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DETECTION OF BACTERIOCIN GENE OF *E. COLI* BACTERIUM ISOLATED OF URINARY TRACT INFECTIONS

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Abstract:

Present research flushed the light on documented studies which were obtained and focused on infections of urinary system caused by bacteria *Escherichia .coli* in human.

There are a variety of pathogens causing infections of urinary system and recurring inflammations but bacteria *E.coli* considered the most important and common.

This research pointed to that bacteria E. coli is originally belong to the normal and benefit microflora present in the body of human particularly in the large intestine of digestive system However, the presence of bacteria in the urinary system produces a variety of infections and inflammations in this system

Keywords: Bacteriocin, Escherichia Coli, Urinary Tructs Infections, Colicins, Microcins

INTRODUCTION

Escherichia coli is a Gram-negative bacteria that is rod-shaped, facultatively anaerobic, and coliform. Escherichia coli is a bacterium found in the lower intestine of warm-blooded animals. The innocuous strains are prevalent in the gut's natural microbiota and can assist their hosts by producing vitamin K2, which aids blood clotting and prevents dangerous bacteria from colonizing the intestine, forming a symbiotic relationship. **(1,2,3)**. *E. coli* is spread through excrement into the environment. The bacterium grows rapidly in fresh feces under aerobic conditions for three days, but its numbers steadily decline after that. (4,5). E. coli and other facultative anaerobes make up about 0.1 percent of the gut microbiota. (6).

This bacterium can be easily and cheaply grown and cultured in a laboratory setting, and it has been intensively studied for more than 60 years. E. coli is a chemoheterotroph, which means it needs a carbon and energy source in its chemically defined media. **(7)**. *E. coli* is the most studied prokaryotic model organism and an important species in biotechnology and microbiology, where it is the host organism for the majority of recombinant DNA research. In perfect conditions, it can be done in as little as 20 minutes. **(8)**.

One of the most common locations for pathogenic E.coli is the urinary system. **(9)** The amount of virulence factorers present in E.coli determines its pathogenicity in urinary tract infections, allowing the bacteria to colonize and penetrate the urinary tract, causing infection, and so it is considered one of the most important pathogens for the urinary system. (10).

Bacteriocin production is one of the virulence factors found in Escherichia coli, and it will be examined in this study.

Gram-negative Enterobacteriaceae produce bacteriocins. Colicins and microcins are ribosome-produced toxins produced by E. coli. **(11).**

The goal of this study was to determine the significance of the bacteriocin biosynthesis gene in E.coli strains that cause urinary tract infections.

E.coli bacterium:

E. coli is a Gram-negative, facultative anaerobic bacterium belonging to the Enterobacteriaceae family. (12). The Gram-negative bacillus Escherichia coli (E.coli) dwells in the large intestine and is naturally removed in the feces. The bacterial genus Echerichia is named after Dr. Theodor Escherich, who first found the species. (13).

It's a highly adaptable bacterial species with both benign commensal strains and pathogenic variants that can cause both intestinal and extraintestinal disorders. (14, 15). As a result, commensal E. coli strains are classified as intestine pathogenic E. coli (IPEC) or extraintestinal pathogenic E. coli (EPEC) (ExPEC) (14, 16).E.coli is a non-pathogenic bacterium that lives in the intestines of many mammals, including humans, and contributes to the microbiota's vital activities. (12, 17). Commensal E.coli isolates from phylogroup A and B1 are largely derived from phylogroup B2 and D. The majority of ExPEC isolates are from phylogroups B2 and D. The majority of ExPEC isolates

are from phylogroups B2 and D. The majority of ExPEC isolates are from phylogroups B2 and D. ExPEC isolates from phylogroup B2 and D ExPEC isolates are the most common. (12, 18, 19). Any of the four phylogroups can cause intestinal and extraintestinal infections, and phylogroups B2 and D have been shown to be regular colonization strains in healthy people. (20, 21).

