Ingeniería Solidaria

QCM Biosensors for pathogen detection in water and food: review of published literature

Biosensores QCM para detección de patógenos en agua y alimentos: revisión de literatura publicada

Biossensores QCM para detecção de patógenos em água e alimentos: revisão da literatura publicada

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Abstract

Introduction: This article is the result of the review "QCM Biosensors for the Detection of Pathogens in Water and Food: A Review,' conducted during the years 2023 and 2024 at the Universidad Distrital Francisco José de Caldas"

Problem: The fast evolution of pathogen detection through biosensors requires a continuous synthesis of literature to provide an integral comprehension of the state of the art to new researchers.

Objective: Perform bibliography research about QCM Biosensors used for pathogen detection in food and water covering a period from 2018 to 2023.

Methodology: The research includes three phases: An explanation of the principles of QCM biosensors, their use in water and food pathogen detection, and their use in industry, with an emphasis on water quality.

Result: QCM biosensors are solid, measure mass changes at the micro and nanometric scales, and are widely used in the food industry due to their accuracy and ease of use.

Conclusion: The review highlights the effectiveness of QCM biosensors when detecting different food contaminants and pathogens. It underlines the practical research necessity and importance of updating review papers to orientate future investigations in this specific area.

Originality: The originality of this review lies on its detailed approach to QCM biosensor use in food pathogen detection.

Limitations: The constant evolution of the field of pathogen detection in addition to the diversity of QCM biosensors and the wide range of pathogens studied may make it difficult to generalize certain findings.

Key words: Pathogens, Biosensors, Food, Detection, Escherichia Coli, Salmonella

Resumen

Introducción: Este artículo es producto de una revisión "Biosensores QCM para la detección de patógenos en agua y alimentos: una revisión" realizado durante el año 2023 y 2024 en la Universidad Distrital Francisco José de Caldas.

Problema: La rápida evolución de la investigación y desarrollo en la detección de patógenos por medio de biosensores demanda una síntesis continua de la literatura para proporcionar a los nuevos investigadores una comprensión integral de lo que se ha logrado hasta la fecha.

Objetivo: Realizar una investigación bibliográfica sobre Biosensores QCM empleados en la detección de patógenos en agua y alimentos entre los años 2018 al 2023.

Metodología: La investigación comprende tres fases: explicación de los principios de los biosensores QCM, su aplicación en la detección de patógenos en agua y alimentos, y sus usos en la industria, enfocándose en la calidad del agua.

Resultado: Los biosensores QCM son sólidos, miden cambios de masa a escalas micro y nanométricas, y se utilizan ampliamente en la industria alimentaria debido a su precisión y facilidad de uso.

Conclusión: La revisión destaca la efectividad de los biosensores QCM en la detección de diversos patógenos y contaminantes en alimentos. Se subraya la necesidad de investigaciones prácticas y la importancia de mantener actualizados los artículos de revisión para orientar futuras investigaciones en este campo específico

Originalidad: La originalidad de esta revisión radica en su enfoque detallado en la aplicación de biosensores QCM para detectar patógenos en alimentos.

Limitaciones: La constante evolución del campo de detección de patógenos además de la diversidad de biosensores QCM y la amplia gama de patógenos estudiados pueden dificultar la generalización de ciertos hallazgos.

Palabras clave: Patógenos, Biosensores, Alimentos, Detección, Escherichia Coli, Salmonella

Resumo

Introdução: Este artigo é produto da revisão “Biossensores QCM para detecção de patógenos em água e alimentos: uma revisão” realizada durante 2023 e 2024 na Universidade Distrital Francisco José de Caldas.

Problema: A rápida evolução da pesquisa e desenvolvimento na detecção de patógenos por biossensores exige uma síntese contínua da literatura para fornecer aos novos pesquisadores uma compreensão abrangente do que foi alcançado até o momento.

Objetivo: Realizar uma pesquisa bibliográfica sobre Biossensores QCM utilizados na detecção de patógenos em água e alimentos entre os anos de 2018 a 2023.

Metodologia: A pesquisa inclui três fases: explicação dos princípios dos biossensores QCM, sua aplicação na detecção de patógenos em água e alimentos, e suas utilizações na indústria, com foco na qualidade da água.

Resultado: os biossensores QCM são robustos, medem mudanças de massa em micro e nanoescalas e são amplamente utilizados na indústria alimentícia devido à sua precisão e facilidade de uso.

Conclusão: A revisão destaca a eficácia dos biossensores QCM na detecção de vários patógenos e contaminantes em alimentos. Destaca-se a necessidade de pesquisas práticas e a importância de manter os artigos de revisão atualizados para orientar pesquisas futuras neste campo específico.

Originalidade: A originalidade desta revisão reside no seu foco detalhado na aplicação de biossensores QCM para detectar patógenos em alimentos.

Limitações: A constante evolução do campo de detecção de patógenos, além da diversidade de biossensores QCM e da ampla gama de patógenos estudados, pode dificultar a generalização de certos achados.

Palavras-chave: Patógenos, Biossensores, Alimentos, Detecção, Escherichia Coli, Salmonella

1. INTRODUCTION

A great number of diseases can be contracted through the consumption of food and water contaminated with pathogens [1], chemicals or toxins, making monitoring of the same a challenge for food and water industry and the health sector [2]. In light of this, society has become more demanding, generating efforts from state entities and scientific communities to innovate and advance on developing new techniques to better control safety and quality of food and water [3].

The best way to face the problem of diseases related to food and water consumption is through prevention (water quality, and safe food) [4]. Therefore, it is considered necessary to evaluate and propose alternatives to improve water supply and mitigate public health problems. A fundamental objective is to reduce uncertainty regarding water resources and their utilization, in order to enhance risk management and ensure water quality [5]. To attain the purposes described above, it is fundamental to define models and methods, and develop tools that permit carrying out the necessary prevention activities [6]. However, a series of barriers related to cost, time and effectiveness of mechanisms to improve water supply quality for human consumption have been appearing along the way [7].

Biosensors are technological devices that analyze chemical or biological parameters; they are differentiated from other transducer-based sensors in their capacity to detect single analytes [8]. In food and water industry, biosensors are used on assurance of quality at a physiochemical, microbiological, bromatological and sensory level, both in raw materials and finished products, guaranteeing the safety of distributed products [9]. Research in this field has demonstrated the effectiveness of QCM biosensors in pathogen detection like Salmonella and Escherichia coli, as well as in toxin identification, included Ochratoxin A, pesticide detection, vet medicines and many others. Their use has also been extended to the detection of heavy metals like cadmium, volatile agents, evaluation in eggs and disease diagnosis on poultry feed. These advances highlight the versatility and potential of QCM sensors on various crucial uses for food safety.

