Review Article

Prevalence of $bla_{\text{CTX-M}}$, bla_{TEM}, and bla_{SHV} Genes of Extended-Spectrum Beta Lactamase-Producing *Escherichia coli* in Aquaculture in Asia: A Systematic Review

Allysah Rhein C. Tolentino*, Alyanna Renae P. Opeda, Lorraine L. Naniong, Lea Janine I. Paralejas, Faith Marie M. Porciuncula, Irah Mae A. Getuiza, Czarene Bon Harvey G. Evangelista, Charlene Princess S. Tolenada

Department of Medical Technology, Institute of Arts and Sciences, Far Eastern University, Manila, PHILIPPINES.

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ABSTRACT

Extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (ESBL-EC) isolates identified by their virulence factors and pathogenicity constituted a significant threat to public health in aquaculture and other water sources not only in developing countries but in Asian countries. Asia dominates aquaculture globally. Aquaculture products are internationally traded commodities that could be a significant contributor to the emergence of antibiotic-resistant bacteria in the aquatic environment when found to be contaminated. Therefore, the researchers aim to determine the presence of ESBL-EC genes in aquaculture and its potential health risks in human transmissions. Experimental and scientific studies that reported the presence of $bla_{\text{CTX-M}}$, bla_{SHV} and bla_{TEM} genes of ESBL-EC in Asia aquaculture were reviewed from 2016 to 2022. A total of eight (8) studies were included in this review which revealed the presence of ESBL-EC genes in the South (68.0%), West (18.9%), Southeast (12.5%), and East (0.6%) Region of Asia, with the former having the highest proportion. Among the genes detected, $bla_{\text{CTX-M}}$ is the most isolated followed by bla_{SHV} and bla_{TEM} genes. The domination of Asia in aquaculture production globally has shown increased importance in effectively dealing with environmental and anthropogenic issues that allow the interactions among diverse bacteria in the aquatic environment leading to the transmission, acquisition, and rapid spread of ESBL-EC resistance genotypes in the aquaculture.

Keywords: Aquaculture, Asia, *blaCTX-M*, Contamination, ESBL-producing *E. coli.*

Correspondence:
Ms. Allysah Rhein C. Tolentino,
Department of Medical Technology, Institute of Arts and Sciences, Far Eastern University, Manila, PHILIPPINES.

Email: 2019095701@feu.edu.ph

INTRODUCTION

Extended-spectrum β-lactamase (ESBL)- producing *Escherichia coli* (ESBL-EC) isolates identified by their virulence factors and pathogenicity constituted a potential threat to public health in aquaculture and other water sources not only in developing countries, but in Asian countries.[1] Hundreds of types of β-lactamase enzymes have been discovered, and one or more of these enzymes may be encoded by genes in each ESBL bacteria. The antibiotic-resistant gut bacterium *E. coli* is prevalent in humans and animals which can release ESBL-EC genes into water sources.[2] Among the ESBL-EC genes found in aquaculture, the most predominant are $bla_{\text{CTX-M}}$, bla_{SHV}, and bla_{TEM} which the former is considered a new class of ESBL.[3]

Aquaculture, a controlled process of cultivating aquatic organisms for human consumption, is a practice dominated by Asian countries in regions such as East Asia, Southeast Asia, and South Asia, in which China is the largest producer of aquaculture products.[4] And although Asia is the world's greatest aquaculture producer, fish infection susceptibility spreads quickly due to inadequate sanitation and fish contamination from diseased marine species.[5] Thus, aquaculture

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is susceptible to increasing *E. coli* gene production, which causes human diseases as well as marine animal infections or the potential for the fish kill.

As a product for human consumption, strict sanitary conditions must be met, however several research done in Asia have shown high numbers of aquaculture products infected with *E. coli*. Such products become vehicles of disease transmissions and sources of foodborne infections[6] that may cause a severe outbreak of ESBL-EC.[5] Hence, this paper aims to determine the presence of ESBL-EC genes in aquaculture, along with its potential health risks in human transmissions. As such, this review paper will assess the prevalence of ESBL-EC genes in aquaculture to provide an outlook of the practice that can be used in developing strategies to improve the safety and quality of aquaculture products fit for human consumption.

