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The Protective Impact of Prebiotic or Probiotic on Experimental Infection of Broiler Chickens with *E. coli* O78

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Abstract

RECENTLY, Escherichia coli (*E. coli*) exhibited a wide range of antibiotic resistance thus the world is directed to pan the usage of antibiotics and to use antibiotic-safe natural alternatives. Therefore, this study aimed to evaluate the effectiveness of prebiotics and probiotics as a preventive measure to reduce the risk of colibacillosis experimental infection in broiler chicks. 140, one day old broiler chicks were randomly allocated into 7 groups, 20 birds each, as follows; groups 1-2 and 3-4 were given prebiotic and prebiotic in drinking water from the 1st to the 5th days of life then at the 6th , and 7th days groups 1, 3, and 5, as well as groups 2, 4, and 6 were infected orally each chick with *E. coli* O78 full drug-sensitive (strain 1) and extreme drug resistance (strain 2), respectively. Groups 5 and 6 were infected with strain 1, and strain 2 infected positives, respectively while group 7 was the control negative group. The results showed that both prebiotic and probiotic have a positive impact on the birds' growth performance, enhance the immune organ weight and histological structure, as well as improve the humoral immune response against commercial vaccines, and improve the morphometric structure of the intestinal villi in experimentally infected chickens with two different *E. coli* O78 strains. In conclusion, it is recommended to use prebiotics and probiotics at the first five days of birds age to reduce the risk of possible E. coli field infection.

Keywords: Antibiotic resistant; Fructo-oligosaccharide; *E. faecium; L. acidophilus; L. subtillis*.

Introduction

Colibacillosis can lead to high mortality, reduced growth, and economic losses in commercial poultry production [1-3]. *Escherichia coli* (*E. coli*) O78 is a serotype of pathogenic *E. coli* that is a significant cause of colibacillosis, a major disease affecting broiler chickens [4, 5].

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [6]. Prebiotics are non-digestible food ingredients that selectively stimulate the growth and/or activity of beneficial bacteria in the gut [7]. Probiotics and prebiotics have been investigated for their potential to protect broiler chickens against *E. coli* O78 infections [8].

Several studies have demonstrated the protective effects of probiotics against *E. coli* O78 in broiler chickens, a study by Timmerman et al [9] found that supplementing the diet of broiler chickens with a multi-strain probiotic significantly reduced the incidence of colibacillosis caused by *E. coli* O78 and the authors hypothesized that the probiotic strains, which included Lactobacillus and Bifidobacterium species, were able to outcompete the pathogenic *E. coli* for nutrients and attachment sites in the gut. Mountzouris *et al*. [10] reported that a probiotic containing Bacillus, Lactobacillus, and Enterococcus strains was effective in reducing the colonization and shedding of *E. coli* O78 in broiler chickens. The proposed mechanisms of action included the production of antimicrobial compounds, competitive exclusion, and the modulation of the immune system, Zhang *et al.* [11] found that supplementing the diet of broiler chickens with the prebiotic fructo-oligosaccharide (FOS) significantly reduced the incidence of colibacillosis caused by *E. coli* O78 through promoting the growth of beneficial bacteria, such as Lactobacillus and Bifidobacterium, which outcompeted the pathogenic *E. coli*.

Probiotics and prebiotics have been shown to be effective in reducing both incidence, and severity of

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E. coli O78 infections in broiler chickens, through competitive exclusion [12], produce antimicrobial compounds like bacteriocins, organic acids, and hydrogen peroxide, and these compounds can directly inhibit the growth and survival of *E. coli* O78, thereby reducing the pathogen's ability to colonize and cause infection in the host [13, 14]. Probiotics stimulate the production of antibodies, increase the activity of phagocytic cells, and enhance the production of cytokines and other immune modulators [15], as well as, promoting the growth of beneficial bacteria and maintaining a healthy gut microbiome, probiotics and prebiotics may also improve the integrity and function of the intestinal epithelial barrier [16]. Some studies have suggested that probiotics and prebiotics may downregulate the expression of virulence factors in *E. coli* O78, such as adhesins and toxins by reducing the pathogen's ability to attach to host cells, and produce harmful effectors, these sup

Nava et al [18] reported that the inclusion of a multi-strain probiotic formulation in the diet of broiler chickens infected with *E. coli* O78 led to improved growth performance, reduced intestinal lesions, and lower pathogen load in the gut. The researchers suggested that the probiotic strains were able to exclude *E. coli* O78, produce antimicrobial compounds, and stimulate the host's innate and adaptive immune responses, thereby mitigating the negative impacts of the infection [18, 19]. Abd Elatiff *et al*. [20] found that probiotics were of great value in protection against the *E. coli* infection and improve chicken performance parameters. Its effect on feed intake, weekly body weight gain and feed conversion rate (FCR). Prebiotics (Lysozyme and Betaine) which could improve antibody titers of inactivated ND and AI vaccine [21]. An increase in the humoral immunity against Newcastle disease (ND) was noticed after ND vaccination. The geometric mean (HI) was 5.9 and 4.2 for probiotic and prebiotic, respectively [8].

Multidrug resistance was detected in the form of resistance to 42%-83.3% of tested 12 antibiotics. Three isolates 15% tested isolates showed a relationship between phenotype and genotype and 85% showed irregular relation. Strains are sensitive and show resistant genes (P-G+) presented in three isolates for AMP (beta-lactam), one for ERI (Macrolide), as well as 5 isolates for trimethoprim (pyrimidine inhibitor). *E. coli* isolates had resistance and lacked gene (P+ G-) reported meanly in one isolate for CN (aminoglycoside), two isolates for tetracycline, 4 isolates for ERI, 7 isolates for trimethoprim, and 8 isolates for aminoglycoside [22]. Ahmed et al. [5] stated that the most predominant isolated serotypes were O91, O128, O78, O124, O2 and O44. These strains were related to EHEC, EPEC, ETEC, and EIEC. These *E. coli* isolates are multidrug resistant (MDR) to extensively drug-resistant (XDR).

In addition to their direct effects on *E. coli* O78, probiotics and prebiotics may promote a healthy and balanced gut microbiome, these supplements can enhance the overall resilience of the chicken's intestinal ecosystem, making it less susceptible to colonization by pathogens like *E. coli* O78 [23].

Inconsistent results across different studies and field conditions can also be a limitation, the effectiveness of probiotics and prebiotics in controlling *E. coli* O78 can be influenced by a variety of factors, including the host animal's health status, gut microbiome composition, and environmental conditions [12, 17]. The use of probiotics and prebiotics may need to be integrated with other control measures, such as biosecurity, vaccination, and good management practices, to achieve effective control of *E. coli* O78 in commercial poultry production [13].

Probiotics in adequate amounts can confer health benefits to the host animal [24]. Certain probiotic strains have demonstrated the ability to inhibit the growth and pathogenicity of the pathogen, thereby improving the overall health and performance of infected chickens [25]. Dahiya *et al*. [26] found that the supplementation of Lactobacillus-based probiotics in the feed of broiler chickens challenged with *E. coli* O78 resulted in significantly higher body weight, improved feed conversion ratio, and reduced mortality rates compared to the infected control group. Baurhoo *et al*. [27] investigated the effects of MOS prebiotic on broiler chickens challenged with *E. coli* O78 and found that the prebiotic supplementation improved gut morphology, increased the population of beneficial bacteria, and reduced the intestinal colonization of the pathogen, leading to better growth performance and feed efficiency in the infected birds.

The dimensions of intestinal villi, including their length, width, and depth, are closely related and can provide valuable insights into the overall intestinal health and nutrient absorption capacity of chickens [28, 29].

Therefore, this study aims to detect the role of prebiotic and probiotic in prevention of experimental infection with *E. coli* O78 extreme resistant and sensitive strain in broiler chickens

Material and Methods

Chicks

One hundred and forty (140) commercial broiler (Arbor Acres plus) chicks were bought as hatched from Cairo poultry Co hatchery. The chicks were caged hygienically in experimental cages Poultry Department, Faculty of Veterinary Medicine, Cairo University under the requirement of the breed manual, on wood saving deep litter and given feeds and water *ad-libitum* under strict sanitary and biosecurity standards.