A reviewing of existing literature has found valuable studies that include different methodologies and technologies for pathogen detection using biosensors [10]–[22]. However, to date, a thorough and specific evaluation, exclusively focused on Quartz Crystal Microbalance (QCM) sensors and in this context, has not been performed.

It is important to highlight that, although significant advances in food and water pathogen detection have been made, no recent reviews have been identified that focus exclusively on applicability and effectiveness of QCM biosensors to this purpose.

Despite the relevance of QCM biosensors to pathogen detection, it is evident that a gap exists in the literature in terms of specific current reviews focused only on this sensor. This review aims to address that gap and provide an up-to-date and detailed review on QCM biosensors used for food and water pathogen detection.

2. MATERIALS AND METHODS

2.1 QCM biosensors operation principles

Biological sensors typically rely on chemical interactions as their means of detection, but, in this case, interactions that generate detectable reactions occur between device molecules and the biomolecules of interest [23]. Interaction types that can occur are: antibody-antigen, enzyme-substrate, microorganism-culture medium or DNA chains that generate variations in one or more physicochemical properties that result in pH changes, electron/heat transfers, optical changes or mass property variations that are detected by a transducer [9].

Thus, it can be said that biosensors are composed of two essential elements: a biorecognition component (bio-receptor) that comes into contact with an objective analyte, and a transducer that transforms an input energy into another output energy [24]. The biosensor can be an enzyme, antibody, receptor, organelle, bacteria, cell, tissue or mimetic compound. The transducer can be an electrode, QCM (Quartz Crystal Microbalance), or photometric/acoustic/thermometric detector. The formation of a chemical compound, mass change, REM, sound or enthalpy change generates an electric signal, which, in turn, provides analysis information (presence or not of the studied analyte) through a monitoring system to which the transducer is connected [25], as seen in Illustration 1.

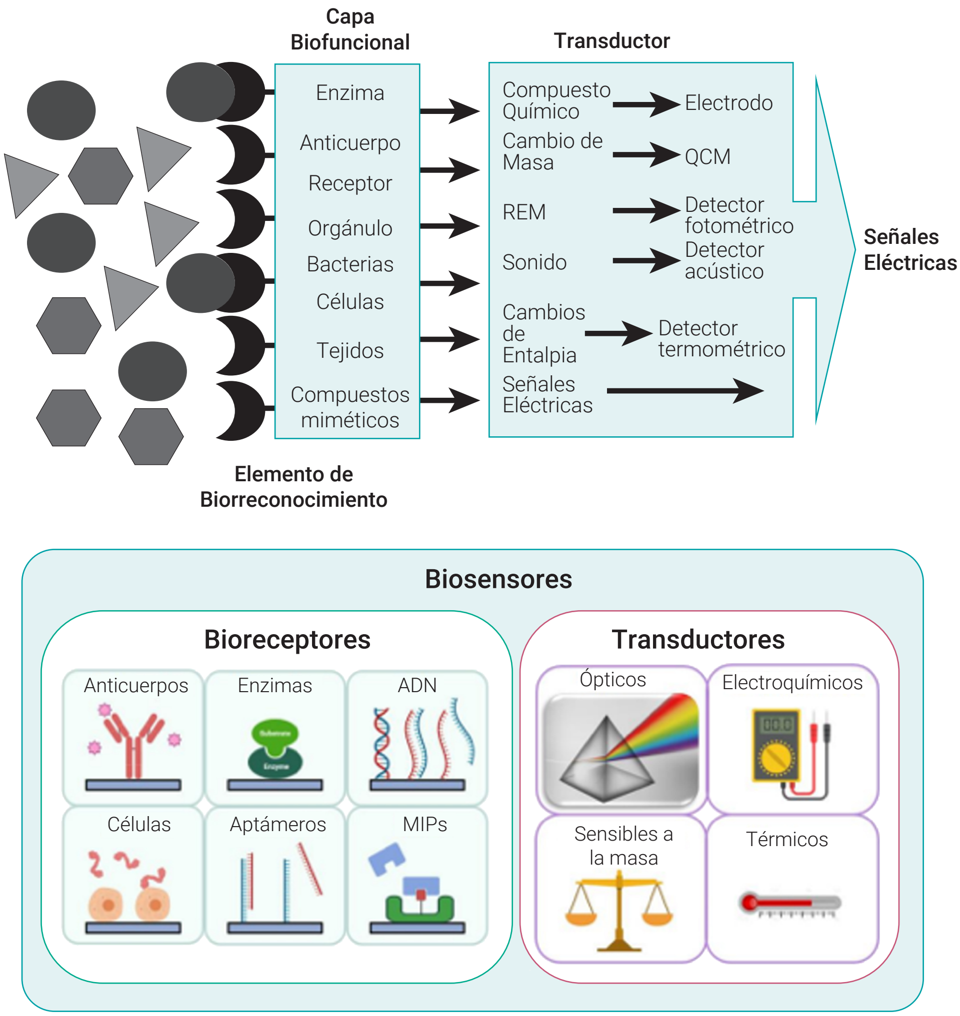

Figure 1. Operating mechanism of a Biosensor, incorporating different compounds that may be used

Source: [26].

Considering the above, biosensors can be operated by transducers that are categorized into classes and subclasses [27], presented in Illustration 2, which are more commonly used for environment and food contaminant detection. It is important to mention that biosensors in the nano line, are widely used in activities like quantitative detection of microorganisms transmitted by food on edible items, pesticides on agricultural crops and environment, food and water toxin detection and detection of xanthine and polyphenols alcoholic and non-alcoholic beverages [28]. QCM have another uses in fields such as ocular disease detection through measuring biomolecule concentrations in tears [[29], and even in the detection of other infecting potentially serious bacteria like Tuberculosis [30].

