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Aptamer-Based Quartz Crystal Microbalance Biosensor for Histamine

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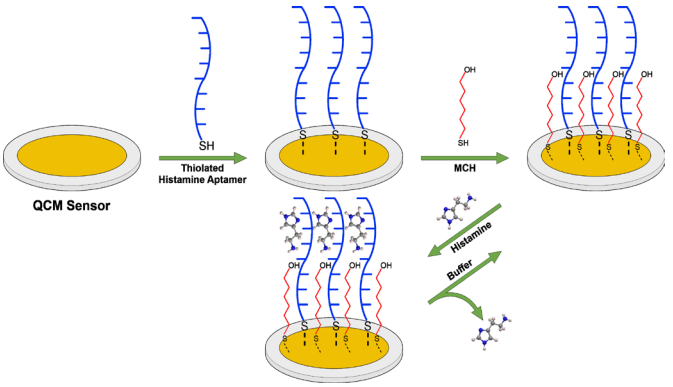
Graphical Abstract



Abstract

Histamine is a biogenic amine commonly associated with food spoilage and allergic reactions, making its rapid and accurate detection critical for food safety. This study aimed to develop a quartz crystal microbalance (QCM) biosensor using a histamine-specific aptamer as the recognition element. The thiol-modified aptamer was immobilized on the gold electrode of the quartz crystal, and the surface was characterized by scanning electron microscopy with energy-dispersive X-ray spectroscopy (SEM-EDS). Adsorption behavior was investigated through equilibrium binding experiments and Langmuir isotherm analysis, while key variables—such as sample pH, aptamer concentration, and immobilization time—were optimized to enhance sensor performance. The biosensor exhibited a linear response in the range of 0.01–1 mg/L (R^2 = 0.995) and a limit of detection of 0.0071 mg/L. It demonstrated high selectivity, with selectivity factors exceeding 15 against structurally related analogs, as well as good repeatability and recovery rates (99–109%) when tested with fish sauce samples. These findings indicate that the developed aptamer–QCM biosensor is a practical, selective, and sensitive platform for histamine detection in food safety applications.

Keywords: aptamer, biosensor, food safety, Langmuir isotherm, QCM

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Introduction

Histamine, one of the most common biogenic amines, plays a critical role in the body's immune and inflammatory responses but can also pose serious health risks when consumed in excess through food. Ingestion of elevated levels of histamine can trigger histamine intolerance or scombroid poisoning, a foodborne toxic reaction often mistaken for food allergies. This condition results from the overproduction or ingestion of histamine, leading to symptoms such as skin flushing, headache, urticaria, abdominal cramps, hypotension, and, in severe cases, respiratory distress [1,2]. The U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) recommend a maximum histamine level of 50 mg/100 g of fish and fishery products to avoid toxic effects [3]. Histamine contamination in food occurs mainly through the enzymatic decarboxylation of the amino acid histidine by bacterial histidine decarboxylase [4,5]. Once formed, histamine is remarkably stable and resistant to common food processing methods such as smoking, freezing, and heat treatment [6].

Quantitative analysis of histamine in food is therefore critical for ensuring food safety and preventing histamine-related illnesses. Conventional analytical techniques for histamine determination include capillary electrophoresis [7], thin-layer chromatography [8], gas chromatography, and high-performance liquid chromatography (HPLC) [9,10]. Although these methods are well-established and provide high accuracy and sensitivity, they are costly, require skilled personnel, and are limited to well-equipped laboratory settings. To address these limitations, alternative approaches—such as fluorometric assays, including those based on molecularly imprinted polymers [11], and immunoassays—have been widely explored as rapid, cost-effective, and reliable screening tools for food safety applications. Nevertheless, these methods are often reagent-dependent, labor-intensive, and may have restricted applicability for rapid, on-site detection.