Ration

All chickens were fed on the same commercial broiler pelleted ration kindly supplied by Cairo poultry Co. poultry company based on the NRC [30], and clean water *ad-libitum*. The starter ration which holds 23% Crud protein was given to the chickens for the first two weeks, followed by the grower (contain 21% Crud protein) ration for the next two weeks, and finally the finisher (contain 19% Crud protein) ration for the last week.

E. coli strains

Enteropathogenic *E. coli* O78 isolated from infected chicken flocks, two strains, strain 1 was antibiotic resistant, and strain 2 was sensitive [5].

Vaccines and vaccination

The birds were vaccinated with Groups 1-6 were vaccinated against ND at 1- day- old with inactivated via s.c injection and La Sota virus at 17th day of age via eye drop, the vaccine was produced by Boehrimger Ingelhiem "Volvac" Lot No 2207062C1A.

Additives

The following two different commercial products including probiotics bacteria, probiotics yeast, organic acid, and one symbiotic were used in drinking water for five days before infection (day 9: day 13). Doses were used in drinking according to the manufacture guide.

Probiotic. Protexin®: It is Commercial probiotic manufactured by ADM Protoxien LTD, UK (Batch no. 124496) holds per kg: *Enterococcus faecium* (NCIMB 11181) 4b 1708. <1.0% Total Viable Count 2x10^{12} CFU/kg. Ingredients: Dextrose up to 1kg. Crude Protein < 1.0%. Crude Fiber < 1.0%. Crude Oil < 1.0%. Crude Ash < 1.0%. Trace. It was used in dose 1 gm/2 L water/day.

Prebiotic: Amino-Zyme®: It is commercial product manufactured by 2M group, Egypt (Batch no. 2389). It is composed of Beta glucan 48.6 gm, Fructo-oligosaccharide 8.3 gm, DL-methionine 0.5 gm, L-carnitine 15.3 gm, L-lycine HCL 4.47 gm, Mono propylene glycol 45.25 gm, Purified water up to 1 liter. Also hold: Spirulina, L-valine, Taurine, Thereonine, L- arginine, Leucine, Isoleucine, *Lactobacillus acidophilus, Lactobacillus subtillis,* Bifidobacterium, Phytase, Protease, Amylase, Xylase. It was used in dose 1ml / L water/day.

Experimental design

The used 140 chicks were randomly divided into 7 groups (1-7); 20 chicks each. Each group was reared in separate disinfected room on deep liter. Groups 1-2 and 3-4 were given prebiotic and prebiotic in drinking water from the 1st to the 5th day of life. At the 6th and 7th days groups 1,3 and 5, as well as groups 2, 4, and 6 were infected orally each chick with 3.5X10^{7}CFU /ml of *E. coli* O78 full drug sensitive (strain 1) and extreme drug resistance (strain 2), respectively [5]. Groups 5, 6, and 7 were the strain 1 infected positive, strain 2 infected positive and control negative control groups, respectively. Groups 1-4 were treated infected groups. All groups were subjected to daily observation for signs of mortality.

Clinicopathological Examination

Chickens in all groups were checked daily for clinical signs and mortality. Clinical signs observed, mortality and the pathological findings in dead birds were recorded. The cumulative mortality rate was calculated as the total number of deaths in chickens/ group divided by the total population in the same group.

Organ body weight ratio and bursal index

Organ body weight ratio (OBW ratio) = organ weight/ Body weight X 100 [31]., while the Bursal weight index (BW index) = BW ratio of infected group/ BW ratio of control group [32]. The bursa considered atrophied when BW index less than 0.7 [33, 34].

Detection of NDVHI Antibody

a. Blood samples for serum:

Blood was collected from the jugular vein at 1st day and day 14th to detect MDABs while from wing vein 21 days post vaccination to HI determine antibody titer, and serum was obtained after centrifuging at 3000 rpm for 10 min and stored at −20°C for further analysis.

b. Haemagglutination inhibition (HI) assay

Sera were obtained from all groups at 35 days of age (21 days post vaccination) were tested by HI assay. The HI assay was carried out using (La Sota strain) according to standard procedures with 4 Hemagglutinating units' virus/ antigen in 0.050 ml and HI titer ≤ 2 Log-$_2$ considered negative [35].

Broiler growth Performance Parameters

During the experiment (14, 21, 28, and 31days of age) (Table 1), chicks were individually weighed weekly. The cumulative weekly average live body weight gain (BWG) was calculated. Feed intake (FI) was calculated weekly and calculate average weekly intake/ bird, so it was expressed as (g/bird/week). To determine the feed conversion ratio (FCR), it has been determined on a weekly basis by dividing the average amount of feed consumed by each bird by the average amount of gain in weight [36].

Histological investigations

For histopathological evaluation: bursae, thymus, spleen, cecal tonsils and the middle region of the cecum were fixed in 10% formalin, embedded

in paraffin blocks that sectioned using a microtome into slices of 4–6 µm thickness then stained with Hematoxylin and Eosin (HandE) stains [37]. The percentage of scoring system for estimated tissues was determined and compared between the experimental groups across a range of 0 to 4 according to the severity as the following 0 means (normal), 1 means (1–25%), 2 means (26–50%), 3 means (51–75 %), 4 means (76–100%) of estimated lesions included lymphoid necrosis and/or lymphocytic depletion, edema and infiltration of plasma cells as well as heterophils. Total mucosal thickness, including the mucosal epithelium and lamina propria of the intestine was determined by morphometric analysis. The intestinal mucosa was measured at 5 representative points in each cecum using ImageJ software. The mean of mucosal thickness was calculated for three birds per group [38].

Statistical analysis

Statistical analysis was performed using one-way ANOVA

Results and Discussion

E. coli O78 is considered as a serious pathogen inducing financial losses in the poultry production sector [39]. Most *E. coli* strains showed a broad-spectrum resistance against most of the commercial antibiotics [5]. The world directed to the usage of antibiotic alternatives including probiotic, prebiotic, symbiotic, postbiotic, herbal extract, essential oils, phytogenic products etc., to enhance birds' productivity and decrease the incidence of multidrug resistance [40]. Thus, the current study aimed to evaluate the usage of prebiotics and probiotics as preventive tools against the experimental infection with two pathogenic multidrug resistant *E. coli* O78 in broiler chickens.

As seen in Table 1 and Figure 1, at the end of the experiment (31 days old) the ABWG (gm) showed a significant reduction in group 2 (1429), followed by group 3 (1531), then group 6 (1564), and group 5 (1633) when compared to group 7 (1746.8). On the other hand, group 1 and group 4 revealed an improvement in ABWG when compared with group 7 (1746.8). Regarding the FCR, group 1 showed a significant improvement in group 4 (1.53) and group 1 (1.54) when compared to group 7 (1.43). Also, it was noticed that group 6, 5, 3 and 2 showed a slight improvement in FCR as 1.60, 1.63, 1.67, respectively when compared with group 7 (1.43). From the -mentioned data, it was observed that the supply of prebiotics and probiotics have a positive impact on ABWG, and induce a reasonable improvement in FCR. Our results in concur with Youssef *et al*. [41] who found that the dietary inclusion of symbiotic (Fructo-oligosaccharides, *E. faecium*, *P. acidilactici, B. animalis*, *L. salivarius* and *L. reuteri*) significantly improved birds FBW and enhances FCR. These results could be explained as important elements of gut health include an environment that supports enzymatic digestion, a population of beneficial gut bacteria, and the preservation of the intestinal epithelium's natural morphology and the increased surface area for nutrient absorption contributes to the improved gut shape. Furthermore, it is beneficial to enhance the intestinal health and productivity of broiler chickens by adding prebiotics, probiotics, or synbiotic to their food [42].

Regarding the recorded to-body weight ratios (Table 2, Figure 2). Prebiotic and probiotic-treated groups (1-4) had higher liver, intestine, proventriculus, and gizzard to-body weight ratios compared to the non-treated infected groups (5 and 6) and those were lower than non-treated, non-infected control group (7) these results were in concur with Shinde *et al*. [43] The diet of broiler chickens resulted in a significantly higher relative weight of the liver [44]. Probiotics (Lactobacillus, Bifidobacterium, and Enterococcus species) have a beneficial impact on organ-body weight ratios in chickens [45]. Probiotic supplementation was believed to promote the growth and development of the intestinal tract, thereby improving nutrient absorption and overall organ function [46]. These findings suggest that the dietary supplementation of prebiotics and probiotics helped to maintain the relative weights of the liver, intestine, proventriculus, and gizzard in broiler chickens challenged with *E. coli* O78, compared to the non-treated, infected groups [47, 48], also these dietary supplements were able to support the growth and development of these important digestive and metabolic organs [49].

