the unique intrinsic properties of the biosensor, the incorporation of nanomaterials generally increases the sensitivity and stability of enzyme-based biosensors. Nanomaterials are widely engaged in the immobilization of enzymes that inherently facilitate enzyme-nanomaterial interaction mechanisms, as illustrated in Figure 5. Enzymatic immobilization on nanomaterial-based optimization and stable design can significantly increase the enzymatic catalytic performance and kinetics of electron transfer, thus providing a large surface to volume ratio for increasing the rate of enzyme adsorption. They can also act as redox enzymes by conjugating with biomolecules for biorecognition [80].

The development of biosensors in the analysis of food and beverages also involves gold nanoparticles (AuNPs) that have been found to contribute to the electrical and conductivity properties of electrical wiring [62]. Particularly in biosensor applications, metal nanoparticles or their composites, graphene, and carbon nanotubes (CNT) have been investigated for electrochemical detection of biomolecules, including biogenic amines (BAs) [31,68,68,39]. In the case of carbon nanomaterials, the presence of sp^2-hybridized materials help in enhancing the conductivity of the electrode surface [82]. In addition, most of these nanomaterials bear carboxylic acid or

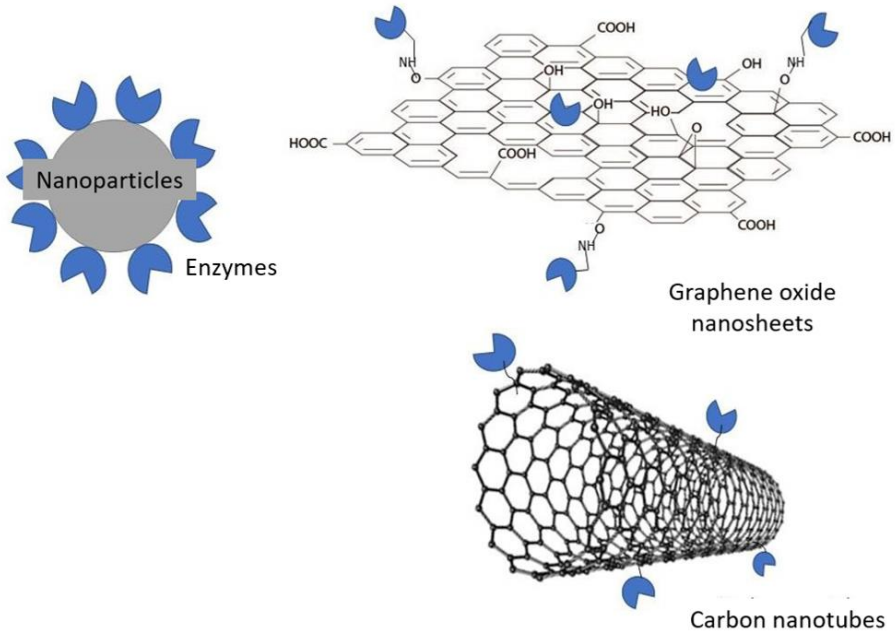


Figure 5. Enzyme immobilization on different nanomaterials.

amine functional groups, and the conjugation of a bioreceptor with nanomaterials can be easily achieved [55,54]. The detection of histamine by electrocatalytic activity, which facilitates electron transfer between electroactive species and the electrode surface of carbon nanotubes, has also been explored.

6.2. Mediators

Mediators are also known as agents for electron exchange and act as a shuttle between the enzyme active site and the electrode surface to promote the electron transfer rate. Therefore, it is also called a mediated electron transfer (MET). A redox mediator is used to decrease the distance between the enzyme redox centre and the electrode, thus facilitating the electron transfer rate. Applying a suitable immobilization operation for enzymes, including the mediator, appears to be the most popular approach for naturally-occurring analytes. Besides, the mediator can increase while improving the electron transfer of the system which reduces the necessary potential window of the system, minimizing effects from interferents, thus enhancing selectivity [35].

Numerous mediators were used in the identification of different BAs, for example, hydroxy-methyl ferrocene (HOMeFc) with monoamine oxidase (MAO) and horseradish peroxidase (HRP) and Prussian blue (PB) using diamine oxidase (DAO) [83]. Ferrocene is an example of a mediator that allows detection at low operational potentials. Potassium hexacyanoferrate was used as the mediator in research by Rahimi et al. [84] because it provided better electrical communication between the embedded redox centre of the tyramine and the tip surface. Tetrathiafluvalene (TTF) has been used as an electrochemical mediator to decrease the working potential for amperometric measurements in a study of selectivity based on the use of TTF as a mediator [57].

CONCLUSION AND FUTURE PERSPECTIVES

In recent times, the presence of biogenic amines (BAs) in food has been widely studied due to their potential for toxicity. Histamine, putrescine, cadaverine, tyramine, tryptamine, spermine and spermidine are the most important BAs. A rapid, sensitive, green, and easily adaptable method is required to detect BAs in food samples, even at low concentrations. Considering the content of BAs and food quality control procedures, enzyme-based electrochemical biosensors are ideal. These are preferred over other analytical methods as they provide rapid *in-situ* and cost-effective analyses. A recent study also highlighted that biosensors were developed with the current trends in analytical chemistry. Nanomaterials have been developed as competent immobilization matrices for enzymes and biocatalyst applications which are preferred over chemical catalysts. Furthermore, a mediator capable of improving electron transfer reduces the necessary potential window of the system by reducing interference to improve selectivity. In achieving food safety, ensuring the quality and safety of food requires the commitment and involvement of multiple domains such as public institutions, production sectors, and commercial processors. All these would significantly impact the health of the consumer. From a future research perspective, essential research efforts should be continued in the field of analysis and determination of BAs in foods. Simultaneous determination of all BAs must be focused on different complex matrices to solve extraction and interference problems. Also, advances need to be made to develop more accurate, swift, simple, and unified determination methods that can easily be transferred to laboratories, industry and public administration.

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