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*Article*

# Potential of Colicin as an Antibacterial Agent in *Escherichia coli*

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**Abstract.** The development of antibiotics calls for the critical consideration of instances of resistance. Infectious disorders brought on by resistant bacterial infections could affect the entire world. It is believed that the protein that the bacteria generate may one day replace antibiotics as an alternative antibacterial agent. Both Gram-positive and Gram-negative bacteria have the ability to manufacture bacteriocin. The bacteriocin type produced by *Escherichia coli*, notably colicin, has been demonstrated to inhibit the same bacteria through various essential methods. Colicin, a substance made by an *E. coli* cell, is also capable of protecting itself from attack; however, this defense mechanism has not yet been identified. The traits of colicin and the method by which it functions as a different antimicrobial agent to inhibit other bacteria will be covered in this article. We analyze the potential of colicin as an antibacterial agent in *E. coli* using PRISMA methods from diverse academic sources. Here, we found that the structure of the colicin, namely its central receptor domain, aids in the recognition of target cells. Promising results were found in recent studies on the antibacterial effects of the *E. coli* and colicin combination.



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## 1. Introduction

*Escherichia coli* (*E. coli*) is easy to detect, Gram-negative bacteria, and susceptible to genetic modification. Based on the diversity of genomes, which range from commensal bacteria to pathogenic bacteria that cause diseases, it is possible to observe the diversity of *E. coli* bacteria. Symbiotic or non-pathogenic bacteria are found in the normal flora of the organism's gastrointestinal tract. Pathogenic variations are also classified as extraintestinal and diarrheal pathogens. These variations come in

facultative and obligate pathogen varieties [1-2]. Outside of its normal environment, this facultative bacteria can operate as an opportunistic pathogen and cause numerous extra-intestinal diseases [2-3].

Multidrug-resistant microorganisms are challenging to cure and provide a significant risk to civilization. It is essential to discover new antimicrobial medications to combat the growth of resistant microbes and the limitations of the present antibiotic development techniques. Due to its high cytotoxic action against clinically significant bacteria, minimal oral toxicity to hosts, and ability to be both broad- and narrow-spectrum, a subset of antimicrobial peptides/proteins known as bacteriocins is regarded as a viable antibiotic alternative [2][4-5]. Direct contact, targeting of nearby cells, or environmental secretion, such as that of bacteriocin, can all result in the production of cytotoxic proteins [6].

Bacteriocins are compounds synthesized by bacteria from ribosomes. This compound exhibits antimicrobial activity against other bacterial species. *E. coli* and other Gram-negative bacteria in the Enterobacteriaceae family that are linked to them produce the high molecular weight (>20 kDa) protein colicin in reaction to stress. Four different mechanisms of colicin lethality have been identified to date: cytoplasmic membrane depolarization (porogen colicin), nonspecific DNase activity, targeted RNase activity, and suppression of colicin biosynthesis [7-9].

Colicin is created by strains of *E. coli* in a complex with high affinity for immune proteins, which prevents colicin from having any harmful effects on the bacteria that make it. Colicin can be classified according to its mechanism of entry into target cells and its cytotoxic mechanism, namely pore conformation, DNase (colicin E2, E8, E9, E7), RNase (E3, E6, E4) and tRNase [10-12]. Colicin enters cells by binding to a number of proteins found in the OM of *E. coli*, including OM receptors and periplasmic proteins. Both the active transport of complex substances into the cell and the passive entry of small molecules are usually carried out via the nutrition receptors on the outer membrane [13-14]. Colicin can be used as an alternative antimicrobial agent that can prevent the growth of *E. coli* bacteria [12][14]. In this article, we will discuss the characteristics and mechanisms of the antibacterial agent produced by colicin.

## 2. Experimental Section

Between April and August 2021, the authors of this literature review searched any databases that contained scientific articles or research findings, including PubMed, Science Direct, and Google Scholar. Only studies that met the aforementioned search criteria were included in systematic reviews. The search terms utilized in this case included (1) *Escherichia coli* (*E. coli*), (2) bacteriocin, (3) colicin, (4) colicin mechanism, or (5) colicin as an antibacterial agent. A duplicate article was the exclusion criteria, but there were no limits for the year of publication or study. We made an effort to analyze recent studies to learn more about the most recent findings on colicin in *E. coli*, particularly as an antibacterial agent.