Broiler chickens infected with APEC exhibited a significantly lower relative weight of the proventriculus and gizzard, compared to the uninfected control group. The authors suggested that the APEC infection may have compromised the development and function of these organs, leading to an imbalance in the organ-body weight ratio [50]. Cançado *et al*. [51] found that broiler chickens infected with AEPEC O78 exhibited a significantly lower relative weight of the spleen, compared to the uninfected control group. The lower organ-to-body weight ratios observed in the non-treated, infected groups suggest that the E. coli O78 infection, particularly the antibiotic-resistant strain, had a more detrimental effect on the normal growth and functioning of these organs, potentially leading to reduced nutrient utilization and overall performance in the affected birds [52, 53].

The organ-body weight ratio is an important indicator of the overall health and development of chickens. The available evidence suggests that prebiotics and probiotics can have a positive effect on the organ-body weight ratio in broiler chickens,

particularly by promoting the development of immune-related organs, such as the spleen and bursa of Fabricius. Conversely, pathogenic bacterial infections, like AEPEC O78, can have a detrimental impact on the organ-body weight ratio, potentially due to the disruption of the normal growth and development of these vital organs. Understanding the modulation of organ-body weight ratio by dietary supplements and pathogenic challenges is crucial for optimizing the overall health and performance of broiler chickens in commercial production [44, 45, 51].

Groups corded geometric means of hemagglutinating antibody (HI) titres against Newcastle disease in sera of chickens (Table 3, Figure 3) proved that prebiotic and probiotic treated infected groups showed titres (7.70 to 8.2) close to the control negative groups (7.9), while the infected groups 5 and 6 showed the lowest titres (7.1-7.2). Prebiotics and probiotics help to improve and restore the immune system activity to produce antibodies. The inclusion of a prebiotic in the diet of broiler chickens resulted in a significantly higher antibody titer against the ND vaccine; the authors attributed this effect to the ability of prebiotics to modulate the gut microbiome and enhance the immune system's responsiveness to vaccination [44]. Probiotics have been shown to positively influence the antibody response to ND vaccination in chicken's broiler chickens fed a probiotic mixture (Lactobacillus, Bifidobacterium, and Enterococcus species) had significantly higher ND antibody titers [10]. The infection with AEPEC O78 had resulted in lower antibody against ND vaccine. Effect of *E. coli* infection on antibody response to ND vaccine in chickens was also reported by Beal et al. [50] found that broiler chickens infected with APEC exhibited significantly lower ND antibody titers compared to the uninfected control group. The was suggested that the APEC infection may have compromised the chickens' immune system, leading to a reduced ability to mount an effective humoral response to the ND vaccine [54, 55].

Examined tissue section prepared from nontreated control chicken at the 6th day of life, intestine, liver and spleen showed showing normal histological structure. Sections of probiotic treated for 5 days showing intestinal goblet cells hyperplasia and moderate length villi (Figure 4A), liver showed mild vacuolation of hepatocytes (Figure 4B) while spleen showing mild depletion of periarteriolar lymphoid aggregation (Figure 4C). Prebiotic treated group: intestine showing normal histological structure (Figure 4D), mild vacuolation of liver hepatocytes (Figure 4B), while well populated periarteriolar lymphoid aggregation and lymphoid follicles were detected in spleen (Figure 4E).

Histopathological examination of prebiotic or probiotic treated or non-treated strain 1 infected chicken groups revealed that the intestinal section showed moderate leukocytes infiltration in lamina propria and submucosa (Figure 5A) in probiotic (group 1). Probiotic treated showing goblet cells hyperplasia and mild leukocytes infiltration in lamina propria and submucosa group 2 (Figure 5B), while the non- treated infected group 5 showing necrosis and sloughing of intestinal villi with severe leukocytes infiltration in the submucosa (Figure 5C).

Intestine of chicken group 3, those given prebiotic before infection with E. coli O78 strain 2 showing epithelial hyperplasia and moderate leukocytes infiltration in lamina propria and submucosa (Figure 5D), while those given probiotic (group 4) showing mild leukocytes infiltration in the submucosa (Figure 5E) to necrosis and sloughing of intestinal villi with severe leukocytes infiltration in the submucosa (Figure 5F). Furthermore, the infected group 6 showing epithelial sloughing at the tips of villi with moderate leukocytes infiltration in lamina propria and submucosa (Figure 5G) as well as sloughed villi and severe leukocytes infiltration in lamina propria, submucosa and tunica musculosa (Figure 5H).

Liver of prebiotic and probiotic pretreated chickens followed by infection with *E. coli* O78 showed mild periportal leukocytes infiltration (Figure 6A). Strain 1 infected nontreated group 5 showing severe periportal leukocytes infiltration (Figure 6B) and group 6 that infected with strain 2 moderate periportal leukocytes infiltration (Figure 6C). The non-treated non-infected group 7 showed normal histological structure (Figure 6D).

Spleen sections of all treated groups 1-4 and infected with either strains 1 or 2 showing well populated periarteriolar lymphoid sheath and follicles (Figure 7A). Strain 1 infected nontreated (group 5) mild depletion of periarteriolar lymphoid sheath (Figure 7B), while those infected with strain 2 (group 6) showed moderate depletion of periarteriolar lymphoid sheath (Figure 7C). Spleen of control negative group 7 was normal histological structure (Figure 7D).

Intestinal villi are finger-like projections that line the small intestine of chickens and other animals; those play a crucial role in the absorption of nutrients from the digested food [56]. The morphology and dimensions of intestinal villi can provide valuable insights into the overall gastrointestinal health and nutrient absorption capacity of chickens [57]. Regarding the intestinal villi measures (Tables 4), chicken groups supplemented with probiotic villi length, width and depth 471.93± 44.9, 167.47 ± 44.07, and 164.86± 38.27; respectively, then prebiotic (length:451.33 ± 34.2, width: 140.04 ± 39.70, and depth: 101.54 ±

23.73). The non-supplemented group showed the lowest values (length:445.68 ± 24.7, width: 113.31± 21.83, and depth: 94.65 ± 8.60). These results indicated that prebiotic or probiotic administration to broiler chicken improve the intestinal villi measurements. In chickens the increase in the height and width of the villi of the small intestine directly reflects an increase of the absorption area of the small intestine, and thus an increase of the mucosal surface area of the small intestine [58]. Longer and wider villi are generally associated with improved nutrient absorption and better intestinal health [58]. By organized studies it was found that the length of intestinal villi in broiler chickens increased significantly when the birds were fed a diet supplemented with probiotic bacteria or essential oils [59, 60]. Inclusion of a probiotic and prebiotic in the diet of broiler chickens resulted in an increase in the width of intestinal villi [61]. The depth of intestinal villi, which represents the distance from the tip of the villi to the base of the crypt, is another important measurement that can be influenced by various factors. Probiotics in the diet of broiler chickens led to an increase in the depth of intestinal villi [62]. The increase in length is associated with an increase in both width and depth. Several studies have reported a positive correlation between the length and width of intestinal villi in chickens, probiotics or prebiotic (enzymes) supply to broiler chickens diet led to concurrent increases in both villi length and width [63].

The depth of intestinal villi, represents the distance from the tip of the villi to the base of the crypt, is also closely related to the villi length. Longer villi are generally associated with a greater depth [64], and increases in both parameters in response to dietary changes [65].

Based on the histological changes observed in intestine, probiotic treated group for 5 days where intestine showed hyperplasia of goblet cells and moderate length villi (Figure 4A). Liver showed mild vacuolation of hepatocytes (Figure 4B). Spleen showed mild depletion of periarteriolar lymphoid aggregation (Figure 4C). The hyperplasia of goblet cells and moderate increase in villi length suggest enhanced intestinal barrier function and nutrient absorption capacity. Increased goblet cell activity can lead to greater mucus production, potentially improving gut defense against pathogens and maintaining intestinal homeostasis [66, 67]. The morphological changes in the intestine may indicate improved digestive and absorptive efficiency, which could enhance growth performance and nutrient utilization in the chickens [58, 68].

