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CINNAMON NANO PARTICLES (CNPs) AS FEED ADDITIVES ON RABBIT GROWTH PERFORMANCE, IMMUNITY, ANTIOXIDANT CAPACITY, AND RESISTANCE TO *ESCHERICHIA COLI*

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ABSTRACT

The use of antibiotics in the poultry industry has been restricted. As a result, the phytogenic feed additives have been increasely utilized to serve this purpose, as well as for other benefits. This study aimed to investigate the effects of cinnamon nanoparticles (CNPs) on rabbit growth performance, immunity, serum biochemistry, blood hematology, cell histology, and protection against *Escherichia coli O25*.Therefore, sixty healthy weaned white New Zealand rabbits (35 days old) were separated into six equal groups. The rabbits were acquired from a private farm in Kafrelsheikh Governorate and acclimated for two weeks before the starting of the experiment. The rabbits groups were divided according to CNPs supplementation with or without antibiotic and experimental infection. According to our findings, the rabbits that received CNPs exhibited improved growth performance, P.M. lesions, bacterial re-isolation outcomes, and clinical symptoms. The hepatic and reno-protective effects of CNPs may be supported by decreases in the activities of serum ALT and AST and increases in the level of total protein and albumin, counts of total white blood cell and lymphocyte, and activities of antioxidant enzyme (SOD and CAT). The histopathological analysis showed that the positive control group had apparent pathological changes, such as interstitial nephritis, hepatic coagulative necrosis, and interstitial pneumonia with mononuclear cell infiltration. However, the superior effect was observed in the CNPs and streptomycin-treated group with milder to moderately altered tissue conditions. Thus, under current experimental conditions, dietary CNPs improved growth performance, antioxidant activity, and protection against experimental infection without pathological lesions.

Key words: *E. coli* infection; growth performance; health status; cinnamon nanoparticles (CNPs); rabbits.

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INTRODUCTION

Rabbit production is a rapidly growing livestock industry worldwide. One good source of animal protein that can help compensate for the global shortage of red meat is rabbit meat (Dalle Zotte and Szendro, 2011). In rabbit breeding operations, digestive tract infections are one of the primary pathogenic issues and cause large economic losses (Saravia *et al.,* 2017). Many infectious illnesses, including bacterial, viral, and parasitic illnesses, can affect domestic rabbits (Langan *et al.,* 2000; Lennox and Kelleher, 2009).

The gastrointestinal tracts of warm-blooded animals are frequently home to the commensal bacteria *E. coli* (Swennes *et al.,* 2012). Nonetheless, some *E. coli* strains have the potential to become virulent in immunocompromised hosts, leading to diarrhea and other intestinal disorders (Croxen *et al.,* 2013). One of the primary pathological issues and the cause of large financial losses in the rabbit breeding industry is digestive infections (Boullier and Milon, 2006). Enteropathogenic *E. coli* (EPEC) is the most prevalent serovar in rabbits; it causes mucoid or bloody diarrhea, dehydration, and lethargic behavior (Swennes *et al.,* 2012). In neonatal New Zealand rabbits, *E. coli* was found to cause diarrhea (Hamed *et al.,*2013). The virulence-associated genes of this bacterium allow some serotypes to cause extraintestinal or intestinal diseases. Diarrheagenic *E.coli* strains are those serotypes that typically cause enteric infections; their pathogenesis is linked to specific virulence traits that differ according to the pathotype (Xia *et al.,* 2010). The only class of *E. coli* known to cause acute intestinal disease in rabbits is EPEC, characterized by inflammatory lesions in the gut where the bacteria are present (Licois, 2004).

Antibiotic resistance has become the greatest threat to human health and livestock production and is mostly caused by the widespread use of antibiotics as animal growth promoters (Millman *et al.,* 2013; Mitchell *et al.,* 2013).

To enhance animal performance, a wide variety of feed additives can be added to the diets of animals and poultry. Due to their adverse effects, several nations now avoid the use of antibiotics. Currently, growth promoters derived from herbal sources (photogenic extracts) are widely used because of the global ban on nutritional antibiotics and consumer awareness, which has created a need for safe and natural feed additives to improve farm animal productivity (Zeweil *et al.,* 2016 a and b). According to Szabóová *et al.* (2008), using phyto-additives and their extracts in rabbit husbandry reasonably enhances welfare and health.