These keywords were searched across all databases and returned 103 articles in total. We also eliminated 15 duplicate articles. From the abstract through the full-text publications, there were articles with the potential to be screened. Out of the 88 prospective articles, forty were disqualified because they failed to satisfy the requirements for inclusion. As a result, 48 articles met the requirements for inclusion and were ready for review. Figure 1 shows the workflow for selecting articles.

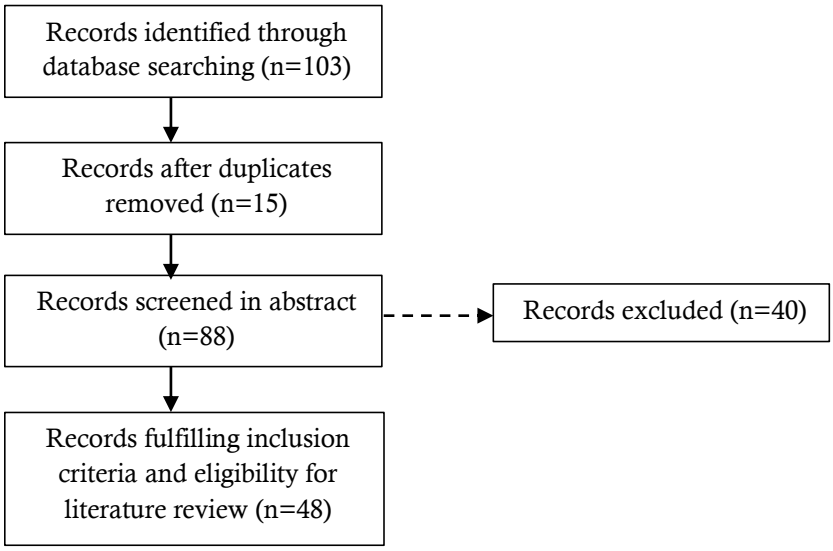


**Figure 1.** PRISMA workflow

## 3. Results and Discussions

### 3.1 *Escherichia coli*

*Escherichia coli* is a rod-shape Gram-negative bacteria of the family Enterobacteriaceae, 1-3 x 0.4-0.7 x 0.6-0.7 µm in size, no spores, some motile (peritric flagella) or is non-motile and facultative anaerobes. Other biochemical features include indole production, no citrate fermentation, methyl red positive and negative urease test, and Voges-Prokauer reaction [15-17].

Gram-negative enterobacteria possess complex surface antigens that play an important role in pathogenicity and also underlie the immune response. These antigens are based on a serum sample, namely the H (flagella), K (cystic), and O (somatic or cell wall) antigens. Not all species carry H and K antigens, except the O antigen, a lipopolysaccharide associated with endotoxin shock. Most Gram-negative species in the gut exhibit subspecies or serotypes caused by minor changes in the chemical structure of the H, K, and O antigens [17-20].

*Escherichia coli* is a normal flora of the gastrointestinal tract. A healthy person has more than one billion *E. coli* cells in the digestive tract. Despite the fact that the majority of *E. coli* strains are benign, some among them are virulent and can cause fatal conditions like sepsis, meningitis, and bloody diarrhea [20-22]. *E. coli* is divided into pathogenic types according to the type of pathogenicity and the clinical signs it causes [22-23].

Macromolecule transport is impeded by the OM of *E. coli*. Colicin and phages have developed to parasitize a variety of OM receptors that are essential for the cellular uptake of food components such as metals, carbohydrates, vitamins, and nucleosides. A plasmid created by *E. coli* contains the antibacterial toxin colicin, which is intended to attack other *E. coli* cells [24-26]. Bacteriocins are substances that bacteria produce and have antibacterial properties. Several bacteriocins generated by Gram-negative bacteria, also known as colicins and microcins, have demonstrated bioactivity against cancer cells in both in vitro and in vivo cases. In cancer cells, bacteriocins had a significantly different inhibitory effect than on normal cells. Bacteriocins may therefore be suitable for particular anticancer weapons [7][27].

