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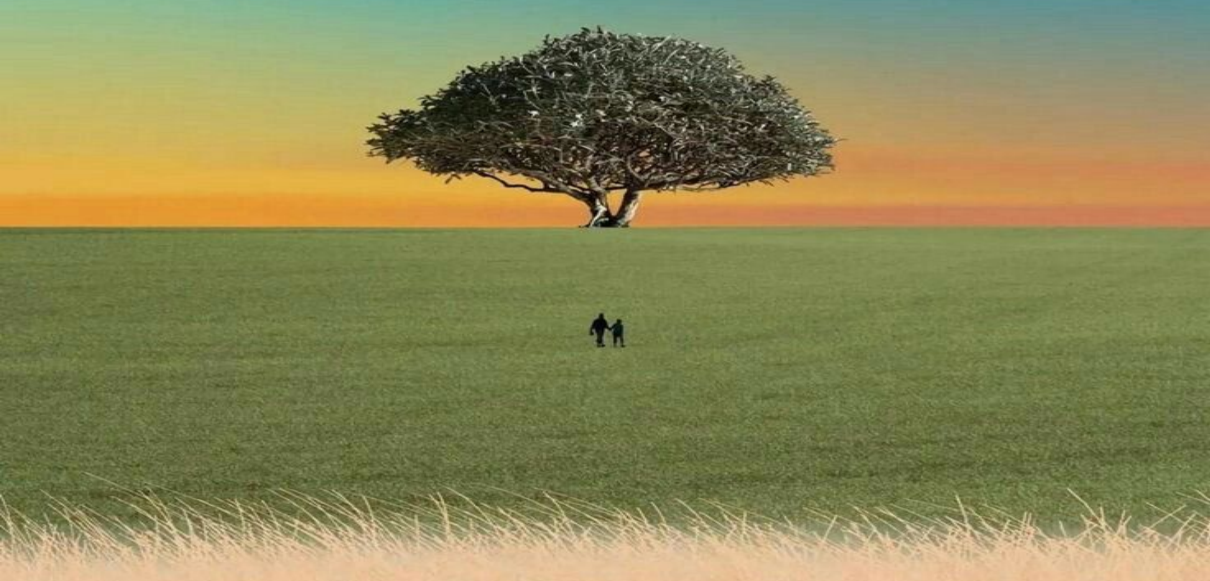

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THE ZOONOTIC ROLE OF *ESCHERICHIA COLI* AND ITS PUBLIC HEALTH SIGNIFICANCE

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1. INTRODUCTION

Escherichia coli is the most significant species within the genus Escherichia, belonging to the family Enterobacteriaceae. It constitutes a part of the normal flora of the gastrointestinal tract in humans and animals. Despite being considered beneficial due to its role in suppressing pathogenic bacterial populations and contributing to vitamin synthesis, *E. coli* is frequently isolated as either a primary or secondary pathogen in various disease cases. Equipped with virulence factors such as flagella, capsules, cell wall components, fimbrial antigens, and the production of colicins, enterotoxins, cytotoxins, hemolysins, and aerobactin, E. coli is capable of causing a wide range of infections, including enteric diseases, septicemia, urinary tract infections, and mastitis.

2. ETIOLOGY

Escherichia coli was first isolated by Theodor Escherich in 1885 from the feces of a child with diarrhea and was initially

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described as *Bacterium coli commune*. Later, it was renamed Escherichia coli in honor of the researcher (Brenner, 1984). *E. coli* is a facultative anaerobic, Gram-negative, rod-shaped microorganism measuring approximately 1.1–1.5 × 2.0–6.0 µm. Most strains possess a capsule or microcapsule. Besides *E. coli*, other species in the genus Escherichia within the family Enterobacteriaceae include E. hermannii, E. fergusonii, E. blattae, and E. vulneris (Koneman et al., 1997, Adeolu et al., 2016).

The organism is capable of both respiratory and fermentative metabolism, and certain strains produce a thin slime layer. Although *E. coli* is actively motile via peritrichous flagella, non-motile strains also exist. The optimal growth temperature is between 37°C and 44°C, with an optimal pH of 7.0–7.2. The bacterium is non-spore-forming and easily cultivable on general-purpose media. On nutrient agar, *E. coli* forms flat, convex, gray, and shiny colonies; on MacConkey agar, it produces dry, pink-red (lactose-positive) colonies surrounded by precipitated bile salts, typically measuring 2–3 mm in diameter. On eosin methylene blue (EMB) agar, it forms lactose-positive colonies with a characteristic metallic sheen. Older cultures may display rough (R-type) colonies, and occasionally mucoid (M-type) colonies. Some strains exhibit hemolysis on blood agar. Biochemically, *E.coli* is oxidase-negative and chemoorganotrophic, fermenting glucose, maltose, mannitol, xylose, rhamnose, arabinose, sorbitol, trehalose, and glycerol to pyruvate, which is further metabolized to lactic acid and formic acid. Fermentation of sucrose, salicin, dulcitol, and raffinose varies among strains, whereas fermentation of adonitol, inositol, and cellobiose is rare. The organism is positive for indole production, nitrate reduction, and methyl red activity but negative for Voges-Proskauer reaction, citrate utilization, hydrogen sulfide production, and urease activity (Holt et al., 1994; Carter et al., 1995, Ranjbar & Farahani, 2021).

Serotyping studies have revealed that *E. coli* possesses more than 182 somatic (O) antigens, over 100 capsular (K) antigens, and approximately 60 flagellar (H) antigens (Blanco et al., 1996; Parma et al., 2000). The O antigens, part of the lipopolysaccharide (LPS) structure, are highly resistant. The first region of the O antigen consists of repeating oligosaccharide units, the variability of which leads to the diversity of serotypes among genera such as Escherichia, Salmonella, and Shigella. The second region comprises core polysaccharides specific to each genus, while the third region, lipid A, contains a disaccharide linked to five or six fatty acids and is connected to the core by 2-keto-3-deoxyoctonate (KDO), an eight-carbon sugar. The carbohydrates in the first region facilitate bacterial adhesion to host tissues during infection and protect against the bacteriostatic effects of serum. O antigens are resistant to heat (110°C for 2.5 hours), alcohol (96% for 4 hours), and acids, but they are sensitive to formaldehyde. Some O antigens of *E. coli* cross-react with Salmonella, Shigella, Citrobacter, Providencia, Vibrio species, human blood group antigens, and mammalian cells (Carter et al., 1995; Blanco et al., 1996; Joensen et al., 2015).

Capsular antigens, composed of polysaccharides, prevent agglutination with O antisera. For effective agglutination, the capsule must be removed or denatured, often by heating at 120°C for 2 hours. Capsular antigens are categorized into three components symbolized as A, B, and L. Certain K antigens contribute significantly to virulence. The K1 antigen *of E. coli*, a polymer of N-acetylneuraminic acid, is particularly associated with neonatal meningitis, bacteremia, and urinary tract infections (Carter et al., 1995; Blanco et al., 1996; Joensen et al., 2015).

Flagellar antigens (H) are protein-based structures sensitive to heat, acid, and alcohol, but resistant to formaldehyde, and are known to produce rapid agglutination reactions with specific H antisera (Carter et al., 1995; Blanco et al., 1996; Joensen et al., 2015).

E. coli also exhibits the ability to agglutinate leukocytes, erythrocytes, yeast cells, and pollen grains, primarily through the action of fimbriae, which play a critical role in bacterial adhesion to host tissues. Fimbriae are long, filamentous protein polymers approximately 2–7 nm in diameter and are closely associated with pathogenicity. Their expression can be inhibited at temperatures below 18°C or in the presence of certain inhibitory substances in the growth medium (Koneman et al., 1997; Holt et al., 1994; Parma et al., 2000; Joensen et al., 2015).

Among the identified fimbrial types, mannose-sensitive fimbriae (Type 1) are commonly present in nearly all E. coli strains and mediate adherence to mannose-containing receptors, facilitating attachment to epithelial surfaces such as the oral cavity and vaginal mucosa, although they are not directly implicated in disease development (Holt et al., 1994; Carter et al., 1995). In contrast, mannose-resistant fimbriae, including S fimbriae and P fimbriae, contribute significantly to pathogenicity. S fimbriae, commonly found in bacteremia-causing strains, facilitate binding to receptors in the choroid plexus and vascular endothelium of the brain ventricles (Koneman et al., 1997). P fimbriae, named for their affinity to P blood group antigens, are predominantly detected in uropathogenic strains, present in approximately 70% of pyelonephritis cases, 36% of cystitis cases, and 19% of strains isolated from the colon (Holt et al., 1994; Carter et al., 1995 Joensen et al., 2015).