MATERIALS AND METHODS

Search Methods

All research articles regarding the presence of ESBL-producing *E. coli* in aquaculture in Asia were retrieved from American Society for Microbiology, Elsevier, Frontiers in Microbiology, Hindawi, International Journal of Veterinary and Animal Research, Multidisciplinary Digital Publishing Institute, Microbial Drug Resistance, Saudi Journal of Medicine and Medical Sciences, ScienceDirect, and Society for Applied Microbiology. All articles used in writing this review were retrieved from the local and international references that contain the keywords provided. English is the main language used in the review. The search terms used were the following: Molecular identification, ESBL, *E. coli*, *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$, and *bla*$_{\text{TEM}}$, resistance genes, antibiotic-resistant bacteria, antibiotic resistance, gram-negative bacteria, drug resistance, aquaculture, fish bacteria, Asia. Boolean operators "OR" and "AND" were utilized in the search to have more focused results in searches. References were processed using Mendeley Reference Manager.

Selection Criteria

The inclusion criteria included in this review were quantitative, descriptive, cross-sectional, and experimental articles from the year 2016 to 2022 that reported the presence of *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$, and *bla*$_{\text{TEM}}$ genes of ESBL-EC in aquaculture in Asia. Articles that discussed other predominant genes of ESBL-EC isolates not related to aquaculture or fish farming, isolates not screened for the presence of ESBL-EC gene, antibiotic profiling, other pathogenic bacteria, and other resistance genes were excluded from the reference selection. Outdated, duplicate, and inaccessible articles were omitted in the selection.

Data Collection Analysis

All obtainable data from selected quantitative, descriptive, cross-sectional, and experimental journal articles were extracted to investigate the prevalence of *bla*$_{\text{CTX-M}}$, *bla*$_{\text{TEM}}$, and *bla*$_{\text{SHV}}$ genes of ESBL-EC in aquaculture in Asia. The researchers independently screened and assessed the abstract of the searched articles through the use of specific criteria needed for the review. The researchers used the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as the basis of filtration to ensure that the articles used are relevant and valid. The PRISMA diagram (Figure 1) shows the detailing process that prompts the inclusion of studies in the review. The data set of this review, including the title, the DOI or link, the genes present, the year of publication, and the location of the study were gathered into a Microsoft Excel spreadsheet for further analysis.

RESULTS

Several research studies discussed the presence of ESBL-EC and the genes *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$, and *bla*$_{\text{TEM}}$ in aquaculture. However, limited studies are done in Asia. The researchers collected 51 studies, but only 8 articles met the standard for inclusion. Based on the data shown in Figure 2. South Asia has the highest proportion of ESBL-EC present among other Asian regions. A total of 704 were isolated and confirmed to be positive for

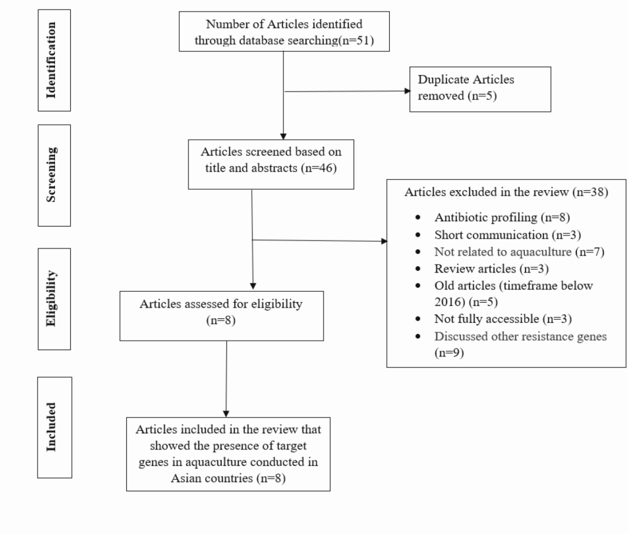

Figure 1: Flowchart of inclusion and exclusion process of articles qualified in the review.

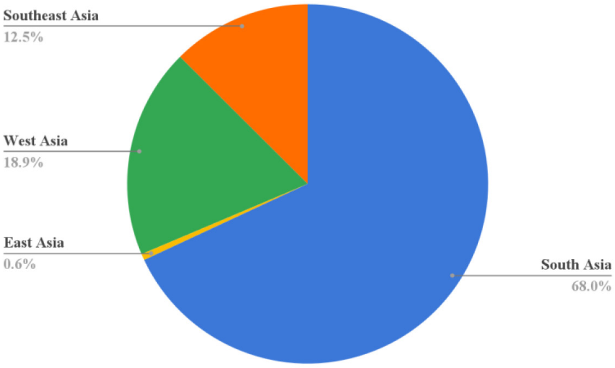

Figure 2: Prevalence of ESBL *E. coli* in aquaculture in Asia.