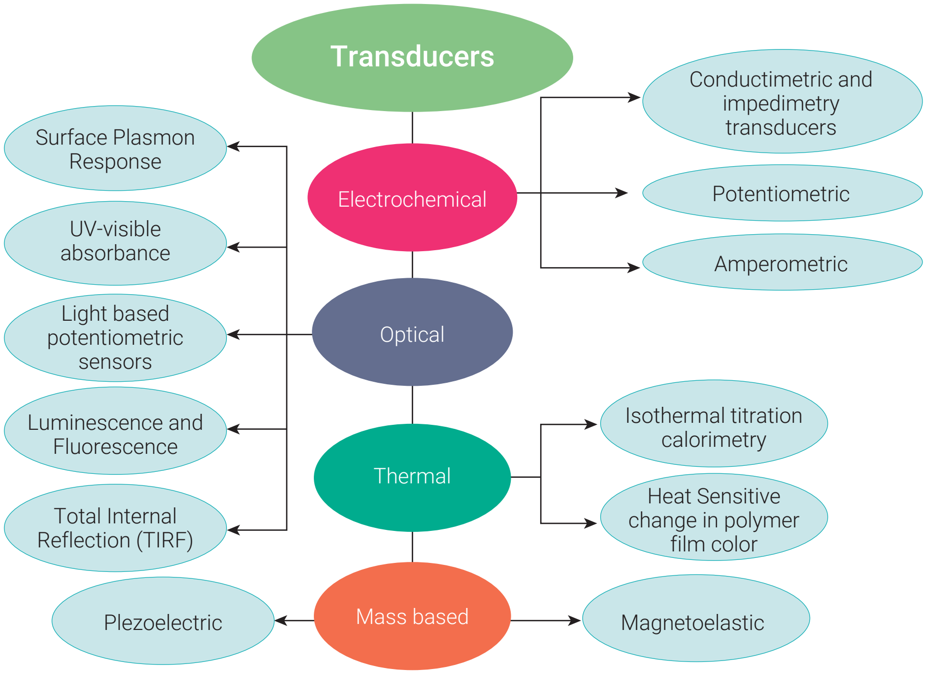

Figure 2. Classes and subclasses of biosensors according to transducer type
Source: [31].

2.2 QCM biosensors, characteristics

Although, as noted above, biosensors can detect analytes via a number of different methods (electrochemical, optical, mass etc.) [27], this research will focus on mass sensors, being devices that exploit the piezoelectric effect, leveraging Quartz Crystal Microbalance (QCM) [32] for solid and liquid sample analysis. Recent analysis methods based on piezoelectric biosensors have been used as promising screening mechanisms, classified as a complementary technique used, like chromatography, for its easy use, cost and fast analysis [3].

QCMs work with mass transducers (also named gravimetric, piezoelectric or acoustic), and are characterized for having a high sensitivity to physicochemical phenomena, which results in high accuracy measurements [33]. These kinds of sensors are used to measure little mass changes at the micro and nanometric scales; changes that wouldn't be possible with a conventional balance. When a mass change is generated, a pressure is generated over the sensor that produces an electrical signal [34]. These kind of QCM biosensors are often used at the industrial, biological and engineer level [35]; their ease of use and accessibility (derived from its low cost) make them the most used biosensor type in the food industry.

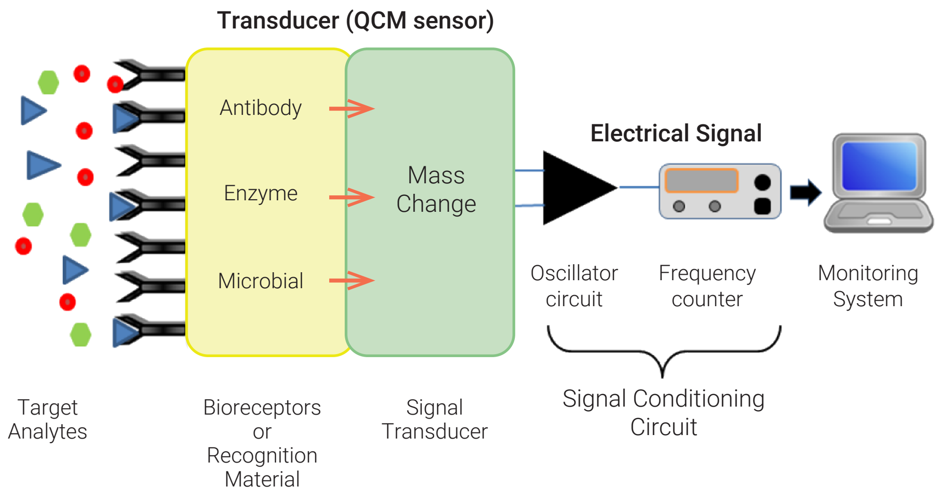

Figure 3. QCM sensor working mechanism
Source: [14].

As seen in Illustration 3, objective analytes come into contact with bioreceptors like antibodies, enzymes and/or microbes that, via QCM sensor detects a mass change that is then converted into an electrical signal that is transmitted to the monitoring system. According to authors like José Montoya and Juan Salinas, QCM biosensors work from immunoreactions in which a molecule of an antigen, located on the sensor's surface, is passed through a solution that contains an antibody (conjugated according to antigen), to generate an antigen-antibody reaction [36] that causes increases the deposited mass on the sensor; this mass variation is turned into a frequency variation by the QCM sensor.

Other authors conceive the QCM biosensors' operation as elements that operate as a microbalance that characterizes mass depositions in the crystal electrode. By depositing a very thin layer of material over a quartz crystal, both the material and the crystal start vibrating at equivalent frequencies; a starting resonance frequency. As deposited mass increases, the resonant frequency increases [33]. Illustration 4 is a graphic representation of this relationship: Left image - the vibration frequency of a quartz crystal (f0), Right image - the way frequency decreases with a mass deposit on its surface to a f1 frequency derived from an inertial increase of the resonant system; thus observing a frequency shift Δf= f1- f0 [37].

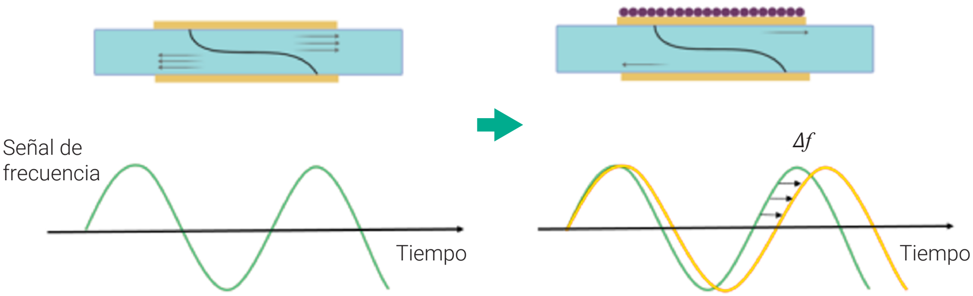

Figure 4. Frequency changes representation when a mass is deposited over a quartz surface
Source: [38].

According to the above, when quartz crystal transducer biosensors are used, calibrations are based on monitoring frequency changes of obtained signals; when there are no analytes to be detected, the frequency must be observed to be practically unaltered, while on a bio recognizing event, the frequency must come down [37].