Additionally, some strains produce adhesins capable of binding to areas independent of P blood group or mannose-containing sites, significantly contributing to the pathogenic process. These adhesins also interact with Dr blood group antigens and have been implicated in cases of cystitis (Koneman et al., 1997; Holt et al., 1994; Carter et al., 1995; Joensen et al., 2015).

Other fimbrial types, including K99, K88, colonization factor antigens (CFA), CS, F41, and 987P, are also of considerable importance, providing pathogenic *E. coli* strains with the ability to specifically adhere to and colonize different epithelial surfaces, thereby facilitating infection (Koneman et al., 1997; Holt et al., 1994; Carter et al., 1995; Joensen et al., 2015).

3. EPIZOOTIOLOGY

Studies conducted to determine the epidemiology of *Escherichia coli* have demonstrated that the bacterium can be found in almost all environments and is capable of maintaining viability under a variety of environmental conditions. Among different strains, the VTEC O157 serotype has been shown to exhibit greater resilience, surviving for up to 50 days in feces, 130 days in soil, and up to nine months in ground beef stored at temperatures between –80°C and –20°C, while retaining its infectivity throughout this period (Çabalar et al., 2001).

Cattle and sheep, along with other farm animals, are recognized as significant reservoirs in the transmission of the pathogen to humans and other animals. In addition, various food products such as fruit juices, inadequately cooked meat products like hamburgers and sausages, raw milk, yogurt, cheese, slaughterhouse waste-contaminated water, and vegetables such as lettuce, potatoes, and radishes have been reported to pose a risk for the transmission of pathogenic *E. coli* strains.

Despite the widespread presence of VTEC strains, the development of disease requires the presence of specific virulence factors, including the eaeA (intimin), E-hlyA (hemolysin), uidA (beta-glucuronidase), fliC (H7 flagellin), KatP (catalase-peroxidase), EspP (protease) genes, shiga toxins (Stx1 and Stx2), and the Mp plasmid (Vidotto et al., 1990; Keene et al., 1997; Chapman et al., 2000; Maclure, 2000; Chapman et al., 2001; Tolun, 2002).

Escherichia coli O157:H7 has been responsible for outbreaks in various regions across the world. Since its first identification, numerous outbreaks have been reported, predominantly associated with the consumption of contaminated food and water or through direct contact with infected animals. In 1982, two separate outbreaks occurred in the United States, each linked to hamburgers served at fast-food restaurant chains, resulting in 26 and 21 cases, respectively. Subsequent years saw further incidents: in 1984, a hamburger-related outbreak in a nursing home in the United States affected 34 individuals, resulting in four deaths, while a 1985 outbreak in Canada linked to person-to-person transmission and contaminated sandwiches caused 73 cases, 12 cases of hemolytic uremic syndrome (HUS), and 19 deaths. Other notable outbreaks included those associated with contaminated drinking water (1989, USA; 1990, Scotland), unpasteurized apple juice (1991, USA), and raw sprouts (1996, Japan; >9,000 cases, 101 HUS cases, 12 deaths). Outbreaks also occurred in relation to surface water exposure (1993, South Africa), pasteurized milk (1994, England), fruit salads (1995, USA), coleslaw (1998, USA), and spinach (2006, USA). Additional events included infections related to contact with cattle during farm visits (2000, USA), swimming in contaminated lakes (1999, USA), and the consumption of inadequately cooked meat products, raw milk, and colostrum (Chapman et al., 2000; Maclure, 2000; Tolun, 2002; Gülhan et al., 2012; Nuhay&Gülhan 2017).

In addition to domestic and livestock-associated sources, wild avian species have been identified as potential carriers of enteropathogenic *E. coli* strains, posing an emerging risk to human health. Studies have suggested that migratory and local bird populations may harbor pathogenic *E. coli*, thus contributing to environmental contamination and facilitating the transmission of virulent strains to humans, particularly in areas where human and wildlife habitats intersect (Gülhan et al., 2012; Nuhay&Gülhan 2017). The role of wildlife as a reservoir highlights the complexity of *E. coli* O157:H7 epidemiology and emphasizes the need for comprehensive monitoring and control strategies encompassing not only agricultural settings but also natural ecosystems.

4. INFECTIONS CAUSED BY *ESCHERICHIA COLI* STRAINS IN HUMANS

Escherichia coli, which is part of the normal intestinal flora of mammals and poultry, generally coexists in balance with other bacterial groups. As long as this balance is maintained, it does not cause infections. Under normal conditions, it contributes to the regulation of putrefaction and fermentation processes and supports vitamin synthesis. However, in certain circumstances, *E. coli* can become pathogenic to both humans and animals, leading to intestinal infections characterized by inflammation and diarrhea. Moreover, when it colonizes extraintestinal tissues, its clinical significance increases. Notably, *E. coli* can cause serious infections when it reaches the urinary tract, gallbladder and bile ducts, lungs, peritoneum, and meninges (Neil MA, 1994; Jiang ZD et al., 2000; Güler L et al., 2002; Shrestha, Miao, & Mehershahi, 2023).

Infections caused by *E. coli* are classified into two main groups: intestinal and extraintestinal infections.

4.1. Intestinal Infections Caused by *Escherichia coli* Strains

Escherichia coli is capable of causing a wide range of intestinal infections in humans, presenting with symptoms that vary from mild diarrhea to severe, cholera-like enteritis with significant fluid loss. These infections are classified into distinct pathotypes based on their virulence mechanisms and clinical manifestations. The major diarrheagenic *E. coli* groups include: enterotoxigenic *E. coli* (ETEC), which is a common cause of traveler's diarrhea; enteropathogenic *E. coli* (EPEC), typically associated with infantile diarrhea; enterohemorrhagic *E. coli* (EHEC), known for causing hemorrhagic colitis and hemolytic uremic syndrome; enteroinvasive *E. coli* (EIEC), which invades intestinal epithelial cells and leads to dysentery-like illness; enteroaggregative *E. coli* (EAggEC), associated with persistent diarrhea particularly in children; and diffusely adhering *E. coli* (DAEC), which is linked to chronic diarrhea in certain age groups (Erensoy & Tokbaş, 1992; Jiang et al., 2000; Mutlu, 2001; Jafari et al., 2021).

4.1.1. Enterotoxigenic *Escherichia coli* (ETEC) Infections

Enterotoxigenic *Escherichia coli* (ETEC) is recognized as one of the most common causes of acute bacterial diarrhea worldwide, particularly affecting children under the age of two in developing countries. ETEC strains are prevalent in regions such as India and Bangladesh, where they can cause cholera-like illness in adults. Although individuals residing in these areas typically possess acquired immunity, tourists visiting from non-endemic regions are susceptible to what is commonly known as traveler's diarrhea. ETEC has been implicated in 11% to 72% of traveler's diarrhea cases. This condition is characterized by symptoms such as diarrhea, nausea, abdominal cramps, and low-grade fever, typically following the ingestion of water or food contaminated with *E. coli*. Poor hygiene practices and unsafe water sources play a major role in the transmission and spread of the infection. The infectious dose in contaminated food is relatively high, with 10^6–10^8 CFU/mL of *E. coli* being sufficient to cause disease in healthy individuals. Gastric acid serves as a protective barrier against infection (Erensoy & Tokbaş, 1992; Jiang et al., 2000; Mutlu, 2001; Jafari et al., 2021).

The pathogenesis of ETEC infections is primarily mediated by the production of enterotoxins. ETEC strains produce two main types of enterotoxins: heat-labile toxin (LT), which is inactivated at 60°C for 30 minutes, and heat-stable toxin (ST), which remains active even after exposure to 100°C for 15 minutes (Gülhan et al., 2009). Strains may produce either or both toxins. In addition to toxin production, the pathogenicity of ETEC involves the presence of colonization factors known as CFA (Colonization Factor Antigens), which mediate bacterial adhesion to the intestinal epithelium. These fimbriae prevent the elimination of bacteria by intestinal peristalsis. To date, five CFAs have been described, with CFA/I and CFA/II being the most commonly produced by ETEC strains (Frey et al., 2000; Johnson et al., 2002; Jafari et al., 2021).