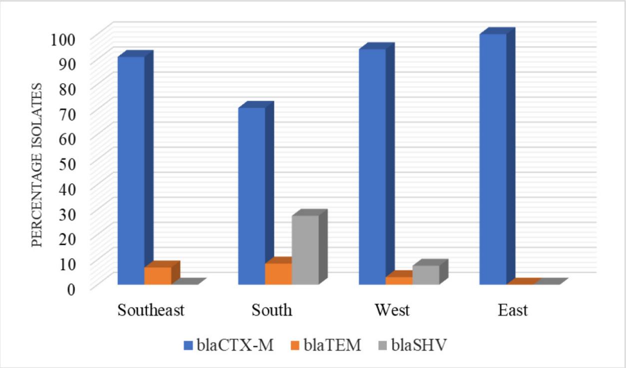

Figure 3: Prevalence of $\mathit{bla}_{\text{CTX-M}}$, $\mathit{bla}_{\text{TEM}}$, and $\mathit{bla}_{\text{SHV}}$ in aquaculture in Asia.

the ESBL-EC gene. Among the isolates, 68.0% were from South Asia, 18.9% from West Asia, 12.5% from Southeast Asia, and 0.6% from East Asia. Unfortunately, due to the lack of studies, data from North, Northeast, Northwest, and Southwest were not provided.

Aquaculture samples from different regions of Asia were utilized to detect the presence of ESBL-EC genes. Among the genes detected, $\mathit{bla}_{\text{CTX-M}}$ is the most isolated. In Southeast Asia, 90.91% of isolates were $\mathit{bla}_{\text{CTX-M}}$, 6.82% were $\mathit{bla}_{\text{TEM,}}$ and no $\mathit{bla}_{\text{SHV}}$ isolate was detected. The majority of these samples came from Vietnam. In South Asia, 70.56% were $\mathit{bla}_{\text{CTX-M}}$, 27.48% were $\mathit{bla}_{\text{SHV}}$, and 8.40% were $\mathit{bla}_{\text{TEM}}$ isolates. The samples tested for the research studies mostly came from India. The gene $\mathit{bla}_{\text{CTX-M}}$ remains the highest portion of isolates with 93.98% in West Asia, particularly in Turkey, whereas $\mathit{bla}_{\text{SHV}}$ has a percentage of 7.52% and 3.01% of the $\mathit{bla}_{\text{TEM}}$ gene. Isolates from East Asia show a 100% positive result of $\mathit{bla}_{\text{CTX-M}}$ and no result of $\mathit{bla}_{\text{TEM}}$ and $\mathit{bla}_{\text{SHV}}$. The samples were taken from freshwater fish in the wet markets of Hong Kong. Figure 3 shows the summary of the presence of the gene in each region of Asia.

DISCUSSION

The presence of $\mathit{bla}_{\text{CTX-M}}$, $\mathit{bla}_{\text{SHV}}$, and $\mathit{bla}_{\text{TEM}}$ among the ESBL-EC isolates found in the aquaculture in Asia serves as a significant indicator of the implementation of sanitation protocols involved in the aquaculture production. The domination of Asia in aquaculture production globally has shown increased importance in effectively dealing with environmental and anthropogenic issues; thus, this systematic review highlights the factors contributing to the emergence of ESBL-EC genes in aquaculture in Asia.

Prevalence of ESBL *E. coli* in aquaculture in Asia

Among the four regions screened in Asia, South Asia, notably the country of India, is found to have the highest prevalence of ESBL-EC in aquaculture settings. According to current reports, India's aquaculture industry is still the world's second-largest,[7] and it was the leading exporter of farmed shrimps in 2018.[8] Furthermore, India ranked as the second country to utilize antimicrobial treatments in aquaculture settings in Asia-Pacific Region.[9] This suggests that the high prevalence of ESBL-EC is predominantly attributed to the usage of antibiotics in aquaculture.