The prebiotic treated group showed intestine showed normal histological structure (Figure 4D). Liver showed mild vacuolation of hepatocytes (Figure 4B). Spleen showed well-populated periarteriolar lymphoid aggregation and lymphoid follicles (Figure 4E). Liver changes including mild vacuolation of hepatocytes observed in the liver could be a sign of increased metabolic activity or lipid accumulation [69]. This may reflect adaptations in liver function to accommodate changes in nutrient absorption and metabolism due to the prebiotic treatment [70]. The mild depletion of periarteriolar lymphoid aggregation in the spleen of the 5-day prebiotic-treated chickens may indicate a temporary modulation of the immune system [71, 72]. However, the well-populated periarteriolar lymphoid aggregation and lymphoid follicles observed in the probiotic-treated group suggest a normalized or enhanced immune response [73, 74]. These splenic changes could reflect an adaptive immune response to the probiotic supplementation, potentially enhancing disease resistance and overall health [75, 76].

Overall, the observed histological changes suggest that prebiotic supplementation may have beneficial effects on intestinal function, liver metabolism, and immune system regulation in the chickens [42, 77].

The histopathological examination of the chicken intestinal sections revealed distinct pathological changes in the different treatment groups infected with *E. coli* O78. In the probiotic-treated group 1, the intestinal section showed moderate leukocyte infiltration in the lamina propria and submucosa (Figure 5A) [43]. This indicates an inflammatory response to the *E. coli* infection, which is typically observed in the early stages of an infection [78].

The probiotic-treated group 2 showed goblet cell hyperplasia and mild leukocyte infiltration in the lamina propria and submucosa (Figure 5B) [43]. Goblet cell hyperplasia is a common adaptive response to intestinal inflammation, as it increases mucus production, which can help protect the intestinal epithelium and facilitate the clearance of pathogens. In contrast, the non-treated infected group 5 exhibited more severe pathological changes, including necrosis and sloughing of the intestinal villi with severe leukocyte infiltration in the submucosa (Figure 5C) [43]. This extensive tissue damage and inflammation suggests a more advanced stage of the E. coli infection in the absence of probiotic treatment [78].

For the prebiotic-treated group 3, the intestinal section showed epithelial hyperplasia and moderate leukocyte infiltration in the lamina propria and submucosa (Figure 5D) [43]. Epithelial hyperplasia is a regenerative response to tissue damage, which suggests that the prebiotic treatment helped to mitigate the extent of intestinal injury caused by the E. coli infection [78]. In the probiotic-treated group 4, the intestinal section exhibited mild leukocyte infiltration in the submucosa (Figure 5E) [43]. This indicates a less severe inflammatory response

compared to the prebiotic-treated group 3, potentially due to the immunomodulatory effects of the probiotic strain [78]. The infected group 6, on the other hand, showed more severe pathological changes, including epithelial sloughing at the tips of the villi, moderate leukocyte infiltration in the lamina propria and submucosa (Fig. 5G), as well as sloughed villi and severe leukocyte infiltration in the lamina propria, submucosa, and tunica musculosa (Figure 5H) [43]. These findings suggest that the absence of prebiotic or probiotic treatment resulted in more extensive intestinal damage and inflammation in response to the *E. coli* infection in chickens [43, 79].

The histopathological findings of the liver samples from the different treatment groups provide insights into the effects of prebiotics and probiotics on the hepatic response to E. coli O78 infection in chickens. In the prebiotic and probiotic pretreated groups (3 and 4), the liver sections showed mild periportal leukocyte infiltration (Figure 6A). This suggests that the supplementation of prebiotics and probiotics prior to the *E. coli* challenge helped to attenuate the inflammatory response in the liver, potentially through the modulation of the gut-liver axis. [43]. The non-treated, infected group 5 challenged with strain 1 exhibited severe periportal leukocyte infiltration (Figure 6B). Similarly, the non-treated, infected group 6 challenged with strain 2 showed moderate periportal leukocyte infiltration (Figure 6C). Interestingly, the non-treated, non-infected group 7 showed a normal histological structure of the liver (Figure 6D) [43].

The milder inflammatory response observed in the prebiotic and probiotic-treated groups could be attributed to prebiotics and probiotics can influence the gut microbiome and intestinal barrier function, which can subsequently affect the liver through the gut-liver axis [80]. Prebiotics and probiotics can directly interact with the host's immune cells and modulate their function, leading to a more balanced and less exaggerated inflammatory response in the liver [81]. Dietary supplements have influenced the production of beneficial metabolites, such as short-chain fatty acids, which can have anti-inflammatory properties and contribute to reduced liver inflammation [82].

In the prebiotic and probiotic pretreated groups (1-4), the spleen sections showed well-populated periarteriolar lymphoid sheaths and follicles, regardless of the E. coli strain used for infection (Figure 7A) [43]. This suggests that the dietary supplementation of prebiotics and probiotics helped to maintain the structural integrity and cellular composition of the splenic white pulp, which is crucial for an effective immune response [67]. The non-treated, infected group 5 challenged with strain 1 exhibited mild depletion of the periarteriolar lymphoid sheath (Figure 7B). Similarly, the non-treated, infected group 6 challenged with strain 2 showed moderate depletion of the periarteriolar lymphoid sheath (Figure 7C) [43]. These findings indicate that the E. coli infection, in the absence of prebiotic or probiotic treatments, led to a more pronounced disruption of the splenic white pulp architecture, potentially compromising the immune function of spleen in chickens [8, 83, 84].

Interestingly, the non-treated, non-infected group 7 showed a normal histological structure of the spleen (Figure 7D). The result confirms that the observed changes in the spleen were specifically due to the *E. coli* challenge [43]. The well-preserved splenic architecture in the prebiotic and probiotic-treated groups can be attributed to prebiotics and probiotics can directly interact with immune cells, such as lymphocytes and macrophages, within the spleen, promoting their proliferation and function, thereby maintaining the structural and functional integrity of the splenic white pulp [81], prebiotics and probiotics, leading to a coordinated immune response and the preservation of splenic tissue architecture [85] and dietary supplements may have enhanced the antioxidant and anti-inflammatory status of the host, which can contribute to the maintenance of splenic structure and function [86].

Generally comparing the histological changes due to antibiotic resistant EPAE O78 were more severe than those of antibiotic sensitive strain of the same serotype. This observation is consistent with the general understanding that antibiotic-resistant pathogens can pose greater challenges to the host's immune system, as they are more capable of evading or overcoming the host's defense mechanisms. The increased virulence and adaptability of antibiotic-resistant strains can lead to more severe pathological changes in the target tissues, such as the spleen, compared to their antibiotic-sensitive counterparts [87- 89].

Overall, the histopathological analysis indicates that both prebiotic and probiotic for Enteron pathogenic *E. coli* treatments were able to mitigate the severity of the to modulate the intestinal immune response and reduce lesions [90].

Conclusions

The usage of prebiotics and probiotics at the incubation period (first five days of birds age), could decrease the negative impact of *E. coli* O78 experimental infection in broiler chickens also, they have a positive impact in the birds' final weight, organ body weight ratio, humoral immune response against commercial vaccines, and they improve the intestinal morphometric structure and enhance the immune organ histological structure.

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Ethical approval.

The institutional animal care and use committee of the Faculty of Veterinary Medicine, University of Cairo, Egypt, ensured that the handling of chickens and all experimental procedures were followed all applicable *measures (Vet CU 18042024933).*

Conflict of interests

The authors declare that they have no conflict of interests.

TABLE 1. Cumulative Growth parameters: AFI /gm, ABWG/gm and FCR of prebiotic or probiotic treated chicken groups before infection with *E. coli* O78 strains 1 or 2.