Pathotypes can be assigned to each of the pathogenic E.coli strains, IPEC and ExPEC. This classification is based on the symptoms of the disease as well as pathogenic characteristics such the presence of virulence factors (VFs) (12). The most common ExPEC pathotypes are uropathogenic E.coli (UPEC) and meningitis-associated E.coli (MNEC) (19). It is generally possible to identify the genetic content and morphological features of intestinal non-pathogenic E.coli and IPEC, but discriminating between commensal E.coli and extraintestinal pathogens is difficult (14). ExPEC strains are often found in healthy people's commensal flora and do not cause gastrointestinal sickness (12, 16). Unlike IPEC, ExPEC can cause a wide range of diseases in almost any anatomical niche, including urinary tract infections, bacteremia, meningitis, and intraabdominal infections (19,22).

The urinary tract is the most prevalent site of E. coli infection, accounting for more than 90% of all uncomplicated urinary tract infections (UTIs) (23), Because of the near proximity of the urethra to the anus, it is more common in women (24).

Extra Intestinal Pathogenic *Escherichia coli*

Humans are susceptible to extraintestinal infections, with ExPEC being the most frequent Gram-negative bacteria. Urinary tract infections are the most common, but E.coli is also the leading cause of bloodstream infections (25, 19, 26, 27).

Johnson et al. coined the term ExPEC in 2000 after receiving reports of UPEC and MNEC isolates producing a variety of extraintestinal illnesses. (16). ExPEC's pathogenicity has been related to a number of hypothetical virulence genes, allowing them to infect nearly any extraintestinal tissue (15, 16). Many of these VFs are present on chromosomes, but some are also found on mobile elements, resulting in a wide range of ExPEC pathotypes (12, 17).

Urinary tracts infections (UTIs):

A urinary tract infection (UTI) is an infection that affects all or part of the urinary system (28). When it affects the lower urinary tract, it's called a bladder infection (cystitis), and when it affects the upper urinary tract, it's called pyelonephritis (29). Urination pain, frequent urination, and the need to urinate despite an empty bladder are all indications of a lower urinary tract infection (28). A kidney infection can induce fever and flank pain in addition to the symptoms of a lower UTI (29). Urine can appear bloody at times (30). In both the elderly and the young, symptoms might be vague or non-specific (28) (31). The most prevalent cause of disease is Escherichia coli, however infection can also be caused by other bacteria or fungi. Risk factors include female anatomy, sexual intercourse, diabetes, obesity, and family history (32). Despite the fact that sexual contact is a risk factor, UTIs are not classified as sexually transmitted infections (STIs) (33). A kidney infection normally develops after a bladder infection, although it can also develop as a result of a blood infection (34). Only symptoms can be used to make a diagnosis in young, healthy women (35). Because germs can be present without an illness, diagnosing people with ambiguous symptoms can be difficult (35). If you're in a bad situation or if you're not sure what to do, a urine culture can help.(36).

In uncomplicated situations, UTIs are treated with a short course of antibiotics such as nitrofurantoin or trimethoprim/sulfamethoxazole (30).

A urinary tract infection affects over 150 million people each year (32). They are more common in women than in men (31). In women, they are the most common bacterial infection (37). Up to 10% of women experience a urinary tract infection in a given year, and half of women get at least one infection throughout their lifetime(35) (30). People between the ages of 16 and 35 are the most likely to develop them. The occurrence of recurrences is extremely prevalent (30).

Urinary tract infections have been documented from ancient times, with the first documented description appearing in the Ebers Papyrus around 1550 BC (38).

Causes of UTI

The percent 80–85% of community-acquired urinary tract infections are caused by uropathogenic E. coli from the gut, with Staphylococcus saprophyticus accounting for 5–10 percent. (35) It's possible that they're caused by viral or fungal infections in rare cases (39, 40).

Healthcare-associated urinary tract infections (mainly caused by urinary catheterization) are caused by a much broader range of bacteria, including E. coli (27%) E. coli (11%) Klebsiella (11%) Pseudomonas (11%) Candida albicans (9%) and Enterococcus (7%), among others (30). (41). (42). Blood-borne infections are the most common cause of Staphylococcus aureus urinary tract infections (29). Chlamydia trachomatis and Mycoplasma genitalium can infect the urethra but not the bladder (43). These diseases are typically classified as urethritis rather than a urinary tract infection (44).

Intercourse

In young sexually active women, sexual activity causes 75–90 percent of bladder infections, with the risk of infection increasing with the frequency of sex (35). The term "honeymoon cystitis" was used to describe the occurrence of repeated UTIs during early marriage. In postmenopausal women, sexual activity has little effect on the probability of getting a UTI (35) The use of spermicide, regardless of sexual frequency, increases the risk of urinary tract infections (UTIs) (35). The use of a diaphragm is also associated with the use of a condom without spermicide

or birth control tablets, however neither of these factors increases the risk of a simple urinary tract infection (35) (31) (44) (45).