### 3.2 Colicin

Bacteria have mechanisms to deal with environmental challenges and against competitors for resources. The synthesis of bacteriocins, which are antimicrobial substances, is one process that reacts to the environment and works to prevent the growth and survival of adversaries. Bacteriocin is a host-

specific toxin and is often lethal to strains due to its power to compete for the same resources [7][28]. Colicin is a kind of bacteriocin produced by Enterobacteriaceae. Similar genes and colicine itself were found in gene clusters on plasmids that make colicin. Colicin-producing genes, which create toxins, immunological genes, which create defense-improving proteins that bind to and neutralize toxin proteins, and lysis genes, which create proteins that facilitate the release of colicin, are all members of this class of genes [7][27].

By creating holes in the IM and stopping the manufacture of cell walls and the breakdown of nucleic acids, the bacteriocin colicin, which is generated by *E. coli*, can kill some strains of *E. coli*. Depending on how cytotoxic they are to the host cell, some colicins must pass the inner membrane (IM) of the target cell. The target cell's OM must be attached to and crossed by all colicines. The mode of bactericidal action commonly used to classify colicins is based on the mode of pore formation, nuclease type, and anti-murein synthesis [14].

Colicin was initially identified by Gratia in 1925, who demonstrated that an *E. coli* strain with the letter "V" for virulence emitted compounds detected in its filtrate that were poisonous to strains that were susceptible to them. have the flu. Moreover, Gratia showed how susceptible strains can produce colicin-resistant mutations. The loss of particular surface receptors for this particular colicin, according to Fredericq, is a contributing factor in colicin resistance [29][22]. Colicin enters cells by parasitizing receptors on the OM that are biologically made to bind and import substances. Colicins come in a variety of forms, and each one enters host cells by parasitizing receptors. It is also feasible to classify colicin based on the translocation mechanism that allows it to enter bacterial cells. Tol-dependent bacterial translocation is mediated by the colicin group A (TolA, TolR, TolB, TolQ, and Pal proteins). Colicin group B employs a Ton-dependent system, including ExbB-ExbD and TonB, to fight the T1 phage [30-31].

The migration of colicin across the cell membrane consists of four steps, namely (i) bonding to the OM of *E. coli*, (ii) formation of outer membrane translation by producing transmembrane proteins colicin including the cytotoxicity C-terminal domain, (iii) periplasmic transport and attachment to or insertion into the IM, (iv) enzymatic breakdown of colicins translocated in the cytoplasm including chromosomal DNA hydrolysis and concurrent suppression of DNA synthesis (colicin E2, E9, and E7), and inhibition of protein synthesis by RNase degradation or tRNA (colicin D or E5) [29][32].