The LT toxin, frequently plasmid-encoded in both human- and animal-origin strains, shares structural, antigenic, and functional similarities with the cholera toxin (CT) produced by Vibrio cholerae. Both LT and CT are multimeric proteins consisting of an A subunit and five B subunits. The B subunits mediate binding to epithelial cells, while the A subunit is split into A_1 and A_2 fragments. The A_1 fragment activates intracellular adenylate cyclase, leading to increased levels of cyclic adenosine monophosphate (cAMP). This increase in cAMP within intestinal villus epithelial cells promotes chloride secretion and inhibits sodium chloride absorption. Simultaneously, sodium secretion from crypt cells increases, resulting in significant water and electrolyte loss into the intestinal lumen and, consequently, profuse watery diarrhea (Donnenberg & Kaper, 1992; Galvan et al., 1999; Jafari et al., 2021).

In contrast, the ST toxin is a smaller, non-immunogenic, heat-stable peptide. It is classified into two subtypes: ST_A (ST-1) and ST_B (ST-2). ST_A stimulates guanylate cyclase activity, thereby increasing intracellular cyclic guanosine monophosphate (cGMP) levels, which disrupts electrolyte transport and contributes to secretory diarrhea (Holmes et al., 1986; Majali et al., 2000).

ETEC infections present as non-bloody watery diarrhea accompanied by nausea, abdominal pain, cramps, and low-grade fever. The bacteria do not invade or penetrate the intestinal mucosa. For diagnosis, reference laboratories must identify the presence of enterotoxins and colonization factors through cell culture or other biological systems. In addition, serotyping of isolated strains using specific antisera is recommended. Commercial diagnostic kits that detect LT and ST toxins are also available (Belongia et al., 1993; Andreu et al., 2005;Lui et al., 2017).

4.1.2. Enteropathogenic Escherichia coli (EPEC) Infections

First identified in 1955, enteropathogenic *Escherichia coli* (EPEC) strains do not produce classical toxins in the intestine. However, they cause diarrhea through a unique mechanism known as "attaching and effacing," by which the bacteria adhere tightly to epithelial cells of the small intestine and disrupt the microvilli structure (Keene et al., 1997; Andreu et al., 2005; Martins et al., 2022).

EPEC is most commonly isolated from children under the age of two. Clinically, the infection is characterized by fever, vomiting, and watery diarrhea that may contain mucus but is typically non-bloody. Outbreaks have been reported in hospitals, neonatal wards, and daycare centers. Although lactic acid bacteria in the gut flora increase intestinal acidity through lactose breakdown, which can have protective effects, breast milk has also been shown to exert significant protective action against EPEC infections. EPEC plays an especially important role in neonatal outbreaks and severe, chronic diarrhea cases.

EPEC strains can be identified by their characteristic O serogroups using polyvalent antisera through slide agglutination, enzyme-linked immunosorbent assay (ELISA), or cell culture techniques (Donnenberg, 1992; Andreu, 2005; Martins et al., 2022).

4.1.3. Enteroinvasive *Escherichia coli* (EIEC) Infections

Outbreaks of foodborne diarrhea caused by enteroinvasive *Escherichia coli* (EIEC) have been reported in Southeast Asia, Eastern Europe, and the Americas. EIEC typically causes a dysentery-like clinical picture resembling Shigella-induced enteritis, primarily in children but also in adults. The most distinctive feature of these strains is their ability to invade the colonic mucosa by expressing proteins encoded by a large invasion plasmid. After penetrating the epithelium, the bacteria multiply within epithelial cells and induce cellular damage, leading to ulceration and inflammation of the intestinal mucosa.

For diagnostic purposes, serotyping, ELISA, and the Sereny test based on the development of keratoconjunctivitis in guinea pig eyes are used. Additionally, the invasive potential of EIEC strains can be evaluated using in vitro cell culture models such as Hep 2 and HeLa cells (Donnenberg & Kaper, 1992; Carter et al., 1995; Andreu et al., 2005).

4.1.4. Enterohemorrhagic *Escherichia coli* (EHEC) Infections

Infections caused by EHEC strains are predominantly foodborne. The primary serotype of concern is *E. coli* O157:H7, although other serotypes such as O26:H11, O103:H2, O111:H8, O114:H4, and O126:H11 are also considered significant. The global incidence of infections caused by O157:H7 has been steadily increasing. Higher case numbers are observed during summer months, and the disease most frequently affects individuals under five and over sixty-five years of age. Outbreaks have been reported in nursing homes and childcare centers. Given its association with severe complications—such as hemorrhagic colitis (HC), hemolytic uremic syndrome (HUS), and thrombotic thrombocytopenic purpura (TTP)—EHEC represents a growing public health concern (Belongia, 1993; Maclure, 2000; Parma et al., 2000; Melton-Celsa, 2020).

EHEC strains primarily produce two types of toxins (Gülhan et al., 2009). One of these, Shiga-like toxin 1 (SLT-1 or Stx1), shares approximately 99% similarity with the toxin produced by Shigella dysenteriae type 1. The second, Shiga-like toxin 2 (SLT-2 or Stx2), shows only 55–60% homology with Shiga toxin but is also cytotoxic. Both toxins exert typical cytopathic effects in cell cultures, initially observed in Vero cells, which led to the terms "verotoxin" for the toxin and "verotoxin-producing *E. coli*" (VTEC) for the organism (O’Brien & LaVeck, 1993).

Although the molecular mechanism of verotoxin activity in mammals is not fully elucidated, it is believed that the B subunit of the toxin binds to glycolipid receptors on host cells, facilitating entry. The enzymatically active A1 fragment of the A subunit then inhibits protein synthesis by binding to the 60S ribosomal subunit, leading to cell death. Intraperitoneal administration of the toxin in mice results in hindlimb paralysis and death, while direct administration to the intestines causes selective degeneration of colonic epithelium (Parma et al., 2000). It remains unclear whether *E. coli* O157:H7 produces verotoxin in food matrices or if the ingestion of verotoxins via contaminated food is sufficient to induce disease in humans (Cosancu & Ayhan, 2000; Melton-Celsa, 2020).

4.1.4.1.Hemolytic Uremic Syndrome (HUS)

First described in 1955, the relationship between VTEC and HUS was established in 1985. HUS is the leading cause of acute renal failure in children and is characterized by a clinical triad of acute anuric renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. It exists in both endemic and sporadic forms, with increased incidence in summer and autumn. While it resembles TTP, HUS typically involves abrupt onset of renal impairment and anuria, with disease severity largely determined by the extent and duration of kidney involvement (Karmali et al., 1983; Miyazaki, 1994; Shigematsu, 1997; Peacook et al., 2001; Joseph et al., 2020).

HUS predominantly affects infants, young children, pregnant or postpartum women, and, less frequently, older children and nonpregnant adults. Histopathologically, the disease is marked by fibrin thrombi within glomerular arterioles and capillaries, resulting in fibrinoid necrosis and cortical necrosis. Clinical signs include elevated lactate dehydrogenase (LDH), hematuria, proteinuria, and decreased glomerular filtration. While the Coombs test is usually positive, coagulation tests are typically normal, aside from increased fibrin degradation products. HUS develops in approximately 0–15% of hemorrhagic colitis cases and in around 10% of pediatric patients. In elderly patients, when accompanied by fever and TTP, the mortality rate may approach 50%. Atypical HUS syndromes have also been observed in patients receiving chemotherapeutic agents such as mitomycin or cyclosporine, and in those undergoing bone marrow or stem cell transplantation (Peacook et al., 2001; Gerber, 2002; Chang Hwa-Gan et al., 2004; Joseph et al., 2020).

4.1.4.2.Thrombotic Thrombocytopenic Purpura (TTP)

TTP is more common in adults and is characterized by microangiopathic hemolytic anemia, thrombocytopenia, purpura, and renal involvement. In untreated cases, mortality is high. Approximately 60% of cases occur in women, particularly between the ages of 10 and 40. While chronic forms can persist for years, the most common presentation is an acute fulminant type, often fatal within weeks. Initial symptoms in women may include vaginal bleeding. Laboratory findings include severe thrombocytopenia, fragmented erythrocytes (helmet cells, triangular or distorted forms), anemia (low Hb, elevated reticulocyte count), neurological symptoms, abdominal pain, cardiac arrhythmias due to myocardial involvement, fever, arthralgia, and myalgia. Elevated LDH, jaundice (due to both direct and indirect bilirubin increase), proteinuria, hematuria, elevated urea levels, and hyaline thrombi in microvasculature are also noted. Reticulocytosis is moderate in 20% of cases, and nucleated red blood cells are found in peripheral smears. The Coombs test is rarely positive, and leukocytosis with a left shift is common. The lupus erythematosus (LE) phenomenon is positive in 10–20% of cases. Lymph node biopsy can aid diagnosis. TTP may co-occur with autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, Sjögren’s syndrome, and vasculitis affecting small vessels (Ezra et al., 1996; Joly et al., 2017).