Recent research has focused on biosensor-based detection platforms for histamine, which offer portability, faster response times, and potential for on-site analysis. Various sensing technologies have been investigated, including electrochemical, optical, and piezoelectric sensors [12]. Among these, the quartz crystal microbalance (QCM) sensor has emerged as a promising tool due to its high sensitivity, label-free detection, and capability to measure mass changes at the nanogram level. QCM sensors operate by measuring the change in resonant frequency of a quartz crystal as a result of analyte binding to a functionalized surface [13]. Different recognition elements have been used in QCM sensors, including enzymes, antibodies, molecularly imprinted polymers, and aptamers.

Aptamers are short, single-stranded DNA or RNA molecules capable of folding into unique three-dimensional structures that bind to specific targets with high affinity and specificity [14]. They are generated through the systematic evolution of ligands by exponential enrichment (SELEX) process, which involves iterative rounds of binding, separation, and amplification to isolate the most effective binding sequences [15]. Aptamers offer several advantages over antibodies, such as greater stability, easier synthesis, lower production costs, and the ability to target a wide range of molecules, from small organic compounds to large proteins and even whole cells.

In the development of histamine biosensors, a QCM sensor using one histamine aptamer candidate demonstrated good linearity and sensitivity but suffered from cross-reactivity with histidine [16]. To address this limitation, the present study employs a histamine-specific aptamer (H2) as the recognition element, immobilized on the gold electrode surface via strong sulfur–gold interactions. This approach aims to enhance selectivity, minimize cross-reactivity, and maintain high sensitivity, even in samples with high ionic strength. The resulting aptamer-functionalized QCM sensor holds promise for reliable and rapid histamine detection in food safety monitoring applications [17].

Materials and Methods

Materials. Analytical reagent-grade chemicals were used in this study, and all solutions were prepared with ultrapure water. Histamine, RNase-free water, 99.9% ethanol, 6-mercapto-1-hexanol (MCH), and phosphate-buffered saline (PBS) were purchased from Sigma-Aldrich, Inc. The thiolated histamine-specific aptamer H2 [18] was obtained from Sangon Biotech Co., Ltd. (China). The sulfur-modified aptamer is a derivative of the sequence reported in a previous study [19] and consists of ninety-nine (99) nucleotides with the 5′ to 3′ sequence:

5′-HS$(CH_2)_6$-AGCTCCAGAAGATAAATTACAGGGAACGTGTTGGTTGCGGTTCT TCCGATCTGCTGTGTTCTCTATCTGTGCCATGCAACTAGGATACTATGACCCC GG

Immobilization of the Aptamers. Prior to immobilization, the lyophilized aptamer was centrifuged at 4 °C to collect the pellet at the bottom of the tube. The pellet was then resuspended in 53.2 μL of 0.01 M PBS (pH 7.5) to prepare a 100 μM stock solution. This stock was incubated at room temperature for 30 minutes and vortex-mixed to ensure complete dissolution. A 5 μM working solution was prepared by dilution, heated briefly to 75 °C to promote proper folding, and then cooled to room temperature.

The gold-coated AT-cut quartz crystal (10 MHz, Novaetech S.r.l., Italy) was cleaned sequentially with ethanol and RNase-free water, then dried under nitrogen. The cleaned crystal was immersed in the 5 μM aptamer solution for 16 hours at room temperature to allow thiol–gold binding. Afterward, the crystal was rinsed with ultrapure water to remove unbound aptamer. To block unoccupied gold sites, the crystal was immersed in 1 mM 6-mercapto-1-hexanol in ethanol for 16 hours, followed by rinsing with ethanol [20].

Measurement Procedure. Frequency measurements were performed using the OpenQCM system (Novaetech S.r.l., Italy) connected to a computer (Figure 1). The aptamer-functionalized crystal was mounted in the measurement cell, and PBS (pH 7.5) was circulated until a stable baseline frequency (f_0) was obtained. Histamine solutions of known concentrations were then introduced into the cell, and the frequency shift (f_i) was recorded once stabilization occurred [21].