Group No	Treatment	Age/ days	AFI /gm	ABWG /gm Mean ± SD	FCR
1	Prebiotic + strain 1	14	410	334.3 ± 30,7	1.23
		21	1100	747.7 ± 45.3	1.47
		28	2100	1438.2 ± 89.3	1.46
		31	2500	1627 ± 65.3	1.54
2	Probiotic + strain 1	14	463.5	299.7 ± 15.6	1.56
		21	1150	756.2 ± 3.97	1.52
		28	2020	1096.8± 100.4	1.84
		31	2400	1429.4 ± 78.9	1.68
3	Prebiotic + strain 2	14	425	257.9 ± 42.8	1.65
		21	1050	686.2 ± 37,0	1.53
		28	1800	1175.7± 87.9	1.53
		31	2570	1531.9 ± 161.3	1.67
4	Probiotic+ strain 2	14	415.9	272.9 ± 17.8	1.52
		21	1200	827.1 ± 47.3	1.45
		28	2100	1482.5 ± 86.2	1.48
		31	2510	1645.9 ± 112.4	1.53
5	Strain 1	14	421	261.2 ± 20.3	1.61
		21	1180.7	690.5 ± 53.8	1.71
		28	2010	1240.2 ± 98.6	1.62
		31	2550	1633.6 ± 132,1	1.63
6	Strain 2	14	425	251.2 ± 30.4	1.69
		21	1180	731.7 56.2	1.61
		28	2182	1262.8 ± 43.3	1.73
		31	2508	1564.8 ± 92.2	1.60
7	Control -ve	14	435.5	289.3 ± 20.5	1.46
		21	1100	789.4 ± 44.3	1.39
		28	2110	1481.7 ± 83.6	1.42
		31	2500	1746.8 ± 89.9	1.43

TABLE 2. **Organ body weight ratio of prebiotic or probiotic treated chicken groups before infection with *E. coli* O78 strains 1 or 2**

Group no	Treatment	Age/days	Organ body weight ratio (Mean ± SD)			
			Liver	Intestine	Proventriculus	Gizzard
			Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
1	Prebiotic + Strain 1	6	2.42 0.02	10.48 3.22	0.81 0.11	2.42 0.45
		17	3.87 0.42	12.71 2.98	0.63 0.15	2.97 0.21
2	probiotic + Strain 1	6	2.40 o.71	10.40 3.06	0.80 0.21	2.40 0.16
		17	3.99 0.15	14.29 4.06	1.12 1.01	3.14 0.30
3	Prebiotic + Strain 2	6	2.76 0.32	7.48 2.16	0.79 0.50	2.36 0.72
		17	4.51 1.02	10.58 3.98	0.76 0.26	3.37 0.17
4	Prebiotic+ Strain 2	6	2.54 0. 27	6.88 2.08	0.72 0.24	2.17 0.12
		17	3.15 0.87	11.41 3.11	0.58 0.17	2.35 0.06
5	Strain 1	6	3.33 0.42	7.78 2.13	0.74 0.22	2.22 0.10
		17	3.60 0.18	11.38 4.82	0.54 0.11	2.60 0. 43
6	Strain 2	6	3.17 0.21	7.39 2.53	0.70 0.75	2.11 0.20
		17	3.38 0.17	10.26 4.29	0.61 0.8	2.40 0.22
7	Control -ve	6	3.24 0.13	7.55 1.90	0.72 1.11	2.16 0.31
	Un-treated	17	3.34 0.90	13.86 3.50	0.54 0.19	2.74 0.18

TABLE 3. Newcastle disease geometric mean of HI antibody titers in sera of prebiotic or probiotic treated chicken groups before infection with *E. coli* O78 strains 1 or 2

Group No	Treatment	HI titer distribution								
		0-3	4	5	6	7	8	9	10	11
1	**Prebiotic + strain 1**				1	2	5	1	1	
2	**Probiotic + strain 1**					6	1		3	
3	**Prebiotic + strain 2**				2	1	4	1		2
4	**Prebiotic+ strain 2**			1	1	1	5	1	1	
5	**Strain 1**				3	3	3	1		
6	**Strain 2**		1	1	2	3		1	2	
7	**Control -ve un-treated**				1	4	1	3	1	

TABLE 4. Illustrates the intestinal villi measurements (Mean ±SD) in at the 7th day after administration of probiotic, prebiotic and nontreated group

Tres5ment	Length Mean ± SD	Width Mean ± SD	Depth Mean ±SD
Prebiotic	451.33 ± 34.2	140.04 ± 39.70	101.54 ± 23.73
Probiotic	471.93± 44.9	167.47 ± 44.07	164.86± 38.27
Nontreated negative	445.68 ± 24.7	113.31± 21.83	94.65 ± 8.60

TABLE 5. illustrates the intestinal villi measurements (Mean ±SD) in treated infected chicken groups

Group no	Treatment	Length Mean ± SD	Width Mean ± SD	Depth Mean ± SD
1	Prebiotic + strain 1	1653.46 ± 94.07	137.94 ± 21.23	351.54 ± 86.90
2	Probiotic + strain 1	1174.42 ± 154.50	147.68 ± 20.20	418.15 ± 88.90
3	Prebiotic + strain 2	1181.62 ± 74.30	119.93 ± 22.43	379.79 ± 79.40
4	Prebiotic+ strain 2	1013.24 ± 39.03	135.21 ± 21.23	401.03 ± 65.37
5	Strain 1	1016.65 ±140.00	192.84 ± 19.50	338.40 ± 28.20
6	Strain 2	1603.88 ± 69.57	139.77 ± 14.17	291.44 ± 23.17
7	Control -ve	1111.34 ± 97.17	175.33 ± 21.33	500.69 ± 70.00

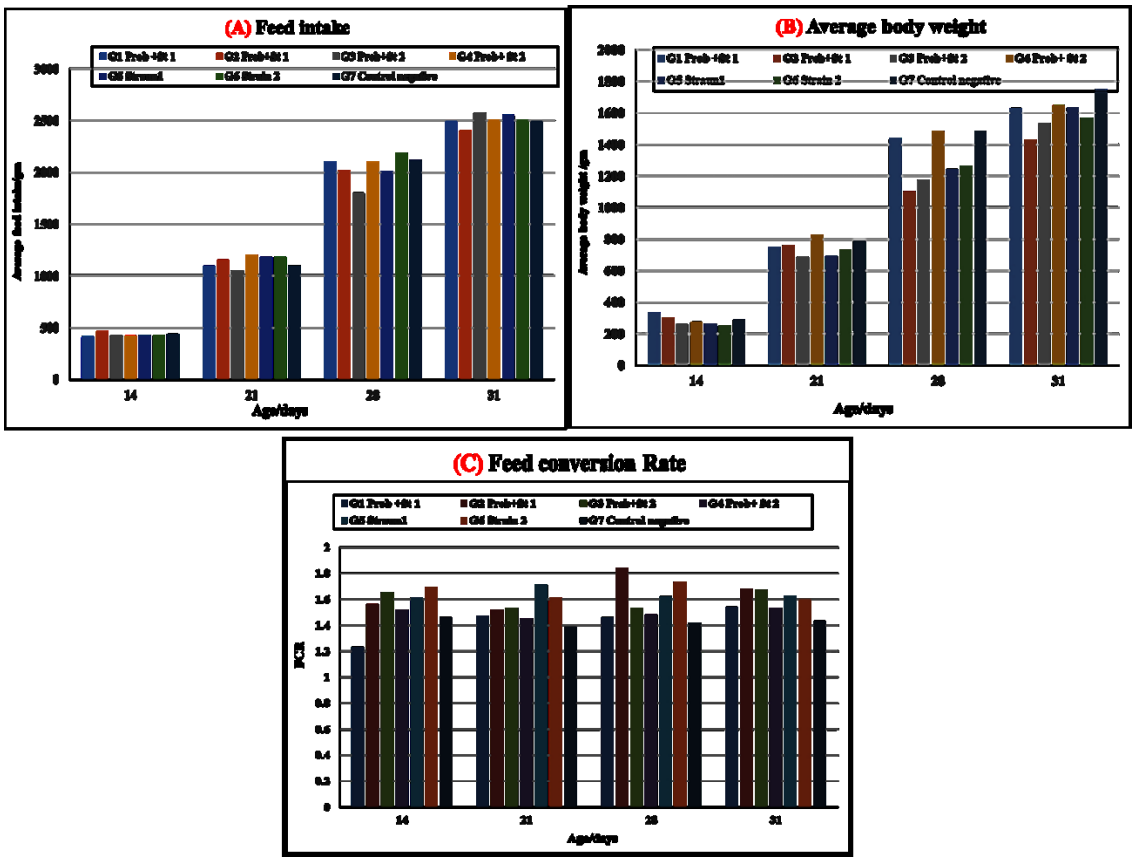

Fig. 1. Cumulative Growth parameters of prebiotic or probiotic treated chicken groups before infection with *E. coli* O78 strains 1 or 2: A: Average feed intake/gm, B. Average body weight/gm C. Feed conversion rate