Plant-derived substances known as phytogenic feed additives (PFAs) are added to animal feed to enhance livestock performance, boost production, and enhance animal food quality (Steiner, 2009). Furthermore, the effectiveness and administration of phytogenic feed additives to livestock must be safe for the environment, the animal, and the user or consumer of the animal product (Windisch *et al.,* 2008). Within the *Lauraceae* family, Cinnamomum zeylanicum, or cinnamon, is one of the earliest known medicinal herbs. Due to its unique scent and potent antibacterial, antifungal, antiulcer, analgesic, antioxidant, and hypocholest-erolemic qualities, cinnamon is employed in the food sector (Mohamed Sham Shihabudeen *et al.,* 2011).

With a variety of uses, the field of nanotechnology has grown and matured in recent years. The vast surface area and nanoscale nature of nanoparticles make them useful tools for understanding their interactions with biological processes. It was discovered that using nanoparticles to control the bioavailability and absorption

of various medications improved their performance (Najafi *et al.,* 2020).

In our study, we assessed how CNPs affect growth, biochemical, immunological, pathological, and growth parameters and *E. coli* infection in developing rabbits.

MATERIALS AND METHODS

Samples

From various rabbit farms inside Kafrelsheikh Governorate, one hundred fecal swabs and samples of internal organs (liver, spleen, and intestine) from healthy and diarrheal rabbits were obtained.

Bacteriological isolation and identification of *E.coli*

E. coli was isolated according to Radwan *et al.* (2021). The gathered specimens were introduced into MacConkey's broth for a 24-hour incubation period at 37°C. After that, MacConkey's agar was streaked with a loopful of broth cultures, and the mixture was aerobically incubated for 24 to 48 hours at 37°C. Then the lactose fermenter (pink) colonies were cultured on eosin methylene blue (EMB) agar media for 18 to 24 hours at 37°C. According to Edward and Ewing (1972), the suspected colonies of *E. coli* were inspected for morphological and cultural traits before being picked up and streaked onto nutrient agar slopes for biochemical identification using oxidase, catalase, indole, citrate, methyl red, Voges Proskauer, hemolysis on blood agar, and urea (Cheesbrough, 1985).

Pathogenicity Testing *In Vitro*:

Congo red dye binding test

The Congo red dye binding assay, described by Berkhoff and Vinal (1986), was used to determine the pathogenicity of the isolates. Trypticase soy agar medium supplemented with 0.15% bile salts and 0.003% Congo red dye was used to cultivate each isolate. According to Reichhardt and Cegelski (2018), colonies that remained white or gray after failing to bind the dye were classified as Congo red (CR-) negative, while colonies that appeared red were classified as Congo red (CR+) positive.

Serological identification of *E. coli* isolates.

One of the Congo red-positive (CR+) samples was subjected to serological identification using a slide agglutination test utilizing polyvalent and monovalent *E. coli* antisera from the Animal Health Research Institute (AHRI), Dokki, Giza, Egypt,for the experimental infection (Edwards and Ewing, 1972).

Identification of *E. coli* isolates and detection of several Virulence genes by PCR:

DNA extraction. A QIAamp DNA Mini Kit (Qiagen, Germany, GmbH) was used to extract DNA from the samples, following the manufacturer's instructions. In brief, 200 µl of the sample suspension was treated for 10 min at 56°C with 10 µl of proteinase K and 200 µl of lysis buffer. Two hundred microliters of 100% ethanol were added to the lysate following incubation. After that, the sample was centrifuged and cleaned according to the manufacturer's instructions. The kit included 100 µl of elution buffer, which eluted the nucleic acid.

Oligonucleotide Primers. The primers were obtained from Metabion (Germany) (Table 1).

PCR amplification. A total of 25 µl reaction volume comprising 12.5 µl of EmeraldAmp Max PCR Master Mix (Takara, Japan), 1 µl of each primer at a concentration of 20 pmol, 5.5 µl of DNase-free water, and 5 µl of DNA template was used. The PCR thermal cycler (2720), from Applied Biosystems, was used to carry out the reaction.