In a study conducted in northwestern and western Mumbai, India, whose seafood samples were collected from retail markets, the unregulated use of antibiotics became the source of the emergence and spread of antibiotic-resistant bacteria.[3,10] In contrast to a study conducted in the state of Kerala's key farming shrimp sector, Kodungallur and Thuravoor, the low prevalence of ESBL-EC are attributed to traditional farming utilizing antibiotic-free commercial feeds in the area.[11] However, the study suggests otherwise, that despite the restrictions in the use of antibiotics, ESBL-EC isolates harboring resistance genes are still evident.[11] Therefore, the source of these bacteria does not solely lie in the unregulated usage of antibiotics but the unregulated release of untreated sewage containing antibiotic residues or diverse types of antimicrobial resistance (AMR) bacteria, which are released from effluents surrounding the area. This is supported by data gathered in Guwahati, Assam's capital city, where fish samples were collected near several institutions such as hospitals, industries, animal husbandry, and poultry farms, all of which contributed to the high presence of ESBL-EC.[12] Moreover, because of a lack of treatment facilities and sufficient sanitation, creeks leading to fishing regions serve as conduits for draining untreated sewage, causing direct contamination[3] and an increase of ESBL-EC isolated in the aquaculture population.

In West Asia, high levels of AMR have been identified in water sources and fish farms that continue to increase throughout the Atatürk Dam on the Euphrates River, Turkey's largest impounded lake, which is contaminated by agricultural, industrial, and domestic effluents[13-14] rapidly. The unconscious usage of antibiotic drugs or vitamins for aquaculture conservation and bacterial disease treatment became the prime reason for the emergence of antibacterial resistance genes among the fish pathogens. Excessive usage of human and animal feces as fertilizers also contributes to the cultivation of resistant microorganisms detected in the fish samples. In another study conducted in the Eastern Province of Saudi Arabia, imported frozen freshwater fish originating from four (4) different countries around Asia, namely India, Myanmar, Thailand, and Vietnam, were collected from various food stores and supermarkets. Among the samples, fish from Thailand (tilapia, catfish and mrigal) have the highest *E. coli* isolates, followed by milkfish from Vietnam and tilapia from India, which have the lowest observed *E. coli* isolates.[15] The observed increase of ESBL-EC prevalence in the retailed imported freshwater fish was due to the high amount of antibiotic usage in the country where the fish products originate.

Southeast Asia has diverse aquaculture; however, destructive overfishing poses a greater risk to long-term development and food safety. The Philippines and Cambodia are two of the most severely impacted countries in terms of destructive overfishing since both employ a destructive fishing technique— poison fishing.[16] The data in Southeast Asia was gathered from Vietnam only (12.5%), which is considered the 4th highest producer of global aquaculture. Vietnam has shown a globally productive national growth throughout the previous years, with the fisheries sector being one of its major contributors. Accordingly, the fish samples were collected from the three provinces in the Mekong Delta-AngGiang, Dong Thap, and Vihn Long.[17] The untreated wastewater from integrated systems, municipal waste, and hospitals may possess high bacterial contamination of resistance genes which possibly contributed to the high proportion of ESBL-EC positive isolates in the region. Thus, Vietnam's seafood industry faces threats from rising commercial pollution, causing environmental and freshwater food safety dangers.[17]

Lastly, there are limited studies conducted in East Asia, hence only 1 data (0.6%) was obtained. It was collected from freshwater fish in 18 wet markets (sampling sites) across Hong Kong's three main regions— Kowloon, Hong Kong Island, and New Territories. However, only a few isolates have been identified. Since East Asian countries are known for having a wet market for cheaper fresh products, ESBL-EC is prevalent in food animals, particularly seafood. Therefore, significant reservoirs of antimicrobial-resistant genes formed, resulting in rapidly increasing AMR in aquaculture.[18]

Prevalence of bla$_{\text{CTX-M}}$, *bla*$_{\text{TEM}}$, and *bla*$_{\text{SHV}}$ genes in ESBL *E. coli* aquaculture in Asia

Generally, ESBLs are plasmid-borne, following plasmid-mediated transfer or bacterial conjugation.[19] This occurs when a donor bacterium expresses its transfer genes located along the plasmid's tra region, which encodes protein factors that assist in the plasmid transfer. The fertility (F) factor mediates the formation of the conjugative pilus (pili) associated with the bacterial T4SS. Protein factors assemble the relaxosome, binding to its OriT to induce a strand-specific cut that will produce the single-stranded Transfer (T)-strand. The T-strand is then converted into double-stranded DNA through RCR. When the relaxosome and the T4CP interact, transfer of the T-strand is initiated by the pilus associated with T4SS. This causes the donor bacterium to extend its pili towards the recipient bacterium, establishing a conjugative bridge that allows for direct genetic material exchange. Upon entry into the recipient cell, the T-strand is coated with SSB to allow the RNA polymerase to synthesize RNA primers. Conversion into a double-stranded DNA plasmid marks the end of plasmid transfer, resulting in the production of a transconjugant cell.[20]

