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Bacteriocins of *Escherichia coli*: A Mini Review

***[1]Umar Umar Abubakar, [1]Umar Nasir Muhtar, [1]Sadiq Haruna**

[1] Department of Microbiology and Biotechnology,
Federal University Dutse.

Email: Uaumar94@gmail.com

Abstract

Bacteriocins are antimicrobial peptides produced by certain bacteria that exhibit potent activities against closely related species, including pathogens. This review aimed to discuss and compare the results of academic research articles focused on the bacteriocins produced by Escherichia coli, shedding light on their diversity, mechanisms of action, and potential applications in various fields. Bacteriocins produced by E. coli strains have been found to vary in terms of their genetic determinants, structures, and modes of action. Through extensive research, several types of E. coli bacteriocins have been identified and characterized, including colicins, microcins, and other related peptides. Some bacteriocins act by disrupting the target cell membrane, leading to cell lysis, while others target essential cellular processes, such as DNA replication or protein synthesis. Understanding these mechanisms provides insights into the potential applications of E. coli bacteriocins as antibacterial agents or probiotics to fight against pathogens. Studies have explored their specific antimicrobial spectra, examining their efficacy against various bacterial strains, including antibiotic-resistant pathogens. Additionally, investigations into their regulation, biosynthesis, and mode of action have contributed to a better understanding of their potential as therapeutic agents. Furthermore, the potential applications of E. coli bacteriocins extend beyond the medical field. Research has demonstrated their ability to control foodborne pathogens and spoilage bacteria, making them promising as natural food preservatives. Moreover, their potential use in biotechnology, agriculture, and environmental protection has been explored, emphasizing their versatility and potential industrial applications. This review paper discussed and compared the results of academic research concerning E. coli bacteriocins, providing insights into their diversity, mechanisms of action, and potential applications. Further studies on E. coli bacteriocins will not only contribute to the understanding of bacterial interactions but may also pave the way for novel antimicrobial strategies and biotechnological advancements.

Keywords*:* Escherichia coli, Bacteriocins, Microcins, Colicins, Antimicrobial peptides

INTRODUCTION

The dramatic rise in antibiotic-resistant pathogens has renewed efforts to identify, develop and redesign antibiotics. Bacteriocins are ribosomally synthesized antimicrobial peptides that are active against other bacteria, either of the same species (narrow spectrum), or across genera (broad spectrum) (Yang *et al.,* 2012). Bacteriocins have been studied and identified in *Escherichia coli* and are coined colicins and microcins (Duquesne *et al.,* 2007). Colicins are high-molecular-mass (30–80 kDa) proteins (Rebuat, 2016) and are tightly controlled by the bacterial Save Our Souls system (Chavan *et al.,* 2007; Inglis *et al.,* 2013). In contrast, microcins, peptides with molecular masses below 10 kDa, are protease and temperature resistant and are reported to resist pH extremes (Duquesne *et al.,* 2007). These characteristics are often associated with bacteriocins of lactic acid bacteria (Rebuat, 2016).

**Author for Correspondence*

Bacteriocins were first identified almost 100 years ago. A heat-labile substance in *E. coli* V culture supernatant was found toxic to *E. coli* S and given the name "colicin" (Hammani *et al.,* 2010). It was thus decided that bacteriocins would be named after the producing species (Negash *et al*., 2020). Since then, bacteriocins have been found among most families of bacteria and many actinomycetes and are described as universally produced, including by some members of the Archaea (Shand *et al.,* 2008). Two main features distinguish the majority of bacteriocins from conventional antibiotics: bacteriocins are ribosomally synthesized and have a relatively narrow killing spectrum (Darbandi *et al.,* 2021). They make up a highly diverse family of proteins in terms of size, microbial target, mode of action and release and mechanism of immunity and can be divided into two broad groups: those produced by Gram-negative bacteria and those produced by Gram-positive bacteria (Gordon *et al.,* 2007, Heng *et al.,* 2007). Bacteriocins are one of the most abundant and diverse classes of antimicrobial molecules, having been detected in all major lineages of Eubacteria and Archaebacteria (Dobson *et al.,* 2013). These molecules are peptides naturally synthesized by ribosomes, produced by both Gram-positive bacteria (GPB) and Gram-negative bacteria (GNB), which will allow these bacteriocin producers to survive in highly competitive microbial environments (Simons *et al.,* 2020). Bacteriocins exhibit antimicrobial activity with variable spectrum depending on the peptide, which may target several bacteria. To address increasing bacterial resistance to conventional antibiotics, bacteriocins are now considered alternative antimicrobials for the treatment of human (and possibly animal) infections (Lawton *et al.,* 2007). Furthermore, since minimally processed foods with no chemical preservatives are in demand by consumers, research into natural antimicrobial agents such as bacteriocins (Abriouel *et al.,* 2011) has been increasing.