Analysis of PCR Products
The PCR products were separated by electrophoresis employing gradients of 5 V/cm on a 1.5% agarose gel (Applichem, Germany, GmbH) in 1 × TBE buffer at room temperature. Fifteen microliters of each product were put into a gel slot for gel analysis. An AA generator 100 bp ladder (Fermentas, Germany) was used to ascertain the fragment sizes. Images of the gel were taken with a gel documentation system (Alpha Innotech, Biometra), and computer software was used to analyze the data.

Table 1: Primer sequences, target genes, amplicon sizes and cycling conditions

Target gene	Primers sequences	Amplified segment (bp)	Primary denaturation	Amplification (35 cycles)			Final extension	Reference
				Secondary denaturation	Annealing	Extension		
tsh	GGT GGT GCA CTG GAG TGG AGT CCA GCG TGA TAG TGG	620	94˚C 5 min.	94˚C 30 sec.	54˚C 30 sec.	72˚C 30 sec.	72˚C 10 min.	Delicato *et al.,* 2003
astA	CCATCAACACA GTATATCCGA GGTCGCGAGTG ACGGCTTTGT	115	94˚C 5 min	94˚C 30 sec.	55˚C 30 sec.	72˚C 30 sec.	72˚C 7 min.	Piva *et al.,* 2003
hlyA	GCATCATCAAG CGTACGTTCC AATGAGCCAAG CTGGTTAAGCT	534	94˚C 5 min.	94˚C 30 sec.	60˚C 40 sec.	72˚C 45 sec.	72˚C 10 min.	Paton and Paton 1998
phoA	CGATTCTGGAA ATGGCAAAAG CGTGATCAGCG GTGACTATGAC	720	94˚C 5 min.	94˚C 30 sec.	55˚C 40 sec.	72˚C 45 sec.	72˚C 10 min.	Hu *et al.,* 2011

Antimicrobial susceptibility of *E. coli* isolates
The disc diffusion method of Bauer *et al.* (1966) was used to determine the antibiotic susceptibility of the isolates. Many discs were utilized, including Ampicillin (AM-10 µg), Streptomycin (S-10 µg), Colistin Sulfate, Cefoxitin (FOX), Doxycycline (DO-30 µg), Ciprofloxacin (CIP-5 µg), and Sulfamethoxazole-Trimethoprim (SXT-25 µg). According to the guidelines provided by the Clinical and Laboratory Standards Institute (CLSI, 2015), the diameter of the inhibitory zone was measured and interpreted.

Preparation of bacterial cultures for experimental infection
Reconstituted *E. coli O25* was cultured for 24 hours at 37°C in 5 milliliters of nutrient broth. After being subcultured on MacConkey's agar, the plates were incubated for 24 hours at 37°C.

Experimental rabbits
After two weeks of adaptation, sixty healthy, weaned, white New Zealand rabbits (35 days of age) were divided into six groups based on Table (2). The rabbits were acquired from a private farm in Kafr elsheikh Governorate. As shown in Table (3) according to (NRC, 1994), the rabbits were fed a basal and balanced diet, and an endless supply of pure and fresh drinking water was provided.

Experimental design:
The experimental design is summarized in Table (2).

Clinical signs and P/M lesions:
All groups were monitored throughout the study for symptoms, postmortem lesions, and mortality.

Table 2: Experimental design

Groups	Treatments
G1	Negative control (non-challenged and non-treated).
G2	Positive control (challenged and non-treated) Challenged orally with 2 ml of saline containing $2x10^7$ CFU /ml *E. coli* O25 at the age of fifty days according to Feldman, 2000.
G3	Non-challenged and fed on a basal diet containing CNPs* 200 mg/kg.
G4	Challenged and fed on a basal diet containing CNPs.
G5	Challenged and treated after infection by 48 hours with antibiotic (streptomycin**) (1gm/liter) for 5 successive days.
G6	Challenged and treated with antibiotic and fed on a basal diet containing CNPs

*The CNPs: According to Bello *et al.* (2015) and Mashkouri *et al.* (2017), cinnamon was purchased from the local market in Kafrelsheikh City, Egypt, and the nanoparticles were made at the Institute of Nanoscience and Nanotechnology, Kafrelsheikh University.
** Produced by medical specialists for usage in accordance with the manufacturer's recommendations for veterinary products and fooder additions (MUVCO).

