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Original Research

Literature review on the genetic variability of Escherichia coli in clinical isolates: relationship with antibiotic resistance and virulence factors

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Abstract

Escherichia coli is a natural flora found in the intestine, but Escherichia coli is also a major repository of resistance genes that may be responsible for treatment failure in humans and animals. This study aims to understand and evaluate the genetic variability of Escherichia coli in clinical isolates and to determine the correlation between genetic variability and antibiotic resistance. This study uses a literature review method. This study presents the results of a search for studies related to the topic, namely the genetic variability of Escherichia coli in clinical isolates and the relationship with antibiotic resistance and virulence factors. The criteria for articles used as data are articles published in the last 10 years, namely from 2015 to 2025. Based on the research that has been done, it can be concluded that genetic variability in Escherichia coli in clinical isolates plays an important role in adaptation, pathogenicity, and antibiotic resistance. Mechanisms such as horizontal gene transfer (HGT), mutations, and genome rearrangements allow E. coli to acquire virulence genes and antibiotic resistance genes, such as genes encoding extended-spectrum β-lactamases (ESBLs) including TEM, SHV, and CTX-M. These genes are often located on mobile plasmids, which support the spread of resistance between bacterial strains and species, complicating infection control and clinical treatment.

Introduction

The genus *Escherichia* is named after the German pediatrician Theodor Escherich and comprises Gram-negative, facultative anaerobic bacilli belonging to the family *Enterobacteriaceae*. The type species, *Escherichia coli* (*E. coli*), is a widely distributed facultative anaerobic bacterium that colonizes the large intestines of humans and warm-blooded animals (Gomes et al., 2016). *E. coli* is a natural commensal flora commonly found in the intestines; however, it also serves as a major reservoir of resistance genes that may contribute to therapeutic failure in both humans and animals. "*Colibacillosis*" is a general term referring to diseases caused by *E. coli*, which typically inhabit the lower intestines of most warm-blooded mammals (Poirel et al., 2018). Although *E. coli* is a dominant facultative flora within the gastrointestinal tract of humans and animals, certain strains have evolved the capability to cause diseases affecting the gastrointestinal system, urinary tract, and central nervous system (Pormohammad et al., 2019).

Antimicrobial resistance is a serious public health concern worldwide. The improper use of antibiotics by humans, industrial practices, and livestock farming, coupled with poor hygiene and

sanitation, as well as inefficient infection prevention and control measures in healthcare settings, are considered significant factors contributing to the emergence and dissemination of antibiotic-resistant bacteria (Pormohammad et al., 2019). Antibiotic resistance in *E. coli* is driven by natural mechanisms whereby bacteria that survive antibiotic exposure proliferate and subsequently inherit and transmit antibiotic-resistant traits (Urban-Chmiel et al., 2022). Antibiotic resistance is acquired through the transfer of resistance genes between bacteria via horizontal mechanisms, including conjugation, transduction, and transformation (Lerminiaux & Cameron, 2019). Gene transfer enables *E. coli* to acquire resistance traits from other bacteria, thereby exacerbating the spread of resistance within bacterial populations (Tao et al. 2022).

Escherichia coli harbors and causes disease by exploiting virulence factors (Kathayat et al., 2021). E. coli possesses adhesins in the form of pili or fimbriae. Adhesins are biopolymers located on the bacterial surface, which enable *E. coli* to recognize, bind, and mediate the attachment of cells and host cells (Epler Barbercheck et al., 2018) and E. coli is capable of evading elimination from bodily fluid flow, such as urine or mucus (Baby et al., 2016).

Escherichia coli exhibits strain diversity and is capable of producing various toxins. The strains of *Escherichia coli* that cause diarrhea in humans include *Enterotoxigenic E. coli* (ETEC), *Enteroaggregative E. coli* (EAEC), *Enteropathogenic E. coli* (EPEC), *Enteroinvasive E. coli* (EIEC), *Diffusely Adherent E. coli* (DAEC), and *Verotoxigenic E. coli* (VTEC). One of the VTEC strains associated with diarrhea, bloody diarrhea, hemorrhagic colitis, and hemolytic uremic syndrome (HUS) is Shiga toxin-producing *Escherichia coli* (STEC) O157:H7 (Lupindu, 2018). Shiga toxin was first identified from the bacterium *Shigella dysenteriae*. Shiga toxin classified into two types, Stx1 and Stx2. Stx1 regulates toxin activity, while Stx2 is involved in mediating toxin binding to the host cell surface and facilitating its entry into the host (Bryan et al., 2015).