The primary treatment for TTP is plasma exchange therapy (plasmapheresis) using 5 L/day of fresh frozen plasma, continued until clinical remission is achieved. Steroids have limited efficacy, but antiplatelet agents (e.g., aspirin, dipyridamole, sulfinpyrazone, dextran) can be used adjunctively. In patients unresponsive to plasma therapy, alternative treatments such as azathioprine, vincristine, or splenectomy may be considered. Long-term monitoring is essential (Ezra et al., 1996; Joly et al., 2017).

4.1.4.3.Hemorrhagic Colitis (HC)

This condition is most commonly associated with *E. coli* O157:H7 and is characterized by acute onset of bloody diarrhea. It affects individuals of all ages and is frequently linked to the consumption of undercooked beef, unpasteurized milk, and dairy products. Cattle are the primary reservoir. Transmission is typically fecal-oral, with higher incidence in children aged 0–2 years. Clinical symptoms include profuse watery diarrhea progressing to visible blood within 24 hours, along with intense abdominal cramping. The incubation period ranges from 3 to 9 days, and the disease duration in uncomplicated cases is generally 2 to 9 days. The pain has been described as more severe than appendicitis and comparable to postpartum uterine contractions (Frey et al., 2000; Jangid et al., 2024).

Fever is uncommon. Microscopy of fresh stool samples may reveal fecal leukocytes. Sigmoidoscopy often shows erythema and edema, while barium enema may reveal the classic "thumbprinting" sign. Up to 51% of HC cases develop HUS, and some may progress to TTP, typically in the second week of illness. HUS is more common in children under five, while TTP occurs more often in the elderly. Diagnosis is confirmed by isolating *E. coli* O157:H7 from stool culture. A distinguishing feature from other infectious diarrheal diseases is the presence of grossly bloody stools (Griffin et al., 1990; Torok et al., 1995; Jangid et al., 2024).

Prevention includes minimizing environmental contamination from infected stool, practicing good hygiene and handwashing with soap, pasteurizing milk, and thoroughly cooking meat products. In uncomplicated cases, supportive treatment with fluid therapy and a soft diet is the mainstay of management (Frey et al., 2000; Jangid et al., 2024).

4.1.5. Enteroaggregatif *Escherichia coli* (EAEC) Infections

EAggEC strains were first identified through epidemiological studies conducted in animals. The term refers to *E. coli* strains that do not produce heat-labile (LT) or heat-stable (ST) enterotoxins, are non-invasive, and are distinguished from ETEC, EPEC, EIEC, and EHEC virotypes based on their O and H antigens. These strains exhibit a characteristic aggregative adherence pattern on HEp-2 and HeLa cells. EAggEC has been isolated from cases of chronic diarrhea in various parts of the world and is known for its high adhesive capacity to intestinal epithelial surfaces.

Although EPEC strains also possess adherence capabilities, they induce localized adherence, whereas EAggEC strains exhibit diffuse adherence, forming bacterial aggregates resembling stacked bricks. These infections can affect individuals of all ages. In children, EAggEC infection typically presents with watery diarrhea, vomiting, dehydration, and less commonly with abdominal pain, fever, or bloody stools.

Diagnosis of EAggEC infections involves the use of DNA probes specific to aggregative adherence-associated genes. Additionally, a liquid-culture aggregation test, which detects the ability of the bacteria to form visible clumps, is employed as a specialized method to distinguish EAggEC strains from other diarrheagenic *E. coli* types (Levine, 1987; Gray, 1995; Cobeljik et al., 1996; Dias et al., 2020).

4.2. Extraintestinal Infections Caused by *Escherichia coli* Strains

The majority of urinary tract infections (UTIs) are bacterial in origin, although in rare cases, viruses and fungi may also be causative agents. More than 95% of UTIs are caused by a single bacterial species. Among bacterial pathogens, uropathogenic *Escherichia coli* (UPEC), which typically originates from the fecal and vaginal flora, is the most common causative agent. UTIs are generally classified into asymptomatic bacteriuria, uncomplicated UTIs, and complicated UTIs (Sobel, 1997; Manges et al., 2001; Russell et al., 2023).

In uncomplicated UTIs such as urethritis, cystitis, and urethro cystitis *E. coli* is the predominant pathogen. Although other microorganisms such as Enterococcus saprophyticus, Pseudomonas aeruginosa, and various Gram-negative bacteria may be involved in complicated UTIs such as cystopyelitis, pyelonephritis, and perinephric abscesses *E. coli* remains the most frequently isolated organism in this group as well. Infections caused by species such as Klebsiella, Proteus, Enterobacter, and Pseudomonas are usually associated with immunocompromised states or underlying conditions.

Notably, in nosocomial (hospital-acquired) UTIs, *E. coli* is the leading pathogen, accounting for approximately 50% of all cases (Barnett & Stephens, 1997; Russell et al., 2023).

Infections of the urinary system are predominantly bacterial in origin, though in rare instances viruses and fungi may also be involved. More than 95% of urinary tract infections (UTIs) are caused by a single bacterial species. Among these, uropathogenic *Escherichia coli* (UPEC)—which originates from the fecal and vaginal flora—is the most frequently isolated pathogen. UTIs are typically classified into asymptomatic bacteriuria (ASB), uncomplicated, and complicated urinary tract infections (Sobel, 1997; Manges et al., 2001; Russell et al., 2023).

In uncomplicated UTIs such as urethritis, cystitis, and urethro-cystitis, *E. coli* accounts for approximately 80% of all cases. Other agents like Staphylococcus saprophyticus are isolated in 10–15% of cases, while Klebsiella pneumoniae and Proteus mirabilis are responsible for a smaller proportion, approximately 3% and 2% respectively. In complicated UTIs—such as cystopyelitis, pyelonephritis, and perinephric abscesses—*E. coli* remains the most frequently identified agent, accounting for 30% of cases, followed by Enterococcus spp. and Pseudomonas aeruginosa, each responsible for about 20% of infections. Coagulase-negative staphylococci are implicated in 15% of cases, while Klebsiella pneumoniae and Proteus mirabilis are isolated at rates of 5% and 4%, respectively. Other Gram-negative organisms, such as Enterobacter spp. and Pseudomonas spp., are typically involved in patients with compromised immune function. In hospital-acquired UTIs, *E. coli* remains the leading pathogen, responsible for approximately 50% of cases (Barnett & Stephens, 1997; Russell et al., 2023).

Asymptomatic bacteriuria (ASB) refers to the presence of significant bacteriuria in individuals who do not exhibit any clinical symptoms. It is defined as the detection of microorganisms in bladder urine that has not been contaminated by urethral or vaginal flora. ASB is particularly relevant in several high-risk populations, including diabetic patients, pregnant women, the elderly, renal transplant recipients, patients with long-term urinary catheterization, children with vesicoureteral reflux, individuals with infected struvite calculi, and those with prosthetic devices such as heart valves or artificial joints (Koneman et al., 1997). In addition, ASB may develop in patients with neurogenic bladder or necrotic urinary tract tumors. *E. coli* is identified as the causative organism in more than 80% of community-acquired ASB cases and is responsible for about 50% of hospital-acquired ASB cases.

In addition to UTIs, *E. coli* is responsible for a variety of extraintestinal infections, including sepsis, meningitis, peritonitis, appendicitis, wound infections, cholecystitis, and cholangitis. These infections are diagnosed by isolating the organism from the appropriate clinical specimens. In the context of UTIs, diagnosis requires isolation of the pathogen from urine samples. During midstream urine examination, quantification of bacterial colony-forming units (CFU) is essential to distinguish between true infection and contamination. The likelihood of infection increases with the bacterial count, which led to the establishment of the concept of "significant bacteriuria." In freshly voided urine, a bacterial count of more than 10^5 CFU/mL is generally accepted as significant bacteriuria, particularly in women where contamination risk is higher. In men, due to the lower likelihood of contamination, a count of more than 10^3 CFU/mL is often considered sufficient to indicate infection. Therefore, the interpretation of significant bacteriuria must be tailored to the clinical context.