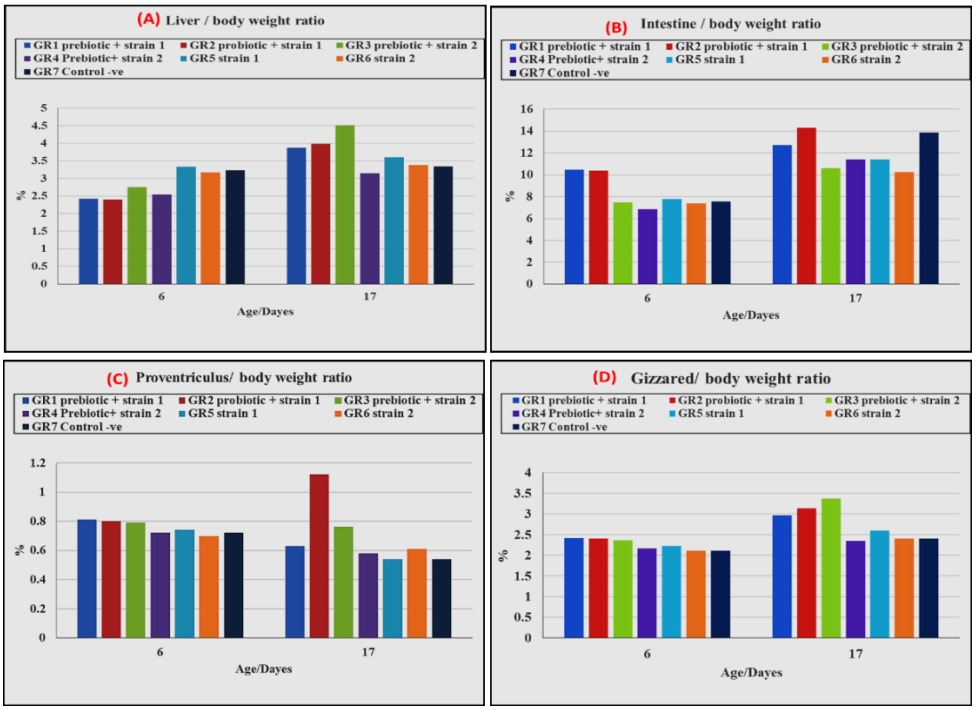

Fig. 2. Organ body weight ratio of prebiotic or probiotic treated chicken groups before infection with *E. coli* O78 strains 1 or 2: A. Liver, B. Intestine, C. Proventriculus, D. Gizzard.

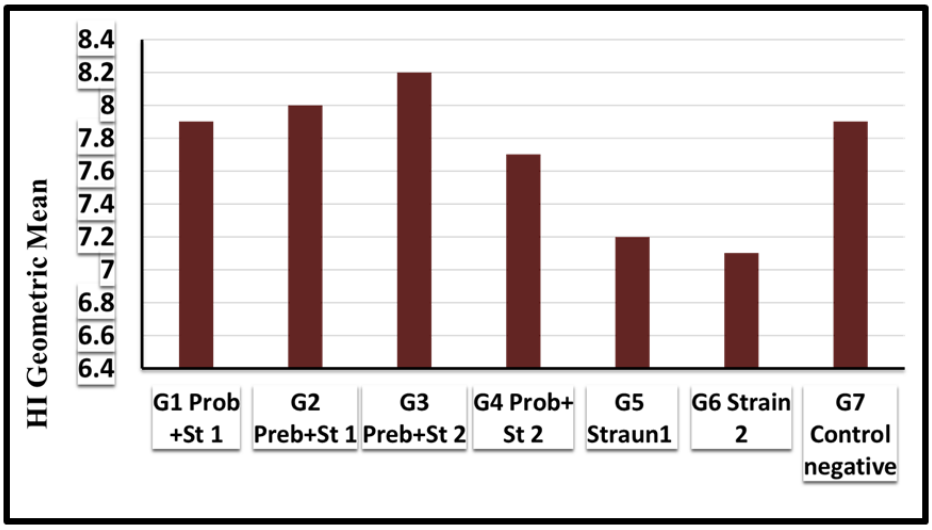

Fig. 3. HI antibody geometric titers against NDV in sera of treated chicken and infected with *E. coli* strains 1 or 2.

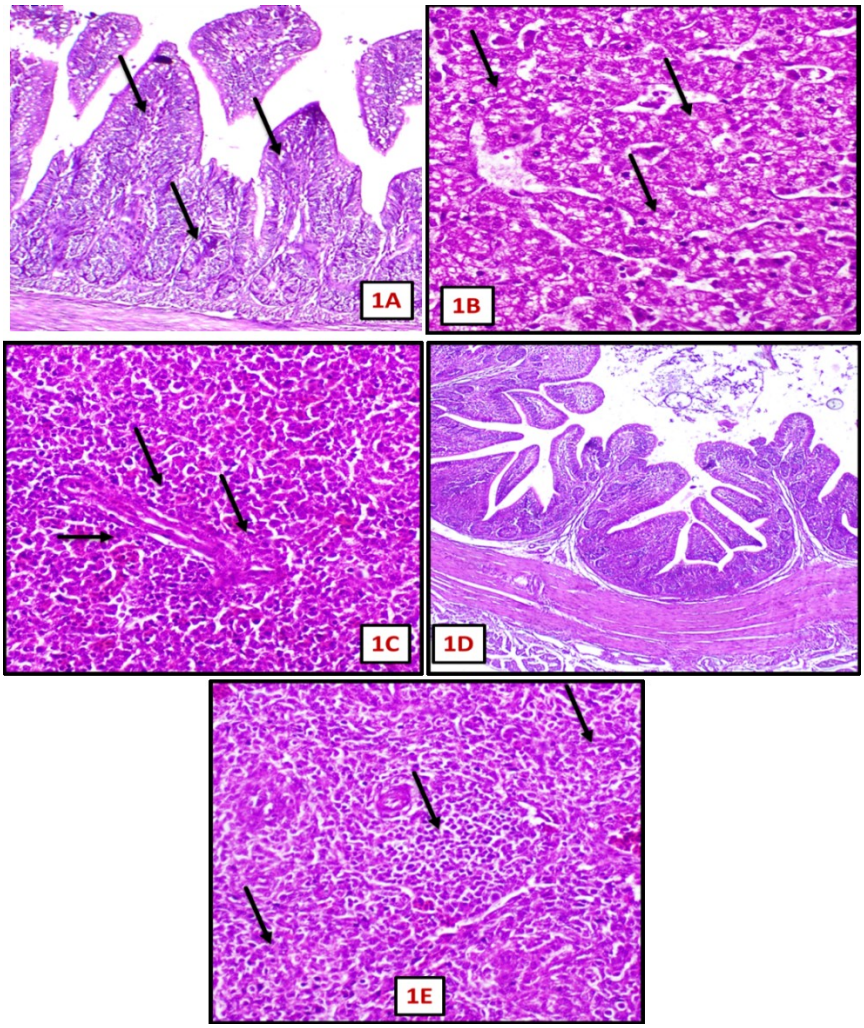

Fig. 4. Tissue section of chicken groups treated with probiotic or prebiotic for 5 days (H&E) showing:

A: Intestine of probiotic: goblet cells hyperplasia (arrows) and moderate length villi (x100).

B: liver of probiotic: mild vacuolation of hepatocytes (arrows) (stain x200) .

C: spleen of prebiotic: mild depletion of periarteriolar lymphoid aggregation (arrows) (x200) .

D: intestine of prebiotic: normal histological structure (x100).

E: spleen of prebiotic: well populated periarteriolar lymphoid aggregation and lymphoid follicles (arrows) (x200).