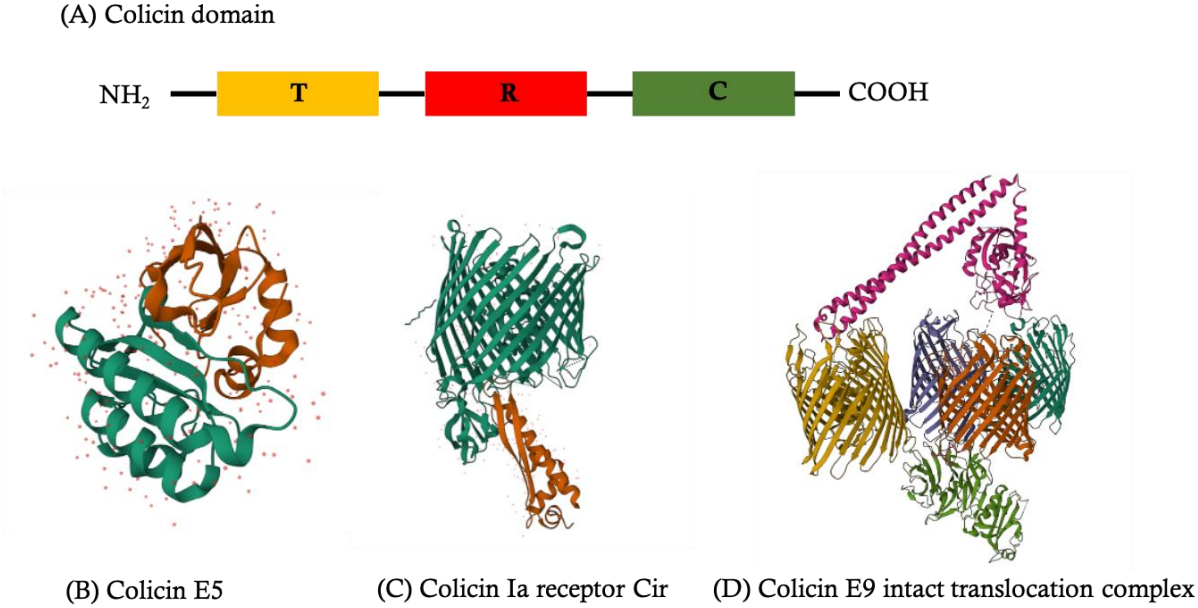


**Figure 2.** Crystal structure and domain of colicin variant (PDB: www.rcsb.org)

Cells are destroyed by the multidomain toxin known as Enterobacteriaceae protein bacteriocin's cytotoxic C-terminal domain, which is encoded on chromosomes or plasmids and is regulated by the toxin's N-terminal section. By depolarizing the cytoplasmic membrane, or cleaving the precursor of the lipid II peptidoglycan in the periplasm, or by cleaving certain tRNAs, rRNAs, or chromosomal DNA in the cytoplasm, cytotoxic activity is exhibited. One of the two routes engaged in the two proton-motive force-linked (PMF) in the IM catalyzes the pathway of the outer membrane. Although Tol-dependent bacteriocins (group A) bind one or more Tol-Pal system components, Ton-dependent bacteriocins bind TonB through the TonB-dependent transporter (TBDT) in the OM [31][33].

### 3.3 Mechanism of Colicin

Colicin makes use of proteins in the inner and periplasmic membranes as well as nutrient transporters that are found in the outer membrane. The three functional domains of colicin are the cytotoxic (C-domain), the core receptor (R-domain), and the translocation (T-domain) [31][32]. The core receptor domain aids in the acknowledgment of target cells by colicins. The translocation domain at the N-terminus allows colicins to pass through the OM into or through the cytoplasm by attaching to cell surface receptor proteins with high affinity, whereas the cytotoxic domain interferes with the target ingredients via the formation or degradation of pores. enzymes. Energy is needed for the release of receptors from the OM and the passage of colicin polypeptides through transducers across the OM for colicin to enter the cell [34-35].

Colicin tightly attach to the major receptor via the R-domain. The T-domain of colicin is capable of interacting with Tol or Ton signaling. Immune proteins are released as a result of this contact. It has been demonstrated that the release of immunogenic proteins partially opens the ColE3 C-domain, enabling it to communicate with OmpF35. The colicin C-domain is then dissociated from the remaining colicin by a protease at the point where the C domain and the R22-domain converge [30][35].