Sex

Because the urethra in women is substantially shorter and closer to the anus, UTIs are more common in women than in men (46). As a woman's estrogen levels fall with menopause, she loses helpful vaginal flora, increasing her risk of urinary tract infections (46). Urinary tract infections are also linked to vaginal shrinkage, which can happen after menopause (47).

Chronic prostatitis/chronic pelvic pain syndrome and chronic bacterial prostatitis can also induce recurrent urinary tract infections in males (not acute bacterial prostatitis or silent inflammatory prostatitis). The risk of infection increases as men age. While bacteria is identified in the urine of older men on a regular basis, it appears that this has no impact on the occurrence of urinary tract infections (48).

Urinary catheters

Urinary catheterization increases the risk of urinary tract infection. Bacteriouria (bacteria in the urine) is a three to six percent daily risk, and medicines are ineffective in preventing symptomatic infections (46). Catheterizing only when absolutely necessary, using an aseptic technique for insertion, and maintaining clear closed drainage of the catheter can all help to limit the risk of infection. (50) (49) (51).

Urinary tract infections are also a risk for men scuba divers who use condom catheters and female scuba divers who use external catching devices for their dry suits (52).

Others

It's likely that a tendency for bladder infections is passed down through the generations. This is assumed to have something to do with genetics. Diabetes, a large prostate, and being uncircumcised are all risk factors (29(35) (53)). (54). In children, urinary tract infections (UTIs) are connected to vesicoureteral reflux (abnormal urine passage from the bladder into the ureters or kidneys) and constipation (55). People with spinal cord injuries are more likely to get urinary tract infections as a result of the constant use of catheters and voiding dysfunction (56). In this demographic, it is the leading cause of infection and hospitalization (56). Furthermore, cranberry juice or supplements appear to be ineffective in terms of prevention and treatment in this demographic (57).

Pathogenesis:

Germs that cause urinary tract infections commonly enter the bladder through the urethra. Infections can spread through the bloodstream and lymphatic system. The germs are assumed to be carried from the colon to the urethra, with females being more vulnerable due to their anatomy. After gaining entrance to the bladder, E. Coli can adhere to the bladder wall and form a biofilm that resists the body's immunological response (30).

Escherichia coli is the most common bacteria that causes urinary tract infection, followed by Klebsiella and Proteus spp. Klebsiella and Proteus spp. are frequently associated to stone disease. Bacteria that are Gram-positive, such as Enterococcus and Staphylococcus, are present.

It has been noticed all across the world that urinary pathogens are becoming increasingly resistant to quinolone antibiotics, which could be the result of quinolone overuse and misuse (58).

Signs and symptoms

Lower urinary tract infection is another name for a bladder infection. Burning during urination, frequent urination (or a need to urinate) in the absence of vaginal discharge, and significant pain are the most common symptoms (35). These symptoms might range from mild to severe, and they usually last six days. There may be some soreness above the pubic bone or in the lower back in healthy women(29) (37). People with an upper urinary tract infection, also known as pyelonephritis, may have flank discomfort, fever, nausea, and vomiting, in addition to the conventional symptoms of a lower urinary tract infection (29) Urine may appear crimson or contain visible pus on occasion (30) (59).

Children

In young children, a fever may be the only sign of a urinary tract infection (UTI) (55) Due to the lack of more visible symptoms in females under the age of two and uncircumcised males younger than a year, many medical societies recommend a urine culture. (55) Infants may not eat well, vomit frequently, sleep more than usual, or exhibit jaundice-like symptoms. Urinary incontinence (loss of bladder control) in older children can occur quickly (55). Bacterial meningitis affects roughly one in every 400 infants aged one to three months who have a urinary tract infection (UTI) (60)

Elderly

Urinary tract symptoms are usually absent in the elderly (31). Some people present with incontinence, a change in mental status, or exhaustion as their sole symptoms (29), whereas others present with sepsis, a blood infection, as the first symptom (30). Because many older people suffer from incontinence or dementia, it might be difficult to diagnose them (31).