Based on the aforementioned background, this study aims to understand and evaluate the genetic variability of *Escherichia coli* in clinical isolates and to determine the correlation between genetic variability and antibiotic resistance.

Method

This study employs a literature review and the PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). It presents a comprehensive search of studies related to the topic, specifically the genetic variability of Escherichia coli in clinical isolates and the correlation between genetic variability and antibiotic resistance.

The criteria for articles included as data are publications from the last 10 years, ranging from 2015 to 2025, accessed through Google Scholar, PubMed, and ScienceDirect.

Subsequently, the author conducted data screening and elimination by thoroughly reading the entirety of each article, resulting in the selection of 18 articles that meet the research topic and specified criteria. The selected articles were then collected and analyzed, including aspects such as author and publication year, research title, research methods, educational level, measured dependent variables, and research findings.

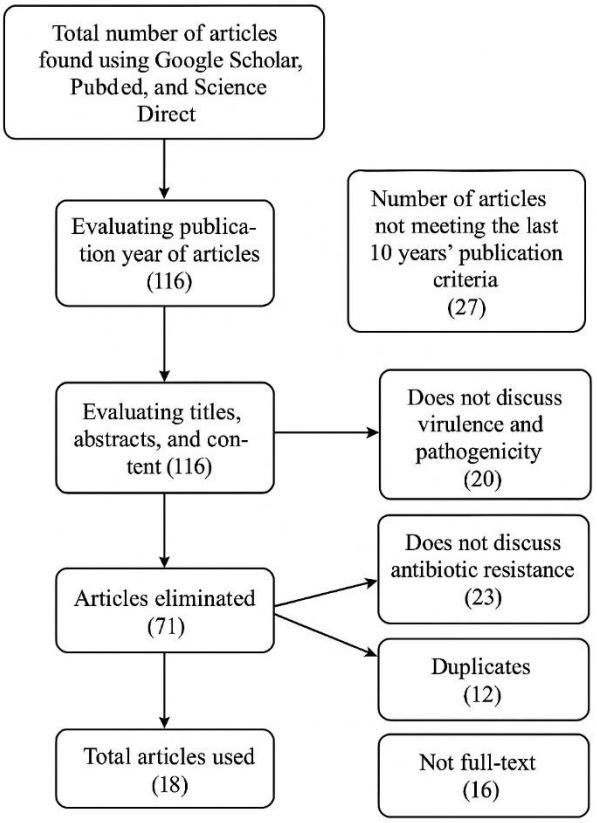

Figure 1. Literature Selection Flowchart Using PRISMA Diagram.

Results and Discussion

3.1. Genetic Variability of Escherichia coli in Clinical Isolates

The genetic diversity of Escherichia coli found in clinical isolates reflects the bacterium's ability to adapt and survive in various environments, such as the human host body (Siniagina et al., 2021). Evolution encoded by horizontally transferred genetics (HGT) has been acquired by several species. E. coli strains have obtained virulence potential factors by acquiring specific loci through HGT, transposons, or phages. Nonpathogenic E. coli can acquire virulence determinants through the horizontal transfer of virulence genes. The genetic exchange occurring in these bacteria contributes to genetic diversity (Javadi et al., 2017).

Genome evolution is a process in which the content and organization of a species' genetic information change over time. This process encompasses various forms of alterations, including point mutations and gene conversion, rearrangements (inversions or translocations), and the deletion and insertion of foreign DNA (integration and transposition of plasmids). These mechanisms appear to be the primary factors driving the genetic adaptation of bacterial organisms to new environments, bacterial populations, and the formation of separate and evolutionarily distinct species. Mechanisms of horizontal gene flux include the transmission of mobile genetic elements such as conjugative plasmids, bacteriophages, transposons, insertion elements, genomic islands, and mechanisms of recombination of foreign DNA into host DNA. Point mutations and genetic rearrangements primarily contribute to evolutionary progression without the creation of new genetic determinants, whereas horizontal gene transfer (HGT) results in highly dynamic genomes. Therefore, HGT can effectively alter the lifestyle of bacterial species. This is particularly true for bacterial pathogens, where virulence is associated with the acquisition of virulence determinants through HGT (Javadi et al., 2017).