Following each measurement, the crystal was regenerated by washing with 20 mM NaOH, rinsing with ultrapure water, and flushing with PBS until the baseline frequency (f_0) was restored.

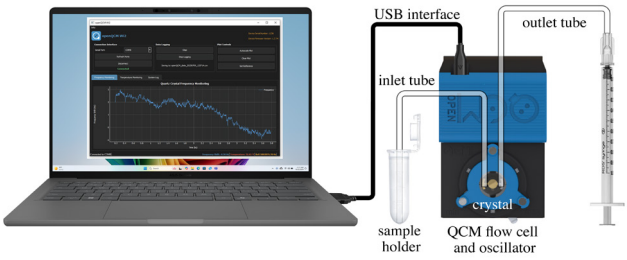

Figure 1. A schematic diagram of the QCM histamine aptamer sensor system.

Measurements were performed in triplicate for each histamine concentration, ranging from 1.0×10^{-5} g/L to 100 mg/L. The frequency change ($\Delta f = f_0 - f_i$) was calculated for each concentration, and the resulting data were used to evaluate sensor performance.

Results and Discussion

Sensor Response and Behavior of the Aptasensor. Upon exposure to histamine solutions, the aptamer-modified QCM sensor exhibited a rapid decrease in frequency, indicating successful binding of histamine to the immobilized aptamer. The frequency shift (Δf) increased with histamine concentration until a levelling off from the sensor's response was observed among the succeeding higher concentrations, and this suggests saturation of available binding sites. This interaction was reversible at pH 7.5, with hydrogen bonding identified as the primary contributing force. Figure 2 shows the response-vs-time curve, illustrating both the rapid association phase and the gradual return toward baseline after rinsing with PBS buffer. The PBS rinse removed nonspecifically bound histamine molecules, consistent with reports that low-ionic-strength phosphate buffers can disrupt weak, non-specific electrostatic interactions [22].

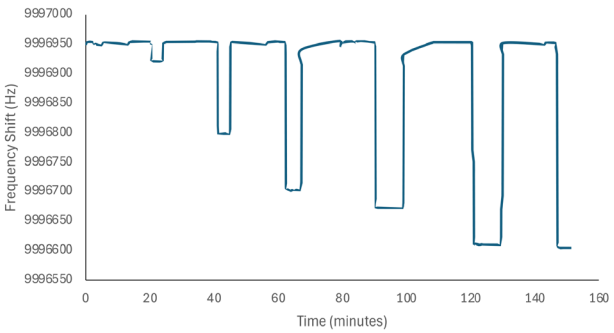

Figure 2. Real-time QCM response curve of the aptamer-functionalized sensor to varying histamine concentrations within the range 0.00001 mg/L to 10 mg/L.

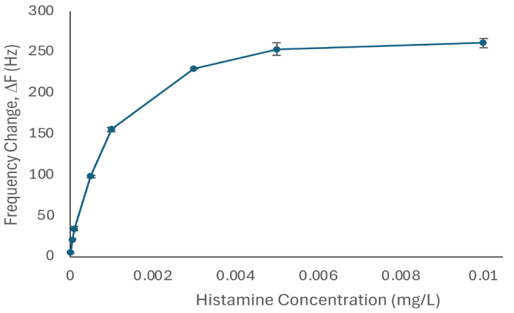

Figure 3. Saturation binding curve of histamine on the aptamer-modified QCM surface.

Binding Capacity and Adsorption Isotherm Analysis. The QCM sensor's binding behavior was systematically evaluated by monitoring its frequency drop in response to varying histamine concentrations, as illustrated in Figure 3. The plot reveals a clear dose-dependent response, with the frequency dropping as histamine concentration increases. This behavior is consistent with the fundamental principle of QCM, where a decrease in frequency is directly proportional to the mass adsorbed onto the crystal's surface. Initially, the response is linear, which is ideal for a sensor in the low concentration range. However, as histamine concentration increases, the curve begins to plateau, eventually reaching a saturation point where the frequency drop ceases to increase. This characteristic saturation binding curve is indicative of a binding process that follows a Langmuir-like adsorption isotherm model.