Table 3: Ingredients and proximate analysis of the experimental diet

Ingredients	Basal diet	Proximate analysis	
Yellow (7%)	9	Dry matter%	89.87
Barseem hay (18.1%)	36.65	Moisture%	10.13
Wheat bran (14.44%)	16.5	Crude protein%	18.62
Barley (12.04%)	16	Ether Extract%	2.95
Soya bean (44.7%)	16	Ash%	9.88
Vegetable oil	1	Crude Fiber% (CF)	16.57
Molasses	3	Nitrogen-free extract (NFE %) **	41.85
Limestone	0.500	Calcium %	1.19
Dicalcium phosphate	0.250	Total phosphorus%	0.69
Sodium bicarbonate	0.300		
vitamins & mineral mixture*	0.250		
DL methionine	0.050		
Salt	0.500		
Total (kg)	100		

* The vitamin and mineral mixture (Multivita Co.) contained vitamin A (12000000 IU), vitamin D3 (2200000 IU), vitamin E (10000 mg), vitamin K3 (2000 mg), vitamin B1 (1000 mg), vitamin B2 (5000 mg), vitamin B6 (1500 mg), vitamin B12 (10 mg), niacin (30000 mg), biotin (50 mg), folic acid (1000 mg), pantothenic acid (10000 mg), iron (30000 mg), manganese (60000 mg), copper (4000 mg), zinc (50000 mg), iodine (1000 mg), cobalt (100 mg), selenium (100 mg), and calcium carbonate ($CaCO_3$) (3000g).
**NFE = Nitrogen free extract and calculated by difference {100 – (moisture% + CP% + EE% + CF% + Ash%)}

Bacteriological investigation:
The lungs, livers, and spleens were removed from the rabbits in each group on the third day, first week, and second week following the infection with *E. coli* for bacterial re-isolation, according to Hamm *et al.* (2016). Additionally, rectal swabs were taken on the 3rd, 7th, and 14th days post-infection from every infected rabbit.

Measurements:
Growth performance parameters
Body weight (BW), weight gain, feed intake (FI), and feed conversion ratio

(FCR) were estimated using the Ensminger and Bomani (1980) equation, and the feed efficiency (FE) was computed using the Brody and Lardy (1946) equation. The growth parameters were calculated using the following formulas:

$$\text{WG (the weight gain, g)} = \text{W2 (final body weight, g)} - \text{W1 (initial body weight, g)}$$

$$\text{FCR (feed conversion ratio)} = \frac{\text{FI (feed intake, g)}}{\text{WG (g)}}$$

$$\text{FE (feed efficiency)} = \frac{\text{W2} - \text{W1}}{\text{FI}} \text{X100}$$

Blood collection and hematobiochemical indices

Blood was drawn from five randomly chosen rabbits from each group, firstly during the first week following infection and the second was after infection from the ear vein. According to Faggio *et al.* (2014), a portion of blood samples containing an anticoagulant (EDTA) was drawn to assess hematological parameters. Hemocytometers were used to count red blood cells (RBCs; ×106/mm³) and white blood cells (WBCs; ×103/mm³), and the cyanmethemoglobin method was used to estimate the Hb concentration (g/100 ml). Thin blood films were placed on sterile slides to measure the differential leucocyte count. Modified Wright's stain was added to the slides once they had had time to dry. The other portion of blood was taken without anticoagulant, and the serum was extracted for determination of biochemical parameters (ALT, AST, total protein, albumin, globulin, urea, and creatinine). The serum antioxidant capacity was determined by measuring the activities of superoxide dismutase (SOD) and catalase (CAT), according to Martin *et al.* (1987) and Aebi (1984), using commercial kits from Bio-Diagnostic Company, Egypt.