bla$_{\text{CTX-M}}$

Among the given data, *bla*$_{\text{CTX-M}}$ is found to be the gene most widely distributed in South Asia (70.56%),[3,10] West Asia (93. 98%),[13,15] and Southeast Asia (47%),[17] The predominance of *bla*$_{\text{CTX-M}}$ distribution worldwide may be the result of the following: (1) families from TEM and SHV arise from the mutation of β-lactamases whereas, the CTX-M family came from bacteria found in the environment,[21] (2) Horizontal gene transfer (HGT) of *bla*$_{\text{CTX-M}}$ genes on conjugative plasmids in *Enterobacteriaceae* is a mechanism by which this gene is transferred. This occurs within the gut of humans, animals, and the environment–as *Kluyvera* spp. is naturally found in the rhizosphere.[22] (3) *bla*$_{\text{CTX-M}}$ genes are carried by various plasmids, in which the predominant group IncF carries the variants CTX-M-15 and CTX-M-14, the most prevalent among various variants of *bla*$_{\text{CTX-M}}$. The IncF family of plasmids is mostly restricted to *Enterobacteriaceae* and has mechanisms that help stabilize the plasmid which, in turn, results in a stable IncF plasmids carried by *E. coli* in the gastrointestinal tract of humans and animals. (4) Transposons and integrons also took part in the dissemination of *bla*$_{\text{CTX-M}}$ genes. IS*Ecp1*, an insertion element most commonly associated with *bla*$_{\text{CTX-M}}$ genes, is responsible for encoding a transposase, an enzyme that promotes the expression of *bla*$_{\text{CTX-M}}$ genes and mobilizes the same gene onto a plasmid. In addition, the propagation of *bla*$_{\text{CTX-M}}$ genes between bacteria and the environment can be made possible by bacteriophage-mediated transduction.[22] (5) The use of antimicrobials in food animals also provides a means for AMR to spread. *bla*$_{\text{CTX-M}}$ variants can be found in the gut of poultry animals as well as raw meat that humans will consume. Unregulated wet markets and animal handling, just like in China, causes the spread of *bla*$_{\text{CTX-M}}$ between humans and animals. The microbial habitat integrated by the extensive use of antibiotics in producing food for animals in China provides optimum conditions for HGT between animal strains and human strains.[22]

bla$_{\text{SHV}}$

Plasmids belonging to incompatibility groups: A/C, F, HI2, I1, L/M, N, and X3; are the main drivers of SHV type.[23] IncA/C plasmids initiate the dissemination of multidrug resistance in *bla*$_{\text{SHV-12}}$ genes among *E. coli*, *Proteus mirabilis* and *Aeromonas cavia*. These plasmids are bigger compared to other replicon types (130 kB), which impose lower conjugation efficacy due to selective pressure for maintenance and are incompatible hosts for the Enterobacteriaceae family.[24] IncF disseminates *bla*$_{\text{SHV-2}}$ genes among *E. coli*. IncHI2 same as IncI1 disseminates *bla*$_{\text{SHV-12}}$ and *bla*$_{\text{SHV-2a}}$ genes, with the latter capable of disseminating *bla*$_{\text{SHV-2}}$ genes among *E. coli serotypes*. IncL/M as well as IncN disseminates the above-mentioned genes in addition to blaSHV-5 and IncX3 which is capable of disseminating *bla*$_{\text{SHV-12}}$ alone among *E. coli*.[23] One reason why the SHV-type ESBL is not prevalent might be because these plasmids are primary carriers of CTX-M type, secondary carriers only to SHV and TEM type.[25]