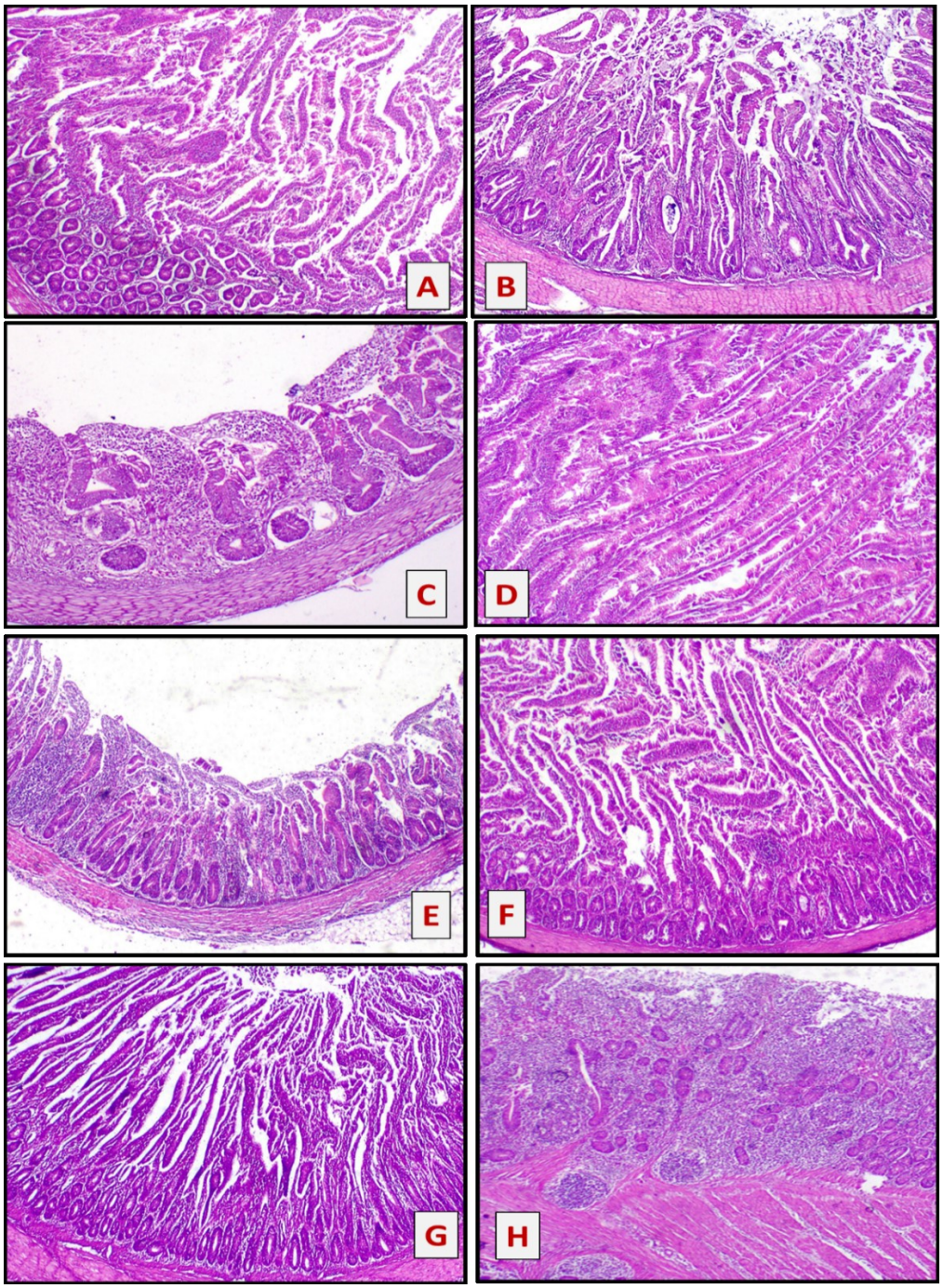

Fig 5. Intestinal sections of prebiotic, probiotic treated and non-treated infected chicken groups with *E. coli* O78 strains 1 or 2 stained H&E:

5A: Group 1, prebiotic: moderate leukocytes infiltration in lamina propria and submucosa (x100). 5B: Group 2, goblet cells hyperplasia and mild leukocytes infiltration in lamina propria and submucosa (x100). 5C: Group 5, necrosis and sloughing of intestinal villi with severe leukocytes infiltration in the submucosa (x200). 5D: Group 3, epithelial hyperplasia and moderate leukocytes infiltration in lamina propria and submucosa (x100). 5E: Group 4, necrosis and sloughing of intestinal villi with severe leukocytes infiltration in the submucosa (x100). 5F: Group 4, mild leukocytes infiltration in the submucosa (x100). 5G: Group 6, epithelial sloughing at the tips of villi with moderate leukocytes infiltration in lamina propria and submucosa (x100). 5H: Group 6, sloughed villi and severe leukocytes infiltration in lamina propria, submucosa and tunica musculosa (x100).

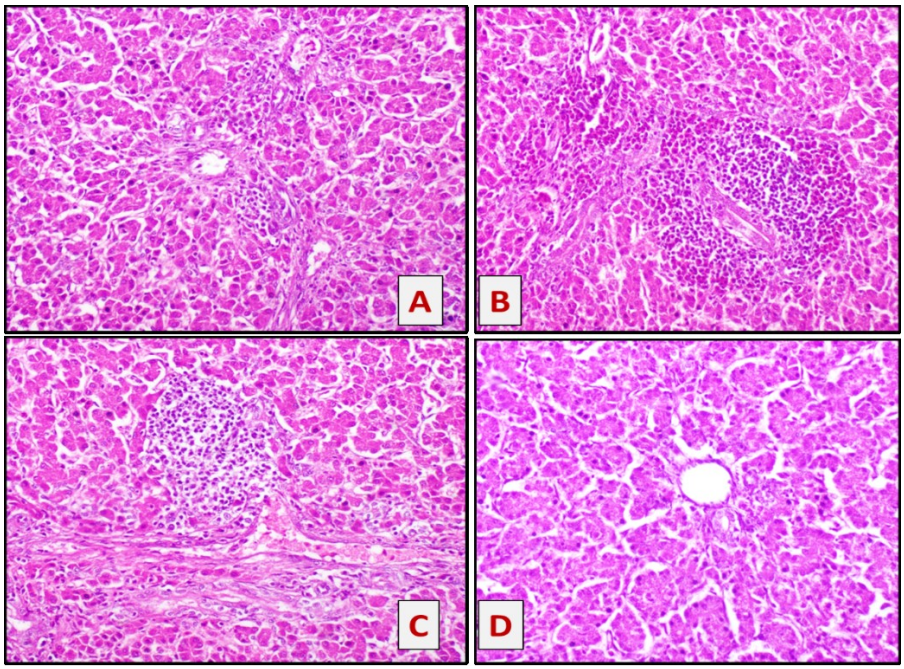

Fig.6. Liver sections of prebiotic, probiotic treated and non-treated infected chicken groups with *E. coli* O78 strains 1 or 2 stained with H&E (x200).

6A Treated groups 1-4 showing mild periportal leukocytes infiltration. 6B: Strain1 infected G5 showing severe periportal leukocytes infiltration. 6C: Strain1 infected G6 showing moderate periportal leukocytes infiltration. 6D: Control -ve G7 showing normal histological structure