Histopathological examination

Samples from the liver, kidney, and lung were collected and fixed in 10% buffered formalin from all experimental rabbit groups. The tissue samples were processed for histopathological evaluation using routine paraffin sections. Sections 4 µm thick were cut and stained with hematoxylin and eosin (H&E) according to Bancroft and Layton (2013).

Biosafety measures

The biosafety procedures followed the pathogen regulation mandate for infectious materials (*E. coli*).

Statistical analysis:

The data were statistically analyzed using one-way ANOVA and Duncan's multiple comparisons test in SPSS (2007) to investigate the significant differences between various treatments concerning the evaluated parameters. Duncan's test indicates a significant difference ($P < 0.05$) between the means with different letters.

RESULTS

Bacterial isolation

From 100 fecal swabs and internal organs (representing 59% of the total), which were taken from apparently healthy and diarrheal rabbits from various rabbit farms in the Kafrelsheikh governorate, 59 *E. coli* isolates were detected as Gram-negative rods and the acquired isolates showed pink colonies and a characteristic green metallic sheen with a black core on MacConkey and EMB media, respectively. The Voges-Proskauer, urease, citrate utilization, and oxidase reduction tests yielded negative results for the suspected *E. coli* isolates. However, the methyl red, indole, and catalase production tests produced positive results. According to the Congo red dye binding test, 17 out of 59 isolates (28% of the total) developed tiny, dark brick red colonies as a pathogenic isolate.

Identification of *E. coli* and detection of several virulence genes by polymerase chain reaction (PCR)

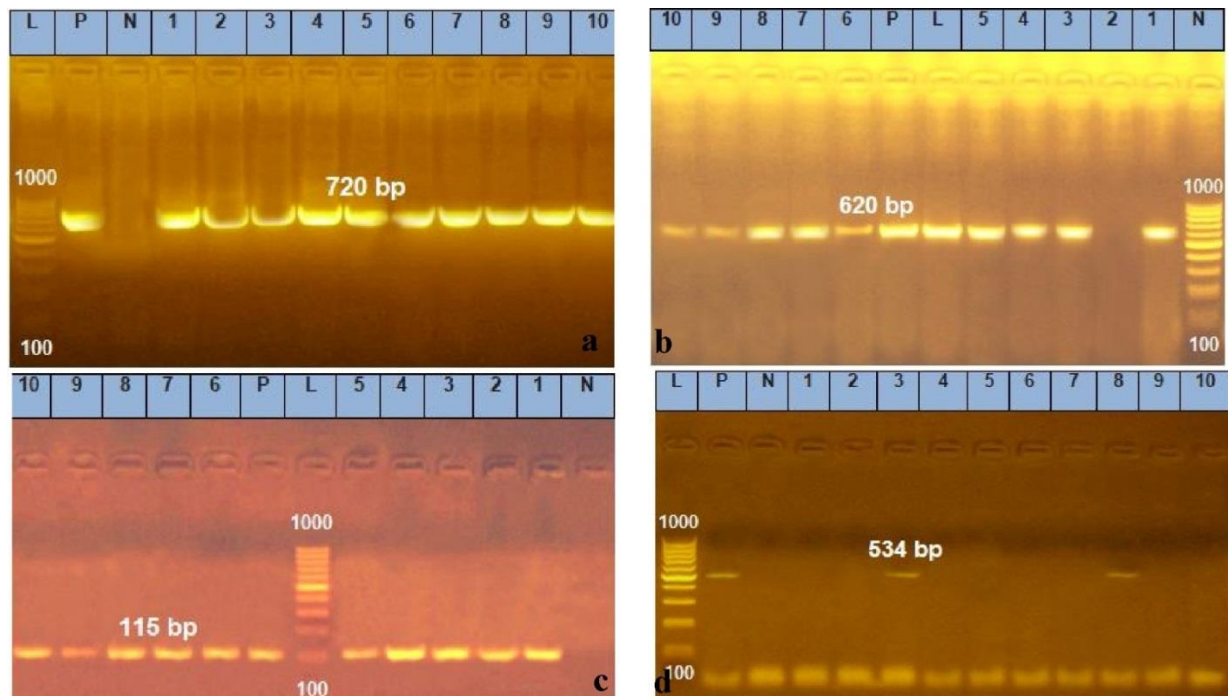

Fig. 1a Agarose gel electrophoresis of PCR amplification products of the phoA gene for characterization of *E.coli*
lane L: 100 bp ladder as a molecular size DNA marker. **Lanes 1, 2, 3, 4, 5, 6,7, 8, 9 and 10:** *E. coli* strains Positive for the *phoA* gene at 720 bp.