E. coli as Producer of Bacteriocin

E. coli produces potent, often highly specific toxins that are usually secreted during stressful conditions and result in the rapid elimination of neighboring cells that are not immune or resistant to their effect (Cameron *et al.,* 2019). Given their often narrow range of activity, it has been proposed that the primary role of bacteriocins is to mediate intraspecific, or population-level, interactions. Bacteriocins have been studied and identified in *E. coli* and are coined colicins and microcins (Duquesne*et al.,* 2007). Colicins are high-molecular-mass (30–80 kDa) proteins (Rebuat 2016) and are tightly controlled by the bacterial SOS system (Inglis *et al.,* 2013, Chavan*et al.,* 2007). In contrast, microcins, peptides with molecular masses below 10 kDa, are protease and temperature resistant and are reported to resist pH extremes (Duquesne*et al.,* 2007; Rebuat 2016). Bacteriocins are unique compared to traditional antibiotics, as they harbour a restricted killing spectrum, targeting specific bacteria or species (Gillor *et al.,* 2008; Kleanthous*et al.,* 2010). The targeted killing of specific bacteria makes producers of these bacteriocins an ideal probiotic.

Functions of Bacteriocins

Bacteriocins may function as colonizing peptides, facilitating the introduction and/or dominance of a producer into an already occupied niche (Riley and Wertz, 2002). Alternatively, bacteriocins may act as antimicrobial or killing peptides, directly inhibiting competing strains or pathogens (Majeed *et al.,* 2011). Lastly, bacteriocins may function as signaling peptides, either signaling other bacteria through quorum sensing and bacterial cross-talk within microbial communities or signalling cells of the host immune system (Czárán *et al.,* 2002; DiCagno *et al*., 2007; Gobbetti *et al*., 2007; Meijerink *et al.,* 2010; Majeed *et al.,* 2011). Among bacterial pathogens, Shiga toxin-producing *E. coli* (STEC) produces a potent toxin (Shiga toxin), which, in conjunction with other factors, causes severe, often foodborne infections in humans (i, 2004; Rahal *et al.,* 2015). Various mitigation strategies for this pathogen have been considered, including vaccines (Stanford *et al.,* 2014), direct-fed microbials

(Stephens *et al.,* 2010), and tannins (Jin *et al.,* 2015), but none have consistent efficacy. Another mitigation strategy being considered to control STEC is using probiotic bacteria to competitively eliminate the pathogens (Askari *et al.,* 2019) as demonstrated by the effective use of *E. coli* to alleviate intestinal infections in humans (Sonnenborn, 2016). Likewise, a colicin-producing *E. coli* isolated from sheep faecal samples was shown to inhibit the STEC O157:H7 (Askari *et al.,* 2019).

Forms of Bacteriocin Produced by *E. coli*

Generally, Gram-negative bacteriocins have been studied and identified in *E. coli* and are coined colicins and microcins (Duquesne *et al.,* 2007).

Colicins

The most extensively studied Gram-negative bacteriocins are colicins from *E. coli* which also serve as a model for the ecology, evolution, function, structure and genetic organization of bacteriocin from Gram-negative bacteria nowadays (Cascales *et al*., 2007). Colicins are high molecular weight toxic proteins that are produced by colicinogenic strains of *E. coli* and some related species of the family *Enterobacteriaceae* (Smajs and Weinstock 2001). Colicins are bactericidal macromolecules produced by certain strains *of Escherichia coli* to kill *E. coli* strains that lack the respective colicin-encoding plasmid. Approximately half of the natural *E. coli* isolates produce one or more of these toxins (Suresh *et al.,* 2014). Apart from their antibacterial activities, pore-forming colicins e.g. colicin A, E1 and N have shown cytotoxic effects on several cancer cells such as breast, bone, colon and gastric cancers (Smarda *et al.,* 2001; Chumchalová and Smarda 2003; Kaur 2015; Arunmanee *et al.,* 2020; Fathizadeh *et al*., 2021). They are usually encoded by colicinogenic plasmids and kill other cells by a variety of mechanisms such as membrane permeabilization, nucleic acid degradation or protein synthesis inhibition (Padilla *et al*., 2006). In 1953, it was suggested that the ability to produce colicin resides in an extrachromosomal genetic element, named the colicinogenic factor, after demonstration that the detertminant for colicinis transmitted in mating experiments (Cascales *et al.,* 2007).

Lancaster *et al*., (2007) and Arunmanee *et al.,* (2020) also reported that the cytotoxicity of Colicins was more specific towards cancer cells than normal cells (Smarda *et al.,* 2001; Chumchalová and Smarda 2003; Kaur 2015; Arunmanee *et al.,* 2020; Fathizadeh *et al*., 2021). The 3D structures of the different types of colicins are depicted in Figure 1.