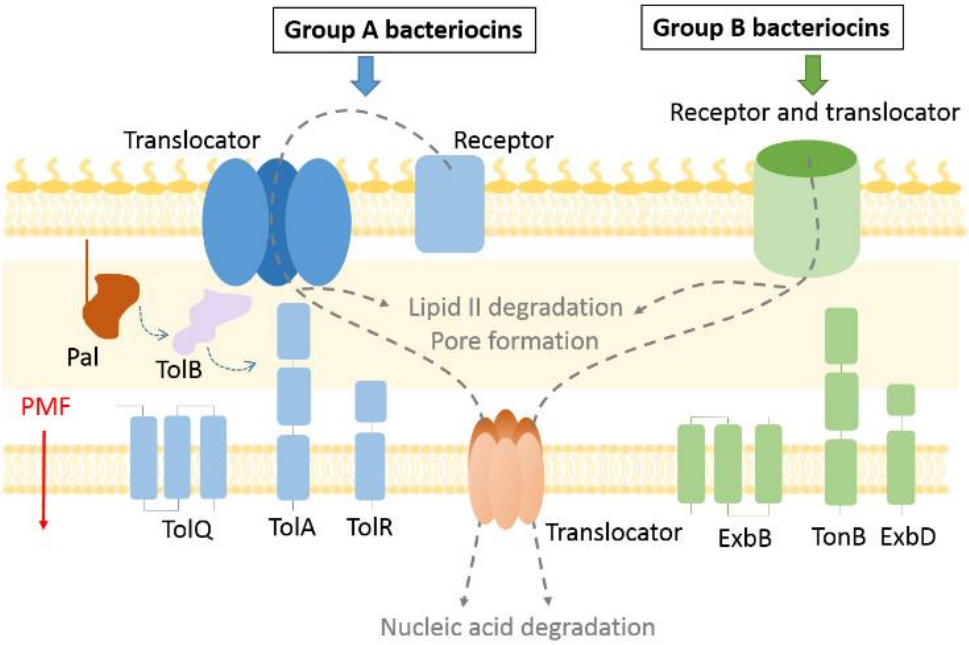


**Figure 3.** Mechanism of colicin group A and B [43]

The development of pores of soluble toxins transported to the plasma membrane's interface by attaching to sugars, lipid, or receptor components is the general method by which membrane pores are formed. Two different paths are used to create the membrane's final pore after the PFT is

concentrated on the membrane's surface. PFT oligomerizes and inserts into the plasma membrane synergistically by sequential oligomerization mechanisms, forming partial or total holes, and both are active. In the α-PFT and β-PFT pathways, transmembrane holes are formed that exhibit different characteristics and trigger cellular responses [36-37].

Colicin E1 causes cytotoxicity in *E. coli* or closely related species by forming ion channels and depolarizing the cytoplasmic membrane [37-38]. OmpF and TolC form a stable trimer on the bacterial OM. Each monomer in the OmpF cutter can form mildly cation-selective ion-permeation channels and requires BtuB for group A colicin activity. Colicin E1 activity depends on both BtuB and TolC working together. OmpF is necessary for colicin N activity alone. TolC is a trimer protein in the OM and spans the periplasmic space as a α-helix pathway [32][37].

**3.4 Colicin as Antibacterial Agent**

Antibiotic resistance is causing concern worldwide. The utilization of drugsfor the therapy of contagious illness has resulted in the appearance of MDR bacteria, necessitating the development of new antibiotics. The establishment of bacterial strains that are resistant to treatment in hospitals may be prevented by the use of combination antimicrobial agents in diverse infections [39-40]. Bacteriocin is a good candidate for antibacterial therapy. Gram-positive and Gram-negative bacteria's lipoteichoic acids and lipopolysaccharides have binding sites on their outer membrane surfaces that let cationic antimicrobial peptides enter the target cytoplasmic membrane. The adhesion of antimicrobial peptides to the OM bacteria is facilitated by electrostatic interactions between cationic molecules and negatively charged spots on the membrane. Many bacteria create bacteriocins, peptides, or proteins that are produced by ribosomes and have a variety of antimicrobial effects [38][41].

Colicin possesses cell-killing action, making it a suitable substitute for antibiotics. In contrast to the majority of traditional antibiotics, which inactivate bacterial growth, colicin damages biological components. microorganisms by preventing DNA replication, cell wall biosynthesis, and protein synthesis (e.g., with kanamycin and penicillin) (eg, ciprofloxacin) [31][35]. Colicin has the power to eradicate so-called persistent non-proliferative cells, which are capable of resisting antibiotic therapy by becoming metabolically dormant. Furthermore, colicin poses no risk to humans because it exclusively eliminates bacteria that have receptors such as FhuA, BtuB, Cir,and OmpF that are absent from human cells. Colicin's cell-killing kinetics are quick and can eliminate dangerous germs while they are still developing, preventing the growth of bacteria that are persistent or resistant. It is possible to engineer novel colicins by mixing them with different bacteriocins in several colicin areas [32][34].