Fig. 1b Agarose gel electrophoresis of PCR amplification products of the *tsh* gene for characterization of *E. coli*
lane L: 100bp ladder as a molecular size DNA marker. **lanes1, 3, 4, 5, 6,7,8,9 and 10:** Positive *E. coli* strains for the *tsh* gene at 620 bp.

Fig. 1c Agarose gel electrophoresis of PCR amplification products of the *astA* gene for characterization of *E.coli*
lane L: 100 bp ladder as a molecular size DNA marker. **lanes1,2, 3, 4, 5, 6,7,8,9 and 10:** *E. coli* strains Positive for the *astA* gene at 115 bp.

Fig. 1d Agarose gel electrophoresis of PCR amplification products of the *hlyA* gene for characterization of *E.coli*
lane L: 100 bp ladder as a molecular size DNA marker. **lanes 3 and 8:** *E. coli* strains Positive for the *hlyA* gene at 534 bp.

Antimicrobial susceptibility of the *E. coli* isolates:

The results indicate that cefoxitin, streptomycin, ampicillin, and amikacin exhibited the highest levels of antimicrobial sensitivity to the isolated *E. coli*. As indicated in Table (4), the isolates were immediately sensitive to colistin sulfate and resistant to ciprofloxacin, sulfamethoxazole/trimethoprim, and doxy-cycline.

Table 4: Antimicrobial sensitivity of *E.coli*

Antimicrobial agents	Resistant		Intermediate		Sensitive	
	No.	%	No.	%	No.	%
Colistin sulphate	0	0	8	80	2	20
Doxycycline	7	70	3	30	0	0
cefoxitin	0	0	0	0	10	100
Streptomycin	0	0	2	20	8	80
ciprofloxacin	1	10	3	30	6	60
Ampicillin	0	0	2	20	8	80
sulfamethoxazole/trimethoprim	8	80	0	0	2	20
Amikacin	2	20	1	10	7	70

Effect of CNPs treatment on the *E.coli* re-isolation rate

Before infection, the experimental rabbits were checked as free from *E. coli.* Bacterial shedding started on the third day after infection, peaked in the first week, and then gradually stopped exhibiting clinical symptoms in the second week. Compared to that in the non-treated groups, the re-isolation rate was lower in the group treated with CNPs or antibiotics alone and in the groups treated with the combination of CNPs and antibiotics.

Table 5: Effect of CNP treatment on *E.coli* re-isolation rate

Group	Treatment	Re-isolation rate					
		3rd post-infection		1st week post-infection		2nd week post-infection	
		No	%	No	%	No	%
G1	Non-treated+ non-challenged	0/10	0	0/10	0	0/10	
G2	Non-treated+ challenged	4/10	40	10/10	100	3/10	30
G3	Treated with CNP + non-challenged	0/10	0	0/10	0	0/10	0
G4	Treated with CNP + challenged	3/10	30	5/10	50	2/10	20
G5	Treated with antibiotic+ challenged	2/10	20	4/10	40	1/10	10
G6	Treated with antibiotic+ CNP+ challenged	0/10	0	2/10	20	0/10	0

Effect of CNPs supplementation and *E.coli* infection on feed parameters

As shown in Table 6, we found significant ($p < 0.05$) differences between the groups of growing rabbits fed a diet containing CNPs and the control group in growth performance parameters (body weight, weight gain, feed intake, feed conversion ratio, and feed efficiency). All rabbits fed CNPs-supplemented diets showed the highest body weight, weight gain, and feed conversion ratio; in contrast, the control groups, the control +ve or -ve, showed the lowest final body weight and weight gain.