It is reasonable to obtain a urine culture when someone exhibits signs of systemic infection but is unable to explain urinary symptoms, such as when advanced dementia is present (61). Fever, chills, and a raised white blood cell count are all systemic signs of infection, as is a temperature increase of more than 1.1 °C (2.0 °F) from normal (61).

Symptoms of urosepsis

E. coli is one of the most common causes of bacteremia and is frequently connected to urinary tract infections, especially when there is a blockage. Non–life threatening E. coli bacteraemia can produce fever, tachycardia,

tachypnoea, and disorientation in addition to the symptoms of a urinary tract infection. E. coli bacteremia can cause septic shock, hypotension, and hypothermia. In severe cases, uremia, liver failure, acute respiratory distress syndrome, coma, and death can all occur. The systemic response to endotoxin (cytokines) or lipopolysaccharides in bacteremia might cause disseminated intravascular coagulation and death (23).

After a 12-month period following an initial E coli infection, the recurrence rate is 44 percent (23). Bacterial reservoirs within urothelial cells could have a function. In both animals and women with recurrent cystitis, uropathogenic E. Coli have been shown to penetrate and colonize the epithelial cells of the bladder epithelial cells (62). (63). When they are shed, they can defy treatments and the body's immune systems, only to recolonize the bladder and produce severe acute illness (64).

Epidemiology and risk factors for E. coli UTI

Because of the urogenital tract's close closeness to the anus in females, the male urethra's larger length, and the antibacterial activity of prostatic fluid in men, urinary tract infection is more common in females than in males (65, 66). Because of the functional, hormonal, and anatomical changes that occur during pregnancy, pregnant women are prone to UTI (67). A urinary tract infection (UTI) during pregnancy can lead to serious complications for both the mother and the baby, including sepsis, preterm labor, and premature birth (67). Asymptomatic bacteriuria (ASB) induces symptomatic cystitis in 30% of patients, and up to 50% of patients develop pyelonephritis if left untreated (66). Furthermore, ASB has been associated to fetal growth retardation and low-birth-weight newborns (66). UTI has been connected to as much as 27% of all pregnancies

The most frequent bacterial ailment in children is a urinary tract infection (UTI), which outnumbers bacterial meningitis, pneumonia, and bacteremia (68). Males are more prone than females to UTI, which affects roughly 1% of babies under the age of three months. Because 10–15 percent of children with UTI have irreparable kidney damage, which can lead to other chronic illnesses like hypertension and renal insufficiency, adequate and quick UTI therapy is crucial in children (69,70). The tendency for UTIs to recur after an initial acute infection, often a few weeks or months later, is a problem in UTI treatment. Within 6 months of the initial episode, 20–30 percent of women will suffer a recurrent bladder infection, and another 3% will develop a third sickness (71, 72).

E. coli UTI pathogenesis

Pathogenesis of UTIs is a complex process influenced by a range of biological and behavioral factors in the host, as well as pathogen features such as VFs. Epidemiological studies on the role of individual VFs in UTI formation are problematic due to the confounding effect of host factors.

External microbes are kept out of the urinary system by urine flow, secreted and tissue-associated antibacterial compounds, and the bactericidal action of effector immune cells in most noncompromised persons. In most cases, the infected E. coli strain begins in the host's feces and travels through the perineal, vaginal, and periurethral areas to the lower urinary system (i.e., urethra and bladder), where it can colonize (73).

These two processes might not be mutually exclusive, but they could both play a role in UTI etiology (74).

Several proximal external reservoirs for the E. coli infecting strain have been identified, despite the fact that the infecting strain is most usually detected in the host's feces. In communities, UTI outbreaks have been reported (75–76), but there has been no evidence of person-to-person transmission. Epidemics have been linked to food and water (75,76). E. coli from retail meat products and healthy or sick people share a lot of molecular similarities, according to research (75). E. coli has been found to spread within a household, even between sexual partners, among cohabiting humans and their pets (77, 78, 79). urinalysis According to the prevalence hypothesis, E. coli clones with the highest numerical prevalence in feces will be implicated, but the pathogenicity theory suggests that E. coli strains with the highest pathogenicity will be implicated.

The VFs of the invading bacteria and the host's defense mechanisms have an impact on the infection's outcome (80). A variety of host features, such as age, gender, pregnancy, and immunologic status, can predispose to UTI and allow less virulent microorganisms to cause infection (73).