The observed behavior is appropriately termed "Langmuir-like" because, while the data visually fits the Langmuir equation, biological systems like aptasensors do not fully meet the model's strict theoretical assumptions of a perfect monolayer on a completely uniform surface without any molecular interactions. However, fitting the experimental data to this model is a standard and effective practice for extracting quantitative binding parameters. By using a linear transformation of the Langmuir model, as shown in Equation 1,

$$\frac{1}{\Delta f} = \frac{1}{K_A \, x \, \Delta f_{max} \, x \, [ligand]} + \frac{1}{\Delta f_{max}} \qquad \textbf{Equation 1}$$

the experimental data can be plotted (Figure 4) to determine key parameters. From the resulting linearized Langmuir plot (Figure 4), the equilibrium dissociation constant (KD) was determined. The relationship between the association constant (KA) and the dissociation constant is given by Equation 2.

$$K_D = \frac{1}{K_A} \qquad \textbf{Equation 2}$$

The calculated KD of 4.8 x 10^{-4} mg/L indicates an exceptionally high binding affinity between the aptamer and histamine, which is a key performance metric for biosensors. This strong affinity and predictable binding behavior confirm that the developed sensor is a robust platform for sensitive and reliable histamine detection.

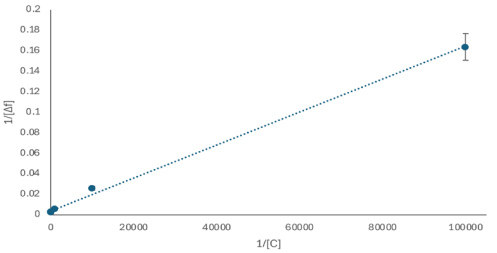

Figure 4. Linear behavior of the linearized Langmuir plots.

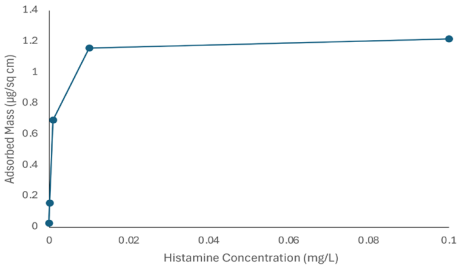

Figure 5. Adsorption isotherm of histamine on the aptamer-modified QCM surface.

Using equation 3, with Δm as the adsorbed mass, Δf as the associated frequency change and C as the crystal's sensitivity constant [4.4 x 10-9 g/(Hz-cm2)] the corresponding adsorption isotherm, shown in Figure 5 was generated.

$$\Delta m = -C(\Delta f) \quad \textbf{Equation 3}$$

This figure describes how the adsorbed mass per unit area of the active sensing layer varies with concentration of histamine in the solution. It also confirms the Langmuir-like behavior of the adsorption and the sensor's saturation capacity.

Characterization of the Aptamer-Modified QCM Surface. SEM-EDS analysis confirmed the immobilization of the thiolated aptamer on the gold-coated QCM surface (Figure 6). The spectra showed characteristic peaks for phosphorus (2.01 keV) and sulfur (2.31 keV), indicating the DNA backbone and the S–Au bond, respectively. Additional signals for nitrogen (0.39 keV) and carbon (0.28 keV) further supported the presence of nucleobases and sugar units. These elemental signatures collectively verify the successful and specific attachment of the aptamer to the electrode surface.

Analytical Performance of the Histamine Sensor. The analytical performance of the aptasensor was evaluated using the linear portion of the dose–response curve within the concentration range of 0.01–1 mg/L. The resulting calibration curve (Figure 7) showed figures of merit comparable to those of TLC, capillary electrophoresis, HPLC, GC, and ELISA-based techniques (Table 1). The sensor exhibited a high coefficient of determination (R^2 = 0.995), surpassing that of TLC and ELISA, and demonstrated a reliable linear relationship between frequency shift and histamine concentration, enabling accurate quantification within this range. The calculated sensitivity, represented by the slope of the curve, was 83.064 Hz/(mg/L).