Table 6: Effect of CNPs supplementation and *E.coli* infection on growth performance parameters every two weeks

Groups	Initial weight	2nd week	4th week	6th week	8th-week
			weight		
G1	955±2	1133.25±7.25^{c}	1422.5±3^{e}	1572.08±1.02^{e}	1764.95±0.15^{e}
G2	960±1	1117.5±1.75^{c}	1219.9±1.4^{f}	1329.6±1.6^{f}	1498.6±0.85^{f}
G3	953±3	1248.25±7.75^{b}	1718.45±0.95^{b}	2179.15±0.93^{b}	2471.48±0.73^{b}
G4	957±2	1137±72.75^{c}	1464.8±2.05^{d}	1696.8±.0.95^{d}	1973.3±0.9^{d}
G5	958±3	1115.75±1.25^{c}	1480.55±1.3^{c}	1889.15±1.2^{c}	2263.65±0.76^{c}
G6	956±4	1340.75±29.75^{a}	1791.95±1.3^{a}	2231.25±0.5^{a}	2715.52±0.73^{a}
			Weight gain		
G1	-	41.25±0.5^{d}	123±0.5^{d}	67.83±1.08^{e}	101.5±0.75^{e}
G2	-	37.5±0.75^{e}	56±2^{e}	60.2±1.65^{f}	90.5±1.22^{f}
G3	-	96.33±0.39^{b}	247.7±0.8^{a}	279.03±0.2^{a}	140±2^{c}
G4	-	41±1^{d}	164±1.75^{c}	106.25±0.5^{d}	112±1^{d}
G5	-	58±1^{c}	215±1.25^{b}	215±0.7^{c}	208±1^{b}
G6	-	187±0.5^{a}	246.2±1.3^{a}	269±1.25^{b}	292.6±1.1^{a}
			Feed intake		
G1	-	641.67±0.92^{e}	998.68±0.42^{c}	685±1^{e}	902.7±0.45^{c}
G2	-	656.67±0.92^{c}	759.92±1.17^{f}	633.3±0.55^{f}	819.02±0.9^{e}
G3	-	650±0.5^{d}	1083.67±1.42^{b}	850.67±0.11^{c}	618.67±0.43^{f}
G4	-	583.33±0.48^{f}	1114.7±0.45^{a}	988±1^{b}	899.33±1.58^{d}
G5	-	750±1^{b}	994.7±1.2^{d}	1134±2^{a}	1102.7±2^{a}
G6	-	823.3±2.45^{a}	836.67±1.42^{e}	791.67±0.72^{d}	988.67±1.17^{b}
			FCR		
G1	-	15.56±0.03^{b}	8.1±0.35^{b}	10.1±0.15^{a}	8.9±0.53^{a}
G2	-	17.5±0.25^{a}	13.57±0.12^{a}	10.52±0.09^{a}	9.05±0.01^{a}
G3	-	6.75±0.5^{e}	4.37±0.13^{d}	3.05±0.14^{d}	4.4±0.17^{d}
G4	-	14.23±0.14^{c}	6.8±0.01^{c}	9.3±0.01^{b}	8.03±0.01^{b}
G5	-	12.93±0.18^{d}	4.6±0.35^{d}	5.27±0.04^{c}	5.3±0.05^{c}
G6	-	4.4±0.15^{f}	3.07±0.45^{e}	2.94±0.02^{d}	3.36±0.044^{e}
			FE		
G1	-	0.06±0.01^{c}	0.12±0.010^{d}	0.099±0.002^{e}	0.11±0.01^{d}
G2	-	0.057±0.002^{c}	0.074±0.001^{e}	0.095±0.002^{e}	0.11±0.01^{d}
G3	-	0.148±0.001^{b}	0.23±0.002^{b}	0.328±0.002^{b}	0.23±0.002^{b}
G4	-	0.07±0.01^{c}	0.15±0.002^{c}	0.108±0.002^{d}	0.13±0.002^{d}
G5	-	0.077±0.002^{c}	0.22±0.001^{b}	0.190±0.002^{c}	0.19±0.002^{c}
G6	-	0.227±0.002^{a}	0.29±0.020^{a}	0.339±0.002^{a}	0.30±0.001^{a}

The values are expressed as a mean value ± standard error. The means with distinct letters in the same column differ significantly at $P < 0.05$.