3.2. Correlation Between Genetic Variability and Antibiotic Resistance

Extended-spectrum β-lactamases (ESBLs) are β-lactamase enzymes produced by Gram-negative bacteria that hydrolyze or degrade aztreonam, penicillins, and first, second, and third-generation cephalosporins, such as ceftriaxone, cefotaxime, and ceftazidime. This degradation renders these antibiotics less effective in the treatment of bacterial-related diseases, leading to resistance (Ugbo et al., 2020). Extended-spectrum β-lactamases (ESBLs) are enzymes that confer resistance to most β-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam. Escherichia coli is a multidrug-resistant (MDR) bacterium and an ESBL producer, capable of causing life-threatening infections (Pormohammad et al., 2019).

Patients infected by organisms producing extended-spectrum β-lactamases (ESBLs) generally exhibit worse outcomes compared to those infected with non-ESBL-producing organisms. The genes encoding ESBLs are typically located on highly mobile plasmids, which can also harbor resistance genes against several unrelated classes of antimicrobials, such as plasmid-mediated quinolone resistance (PMQR) genes and aminoglycoside resistance genes (Ugbo et al., 2020).

The distribution shift of various plasmid-mediated TEM and SHV genes among ESBLs has occurred in Africa and Europe, with a dramatic increase in CTX-M ESBL genes over TEM and SHV variants. Non-TEM and non-SHV genes, such as PER and OXA types, have also been identified in several countries. The shift in the distribution of plasmid-mediated TEM and SHV genes among different ESBLs has been observed in Africa and Europe, with a significant rise in CTX-M ESBL genes surpassing TEM and SHV variants. Non-TEM and non-SHV genes, such as PER and OXA types, have also been detected in several countries. Plasmid-mediated ESBL genes, including TEM, SHV, and CTX-M, are most commonly found in Klebsiella species, followed by E. coli. These ESBL genes produce enzymes capable of hydrolyzing broad-spectrum cephalosporins and monobactams but remain inactive against cephamycins and imipenem. The CTX-M genes, particularly CTX-M-15, have been implicated in various epidemiological scenarios and have spread across continents due to epidemic plasmids and/or specific epidemic strains (Ugbo et al., 2020).

Class A β-lactamases are the most common group, comprising a large family that includes TEM, SHV, and CTX-M β-lactamases. The detection and identification of ESBL genes can be performed using molecular techniques to facilitate the identification of β-lactamase genes in bacterial isolates (Ugbo et al., 2020).

3.3. Molecular Techniques for Genetic Variability Analysis and Virulence Factors

Whole Genome Sequencing (WGS) is a high-resolution sequencing technique utilized to comprehensively analyze an organism's genome, thereby enabling the examination of genetic variability and the detection of antibiotic resistance genes. The WGS method can be effectively applied within phylogenetic approaches to provide specific insights. In Escherichia coli, the dominance of phylogroup B1 is frequently encountered. Extra-intestinal infections in humans, including sepsis caused by E. coli B1 such as ST58, are notably prevalent. Escherichia coli serves as a valuable indicator organism for monitoring antimicrobial resistance (AMR) contamination and carriage within food products. Agricultural commodities can acquire drug-resistant E. coli through exposure to manure, contaminated irrigation water, and wildlife, particularly birds (Reid et al., 2020).

WGS has been employed to characterize 120 tetracycline-resistant (TET-resistant) E. coli strains isolated from ready-to-eat cilantro leaves, arugula, and mixed salads purchased from two cities in Germany. E. coli was detected both on the day of purchase and after seven days of refrigeration. Cilantro leaves were found to be more frequently contaminated with TET-resistant E. coli, resulting in 102 (85%) sequenced strains. Phylogroup B1 dominated the collection (n = 84, 70%) with multilocus sequence types B1-ST6186 (n = 37, 31%), C-ST165 (n = 17, 14%), B1-ST58 (n = 14, 12%), B1-ST641 (n = 8, 7%), and C-ST88 (n = 5, 4%) frequently identified using WGS techniques (Reid et al., 2020).