Acute cystitis is an infection of the lower urinary tract that produces dysuria and frequent urination among other symptoms. Acute pyelonephritis is an infection that affects the upper urinary tract and causes symptoms such as discomfort in the flanks, fever, and malaise.

Uropathogenic E. coli (UPEC) and virulence factors (VFs)

A vast range of virulence factors that are responsible for the invasion and colonization of the urinary tract, as well as infection, determine the pathogenicity of the E.Coli bacteria that causes UTIs (10). The existence of specific additional traits known as virulence factors determines pathogenicity, or an organism's ability to cause disease (VFs). Pathogens with VFs are able to get beyond host defenses and cause disease. Despite the discovery of many VFs in UPEC, experimental and epidemiological studies have shown that none of them uniquely denes these disease.

UPEC VFs have functional categories including as adhesins, poisons, iron acquisition pathways, protectins, and bacteriocin production. VFs are encoded by genes on chromosomes or plasmids, with some being fully chromosomal and others plasmid-based (81).

Bacteriocins production

Animals, plants, insects, and bacteria create antibacterial chemicals such as hydrogen peroxide, fatty acids, organic acids, ethanol, antibiotics, and bacteriocins. Antimicrobial peptides (AMPs) or proteins produced by bacteria are known as bacteriocins. A lack of nutrients in the environment triggers microbial synthesis of a variety of

bacteriocins in order to compete for space and resources. Bacteriocin genes encode ribosomally produced antimicrobial peptides or proteins that kill related (narrow spectrum) or unrelated (wide spectrum) microbiotas as part of bacteria's natural defensive system (82). Bacteriocins are produced by nearly all bacteria, the vast majority of which are unknown (83).

As a result, VFs can be transmitted vertically or horizontally, further complicating the system and making it difficult to determine the involvement of individual VF genes in UTI etiology (81). The ability of bacteriocins to kill is regarded to be a successful strategy for preserving population and reducing competition in order to get more resources and living space in habitats. Unlike most antibiotics, which are secondary metabolites, bacteriocins are ribosomally produced and susceptible to proteases, and are generally safe for humans and the environment. Because many of the chemical additives used in food may be dangerous, modern society is more conscious of the issue of food safety; as a result, it is profitable to claim natural resources and diet health benefits. Natural foods have a lot of health benefits, but they don't have a lot of calories.

The health benefits of natural foods without chemical additives are becoming more widely recognized; however, the majority of commercially available preservatives and antibiotics are produced through chemical synthesis, and long-term consumption of such products can harm human health by lowering gut bacterial counts. In addition, the use of antibiotics or antibiotic residues in food is forbidden. Unlike chemical preservatives and antibiotics, "generally recognized as safe" (GRAS) bacteriocins such as nisin promise safe usage as a food preservative in vegetables, dairy, (cheese, meats, and other foods by preventing microbial contamination during the manufacturing process (84, 85

The classification of bacteriocins from Gram-positive to Gram-negative bacteria is the subject of this review. The . report also discusses the use of bacteriocin-producing microorganisms and bacteriocins derived from natural resources for human life.

Colicins

Colicins are antimicrobial proteins made by bacteria that can kill closely similar bacterial strains in the environment, reducing competition for nutrients and living space. Colicins have three domains: an amino-terminal translocation (T) domain that facilitates translocation across the outer membrane via the translocator protein; a central receptor-binding (R) domain that binds to a bacterial outer membrane receptor; and a carboxy-terminal cytotoxic (C) domain with antibacterial activity (86; 87).

To avoid poisoning by self-made colicins, specificity immunity proteins will be generated at the same time to inactivate colicins (87). When the colicins recognition receptors protein and the translocators protein system are present on the outer membrane surface of a bacterial cell, the colicins are carried inside the cell and kill the bacteria. Sensitive strains of bacteria are what they're called. Non-receptor protein bacteria are defined as strains that are resistant to a specific colicin. Bacteria with a translocator protein system deficiency are known as tolerant strains. Organisms that produce immunity proteins are known as immune strains. Similar colicins would not kill bacterial strains that are resistant, tolerant, or immune. There are several colicins in sequence, with the majority encoded on plasmids and only a few on chromosomes. Immunity protein, toxin protein, and lysis gene are all encoded by a conventional colicin gene cluster (88, 87).Bacteriocin release protein (BRP) is a lysis protein that triggers the production of colicins in bacteria.