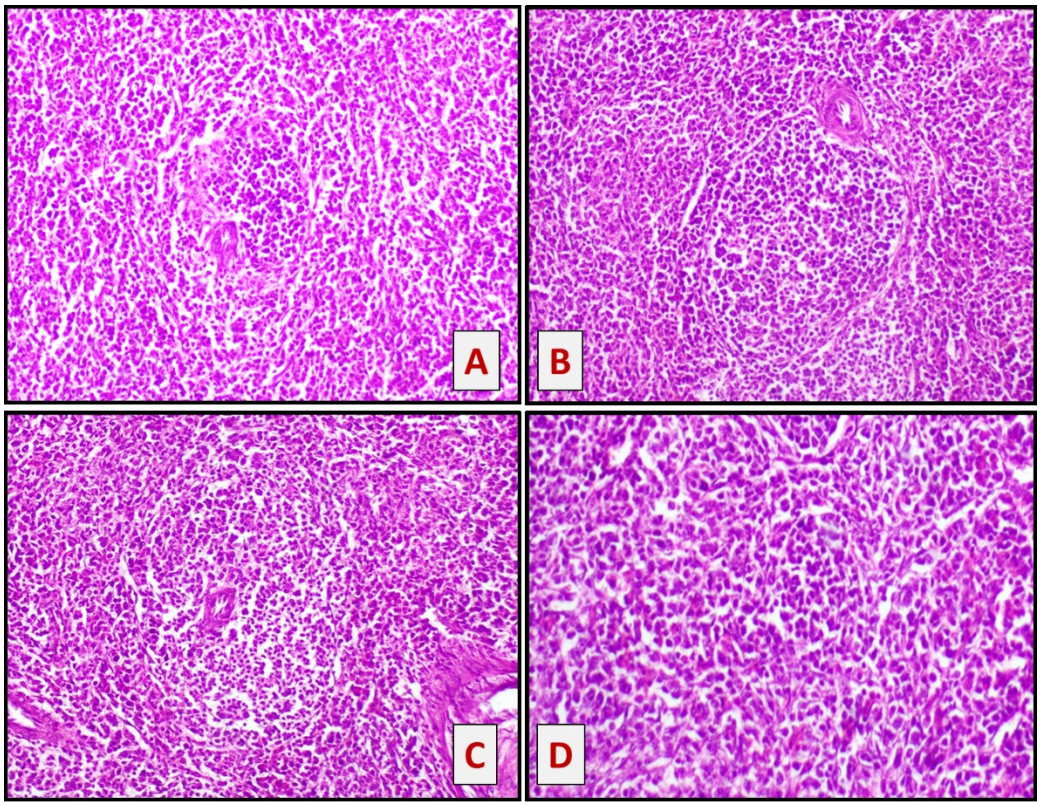

Fig. 7. Spleen sections of prebiotic, probiotic treated and non-treated infected chicken groups with *E. coli* O78 strains 1 or 2 stained with H&E (x200).

7A: Treated infected (Gruops1-4) showing well populated periarteriolar lymphoid sheath and follicles.
7B: Infected Strain 1 (Group 5) showing mild depletion of periarteriolar lymphoid sheath.
7C: Infected Strain 2 (Group 6) showing moderate depletion of periarteriolar lymphoid sheath.
7D: Control -ve showing normal histological structure.

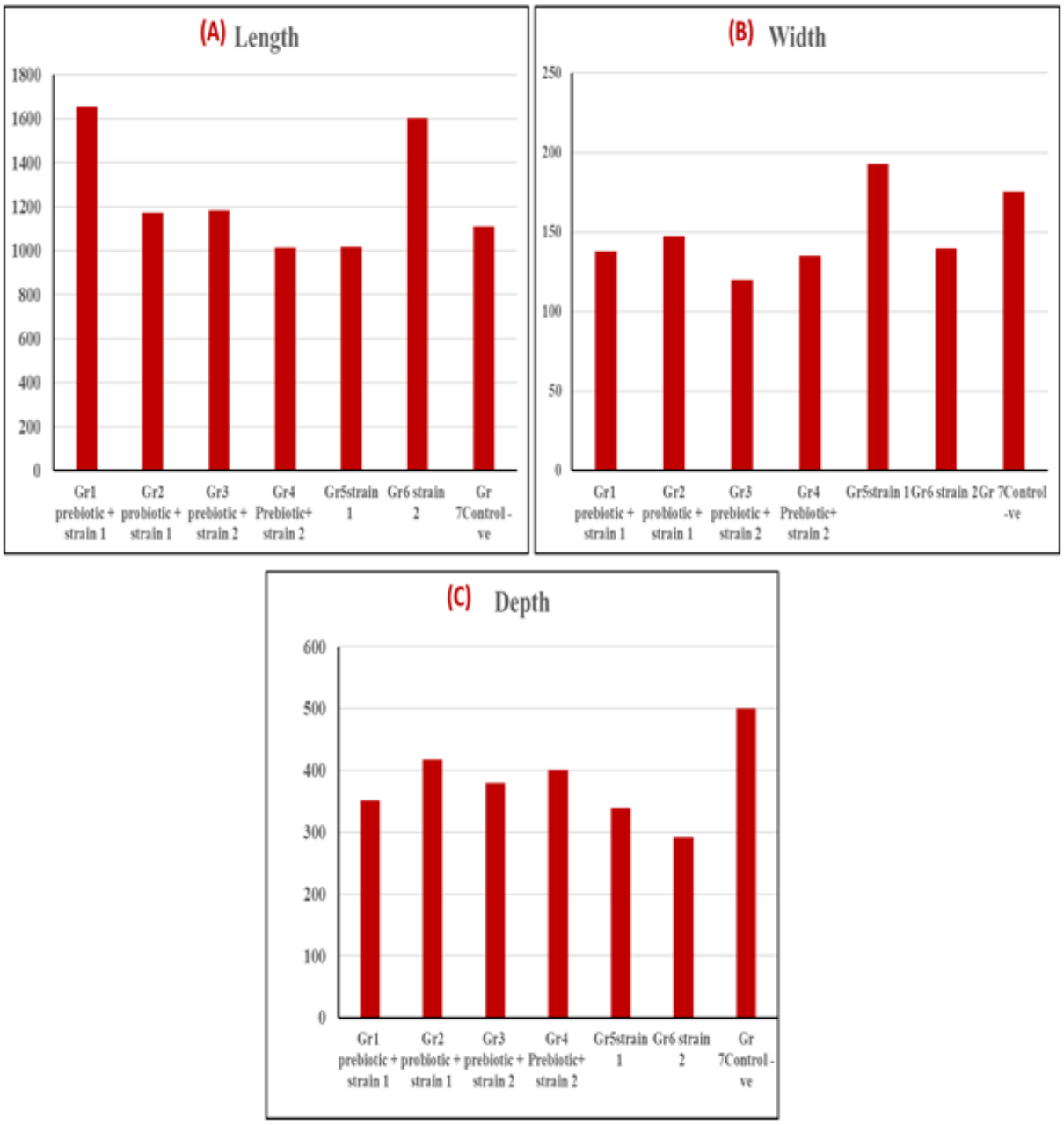

Fig. 4. The intestinal villi measurements (Mean ±SD) in treated infected chicken groups. A. Length B. Width. C. Depth

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التأثير الوقائي للبريبيوتيك أو البروبيوتيك على الإصابة التجريبية لدجاج اللحم بالميكروب القولوني النوع المصلي O78

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الخلاصة

يعد داء العصيات القولونية في الطيور من العوامل المسببة للأمراض الخطيرة التي تسبب خسائر مالية فادحة في قطاع إنتاج الطيور. في الآونة الأخيرة، أظهرت الإشريكية القولونية (E. coli) نطاقًا واسعًا من مقاومة المضادات الحيوية، وبالتالي يتم توجيه العالم إلى استخدام المضادات الحيوية واستخدام البدائل الطبيعية الآمنة للمضادات الحيوية. وهكذا، هدفت هذه الدراسة إلى تقييم فعالية البريبايوتيك والبروبيوتيك كإجراء وقائي للحد من خطر العدوى التجريبية بالعصيات القولونية في فراخ اللحم. تم توزيع 140 فرخاً لاحم بعمر يوم واحد عشوائياً إلى 7 مجموعات تضم كل منها 20 طائراً على النحو التالي: تم إعطاء المجموعات 1-2 و3-4 البريبايوتيك والبريبايوتيك في مياه الشرب من اليوم الأول إلى اليوم الخامس من الحياة، ثم في اليوم السادس والسابع تم إعطاء المجموعات 1 و3 و5 وكذلك المجموعات 2 و4 و6. أصيب كل فرخ عن طريق الفم بالإشريكية القولونية O78 الحساسة للأدوية الكاملة (السلالة 1) والمقاومة الشديدة للأدوية (السلالة 2) على التوالي. أصيبت المجموعتان 5 و 6 بالسلالة 1، والسلالة 2 إيجابية، على التوالي، بينما ظلت المجموعة 7 كمجموعة سيطرة سلبية. أظهرت النتائج أن كلاً من البريبايوتك والبروبيوتيك لهما تأثير إيجابي على أداء نمو الطيور، ويعزز وزن العضو المناعي والبنية النسيجية وكذلك تحسين الاستجابة المناعية الخلطية ضد اللقاحات التجارية ويحسن التركيب المورفومتري للزغابات المعوية تجريبياً. الدجاج المصاب بسلالتين مختلفتين من الإشريكية القولونية .O78 في الختام، يوصى باستخدام البريبايوتكس والبروبيوتيك في الأيام الخمسة الأولى من عمر الطيور لتقليل خطر الإصابة المحتملة بالإشريكية القولونية.

الكلمات المفتاحية: مقاومة للمضادات الحيوية ، فركتو-أوليغوساكاريد، المكورات المعوية البرازية، الملبنة الحمضة، الملبنة الرقيقة.