For symptomatic women, significant bacteriuria is defined as $>10^2$ CFU/mL of coliform bacteria or $>10^5$ CFU/mL for non-coliform species. In symptomatic men, $>10^3$ CFU/mL is considered diagnostic. In asymptomatic individuals, two consecutive urine specimens with $>10^5$ CFU/mL are required. For patients with indwelling urinary catheters, a threshold of $>10^2$ CFU/mL of coliform bacteria is sufficient for diagnosis (Andreu et al., 2005; Russell et al., 2023).

5. TREATMENT OF *ESCHERICHIA COLI* INFECTIONS

Regardless of the specific pathotype, the primary approach in treating enteric *Escherichia coli* infections involves the replacement of lost fluids and electrolytes. In mild cases, oral rehydration is usually sufficient, whereas more severe cases may require intravenous fluid therapy (Villa et al., 2000).

The use of antimotility agents is contraindicated, particularly in ETEC and EIEC infections, as these may exacerbate the disease by prolonging bacterial retention and toxin exposure in the gut. In ETEC-associated diarrhea, bismuth subsalicylate may help alleviate symptoms; although the exact mechanism is not fully understood, animal studies have demonstrated its potential to inhibit enterotoxin production (Frey et al., 2000; Kakoullis et al., 2020).

While the role of antimicrobial therapy in *E. coli* infections remains somewhat controversial, clinical studies involving travelers' diarrhea have shown that agents such as doxycycline, trimethoprim-sulfamethoxazole, and ofloxacin can shorten the duration of symptoms to 24–36 hours. However, due to the potential for plasmid-mediated co-transfer of enterotoxin and multidrug resistance genes in ETEC strains, antibiotic use should be avoided unless absolutely necessary.

Given that EIEC infections clinically resemble shigellosis, it has been suggested that indications for antimicrobial therapy in shigellosis may also apply to EIEC-related cases. Nevertheless, this assumption is not yet supported by sufficient clinical data (Frey et al., 2000).

In contrast, the use of antibiotics in EHEC infections is not only ineffective but may also increase the risk of adverse outcomes, such as hemolytic uremic syndrome, due to enhanced toxin release.

For extraintestinal *E. coli* infections, targeted antibiotic therapy is essential and should be guided by the results of antimicrobial susceptibility testing (Ezra et al., 1996; Kakoullis et al., 2020).

6. CONTROL AND PREVENTION OF *ESCHERICHIA COLI* INFECTIONS

Due to its presence as a natural component of the intestinal microbiota, preventing *Escherichia coli* infections can be challenging. As with other fecal–oral transmitted infections, personal hygiene plays a critical role in prevention. Individuals should consume clean water and properly prepared foods, boil drinking water when contamination is suspected, and thoroughly wash fruits and vegetables. Special attention should be given to the preparation and thorough cooking of processed foods such as hamburgers. When consuming milk or dairy products, it is essential to ensure adequate pasteurization or boiling (Ezra et al., 1996; Keene et al., 1997; Peacook et al., 2001; McNeilly et al., 2015).

To prevent hospital-acquired *E. coli* infections, rigorous implementation of cleaning, disinfection, and sterilization procedures is necessary. Both patients and healthcare personnel must adhere strictly to personal hygiene protocols, with particular emphasis on proper hand hygiene (Miyazaki, 1994; Peacook et al., 2001; McNeilly et al., 2015).

Immunization strategies against *E. coli* infections are not yet sufficient for effective protection. However, several studies have demonstrated that prophylactic administration of chemotherapeutic agents such as fluoroquinolones and trimethoprim-sulfamethoxazole may be effective in preventing traveler’s diarrhea by suppressing the anaerobic intestinal flora. Despite these findings, widespread prophylactic use cannot be recommended given the large number of global travelers and the potential for antimicrobial resistance (Frey et al., 2000; Villa et al., 2000; McNeilly et al., 2015).

Additionally, in cattle, two commercially available vaccines—Econiche and Epitopix—have been developed for the prevention of *E. coli* O157:H7 infections, aiming to reduce bacterial shedding and zoonotic transmission risk.

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BALIK MİKROBİYOTASI VE FLAVOİDLER ARASINDAKİ İNTERAKSİYON

Altuğ KÜÇÜKGÜL[1]

1. GİRİŞ

Sindirim sistemine dâhil birçok mikroorganizma (bakteri, virüs vb.) canlının mikrobiyotasını oluşturmaktadır. Sağlığımız üzerinde pozitif etkileri olan bu mikroorganizmalar sindirim sisteminden bağışıklık sistemine kadar birçok fonksiyonda önemli rol oynamaktadır. Ayrıca hastalıklardan korunmada ve metabolizmanın sağlıklı sürdürülmesinde kritik önem arz etmektedir.

İnsanlarda ve diğer memelilerde büyük ve karmaşık bir mikrobiyota topluluğu raporlanmışken balıkların bağırsak bakteri topluluğunun diğer omurgalılarınkinden (yani sürüngenler, kuşlar ve memeliler) önemli ölçüde farklı olduğu buna rağmen sağlık üzerinde önemli etkileri olduğu bildirilmiştir.

Balıklarda mikrobiyota bileşiminin ve konak-mikrobiyal etkileşiminin özgüllüğü, balık mikrobiyotası araştırmalarının önemini vurgulamaktadır. Bundan dolayı mikrobiyotanın balık sağlığı, performans ve diğer fizyolojik işlevleri üzerindeki etkilerini kapsayan birçok çalışma yürütülmüştür Chiarello ve ark., 2018; Rawls ve ark., 2004). Bu çalışmalardan mikrobiyotanın balık besleme üzerindeki etkileri, balık konağı ile mikrobiyotanın etkileşimi, mikrobiyotanın bağışıklık ve diğer fizyolojik işlevlerin düzenlenmesindeki rolü önemli araştırmalar

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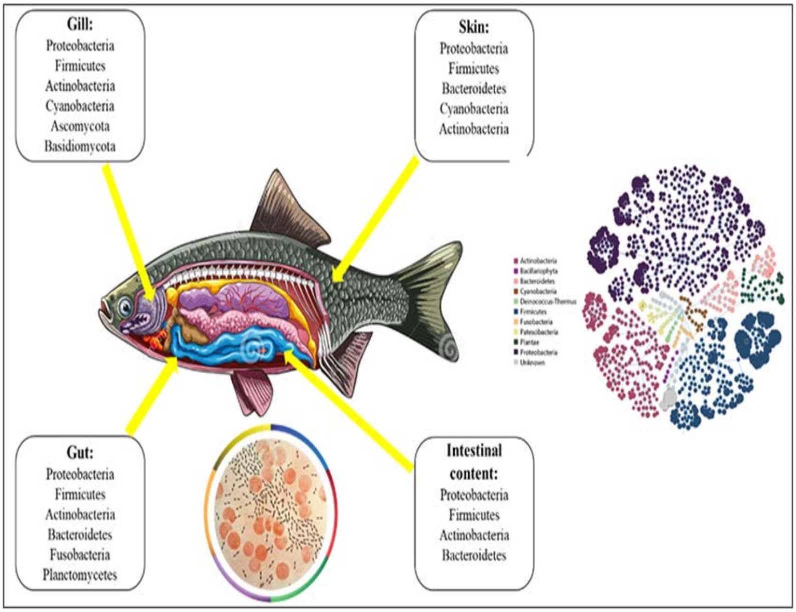
olarak bildirilmiştir (Kokou ve ark., 2019; Walburn ve ark., 2019; Li ve ark., 2022). Görünen o ki su ürünleri yetiştiriciliği endüstrisinde balık mikrobiyota araştırmaları metabolik hastalıklar, su kalitesi ve antibiyotik kaynaklı problemlerin üstesinden gelmede çevre dostu ve yeşil çözümler sunmaktadır. Mikrobiyotadan türetilen probiyotikler ve karşılık gelen prebiyotikler (Wang ve ark., 2021), ayrıca balıkların derisi, solungaçları ve diğer mukozal yüzeylerinin mikrobiyotası hakkında birçok çalışma sektördeki güncel araştırmalardandır (Legrand ve ark., 2018; Llewellyn ve ark., 2014).