Colicins are categorized into two groups: group A and group B, based on their capacity to cross the outer membrane (translocator) system. Through infiltrate the outer membrane of sensitive bacteria, Group A colicins, such as colicins E1 to E9, colicin A, K, N, and others, require the Tol protein system (Tol system). Group B barteriocins, such as colicin 5, 10, B, D, M, V, Ia, Ib, use the Ton system (Ton system) to permeate the outer membrane of sensitive bacteria (89,87). Colicins of group A are encoded on small plasmids with a lysis gene and can be released from bacteria, whereas colicins of group B are encoded on large plasmids without a lysis gene and cannot be released from bacteria (86).

Colicins are divided into three classes based on how they kill bacteria once they enter the target cell: (1) Pore-forming colicins: the formation of pores or channels in the inner membrane causes cytoplasmic compound leakage, electrochemical gradient destruction, ion loss, and cell death. (2) Nuclease-type colicins: colicins that incorporate DNase, 16S rRNase, and tRNase to digest bacteria's DNA and RNA non-specifically. E2–E9 colicins are among them. (3) Peptidoglycanase colicins: these proteins digest the peptidoglycan precursor, inhibiting peptidoglycan synthesis and ultimately killing the bacterium (86).

Microcins

Microcins are antimicrobial peptides with a low molecular weight (less than 10 kDa) that differ from colicins, which have a molecular weight of 25–80 kDa. Microcins are made from precursor peptides such as the N-terminal leader peptide and core peptides. Microcin precursor peptides may or may not undergo post-translational modification during the maturation process to become an active microcin. Enterobacteriaceae, which have strong heat, pH, and protease tolerance, create the majority of microcins (90). Pore-forming, nuclease, such as DNase and RNase activities, and protein synthesis or DNA replication inhibitors are among the bactericidal methods used by microcins.

Microcins have no lysis genes and are secreted from bacteria via the Type I ABC (ATP binding cassette) transporter secretion system, which is made up of many proteins (91).

Based on their molecular weights, structural disulfide linkages, and post-translational modifications, microcins are separated into two classes. Class I microcins, such as microcin B17, C7-C51, D93, and J25, are low-molecular-weight peptides that have been post-translationally changed (5 kDa). The molecular weight of class II microcins (5–10 kDa)

is higher than that of class I microcins. Class II microcins are further divided into two subclasses: class IIa and class IIb. Class IIa microcins such as microcin L, V, and N require three separate genes to synthesize and assemble functional peptides. Microcins in class IIb, such as E492, M, and H47, are linear peptides with or without post-translational modifications at the C-terminus (92).

Real-Time PCR for Gene Expression Analysis

Dr. Kary Mullis pioneered the polymerase chain reaction (PCR) in 1983, and since then, many different forms of PCR have been produced.

One of them, called "Real-time PCR" or "fluorescence based PCR," allows us to, among other things, quantify nucleic acids extracted from cells or tissues, compare different stages of infection, detect chromosomal translocations, genotype single nucleotide polymorphisms, and determine gene expression levels in samples. Real-time PCR has emerged as the most precise and sensitive technology for detecting and quantifying nucleic acids. To comprehend underlying cellular mechanisms and find variations in gene expression levels in response to certain biological stimuli (e.g., growth factor or pharmacological agent), quantitative gene expression study using quantitative PCR (qPCR) is necessary (93, 94). The emergence of Real-time PCR technology has made nucleic acid quantification much easier (94, 95). It's generally used for one of two things: identifying gene expression as a main investigative tool or validating DNA microarray results as a secondary technique (96).

CONCLUSIONS

1- The findings of this study add to the growing body of evidence that pathogenic E. Coli that infects the urinary system is caused by abnormal intestinal flora.
2-there are many causes of urinary tract infections but *E. Coli* is considered the main one.
3- The absence of implementation of appropriate hygiene measures may make it easier for uropathogenic E. Coli to spread and persist.
4-there are risk facters and virulance facters of infection with *E. Coli* that determine its pathogenisity.
5- The establishment of dangerous E. Coli strains is fueled by genetic material and virulence factors.
6-bacteriocins production is important virulance facter that enhance the pathogenisity.

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