Just as quartz crystals work with solid materials, they also work in fluids, however, viscoelasticity changes can generate crystal resonance frequency changes which can be easily mistaken for a frequency change due to mass increase [37]. For this reason, in the case of viscoelastic fluids, besides the measurement of crystal resonance frequency change it is necessary to measure another variable that is the half width half band – Γ; and, finally, for pseudoplastic fluids, a mathematical model is also required that shows the viscosity behavior as a function of different shearing velocities.

This review was carried out following a bibliographic approach and literature reviewing. In the first phase, a thorough research was carried out related to QCM biosensors and their role in food and water pathogen detection. Academic databases and research repositories were accessed, as well as governmental and scientific information sources. Papers and relevant documents were selected according to specific criteria, including investigation quality, QCM biosensors applicability and current publications. Last year's published investigations information was collected.

The second phase proceeds to analyze and synthetize collected literature; QCM biosensor operating principles were evaluated, their use in pathogen detection and their use in industry. Concepts closely related to biosensors were detailed: transducers, QCM biosensor types and biochemical interactions that allow food and water pathogen detection.

3. RESULTS

3.1 Detection of pathogens in food and water through QCM biosensors.

Food contamination can occur in products of a vegetable, animal or synthetic nature that due its manipulation could be exposed to microorganism transmission [39], the most frequent being contamination of a bacterial typology [32]. A systematic organization of collected information was carried out, focusing on their categorization according to the pathogen type. This classification will facilitate a clear and detailed understanding of progress achieved on specific pathogen detection, thus offering an integral vision of recent developments within each area.

3.1.1 Camplylobacter bacteria

In China, Hong Wang and co, developed a fast and sensitive immunosensor to detect a pathogen bacteria called Camplylobacter jejuni, which is one of the main causes of food transmitted human gastrointestinal diseases through poultry and bird consumption. In this research, a QCM biosensor was used that includes magnetic particles (MNB) to isolate the objective pathogen, and gold nanoparticles to amplify the measurement [40]. Results showed that that immunosensor is capable of detecting the bacteria in poultry products with a detection range of 20 to 30 CFU/mL with a total detection time of less than 30 min which turns it into a fast and effective method for main pathogen detection transmitted by poultry-based foods.

3.1.2 *Escherichia Coli*

Among more frequent pathogens found in food is Escherichia Coli (O157:H7), a pathogen that results in a high morbidity rate. Among fast and simple detection mechanisms are QCM sensors [41]; however, it is important to take into account that the right design and selection of specific elements of the biosensor, correct immobilization over the transducer and selection and developing characterization system are essential for the correct operation of these detecting devices [42]. According to the above, the research tries to improve sensitivity and detection limits of piezoelectric biosensors, given that, some design models haven't taken into account the necessity of compensating generated noise from environmental temperature changes, which end up influencing this tool's performance [43].

Gaddi B. Eshun, of New Jersey's technology institute, addresses the global threat that pathogenic bacteria represent, in particular Escherichia coli (E. coli) for food quality and water systems, focusing on a Biosensor design using a derivation of a simple sugar or monosaccharide named mannose for E. coli detection through QCM technology. The research highlights the importance of developing sensitive fast methods to detect the presence of E. coli in contaminated water and food due to its risk to public health. E. coli in its commensal form, resides naturally in the intestinal tracts of hot blood animals. However, infectious strains, as Shiga toxin producers (STEC), can cause hemolytic uremic syndrome (HUS) and acute gastroenteritis. The study mentions an outbreak in 2011 related to E. coli O104:H4, which ended in 810 cases and 39 deaths.

Limitations of usual detection methods drive the necessity of developing faster, more reliable, portable and cheaper methods that do not require reagents. QCM is presented as an potentially cheaper option offering real-time detection. However, it should be highlighted that QCM biosensors have issues related to bacteria detection limits due to sample size and matrix effect interference. In this study, ligands where synthetized (organic compounds capable of binding to a metal center through one or more atoms) derived from mannose like 4-NMBA and 4-TNM, for the detection of E. coli through interaction with lectin FimH. These ligands were characterized using techniques like mass spectrometry, scanning electron microscopy and infrared spectroscopy. Biosensor design involved the modification of a QCM with these ligands to facilitate E. coli detection. Study results show low detection limits and high sensitivity. This approach offers a reliable and cheap method for pathogenic bacteria detection [44].

Another study performed with QCM biosensors to detect E. coli was made by Xiaofan Yu and co in Shenyang city, China. In this study a single strain DNA (ssDNA) aptameter was selected through the SELEX technique of complete bacteria for E. coli O157:H7, with a high affinity (Kd = 10.30 nM) and specificity. The aptameter, named S1, was characterized using GraphPad Prism 5.0 and it was determined that its Kd value was about 10.30 nM.

QCM electrode reusability was investigated, using NaOH for regeneration. It was observed that regeneration efficiency decreases with an increase in NaOH concentration and regeneration time. S1 aptamer specificity for E. coli O157:H7 was evaluated through dot-blot essays, showing high affinity to objective bacteria and a low or null union to other nonobjective bacteria, suggesting its potential to distinguish E. Coli O157:H7 from other food transmitted pathogens.

An aptasensor was manufactured based on QCM for E. coli O157:H7 detection. Successful immobilization of S1 aptamer on the electrode allowed for the detection of various concentrations of E. coli O157:H7, with a linear relationship between frequency change and cell concentration. Aptasensor are highly sensitive and have a great capacity for distinguishing E. coli O157:H7 from other non-objective bacteria. The study also addressed considerations about QCM sensitivity, comparing them to other detection methods and mentioning the necessity of pretreatment of food samples for practical use. In conclusion, S1 aptamer and the QCM aptasensor proved promising for the rapid specific detection of E. coli O157:H7, with potential implications in the food industry and outbreak prevention [45].