Flavoidler bitkilerde bulunan doğal biyoaktif özellikli bileşiklerdir. Birçok meyve ve sebzede glikozitler formunda yaygın olarak bulunmaktadır. Polifenol bileşiklerin geniş bir kısmını oluşturan flavonoidlerin temel yapıları bir heterosiklik piran halkası (C) ve iki aromatik halkadan (A ve B) oluşmakta ve böylece bir dizi biyolojik aktivite sergilemektedir. Bu etkilerden en önemlileri antitümör, antienflamatuvar, antioksidan, antiviral, antimikrobiyal ve bağırsak sağlığı üzerinde olan probiyotik etkileridir (Kubulay ve ark., 2016; Peluso ve srk., 2015; Pei ve ark., 2020). Yapılan çalışmalar göstermişti ki flavoidin alımını takiben konağın bağırsak mikrobiyotası tarafından metabolize edilmekte oksidatif stres, inflamasyon ve bağırsak mikrobiyotası bozukluklarının düzeltilmesinde rol oynamaktadır (Cassidy ve ark., 2017; Han ve ark., 2022). Yapılan son araştırmalar bağırsak mikrobiyotası ve flavonoidlerin arasındaki etkileşim üzerine odaklanmış flavonoidlerin bağırsak mikrobiyotasında yararlı mikropları arttırıp zararlıları engelleyerek etkin bir rol oynadığı bildirilmiştir (Cheng ve ark., 2016; Tian ve ark., 2019).

Bu çalışmada balıklardaki mikrobiyotanın sağlık üzerindeki önemi ve özellikle mikrobiyota ve flavoidler arasındaki interaksiyon üzerinde durulmuştur.

2. BALIKTA MİKROBİYOTA

İnsanlarda ve diğer memelilerde olduğu gibi, balıkların bağırsaklarında büyük ve karmaşık bir mikrop topluluğu bulunur. Sağlık üzerinde pozitif etkileri olan bu mikroorganizmalar canlının mikrobiyotasını oluşturmaktadır.



Resim 2.1. Balıklarda mikrobiyotanın kompozisyonu (Haque ve ark., 2022)

Mikrobiyota canlının genetiği, beslenme alışkanlıkları, gelişim safhaları ve çevre gibi birçok faktörden etkilenebilmektedir. Balıklarda bu durum geçerli olup en önemli faktörlerin başında gıda ve besinler gelmektedir. Yapılan bir araştırmada aynı gölde yaşayan etçil ve otçul balıklar üzerinde bağırsak içerikleri analiz edilmiş; otçul olanlarda Citrobacter, Clostridium Leptotrichia vb. bakterilerce zenginlik, etçil olanlarda ise Halomonas ve Cetobacterium gibi bakteri toplulukları gözlenmiştir. Bu da demek oluyor ki diyetin özellikle bağırsak mikrobiyotası üzerinde etkindir (Liu ve ark., 2016). Balıklarda mikrobiyota ile konak seçiminin bakteriyel topluluğun ana belirleyicisi olduğu bir diğer önemli durum olarak karşımıza çıkmaktadır. Daly ve ark. (2019), farklı çiftliklerden sazan ve gökkuşağı balıklarının bağırsak mikrobiyota içerilerini araştırdı. Elde edilen sonuçlar gösterdi ki yetiştirme ortamları farklı da olsa her iki balık türü içinde bakteri topluluğu tür içi tekdüzeliğe sahipti. Mikrobiyal topluluğu etkileyen bir diğer etken ise çevresel faktörlerdir. Üç omnivor balığın su, tortu ve bağırsaklarındaki bakteri topluluklarını incelendiğinde *Toxabramis houdemeri* ve *Hemiculter leucisculus*'un su mikrobiyotasına, *Oreochromis mossambicus*'un tortuların bakteriyel topluluklarına benzediği raporlanmıştır. Bu durum gösteriyor ki T. houdemeri ve *H. leuisculus* pelajik, *O. mossambicus*'un ise bentik türler olması bu benzerliğin en büyük kanıtıdır (Bi ve ark., 2021). İçinde yaşadığı suyun sıcaklığı, tuzluluğu gibi etkenler balıkların bağırsak mikrobiyotasını etkileyen bir diğer çevresel faktörlerdendir (Hieu ve ark., 2022; Horlick ve ark., 2021). Sıcaklık artışıyla bağırsak mikrobiyotasının çeşitliliğinin azaldığını buna karşın Mycoplasma, Firmicutes ve Tenericutes'un bolluğunun önemli ölçüde Zhou ve ark. (2022) bildirmişlerdir. Bir diğer çalışmada zebra balıklarının karaciğer ve bağırsak epitelinde yağ asit alımı ve lipit damlacıklarının oluşumun uyarılmasında mikobiyotanın etkin olduğu bildirilmiştir (Semova ve ark., 2012).

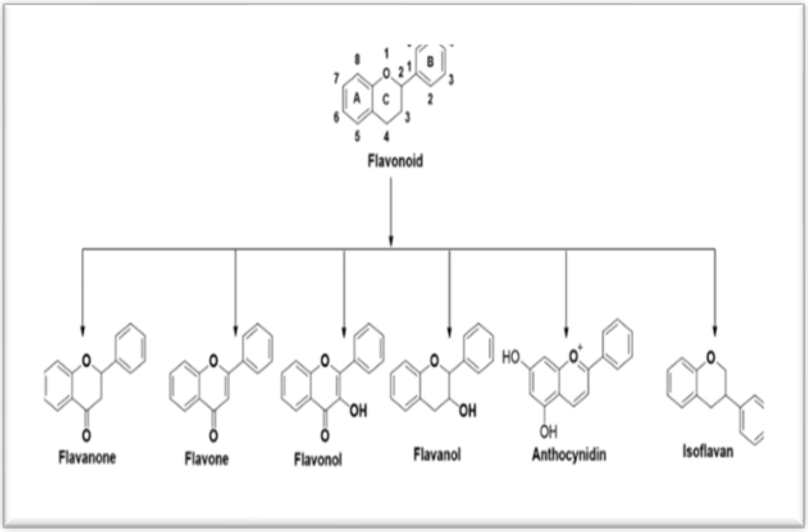
Balık sağlığı ve hastalıklarında önemli olan mikrobiyota balıklarda büyüme, metabolizma, bağışıklık ve hastalık direncinde iyileşme gibi birçok durumda da kilit rol oynamaktadır. Özellikle balıklardaki bakteriyel hastalıkların tedavisinde kullanılan antibiyotikler ekzojen veya endojen mikroorganizmalarla ve bağırsak mikrobiyal topluluklarıyla etkileşime girme şeklini değiştirdiği birçok literatürde raporlanmıştır (Küçükgül ve ark., 2013; Legrand ve ark., 2020; Rosado ve ark., 2019). Öyle ki antibiyotiklerin bilinçsiz kullanımı mikrobiyotanın çeşidi ve miktarı gibi kısa ya da uzun vade d zarar verebilmektedir. Bunun yanında fırsatçı patojenlere (Aeromonas vb.) öncülük edebilmektedir ve doğal olarak balık sağlığı tüm bu durumlardan olumsuz etkilenebilmektedir (Wang ve ark., 2019). Bu konuyu referans gösteren bir araştırmada Bozzi ve ark. (2021) formalin ile tedavi edilen Atlantik somununun bağırsak mikrobiyotasını incelediğinde mikrobiyotanın olumsuz etkilendiğini ve hasta balık mikrobiyotasına sahip olduğunu raporlamıştır. Mikrobiyota ve kommensal bakterilerin balıkların enerji dengesi ve metabolik sağlığı üzerindeki etkisinde rol oynadığı birçok çalışma ile vurgulanmıştır. Bu çalışmalardan biri olan araştırmada, yüksek yağlı bir diyetle beslenen nil tilapyasının bağırsağından örneklenen Citrobacter suşunun konak-mikrop etkileşiminin korunan bir özelliği olan enerji hasadını arttırdığı raporlanmıştır (Zhang ve ark., 2020).

Balık sağlığının korunmasında güçlü bir immünitenin rolü çok büyüktür. Bu bağlamda bağışıklığın düzenlenmesinde mikrobiyal metabolitler ya da bakteriyel bileşenlerinin öneminden bahsetmek gerekmektedir. Kommensal bir bakteri olan *A. veronii* ile konakçısı incelenmiş (zebra balığı) ve bakterinin bağırsakta mevcut iltihap üzerinde iyileştirici etkisi olan immünomodülatör protein olan AimA salgıladığı bildirilmiştir (Rolig ve ark., 2018). Tüm bu veriler ışığında, balık sağlığı ve hastalığında mikrobiyotanın rolü çok önemlidir. Deniz ve tatlı balıklarında mikrobiyotanın gelişimi balıkların içinde yaşadığı suyun, besin içeriklerinin, mevsimlerin, trofik seviyelerinin farklı çevresel koşullarına göre değişim gösterebilmektedir.