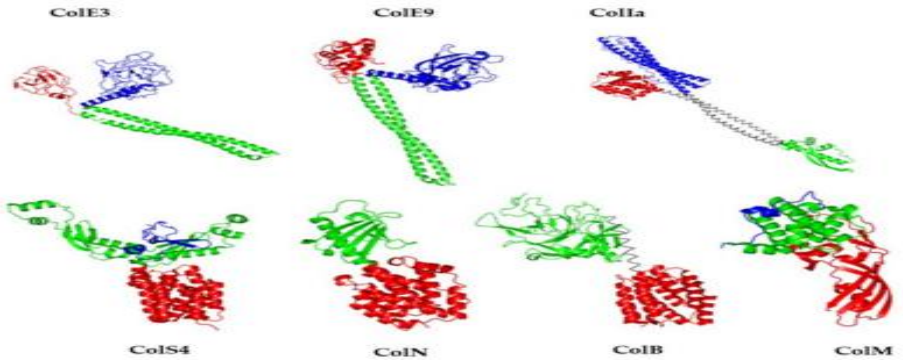

Figure 1: This figure illustrates the Modular organization of colicins, showing 3D structures of different types (ColE3, ColE9, ColIa, ColS4, ColN, ColB, and ColM).

The translocation domain is represented in blue, the reception domain in green, and the activity domain in red. The figure was created using PyMOL software with atomic coordinates from the Protein Data Bank (Cherier *et al*., 2021).

Microcins

Microcins are antibacterial peptides of low molecular weight, < 10 kDa, that are produced by *E. coli*. Like other AMPs, they are secreted under conditions of nutrient exhaustion and exert potent antibacterial activity against closely related species. Microcins are ribosomally synthesized, and some of them are post-translationally modified (Smits *et al.,* 2020). Their biosynthetic cluster encodes a linear precursor peptide, the maturation enzymes that modify the peptide and immunity proteins that are degrading enzymes, binding proteins or transporters [for an in-depth review on microcin biosynthesis see reference (Duquesne *et al.,* 2007); Figure 2 depicts the biosynthetic gene clusters of class I and IIa/b microcins.

Classes of Microcins

Microcins can be classified into class I and class II (Duquesne *et al.,* 2007; Arnison *et al.,* 2013). Class I microcins are usually plasmid-encoded and post-translationally modified. Microcins that belong to class I include MccB17, containing thiazole and oxazole rings, and MccJ25, possessing a lasso topology or MccC7/ C51, containing a nucleotide (Severinov *et al.,* 2011). Class II microcins can be subdivided into IIa and IIb; microcins of class IIa are plasmid-encoded but not modified (MccL, MccV, Mcc24), whereas microcins of class IIb are chromosomally encoded linear peptides with a C-terminal siderophore modification (MccE492, MccM, MccH47 and MccI47) (Vassiliadis *et al*., 2011).

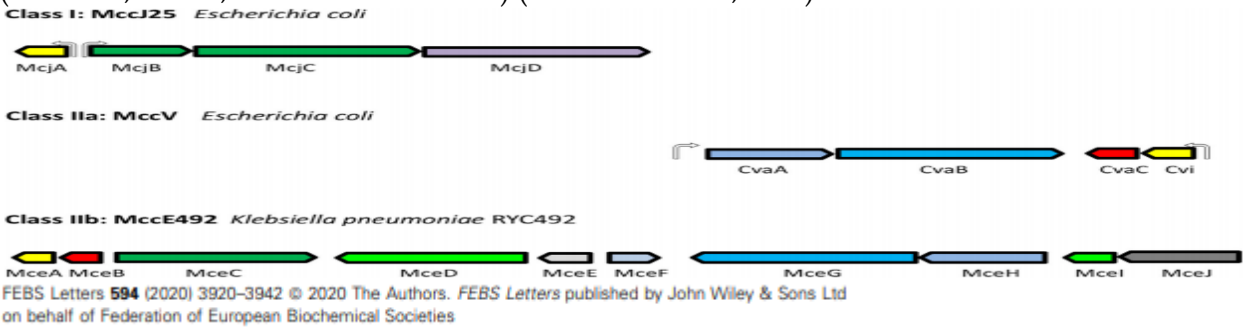

Figure 2: Biosynthetic gene clusters of class I and IIa/b microcins, providing representative examples for each class.

The clusters encompass genes encoding self-immunity proteins, which effectively safeguard against the produced peptides. The colour code represents different elements, such as precursor peptides (yellow), posttranslational modification enzymes (green), and self-immunity through transporters (blue and purple), self-immunity proteins (excluding export) (red), and genes with unknown functions (grey) (Smit *et al*., 2020). Known promoters are indicated by white arrows, and the protein names are specified below the corresponding genes (Smit *et al*., 2020).

CONCLUSION

Given the mounting threat posed by antibiotic resistance, foodborne illnesses and food spoilage, a better understanding of the mechanisms bacteria employ to evolve resistance, persistence as well as pathogenesis is urgently needed. The solution to this alarming threat lies with bacteriocins produced by *E. coli*. Colicins and microcins produced by this bacterium can be used to reduce the intensity of antibiotic resistance, foodborne illnesses and food spoilage because they are potent against *E. coli* 0157:H7 which is a major cause of food spoilage and food poisoning and other closely related members of Enterobacteriaceae such as pathogenic *Salmonella* and *Shigella* among others.

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