In 2020 a detailed comparison of biofilms was performed on developing phases of Escherichia coli (adhesion, maturation, and dispersion) on titanium and gold surfaces. A QCM was used, a reliable and cheap microgravimetric sensor, for real time monitoring of the dissipation and frequency changes during different stages of biofilm development. Although gold is the most common electrode in QCM sensors, titanium electrodes are frequently used, allowing for research into how pathogens interact with different metallic substrates [46]. WCM results were confirmed by atomic force microscopy and violet crystal staining, validating surface sensor effectiveness for microbial biofilm investigation. Due to the ease of modification of substrate type and coating, QCM sensors offer well controlled experimental conditions for studying microbial treatments in surfaces and procedures of eradication, even in mature biofilms. This study demonstrates that QCM devices provide an economic and reliable alternative to conventional microbiological techniques for studying real-time biofilm formation stages, with high temporal resolution and without the necessity of tagging or interrupting procedures. QCM results match with high resolution images provided by atomic force microscopy, as well as with the results of conventional techniques such as violet crystal staining, confirming reliability of surface devices used in this work. It was demonstrated that QCM system allow real-time detailed characterization of bacterial biofilm development stages both in gold and titanium over more than 24 hours, showing effectiveness of this detection platform in comparative studies about biofilm growth in different materials. It also showed that E. coli has a greater affinity and a biofilm formation more abundant in gold sensors when compared with titanium sensors. Insomuch as superficial properties of QCM can be easily modulated and the sensor platform can integrate with microfluidic configurations, this technology offers a wide range of opportunities to investigate properties and biofilm developing, research into specific medications for biofilms, develop antimicrobial treatments on surfaces and designing eradication procedures of biofilm.

3.1.3 Salmonella typhimurium

Salmonella is a pathogenic bacterium of great relevance in food transmitted diseases, given that it has a direct impact on health. Because of this, in Mexico 2022, Doctor José Ortega developed an immunosensor using QCM and a detection method by a direct agglutination technique to detect Salmonella. For immunosensor development, gold nanoparticles were immobilized of two different sizes (25 and 62 nm) with the purpose of comparing detection signal size. Two compounds were synthetized, methyl cysteines, which improved the detection capacity of gold nanoparticles (AuNPs) when combined with them. These cysteines facilitated the orientation of antibodies of Salmonella typhimurium compared with non-treated AuNPs. Frequency changes and intensity of signal allowed for an efficient detection of S. typhimurium. AuNPs size were also investigated and it was found that particles of 25nM offered a better performance in signal amplification and, therefore, on S. typhimurium detection. Results show that specificity of the method is due to the specific monoclonal antibody of S. typhimurium, with AbST-M-AuNPs system being the more efficient in detection limit terms [2].

In 2018, Fulgione Andrea performed a research study, where an innovative method was developed for Salmonella typhimurium detection in food using a biosensor based on QCM modified with polyclonal antibodies anti Salmonella by photochemical immobilization technique (PIT) [47]. The PIT technique turned out to be essential for improving biosensor sensitivity. It was observed that, when antibodies were irradiated with UV light before their interaction with the gold sensor surface, they assumed a preferent orientation that improved interaction with the objective bacteria. This modification improved effectiveness in Salmonella typhimurium detection compared to non-treated antibodies.

QCM measurement procedures stand out for their simplicity and speed. They do not require specialized personnel and can be completed in less than 4 hours. A sample pre-enrichment, performed at 37°C for 2 hours, with minimal preparation steps, makes this method practical and efficient.

In result terms, QCM biosensors show an exceptional capacity to detect Salmonella typhimurium concentrations under 100 UFC/mL in chicken meat samples. Although not intended for accurate quantitative analysis, biosensors offer a valuable qualitative tool for fast identification of food contamination.

Biosensor specificity was confirmed through E. coli testing, where a significative signal was not detected, underlining its capacity to distinguish between different pathogen bacteria. Those findings suggest that QCM biosensors could be applied not just for Salmonella but for other food transmitted pathogens too, thus providing a promising alternative to improving food safety in the whole production chain. In summary, research highlights the effectiveness and applicability of this improved QCM biosensor with PIT technique in the fast detection of food pathogens.

3.1.4 Listeria innocua

In 2020, Veronica Oravczová in Slovakia, developed a biosensor based on DNA for the detection of the pathogenic bacterium Listeria innocua spp., and is based on multi-harmonic QCM technology. Results show that the addition of Listeria innocua to a biosensor modifies the resonant frequency in function of concentration, demonstrating promising specificity and sensitivity. The limit of detection obtained is approximately 1.6 × 103 CFU/mL, with a real-time detection of 30 minutes.

Although results are positive, the author highlights the need for more detailed research to improve detection limits and validate the specificity of the trails, including testing real milk samples. The developed biosensor was compared to a previous study about Lactobacilli acidophilus, highlighting its potential in the fast and specific detection of Listeria innocua in lower concentrations that minimum infectious doses [48].

3.1.5 Burkholderia pseudomallei

Burkholderia pseudomallei is a gram-negative bacterium that causes melioidosis, an infectious disease that can be lethal despite timely treatment. This pathogen is usually found in the ground and water in tropical and subtropical regions, being more prevalent in Southeast Asia and northern Australia. Besides its presence in soil, transmission could include contaminated water ingestion. Rooge Suvanasuthi developed a detection method of type III secretion system gen (TTSS) of Burkholderia pseudomallei using a QCM biosensor without needing genetic amplification. The bacteria causing melioidosis, contains TTSS gen clusters, essential for its pathogenicity. Traditional genetic amplification identified a specific fragment of 540 pb inside genome of B. pseudomallei, flanked by restriction sites BglI, as the effective objective for detection [49]. A QCM-DNA biosensor, using a specific proband to join TTSS1 fragments, demonstrated the capacity to detect bacteria without the use of nucleic acid amplification. The biosensor detection limit was for 0.4 μM of synthetic DNA oligonucleotide. The system could distinguish specific DNA fragments digested with BglI of B. pseudomallei with a signal significatively greater than B. thailandensis. This study provides proof of an effective QCM-DNA biosensor for B. pseudomallei identification without requiring nucleic acid amplification.

3.1.6 Brucella melitensis

In Turkey, a research laboratory for biomaterials and chemical processing designed an QCM aptasensor for the diagnosis and detection of Brucella melitensis in milk and dairy products. Brucella melitensis can be transmitted to humans through the consumption of milk and dairy products or when there is direct contact with sick animals. This bacterium affects mainly sheep and goats, although it is not uncommon for it to be found in cattle, camels and dogs. As a human pathogen, Brucellosis survives in fresh milk for 5 days at 4°C and up to 9 days at -20°C [50]. For this reason, a robust and sensible QCM aptasensor was created, coupled with a magnetic pre concentration system, which turned out to be highly sensitive and fast.

3.1.7 Cryptosporidium

In this study, Cryptosporidium interactions were investigated, a protozoan pathogen transmitted by water, and filter media used on drinking water treatment. To better understand these processes, modified polystyrene microspheres were used to imitate superficial properties of cysts of Cryptosporidium. Molecular level deposition kinetics were studied by QCM-D with dissipation monitoring and at the laboratory level by sand columns. Results show the importance of surface charge and hydrophobicity of Cryptosporidium on its transportation and retention on porous media. Modified microspheres were identified with copolymers as suitable surrogates to evaluate the attenuation of Cryptosporidium in natural and designed aquatic environments. This study contributes to the understanding of how surface characteristics affect Cryptosporidium transport in porous media [51].