3. FLAVOİDLER

Sağlık üzerinde olumlu etkileri olan doğal bileşiklerden flavonoidler bitkilerde düşük molekül ağırlıklı olarak bulunmaktadır (Sghaiera ve ark., 2011). İlk olarak vitamin P olarak adlandırılan flavanoidler daha sonra çeşitli araştırmalarla vitmin aktivitesi sergilemediği bildirilmiş ve doğal biyolojik aktivite sergilediğinden flavanoid ismini almıştır (Chichester ve ark., 1981). Flavanoidlerin yapısı fenolik doğal bileşenlerden iskeleti ise iki fenolik halka içeren 15 karbondan oluşmaktadır ki karakteristik özelliklerini bu halka belirlemektedir (Kocabaş, 2008).

Flavonoidler bitkilerde en çok bulunan sekonder metabolit türdür. Flavanoidlerin sayısı günümüze dek 5000'den fazladır (Bronze ve ark., 2012). Flavonoidler birçok sınıfa ayrılsa da temelde 6 sınıf olarak ele alınmaktadır (Resim 2). Flavanol sınıfında yer alan kateşin, epikateşin formunda bulunan flavanoidler daha çok çeşitli meyve, çikolata, çay gibi gıdalarda bulunmaktadır. Karabuğday, domates, kırmızı şarap gibi gıdalarda ise Luteolin glükozit, Chrysin flavanoidleri formlarında bulunan flavanoidler Flavon sınıfındadır. Myricetin, tamarixetin, quercetin flavanoid formlarında zeytinyağı, dutsu meyveler, soğan, şarap gibi gıdalarda bulunan flavanoidler Flavonol sınıfında yer almaktadır. Turunçgiller ve limon gibi gıdalarda bulunan flavanoidler Flavanon sınıfı bünyesinde bulunmaktadır. Genitsin, daidzin formlarında daha çok soya fasülyesinde bulunan flavanoidler İsoflavone sınıfındadır. Son olarak ise Anthocyanidin sınıfında yer alan Apigenidin, cyanidin formalarındaki flavanoidler kiraz, çilek, dutsu meyvelerde çokça bulunmaktadır (Arts ve ark., 1999).



Resim 3.1. Flavonoidlerin sınıflandırılması (Kumar ve Pandey 2013)

Polifenolik bileşikler, özellikle flavonoidler, antioksidan, antimikrobiyal, anti-inflamatuar, anti-alerjik, antikarsinojenik, anti-hipertansif ve anti-tromboz dahil olmak üzere çeşitli biyolojik aktiviteleriyle yaygın olarak tanınır (Ata ve ark., 2024; Bozkaya ve ark., 2023; Frankel ve ark., 1995; Küçükgül Güleç ve ark., 2014; Vaquero ve ark., 2006). Bilindiği üzere flavonoidler bağırsağa girdiğinde mikrobiyota tarafından anaerobik fermantasyona uğrayıp bir seri işlem neticesinde glikozid hidrolize uğrar, daha kolay emilir ve yeni metabolitler oluşmaktadır. Sonuç itibariyle bağırsak mikrobiyotası flavonoidlerin metabolizmasında önemli rol oynamakta ve flavonoidlerin biyolojik aktivitesi artmaktadır ki biyoyararlanım da biyoaktivite ile ilişkilidir (He ve ark., 2017; Koul ve Kalia, 2016).

Hayvanların bağırsaklarında yer alan mantar, bakteri, arke ve virüslerden oluşan büyük bir mikrobiyal topluluk bulunur ve bu topluluk canlının yaşam aktivitesini yakından etkilemektedir. Özellikle flavanoidlerle takviye bu mikrobiyal topluluğun sayısını arttırmasının yanında mikrobiyal metabolitlerindeki dinamik değişikliklere de yardımcı olmaktadır. Bu nedenle flavanoidlerin mikroorganizmaları nasıl etkilediği ve mikroorganizmalar üzerinde bakteriyostatik etkileri nasıl uyguladığı üzerinde durulması gerekli konuların başında gelmektedir. Flavonoidlerin bakterilerin büyümesini ve metabolizmasını etkileyebileceği Alberto ve ark. (2004) tarafından çalışılmış, yapılarına ve konsantrasyonlarına göre mikrobiyal büyümeyi aktive edici veya inhibe edici bir etki gösterdikleri incelenmiştir. Yapılan bir araştırmada, Kuersetin ve mirisetin gibi flavonoidlerin idrar kaynaklı *Escherichia coli*'nin (E. coli) hidrofobisitesini büyük ölçüde azalttığı ve biyofilm oluşumunu kısıtladığı, böylece bakterilerin konakçıya bağlanmasını önlediği bildirilmiştir (Rodriguez-Perez ve ark., 2016). Bakterilerin popülasyon davranışını düzenlemek için kullandığı bir hücreler arası iletişim süreci olan çoğunluk algılama durumunun flavanoidlerle başlıca düzenleyici hedef genlerinin ekspresyonu üzerinde inhibe edici etkilere sahip olduğu da bir diğer bulguyla desteklenmiştir. Baikalin, kuersetin ve kateşin gibi flavonoidlerin bakteriye l yüzme ve küme hareketliliği üzerinde engelleyici etki gösterdiği raporlanmıştır (Luo ve ark., 2017). Virüsler üzerinde yapılan bir diğer araştırmada, flavonoidlerin retrovirüs HIV'de viral DNA replikasyonunun ters transkriptaz enzimini inhibe ederek veya viral yüzeydeki glikoprotein üzerinde etki ederek virüsün yapışmasını etkileyerek etkisini kanıtladığı bildirilmiştir (Mahmood, 1993).

Canlılarda mikrobiyota özellikle bağırsak mikrobiyotası yüksek şeker ve yağlı diyetlerden olumsuz etkilenmektedir. Bu durumda kurtarıcı rol üstlenen en büyük faktörlerden birisi ise yine flavanoid destekli diyet olmaktadır. Yapılan çalışmalar bağırsak mikrobiyotası üzerinde flavanoidlerin düzenleyici, onarıcı etkilerini kanıtlayıcı bilgiler sunmuş böylelikle konak bağışıklığı, metabolizma ve inflamasyon üzerinde de katkı sağladığı raporlamışlardır. Bir araştırmada, Sun ve ark. (2021), yüksek diyetli yağ ile 12 hafta boyunca sıçanları beslemiş daha sonra sıçanlara mirisetin takviyesi yapmışlardır. Yüksek yağlı diyetin neden olduğu bağırsak mikrobiyotasındaki değişiklikleri mirisetinin önemli ölçüde düzelttiğini bildirmişlerdir. Buna benzer yüksek diyet uygulanan çalışmalarda flavonoidlerle takviyenin bağırsak mikrobiyotasını yeniden şekillendirdiği, probiyotik bolluğunu artırdığı ve patojenik bakteri bolluğunu azalttığı gözlemlenmiştir (Duan ve ark., 2021).

Probiyotik bakteriler canlı bağırsağının doğal sakinleridir, bağırsak mikrobiyotasının dengesini ve patojenlere karşı savunmayı iyileştirerek sağlığı olumlu yönde etkilerler, bu bakterilerin büyümesi ve aktivitesi prebiyotik ile iyileştirilebilmektedir. Probiyotikler içinde bir besin kaynağının çoğunluğu ise flavanoidler oluşturmaktadır. En önemli etkileri ise canlıya hem enerji hem de besin sağlayarak büyümelerini ve üremelerini teşvik etmektedir (Li ve ark., 2023). Ayrıca bağırsak florası içinde çoğalma ve büyüme üzerinde de etkileri olduğu bilinmektedir. Alberto ve ark. (2004) şarapta bulunan *Lactobacillus hilgardii*'nin, normalde şarapta bulunan konsantrasyonlarda gallik asit ve kateşin varlığında büyümeyi uyarıcı bir etki gösterdiğini bildirmiştir. Bunun yanında asit-baz dengesini koruma, bağırsak pH'ını düzenleme, zararlı bakterilerin çoğalmasını engelleme ve probiyotiklerin büyümesine daha elverişli bir bağırsak ortamı yaratma gibi durumlarda yardımcı olan propiyonik asit ve bütirik asit gibi kısa zincirli yağ asitleri üretmek için flavonoidleri metabolize edebilmektedir (Cheng ve ark., 2022; Filannino ve ark., 2015).