bla$_{\text{TEM}}$

Based on the gathered data, *bla*$_{\text{TEM}}$ is found to be the least dominant gene in Asia, present in only 6.85% of the total ESBL-EC isolates. In the family *Enterobacteriaceae*, the expression of the *bla*$_{\text{TEM}}$ gene is linked with four types of promoters (Pa/Pb, P3, P4, and P5), with the P3-type promoter being the most common, while the overexpression of *bla*$_{\text{TEM-1}}$ is associated chiefly with P4 and Pa/Pb promoters. The *bla*$_{\text{TEM-1}}$ gene, which is the most common, is carried by nine IncL/M Plasmids: pKPN-068, pFOX-7a, pENT-d0d, pENT-e56, pNDM-OM, pCTX-M3, pNDM-HK, pEl1573, and pCTX-M360. These IncL/M Plasmids may also be present in the form of integron gene cassettes. This significantly amplifies the “transferability” of resistance genes, which is why the genes can be easily introduced into bacterial chromosomes from IncL/M plasmids through horizontal gene transfer. These plasmids also produce another β-lactamase gene which is also capable of deactivating a vast range of β-lactam antibiotics. The presence of this secondary gene is why the TEM-1 type enzyme has a narrow substrate specificity which may be one of the reasons why the *bla*$_{\text{TEM}}$ gene is not prevalent in the ESBL-EC isolates.[26]

CONCLUSION

Several studies in Asia have shown the prevalence of ESBL producing *E. coli* in aquaculture, mainly in the South, West, East, and Southeastern regions, with the former having the highest proportion among all. The most isolated gene among the ESBL-EC isolates is *bla*$_{\text{CTX-M}}$, followed by *bla*$_{\text{SHV}}$ and *bla*$_{\text{TEM}}$ genes. The latent ability of each gene for transmission of resistance genotypes was considered the leading cause of the rapid spread and acquisition of multiple antibiotic-resistant mechanisms of *E. coli* that results in a wide range of aquaculture contamination. The distribution of the genes in each region reflects the country’s varying regulations for aquaculture production. Excessive usage of antibiotics as growth promoters and for prophylactic measures in aquaculture contributes significantly to the growth of resistant bacteria-harboring resistance genes that are pathogenic to humans. However, the utilization of antibiotic-free commercial feeds suggests otherwise, as ESBL-EC isolates harboring resistance genes still are evident, which leads to the conclusion that the source of these bacteria does not solely lie in the unregulated usage of antibiotics but the unregulated release of untreated sewage. Therefore, the lack of proportion between abundance and inadequacy in the regulations of antimicrobials used and implementation of sanitary protocols in each country’s aquaculture made the potentiality for health risks much harder to break. The prevalence of ESBL-EC genes in aquaculture in Asia jeopardizes the international trade in aquaculture products and public health globally. Being an internationally traded commodity, fishes and the likes increase the probability of the emergence and spread of antibiotic-resistant bacteria in the aquatic environment and the probability of human transmission.

RECOMMENDATIONS

To monitor the status of aquaculture production globally, the researchers would like to recommend that future researchers conduct more studies about the prevalence of ESBL-EC genes and other resistance genes in the aquatic environment, especially in countries where aquaculture production is prevalent.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AMR: Antimicrobial Resistance; **ESBL-EC:** Extended-spectrum beta-lactamase-producing *Escherichia coli*; **IncA/C:** Incompatibility group A and C; **IncL/M:** Incompatibility group L and M; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **T4CP:** Type IV Coupling Protein; **T4SS:** type IV secretion system; **SSB:** Single-Stranded Binding Protein; **OriT:** Origin of Transfer; **RCR:** Rolling Circle Replication.

SUMMARY

Asian countries, known to be the largest aquaculture producers, are susceptible to pathogenic ESBL-producing *E. coli* due to poor sanitation and lack of protocols. Consumption of infected products causes higher morbidity and mortality that threatens public health. Research articles used for this review were retrieved from local and international references and filtered through a selection criterion to ensure validity. Results show that among the four Asian regions included, South Asia has the highest prevalence of ESBL-EC, followed by West Asia, Southeast Asia, and East Asia. This is attributed to the unregulated use of antibiotics, which facilitate the spread of Antimicrobial Resistance among aquaculture products. Within the ESBL family, the most common types detected are *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$, and *bla*$_{\text{TEM}}$, which are generally propagated through plasmid transfer. *bla*$_{\text{CTX-M}}$ was found to be the predominant gene due to several plasmids that primarily carry this gene.

Authors' Contributions

Each author has contributed to the completion of this review paper. Authors A, C, and E contributed to the paper's introduction, while Authors D and G managed the methodology and results. Each author has made a substantial contribution to literature searches, initial and final article screening, and the construction of discussion. Authors A, B, and F took part in thoroughly reviewing and calculating percentage isolates. The abstract and conclusion were constructed by Author A, while Authors C, D, and E accomplished the summary. Authors B, F, and G managed the citation and referencing of the paper. Lastly, Author H supervised and guided the authors in writing the review paper.

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