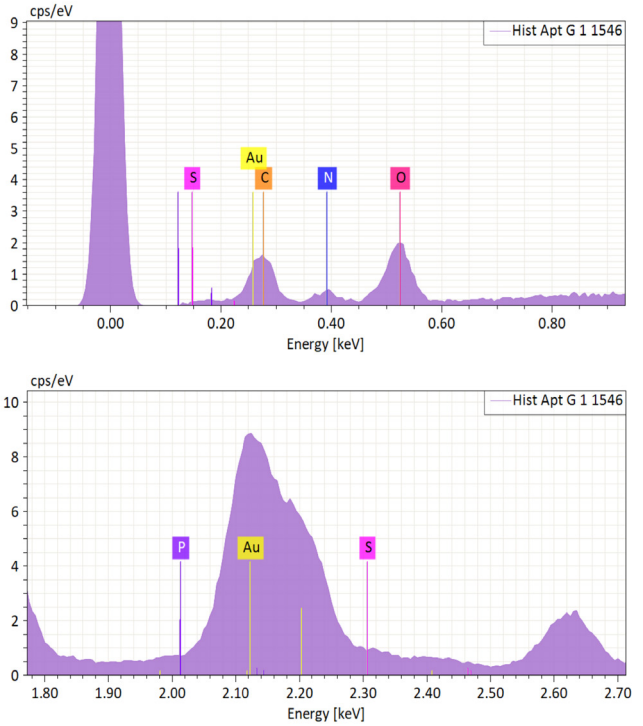

Figure 6. SEM-EDS spectra of the aptamer-modified QCM surface.

Although the linear range was narrower than those reported for TLC and capillary electrophoresis, the aptasensor achieved a lower limit of detection (LOD) of 0.0071 mg/L, confirming its ability to detect trace histamine levels. Moreover, compared with conventional methods, the developed technique offers the advantages of faster response, label-free detection, and competitive performance for histamine analysis.

The sensor's practical applicability was further evaluated in terms of selectivity, reproducibility, and repeatability. Selectivity was examined against potential interferents commonly found in biological and food matrices, including histidine, dopamine, and guanidine, at physiological pH (7.5). The aptasensor demonstrated strong preferential binding to histamine (Figure 8), with selectivity factors of 16, 21, and 24 for guanidine, histidine, and dopamine, respectively, indicating minimal cross-reactivity.

Table 1. Analytical performance of the aptamer-based biosensor as compared with other methods.

Method	Linear Range	R^2	LOD	Reference
TLC	0 -300 mg/L	0.9708	15.75 mg/L	[8]
Capillary Electrophoresis	0.001-1 mg/L	0.9990	5 mg/L	[7]
HPLC	0.16-5.0 mg/L	0.9998	0.10 mg/L	[9]
GC	0.16-5.0 mg/L	0.9999	0.06 mg/L	[9]
ELISA	0-72 mg/L	0.97	0.2 mg/L	[23]
QCM	0.01-1 mg/L	0.995	0.0071 mg/L	This study

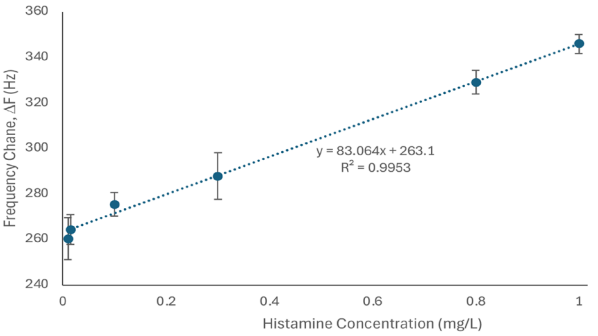

Figure 7. Calibration curve of the aptamer-functionalized QCM sensor.