The Whole Genome Sequencing (WGS) of these hyper-resistant strains enables the identification of single nucleotide polymorphisms (SNPs) and deletions compared to the wild-type (WT) strain. To analyze the contribution of these mutations to the enhanced antimicrobial resistance detected in hyper-resistant strains, derivative strains were created through allele reversal. Food preservation using essential oils (EOs)

is being extensively studied due to the antimicrobial properties of their individual constituents (ICs). Three resistant mutants (designated CAR, CIT, and LIM) of Escherichia coli MG1655 were selected by subculturing with the ICs carvacrol, citral, and (+)-limonene oxide. These derivative strains exhibited increased minimum inhibitory concentration (MIC) values for ICs and simultaneously enhanced resistance against various antibiotics, including ampicillin, trimethoprim, chloramphenicol, tetracycline, kanamycin, novobiocin, norfloxacin, cephalexin, and nalidixic acid, compared to the parental strain (wild-type [WT]) (Chueca et al., 2018).

The role of the SoxR D137Y missense mutation in CAR was confirmed by growth in the presence of several ICs and antibiotics, as well as by its tolerance to ICs but not to lethal heat treatment. In CIT, the increased resistance was attributed to contributions from multiple detected SNPs, resulting in a frameshift in MarR and a GyrB ΔG157 in-frame mutation. Both the frameshift-inducing insertion in AcrR and the large chromosomal deletion identified in LIM were correlated with the hyper-resistant phenotype of this strain. The characteristics of the obtained mutants suggest an intriguing relationship with cellular defense mechanisms previously implicated in antibiotic resistance (Chueca et al., 2018).

Multilocus Sequence Typing (MLST) is a genotypic method used to analyze bacterial genetic variation through sequencing of multiple housekeeping genes. Identifying bacteria at the strain level is crucial in epidemiological studies, as well as in the diagnosis and treatment of bacterial infections. This method is particularly valuable for characterizing bacteria with high genetic variability, such as Escherichia coli and other members of the Enterobacteriaceae family, which can exhibit significant differences in virulence potential. Based on the site of infection, pathogenic E. coli can be classified into two major groups. Intestinal pathogenic E. coli (IPEC), which causes infections in the gastrointestinal tract, and extraintestinal pathogenic E. coli (ExPEC), which causes infections outside the gastrointestinal tract (Abramo et al., 2015).

In the development of the MLST method, the design of universal primer pairs and the selection of optimal restriction enzymes, such as RsaI, are based on in silico comparative analysis of gene sequences encoding 53 E. coli H antigen (flagellin) serotypes. Target genome fragments for MLST are selected through bioinformatics analysis of the complete sequences of 16 E. coli genomes. Initially, seven molecular targets were proposed in this method; however, only five of them were proven effective in genotyping E. coli strains (Kotłowski et al., 2020).

The research findings demonstrate that the MLST method exhibits a high discriminatory power in differentiating E. coli strains. Within a group of 71 tested strains, the fliC RFLP-PCR method identified 29 clusters, while the MLST method revealed 47 distinct clusters. In comparison, the reference BOX-PCR method identified 31 different genotypes. In silico analysis indicated that the discriminatory power of the MLST method developed in this study is comparable to the Pasteur and Achtman schemes and higher than the Clermont method. From an epidemiological perspective, the findings indicate that most patients were infected by unique strains likely originating from environmental sources. However, several strains isolated from patients in various wards, such as pediatrics, internal medicine, and neurology, exhibited the same genotype based on the results of all three methods. This suggests the possibility of bacterial strain transmission between patients within the hospital environment (Kotłowski et al., 2020).

Conclusion

Based on the literature review conducted, it can be concluded that genetic variability in Escherichia coli clinical isolates plays a significant role in adaptation, pathogenicity, and antibiotic resistance. Mechanisms such as horizontal gene transfer (HGT), mutation, and genomic rearrangement enable E. coli to acquire virulence genes and antibiotic resistance genes, such as those encoding extended-spectrum β-lactamases (ESBLs) including TEM, SHV, and CTX-M. These genes are often located on mobile plasmids, which facilitate the dissemination of resistance among bacterial strains and species, thereby complicating infection control and clinical treatment.

Future research can focus on further exploration of horizontal gene transfer mechanisms in vivo. Additionally, developing CRISPR-Cas-based methods to inhibit the expression of antibiotic resistance genes or virulence genes in E. coli could be an innovative approach to controlling Escherichia coli pathogens in the future.

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