3.1.8 Staphylococcus aureus

In 2019, in China, a detailed comparison between two kinds of sensors was performed, specifically Surface Acoustic Wave (SAW) and QCM, with a particular approach in detection of Staphylococcus aureus (S. aureus). Results showed that sensitivities of SAW-Love and SAW-Rayleigh were higher than QCM. Specifically, sensitivities of mass charge of S. aureus were approximately 328.75, 246.88 and 6.25 Hz ng^{-1} for SAW-Love, SAW-Rayleigh and QCM sensors, respectively. The higher operative frequency of SAW sensors allowed for a sensitivity up to 30-50 times higher than QCM.

Additional studies were performed to analyze comparatively the Limit of Detection (LoD) of sensors QCM and SAW-Love with nanoparticles of ZnO. A variation in resonant frequency for S. aureus concentrations of about 2×10^3 to 2×10^9 CFU mL^{-1} was observed. QCM sensors demonstrated a response in a higher concentration range (2×10^8 to 2×10^9 CFU mL^{-1}), while SAW-Love sensors showed responded in a lower concentration range (2×10^3 CFU mL^{-1}). SAW-Love sensors exhibited a significative detection limit of more than 12 kHz to 2×10^3 CFU mL^{-1}, while QCM had a detection limit of only 35 Hz to 2×10^5 CFU mL^{-1}. This means that SAW-Love sensors have a detection limit approximately five orders of magnitude smaller for S. aureus concentrations compared to QCM [52].

3.2 Other QCM sensor use in food industry.

Besides pathogen detection, QCM biosensors are also used in hormonal detection like Oxytocin A. In 2017, at the biotechnology and medical engineering department of Ernst-Abbe university of Germany, the development of an innovator sensor based on a QCM-D dissipation monitoring biosensor and antibodies for fast and sensile detection of Oxytocin A (OTA) in red wine was presented [53]. Oxytocin A is a highly toxic mycotoxin that contaminates different agriculture products, representing a risk to animal and human health. This sensor uses an indirect competitive test with QCM-D, allowing for a simultaneous measurement of frequency and dissipation changes, offering detailed information about mass, conformational changes, and viscoelastic properties of layers in the sensor surface.

For improving sensor sensibility, conjugated secondary antibodies with gold nanoparticles (AuNPs) were applied, reaching a linear detection range of 0.2–40 ng mL–1 with a Limit of Detection (LOD) of 0.16 ng mL–1; within requirements established by Europe Union legislation for OTA in food. It completely eliminated the matrix effect caused by polyphenols in wine and non-specific interactions with sensor surface through an easy pretreatment of wine with polyvinylpyrrolidone (PVP).

Despite the wine component's absorption into the sensor surface, an excellent repeatability detection method was achieved. Compared with other techniques, like High Performance Liquid Chromatography (HPLC) or immunochromatographic tests, QCM-D biosensors offer greater sensitivity, a shorter analysis time and avoid complicated prior cleaning procedures. This method offers a fast, sensitive, and reliable alternative for food and drink micro toxin detection, contributing significantly to food safety and, therefore, to human health.

Oxytocin A, also known as OTA, is carcinogenic and responsible for different diseases. Due to this, an OTA detection method was implemented in Turkey. The proposed method uses a direct immobilization of the OTA on an aminated surface, avoiding use of proteins on the surface. This election resulted in the efficient regeneration of the sensor using a solution of NaOH at 0% and SDS at 1%, which enabled the reusing of the sensor almost 13 times without a significant lack of performance. This capacity of robust regeneration provides a practical cheap solution for continuous monitoring.

QCM was selected for its sensitivity without the need for prior antibody tagging, its low cost and ease of use. OTA direct immobilization on the sensor surface was achieved by activation of carboxyl groups in OTA with EDC/NHC, followed by joining to amino groups generated on the crystal surface. This novel approach contributes to QCM sensor advances for micro toxin detection. This sensor demonstrated an effective detection capacity in a concentration range of 17.2 to 200 ng/mL, covering relevant thresholds for OTA regulation in food and fodder. Election of not using proteins on the surface allowed for a robust regeneration and a successful reusing of the sensor, improving its practical applicability.

In conclusion, this study presents an innovative approach for OTA detection, taking advantage of QCM sensors and highlighting the importance of strategies of direct immobilization without using proteins. The durability of the sensor and its capacity of detecting OTA relevant levels position it as a valuable tool for in-situ monitoring of micro toxins in food and fodder, contributing to food safety and public health [54].

Research was performed in Turkey related to the detection of a selective herbicide belonging to the chemical herbicides group. In this study, a method of specific fast selective and sensitive real time detection of the herbicide 2,4-dichlorophenoxyacetic (2,4-D) was developed by using QCM and surface plasmodial resonance (SPR) covered with polymeric nano film of p (EGDMA-MATrp) molecularly printed. 2,4-D is one of herbicides more widely used and, due to its general use, persistence and high solubility, have contaminated agriculture food products, natural, water and soil resources. The presence of 2,4-D in food and the environment is considered a potential risk to both ecosystems and human health, given that it can cause serious effects like endocrine disruptive activity, cancer, and degenerative changes in the nervous system.

QCM and SPR sensors were used due to their advantages, like high sensitivity, online analysis capacity, fast response times, easy operation, low detection limits and device simplicity. These sensors were modified with p nanofilms (EGDMA-MATrp) molecularly printed, that have the capacity to form specific cavities for 2,4-D. It was demonstrated that MIP-QCM and MIP-SPR sensors were selective and sensitive to 2,4-D concentrations in a range of 0.23–8.0 nM. Reusing of MIP-QCM/SPR sensors was also successfully evaluated by cycles of balanced-adsorption-regeneration.

Additionally, a liquid chromatography method coupled to mass spectrometry in tandem (LC-MS/MS) for quantitative determination of 2,4-D in apple samples was developed and validated. Validation of the method showed accurate and precise results, with low detection limits and good linearity in the studied concentration range.

Actual apple samples were analyzed, and QCM, SPR and LC-MS/MS method results were compared in exact and accurate terms. Three of them provided acceptable results, with recoveries between 87% and 93%. It was concluded that MIP-QCM/SPR sensors are an effective alternative for 2,4-D detection, with advantages like high sensitivity and selectivity, low detection limits and capacity for real-time measurement. These sensors could be useful for 2,4-D detection in natural sources like water, fruits and vegetables, contributing to protection against environmental contamination [55] .