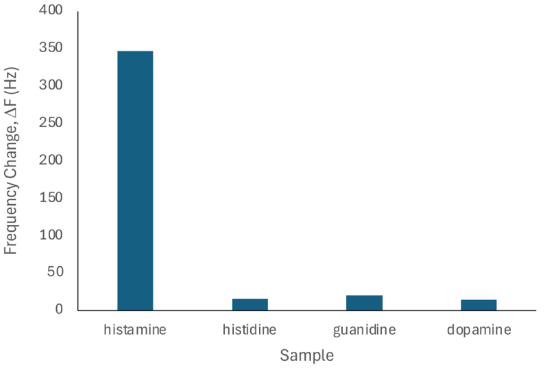

Figure 8. Selectivity of the sensor at 1 mg/L concentration.

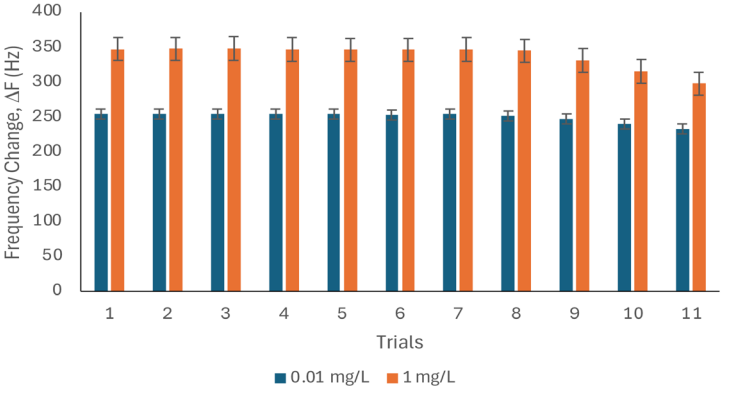

Figure 9. Repeatability test of the QCM aptasensor for histamine detection (n = 11).

Reproducibility was assessed using five independently fabricated QCM crystals, each tested in quadruplicate with 0.01 mg/L histamine. A low %RSD of 2.6% confirmed consistent fabrication and reliable analytical response across devices. Repeatability was evaluated by subjecting a single QCM aptasensor to 11 consecutive measurement cycles, alternating between 0.01 mg/L and 1 mg/L histamine solutions. Stable responses were obtained, with %RSD values of 2.90% and 4.92%, respectively, confirming the sensor's robustness and reusability (Figure 9).

Collectively, these results highlight the aptasensor's high sensitivity, excellent selectivity, and strong reproducibility, establishing it as a reliable and cost-effective platform for quantitative histamine detection. While its current application focuses on condiments, future work should extend testing to histamine-rich foods and allergy-related diagnostics to broaden its practical impact.

Overall, the combined results for selectivity, reproducibility, and repeatability demonstrate that the QCM aptasensor possesses strong analytical performance characteristics. The ability to selectively detect histamine in the presence of structurally similar compounds, coupled with its reliable fabrication and reusability, highlights the sensor's suitability for practical deployment in food quality monitoring and safety assurance.

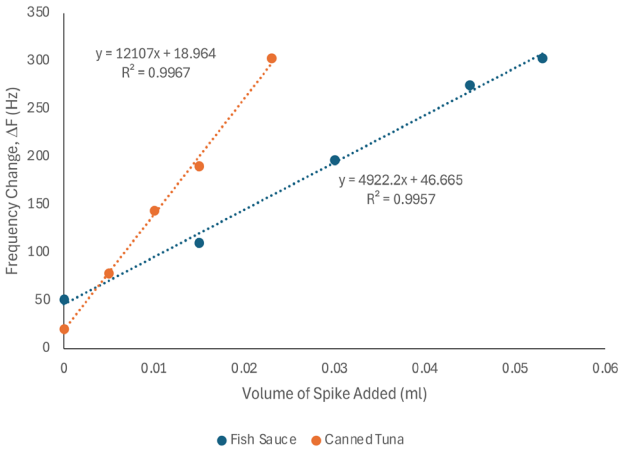

Figure 10. Standard addition calibration curves for the determination of histamine in fish sauce and canned tuna samples using the QCM sensor.