ColE1, a colicin of group A, kills *E. coli*-sensitive cells by creating signaling pathways in the IM. Colicin E-producing bacteria defend themselves by generating immunological proteins that attach to the cytotoxic C-terminus domain and inhibit its function. When ColE1 binds, it occurs in the IM and prevents the formation of deadly holes, but when ColE binds, it does so with high affinity in the cytoplasm and results in the formation of a protein complex that is ejected from the cell. The target bacterial defense mechanisms against colicin rely heavily on the unintentional modification of receptors (resistance) or elements of translocation (tolerance) [24][31].

Since the identification of the antibiotic-deficient colicin E1 fragment with cytotoxic potential C that belongs to many antibiotic classes, colicin E1 has the potential to be an antibiotic. Colicin E1's ability to retain its binding to surfaces is improved by TolC interaction, although it is insufficient. ColE1-T only partially inhibits the antibiotic while ColE1-TR completely inhibits [42-43].

Research conducted by Budiardjo et al [42-43], found that colicin E1 fragments that bind to TolC inhibit the pumping pathways of antibiotics and increase susceptibility to all three antibiotics. In the live cell assay for the flow inhibitor colicin E1, the colorant N-(2-naphthyl)-1-naphthylamine, which is released by AcrAB-TolC efflux, is passively diffused into cells. The CCCP protonophore can deactivate NNN, which prevents proton dynamics and permits NNN to build up in the cell. ColE1-TR successfully increased the antibiotic potency of three different well-known TolC substrates, as it

entirely suppressed the NNN influx. The antibiotic stays contained inside the cell thanks to an efficient TolC node, which lowers the concentration required to stop development.

Various combinations of colicins have been tested by Lobmann et al. [44] to control EHEC contamination in various foods such as meat and it has been reported that there is a reduction in *E. coli* 0157:H7 contamination in fresh pork treated with a mixture of ColM+ColE7. The combined colicin treatment (ColM+E7+Ia+5+K+U) was tested on meat contaminated with USDA "Big7 STEC" mixture plus 104:H4 serotype resulting in a 1-3 log reduction in the bacterial population. In addition, the colicin test is performed on *E. coli* bacteria that are multi-resistant to each type of colicin and the combination of the different types. Colicin E7 and M each significantly reduced the bacterial population in the first 4 hours while the combined colicin (ColE7+M, ColE7+M+E6+E2, and ColE7+M+E6+E2+K+5) can kill bacteria as a whole. The usage of colicin is dose-dependent; for instance, colicin M alone, when employed at concentrations of 5 mg/L as opposed to 0.5 mg/L, provides substantially tighter control of bacteria.

Translocon complex assembly is required for ColE9 import. The BtuB (receptor), OmpF or OmpC (porin translocator), TolB (cytoplasmic target), and Im9 make up the OM part of the translocon (immunoprotein). ColE9 forms the OM translocon by crossing the porin channel and interacting with the PMF-coupled Tol-Pal system in the periplasmic using an intrinsically unstructured N-terminus. Colicin is known to use FtsH, an AAA+ ATPase/protease to get around MI. ColE9 DNase causes nonspecific double-stranded DNA cleavage once within the cell, which kills the cell [43][45].

## 4. Conclusion

*E. coli* produces the protein colicin, which is a response to environmental stress. Colicins are separated into group A colicins (A, N, E1, E3, E6, E7, E9) with a Tol-dependent system and group B colicins (Ia, Ib, B, D) with a Ton-system based on the translocation mechanism during bacterial cell invasion. Colicin has three functional domains, T, R, and C, which aid in target cell recognition, binding to cell surface receptor proteins, pore formation, and enzyme breakdown. The four steps of colicin translocation are binding to gram-negative *E. coli* bacteria's outer membrane, creating translocons on the outer membrane, moving between periplasmic regions, and decreasing enzyme activity. Since colicin's cytotoxicity only works on bacteria, it is not hazardous to humans. To aid in the management of *E. coli* and other related bacterial infections, it is crucial to determine the antibacterial capability of colicin. Combining several colicin types revealed a promising prospect for colicin as an antibacterial agent, but additional research is required.

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