4. BALIKTA MİKROBİYOTA VE FLAVANOİD İLİŞKİSİ

Balıklar su içerisinde yaşayan canlı grubu olarak su ile sıkı bir etkileşim gösterirler ve suda oluşabilecek her türlü olumlu ya da olumsuz duruma karşı etki gösterirler. Balıklarda mikrobiyota ise başta bağırsak olmak üzere balık sağlığını destekleyerek homeostazda vazgeçilmez bir rol oynamakta ve su ürünleri yetiştiriciliği yapılan balıkların refahının iyi bir göstergesi olarak bilinmektedir. Doğal olarak balıkların mikrobiyotasında rol oynayan tüm etmenlerinde bu bağlamda iyi bilinmesi ve öneminin anlaşılması gerekmektedir.

Balık mikrobiyotasında önemli rol oynayan etmenlerden birisi de flavanoidlerdir. Flavonoidler, iskeleti 2-fenilkromon olan, meyve, soğan, kakao ve çay gibi bitkilerden elde edilen büyük bir biyoaktif bileşik grubu olup antioksidan, anti-inflamatuar ve antibakteriyel gibi biyolojik özelliklere sahip olan birçok formda (kuersetin, kateşin, rutin, glisirizin vb.) bulunmaktadır (Georgiev ve ark., 2014; Küçükgül, 2018; Küçükgül ve Küçükgül, 2017; Zhang et al., 2011). Biyolojik özellikleri nedeniyle flavanoidce zengin gıdaların tüketimi vücut sağlığını etkilemekte özellikle nörodejeneratif, kardiyovasküler hastalık ve kanser gibi kronik dejeneratif hastalıklar, oksidatif stres üzerinde koruyucu etkiler göstermektedir (Liu ve ark., 2017). Bir çalışmada, gümüş yayın balığı rutin flavonoid diyetle beslenmiş ve oksitetrasiklin kaynaklı karaciğer oksidatif strese karşı etkili olduğu bildirilmiştir (Londero ve ark., 2020). Bir diğer araştırmada, Jia ve ark. (2019), diyetle uygulanan flavonoidin çipura balığının (*Megalobrama amblycephala*) büyüme performansını önemli ölçüde iyileştirdiğini raporlamıştır. Gökkuşağı alabalığı üzerinde yapılan bir diğer çalışma, krezol veya timolün eklenmesinin balık bağırsağında anaerobik bakteri bolluğunu azalttığını ve laktik asit bakteri bolluğunu azalttığını göstermiştir (Hagi ve ark., 2004). Nil tilapia'sının flavonoidler açısından zengin elma kabuğu ile diyet takviyesi karaciğerdeki kolesterol ve triasilgliserol seviyelerinde bir azalma olduğunu göstermiştir (Qiang ve ark., 2019).

Yapılan bazı çalışmalarda ise dünyada su ürünleri yetiştiriciliğinde önemli bir paya sahip ot sazanının et kalitesinin iyileştirilmesinde flavonoid destekli dietin etkileri araştırılmış, optimum dozajlar belirlenmiştir (Li ve ark., 2014; Zhao ve ark., 2018). Benzer bir çalışmada Xu ve ark. (2021), ot sazanının büyümesi, yem kullanımı ve et kalitesi üzerindeki etkileri araştırmak için diyete RT, QC, BC ve CC eklenmiş ve bu flavonoidlerin etki mekanizmasını gerçek zamanlı floresan kantitatif PCR teknolojisi (RT-qPCR) ile belirlemişlerdir. Diyetsel QC ve RT'nin ot sazanının büyümesini ve et kalitesini desteklediği ve bunun IGF-1/TOR, Nrf2, TGF-β/Smad4 ve PPAR sinyal yollarıyla ilişkili olabileceği araştırıcılar tarafından raporlanmıştır. Gökkuşağı alabalığı, siyah kaya balığı (*Sebastes melanops*) ve beluga mersin balığında (*Huso huso*) üzerinde yapılan bir çalışmada, flavonoid özlerinin eklenmesinin lipid peroksidasyonuyla mücadelede ve plazma kolesterol seviyelerinin canlı organizmada azaltılmasında etkili olduğu gösterilmiştir (Akrami ve ark., 2015). Zhai ve Liu (2013) ise tilapia üzerinde 200-1600 mg/kg kuersetin destekli diet uygulamış lipid üzerinde giderek artan düzenleyici etkiler gözlemlemişlerdir.

Bağırsak mikrobiyotası, bağırsak sağlığını destekleyerek homeostazda vazgeçilmez bir rol oynadığı için su ürünleri yetiştiriciliği yapılan balıkların refahının iyi bir göstergesidir. Flavonoidlerin biyoyararlanımının karmaşık yapıları nedeniyle çok düşük olması ancak %5-10'unun ince bağırsakta emilebilmesine olanak sağlamaktadır. Bu nedenle, flavonoidler etkilerini daha ziyade çok sayıda flavonoid prototip halinde bağırsak yoluna ulaşması ve bağırsak mikroorganizmalarıyla etkileşime girmesiyle göstermektedir (Vg ve ark., 2019).

Balıklarda bağışıklık durumu, yem verimliliği ve büyüme performansı için küçük dozlarda prebiyotik içerikli diyet takviyesinin yararlı olduğu bildirilmiştir (Ganguly ve ark., 2013). Düşük kalorili bir diyetle zebra balığı üzerinde bağırsak epiteli ve karaciğerde yağ asidi emilimini uyaran Firmicutes'in daha yüksek olduğu raporlanmıştır (Semova ve ark., 2012). İnülinin %0,25- %2 konsantrasyonlarının; ot sazanı, atlantik somonu ve tilapia (*Tilapia aureus*) gibi su organizmalarında antimikrobiyal ve immünomodülatör aktivite gösterdiği raporlanmışlardır (Gibson ve ark.,2010; Yukgehnaish ve ark., 2020).

Yapılan çalışmalar göstermiştir ki flavonoid ve flavonoid bileşiklerinin daha iyi emilmesine izin veren karşılıklı bir etkileşimle bakteri kompozisyonunu düzenlediği ve buna karşılık, flavonoid biyoaktivitesi tarafından lipid oksidasyonunda yer alan metabolik süreçlerin modülasyonunda rol oynadığı birçok çalışmayla ortaya konmuştur (Zhang ve ark., 2014, Braune ve Blaut, 2016, Al-Ishaq ve ark., 2021).

5. SONUÇ

Sağlıklı yaşamda önemli değerlerin başında mikrobiyota gelmektedir. Vücudun en değerli rezervuarı olarak bilinen bağırsakta, farklı işlevlere göre genellikle yararlı bakteriler, koşullu patojenik bakteriler ve patojenik bakteriler bulunmakta ve mikrobiyotayı oluşturmaktadır. Bu bağlamda özellikle bağırsak mikrobiyotası önemlidir. Çünkü bağırsaktaki çeşitli bakterilerin büyümesi, çoğalması ve metabolik süreci dinamik bir denge durumunda normal ve düzenlidir. Ancak, bu dinamik denge bozulduğunda, vücudunun beslenme durumu, fizyolojik işlevi ve hastalık direnci değişebilmekte bu da çeşitli sorunlara yol açabilmektedir. Bu veriler ışığında son yıllarda flavonoidlerin başta bağırsak mikrobiyotası olmak üzere genel mikrobiyota üzerinde düzenleyici etkisi olduğu bu etkiyi de esas olarak yararlı bakterilerin büyümesini teşvik ederek ve koşullu patojenik bakterilerin büyümesini engelleyerek böylece floradaki bozukluğu yeniden şekillendirerek yaptığı bilinmektedir.

Balıklarda da mikrobiyota ve flavonoidler arasında çift yönlü bir etkileşim olduğu bilinmektedir. Tüm canlılarda olduğu gibi balıklarda da deri, bağırsak florası karmaşık yapılara sahip flavonoidlerin çoklu metabolik yollarla düşük moleküler ağırlıklı fenolik asitlere metabolize edebilmesini sağlamakta dolayısıyla vücut tarafından emilebilmesini kolaylaştırmaktadır. Böylelikle, diyetlere eklenen flavonoidlerin büyüme performansı, mikrobiyotadaki zararlı bakteriler ve lipit metabolizması üzerine etkileri olumlu olmaktadır.

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