Table 2. Results of real sample analyses.

Sample	Detected Amount of Histamine (mg/L)		Test of significant difference at 95% confidence level
	QCM mean±SD (n=4)	Fluorometric Technique	
Fish Sauce	9.5±0.19	10	No significant difference
Canned Tuna	4.1±0.21	<10	-

Real Sample Analysis. The performance of the QCM aptasensor for histamine detection was evaluated in fish sauce and canned tuna using the standard addition method, providing a basis for comparison with the standard fluorometric technique.

For the fish sauce analysis, a calibration curve was generated by spiking aliquots of the sample with known concentrations of histamine. Extrapolation of the best-fit line to the x-axis gave a histamine concentration of 9.48 mg/L (n = 4) with a standard deviation of ±0.19, which closely matched the 10 mg/L value obtained using the reference fluorometric method (AOAC Official Method 977.13) [24]. A paired t-test showed no statistically significant difference between the two methods ($p > 0.05$), confirming the comparable accuracy of the QCM sensor. In this matrix, the sensor exhibited a limit of detection (LOD) of 0.00021 mg/L, a sensitivity of 4922.2 Hz/(mg/L), and recovery rates of 99–109% (n = 4), indicating excellent accuracy even in a high-salt environment. The combined calibration curves for fish sauce and canned tuna are presented in Figure 10.

For the canned tuna analysis, the sample was homogenized and processed for histamine extraction. A standard addition calibration curve was obtained from spiked aliquots, and the histamine concentration in the unspiked sample was determined to be 4.1 mg/L (n = 4, ±0.21). This value is below the reporting threshold of the fluorometric reference method, which can only quantify histamine at levels ≥10 mg/L. The ability of the QCM aptasensor to measure below this threshold highlights its superior sensitivity. In the canned tuna matrix, the sensor demonstrated a higher sensitivity of 12,107 Hz/(mg/L) and an LOD of 0.00026 mg/L. Percent recovery tests were not performed due to the complexity of spiking and recovering analytes from a solid food matrix. Table 2 summarizes the sensor's performance in detecting histamine in fish sauce and canned tuna compared with the standard method.

Conclusion

The developed aptamer–QCM biosensor demonstrates a robust, rapid, and selective platform for histamine detection in liquid samples, with performance characteristics meeting the stringent requirements of food safety monitoring. Its strong aptamer–histamine binding affinity, coupled with high reproducibility, repeatability, and excellent recovery in complex matrices such as commercial fish sauce, establishes its reliability for real-world applications. The close agreement with a standard fluorometric method underscores its analytical accuracy, while its reusability and minimal sample preparation make it an attractive alternative to conventional laboratory-based assays. Beyond its demonstrated utility in condiment analysis, the platform holds promise for expansion to histamine-rich food products and potentially to clinical diagnostics for allergy-related conditions. These attributes position the aptamer–QCM system as a practical, field-adaptable, and cost-effective solution for routine histamine monitoring, with the versatility to be integrated into broader biosensing technologies.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this work.

Author Contributions

The following researchers made substantial contributions to the work: Conceptualization: George Rabacal, Dharmatov Rahula Albano; Methodology: George Rabacal, Dharmatov Rahula Albano; Data curation: George Rabacal, Lyam Estipona; Formal analysis: George Rabacal, Dharmatov Rahula Albano; Investigation: George Rabacal, Lyam Estipona; Resources: Dharmatov Rahula Albano; Writing – original draft: George Rabacal; Writing – review & editing: Dharmatov Rahula Albano; Supervision: Dharmatov Rahula Albano; Funding acquisition: George Rabacal, Dharmatov Rahula Albano.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

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