QCM sensors could be used too for volatile elements detection. For example, in China, researchers used 4 QCM sensors for eggs classification according to their freshness, based on the number of storage days. In this study a hermetic device was manufactured where 4 sensors were installed in different materials (carbon nanotubes of multiple walls, graphene, copper oxide and polyaniline) for immersion in a sealed chamber and connected to a frequency controller. The Linear Discriminant Analysis method (LDA) surpasses the Principal Compounds Analysis (PCA) in classification procedure, with a 100% accuracy in original data and a 98.8% in five folds cross validation procedure. The regression model PLSR added to KPCA showed a better predictive performance (R2= 0.9136 in calibration set and R2= 0.9547 in validation set). This was the first study that evaluated egg quality with different storage times using a QCM sensor set. Promising experimental results show the QCM technique provides a nondestructive and sensitive method for evaluating egg quality with different storage times. Future investigations should focus on optimization of deposition method and exploration of high sensitivity materials to achieve better properties of detection of QCM sensor gasses [56].

Another agent present in food is cadmium, one of the most contaminating and damaging most heavy metals for the human body. Cadmium consumption can generate cardiovascular diseases or kidney and liver cancer. Thus, researchers from India in year 2018 developed a piezoelectric QCM sensor for the detection of this metal in a liquid medium, especially in water. This study focused on functionalized carbon nanotubes using (ODANCTSs) to catch cadmium ions in water. Carbon nanotubes create a stable layer with amino groups that improve cadmium capturing. It was possible to detect lower concentrations (5 ppb) of cadmium in water, with a proportional range of 20 to 142 ppb. A device was used that measured piezoelectric response and current-tension curves simultaneously, which revealed the adsorption and desorption process of cadmium ions. It was observed that adsorption is slower than desorption [57]. Future works will focus in detecting cadmium on other compounds and tackling problems of sensor selectivity.

When talking about water quality, its analysis and complete evaluation must integrate its associated physicochemical, biological topics and hydrology. Among challenges that are currently present at the water quality level for human consumption is the deficiency of a sampling system for the early detection of contaminants and lack of modernization in detecting systems [58]. Additionally, at the environmental control level, biosensors are also widely used, for example, by water distribution bodies attempting to guarantee both drinkability and flora and fauna life [27]. To respond to the necessities related to water quality, there are different kinds of instrument and methods that have been developed, and QCM is one of them [59]. For human consumption or use in productive processes, analysis of water quality has become essential for health and economic growth [60].

Aquaculture is an economic sector in growth around the world, and of great importance given that it contributes to the nutrition of a growing world population, establishing itself as a high quality protein source [61]. However, there are challenges that are currently associated with environmental contamination, especially with waters, with frequent pathogen outbreaks being observed and with lack of traceability that guarantee assurance of product quality [62]. In response to the necessities above, biosensors are used with frequency in agricultural industry, so the water where fish are raised, aquatic plants, seafood and others, require monitoring processes, because have developed different types of nanotechnologies focused on evaluation of water quality; This significatively affects productivity and quality of their final products [63]. Among enforcements of water quality in aquaculture is the monitoring of physicochemical characteristics of water in shrimp farms [64].

Some studies have shown effectiveness and efficiency of QCM biosensors in the productive process of black cachama (Colossoma macropomum), where an attempt has been made to decrease the mortality rate of fish within the first ten days of life through a control system based on QCM, following the physicochemical parameters of water contained in pond, achieving a decrease in mortality of 21,7% [65]. In addition, in China, a gas sensor was developed for the evaluation of freshness of grass carp fillets refrigerated for a 4-day period. A hydrophobic nano compound was used Cu(I)-Cys with the QCM sensor. This nano compound was applied in a specific amount of 10 μL on each side of QCM [66].

Sensors demonstrated different desirable properties, among which are included reproducibility, hydrophobicity, reversibility, selectivity, and stability with two specific compounds: hexanal and 1-octen-3-ol. These compounds were selected for their relationship with fish quality and its capacity to indicate deterioration process.

It is important to highlight that the sensor exhibited a featured performance even in high relative humidity conditions (80%). Detection of hexanal and 1-octen-3-ol was validated by correlation of frequency changes of QCM with its compound's composition measured by gas chromatography-mass spectrometry (SPME-GCMS). Congruence between sensor results and the reference technique was high, with a correlation coefficient of 0.96. This approach presents promising practical uses, especially for the evaluation of storage time of grass carp fillets over the first 4 days of refrigeration. The sensor's capacity to operate in high humidity conditions makes it particularly relevant for use in environments of storage and transport of food.

Another use for QCM biosensors is in the detection of pesticides and antibiotics in products like honey, which have proven highly effective [37]. In this study, highly sensitive immunosensors were developed based on high fundamental frequency QCMs (HFF-QCM) for the detection of DDT pesticides and carbaryl on honey. The presence of these pesticides in honey have generated concerns, and traditional techniques, like chromatography, although attaining the required limits of detection needed, are not suitable for in-situ implementation in the honey packing industry due to its high cost and necessity of highly qualified personal for its routine operation. Biosensors offer an easier, lower cost and easy-operation alternative for analytical purposes in food enforcements.

On the development of immunosensors HFF-QCM, specific monoclonals were used as immunoreagents on immunocompetent essays with conjugate coating format. Immunosensors demonstrated a notable sensitivity, reaching detection limits of 0.05 μg L–1 for carbaryl and 0.24 μg L–1 for DDT on standard essays. In practical tests with honey samples, detection limits were 8 μg kg−1 for carbaryl and 24 μg kg−1 for DDT, fulfilling the regulated limits.

Analytic performance of these immunosensors was notable, with accurate recoveries (recovery percentages of 94% to 130%) and a great accuracy (variation coefficients in the range of 9% to 36%). It is suggested that these immunosensors could be promising analytic tools for quality control in the honey packing industry, by simplifying and reducing costs of routine analysis of pesticides in this natural food.

Otherwise, instruments for quality monitoring of water are also used in sodium analysis in commercial mineral waters; so that some studies have proposed developing od sensors specifically for those purposes, using a piezoelectric QCM, showing that covering QCM with 5% of bis [(12-crown-4) methyl] dodecyl methylmalonate, 33% of PVC and 62% de NPOE, produces a decreased frequency of around 18 kHz; this is the optimal range for linear calibration for proper monitoring, presenting a performance similar to other methods like atomical absorption [13].

In some studies, water samples were compared to other fluids, like milk, to follow minimal changes in quartz surface signals in presence of samples contaminated with Afloxine B1-BSA (bovine serum albumin), constituting QCM sensors as being much more sensitive mechanisms in water than in milk, associating this result to the fact that temperature changes affect viscosity of this last liquid [67]. Besides its notable role in the detection of pathogens in liquid food, like water, QCMs have been shown to be equally effective in the early identification of microbial contaminants in milk, providing a crucial versatile tool to guarantee food safety in the dairy production chain.

Continuing with milk, Sandro Spagnolo and co, designed a biosensor to detect proteolytic activity of plasmin, a protease important in biological systems, especially in milk. Using QCM with multi-harmonic dissipation (QCM-D), the β-casein was immobilized on the hydrophobic surface of an AT- cut QCM by 1-dodecanotiol. The biosensor demonstrated the capacity to detect plasmin in a concentration range of 0.1 a 20 nM, with a detection limit of approximately 0.13 ± 0.01 nM [68].

β-casein was used as a substrate for monitoring plasmin activity and fast changes in viscoelastic properties of β-casein layer in sub-nanomolar concentrations of plasmin were observed. Viscoelastic properties of β-casein after the action of plasmin and trypsin were compared, revealing differences in layer architecture. In conclusion, the QCM-D multi-harmonic method allowed for the detection of plasmin in sub-nanomolar concentrations, with the additional capacity of analyzing dynamical changes in viscoelastic properties of the β-casein layer along plasmin action. This approach could be beneficial for studying activity mechanisms of protease in surfaces in different conditions.

Alexandra Poturnayova in Russia developed a biosensor based on a QCM to identify plasmin (PLA) in milk, using β-casein as an immobilized substrate on the piezo crystal surface. Cleavage of β-casein induced by PLA in a concentration range of 0.1 to 40 nM results in a resonant frequency increasing series (fs) and a decreasing of motional resistance (Rm). The biosensor demonstrated its effectiveness in raw milk samples and added milk from different animals (cows, goats, sheep). The response of Biosensor for trypsin and α-cimotrypsin was studied. Sensor technology reached a Limit of Detection (LOD) of 167.16 ± 39.36 pM to pH 7.4. This LOD was confirmed by a test of enzymatic immunoassay (ELISA) performed in parallel with Biosensor measurements. Atomic Force Microscopy (AFM) confirmed the cleavage effect of PLA in surfaces covered by β-casein [69].

Milk proteolysis is an important process in which PLA performs a crucial role. Information about PLA activity is vital for guaranteeing product quality and reducing processing costs. Although there are expensive methods to determine PLA activity, this study presents a novel approach using sensor technology, specifically QCM, that allows for the direct detection of the PLA activity in real milk samples. The effectiveness of biosensors has been demonstrated in different types of milk, and results were compared with those obtained by the standard ELISA technique. This approach can be considered as a practical and efficient alternative for routine tests in dairy laboratories.

Technological of Monterrey engineer and science students, performed a study for residual water pathogen detection using QCM biosensors. Residual Water Based Epidemiology (RWBE) stands out as an essential tool for the early detection of outbreaks, like COVID-19, providing real-time data about public and environmental health. In this context, a lack of centralized laboratories in some municipalities prevented efficient processing of RWBE samples. Here, biosensors emerge as potential and reliable solution for monitoring diseases through RWBE. Their paper examines eighteen recent biosensors, evaluating their technical and economic viability for the detection of residual water pathogen agents. The infectious persistence of an outbreak is underlined as a global responsibility and necessitates actions that allow for early detection. The COVID-19 pandemic serves as an example, highlighting the difficulty of identification of infected individuals, especially those that were asymptomatic [70].

In contexts where infrastructure and sanitary coverings are limited, classical strategies of epidemiology result in inefficiency. RWBE, at evaluating the presence of residual water infectious agents, emerges as a promising tool, but current methods depend on centralized laboratories. The paper focuses on the implementation of biosensors for residual water viral pathogen detection. Different types of biosensor are mentioned, with special emphasis based on paper, considered suitable for regions

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with limited resources. Additionally, economical topics are discussed, pointing out that biosensors must meet criteria like being affordable, sensible, specific, easy-to-use and applicable in place. Five potential biosensors are evaluated in detail, considering manufacture costs and necessary materials. They highlight the importance of designing scalable, sensitivity, and economics to implement RWBE in an effective way, especially in communities of low and medium income.

4. DISCUSION AND CONCLUSIONS

Through thorough review of literature, different significant uses of QCM sensors in pathogen detection were identified. Among the detected microorganisms were Salmonella, E. coli, Cryptosporidium, Staphylococcus aureus, Brucella melitensis, Burkholderia pseudomallei and Listeria inoccua. Additionally, multiple uses beyond pathogen detection were explored, such as toxin and contaminant detection, freshness evaluation and metal detection like cadmium. The review reveals significant advances in pathogen detection by using QCM biosensors. QCM technology demonstrates versatility and is effective in addressing the detection of a wide variety of pathogen microorganisms with promising results.

QCM biosensors utilize quartz crystals, however, according to multiple types of use that could be given, effectiveness and sensitivity may vary with design and the condition of the medium which is tested (solid, liquid, temperature, densities, other). Studies also highlight that humidity could significatively affect the performance of QCM biosensors, because the measurement method (immersion, evaporation, spray, other) also can turn into a variable that, through investigative processes, are being manipulated to establish better practices in the use and effectiveness of quartz crystal in water quality evaluation [71].

Constant updating of review papers in QCM food pathogen detection field is essential. Accelerated evolution of investigation and development in this area demands a continuous synthesis of scientific literature to provide new researchers a complete vision of the state of the art. This review underscores the relevance and urgency of updated review papers, that not just consolidate current reaches, but also identify gaps in knowledge and areas that require further investigation. Although the reviewed studies demonstrate promising results in laboratory environments, it is imperative to carry out additional research with an approach orientated to industrial use. Laboratory tests, although essential when validating viability of QCM biosensors, must be complemented with full-scale studies in the food industry. Future research must address ethical and regulatory considerations associated with QCM biosensor implementation in the food industry. Compliance with standards and regulations will guarantee general acceptance and adoption of this technology.

In summary, the next investigation phase must go beyond laboratory validation, heading towards industrial effective use of QCM biosensors in pathogen detection, contributing to improved food safety in a practical, sustainable way.

In general terms we should say that control and monitoring systems like QCM sensors, have a great quantity of uses in different action fields, not just in food and water quality [72], and how effectiveness is widely linked to desired measurement parameters; in this sense, sensor designs that utilize QCMs could and must vary according to conditions and the medium in which they are going to be used to guarantee their effectiveness [73].

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