Effects of CNPs supplementation and *E.coli* infection on hematological parameters

There was a significant increase in WBC counts in group 3, while there was a significant decrease in group 2, but there were nonsignificant differences between groups 4, 5, 6, and group 1 (Table 7). RBC counts and hemoglobin did not significantly differ across the groups.

Table 7: Effect of CNPs supplementation and *E.coli* infection on hematological parameters

group	**RBCs**($\times10^6$/mm³)		**WBCs**($\times10^3$/mm³)		**Hb**(g/100ml)	
	1st wk pc*	At the end of the experiment	1st wk pc*	At the end of the experiment	1st wk pc*	At the end of the experiment
G1	6.18± 0.17	6.18± 0.17	10.77± 1.07 b	10.77± 1.07 b	13.57 ± 0.17 a	13.57 ± 0.17
G2	5.67± 0.25	6.12± 0.230	6.23± 0.14 d	7.86± 0.33 d	11.20± 0.20 b	12.37± 0.49
G3	6.19± 0.19	6.19± 0.19	15.60± 2.97 a	15.60± 2.97 a	12.23± 0.53 a	12.23± 0.53
G4	5.93± 0.11	5.973± 0.13	9.16± 0.17 c	10.57± 1.14 b	12.20± 0.17 a	11.93± 0.16
G5	6.20± 0.25	6.14± 0.18	9.00± 0.17 c	9.10± 0.94 c	12.57± 0.80 a	11.70± 0.26
G6	6.29± 0.13	6.11± 0.29	10.20± 0.56 b	11.27± 0.43 b	12.83± 0.40 a	12.00± 0.88

The values are expressed as a mean value ± standard error. At (P < 0.05, means with various letters in the same column differ significantly), pc* (post-infection).

Effect of CNPs supplementation and *E.coli* infection on deferential leucocyte count

There were significantly decreased lymphocyte counts in group 2. Furthermore, group 2 had a notable increase in neutrophil counts, but group 1 and the other groups showed nonsignificant differences in neutrophil counts. However, the mixed cell count increased in the other groups to reach group 1, whereas it decreased in group 2 (table 8).

Group	**Lymphocyte**		**Neutrophil**		**Mixed cell**	
	1st wk pc*	At the end of the experiment	1st wk pc*	At the end of the experiment	1st wk pc*	At the end of the experiment
G1	5.46± 0.76 a	5.46± 0.76	2.06± 0.08 d	2.93± 0.12 c	3.36± 0.56 a	3.36± 0.56 a
G2	3.00± 0.11 b	5.63± 0.59	6.10± 1.30 a	6.10± 1.30 a	1.13± 0.03 d	2.00± 0.55 b
G3	5.20± 0.36 a	5.20±0.36	3.36± 0.41 b	3.36± 0.41 b	2.20± 0.45 b	2.20± 0.45 b
G4	5.40± 0.20 a	4.03± 0.17	2.23± 0.23 c	1.83± 0.12 e	1.53± 0.08 c	2.00± 0.10 b
G5	5.56± 0.29 a	4.80± 0.72	2.50± 0.20 c	2.06± 0.40 d	2.13± 0.08 b	2.23± 0.40 b
G6	5.06± 0.12 a	5.10± 0.40	2.03± 0.26 d	3.33± 0.40 b	1.90± 0.11 c	2.83± 0.48 a

Table 8: Effect of CNPs supplementation and *E.coli* infection on deferential leucocyte count

The values are expressed as a mean value ± standard error. At (P < 0.05, means with various letters in the same column differ significantly), pc* (post-infection).

Effects of CNP supplementation and *E.coli* infection on antioxidant enzymes

The antioxidant enzymes (SOD and CAT) activities in the current study were significantly increased in groups 3 and 6. Following *E. coli* inoculation, the antioxidant enzymes (SOD and CAT) activities in groups 5 and 4 were increased to reach group 1 (Table 9).

Effects of CNPs supplementation and *E.coli* infection on liver enzymes

Results showed that there were significantly higher liver enzyme levels (ALT and AST) in group 2 than in other groups, while group 3 showed significantly lower liver enzyme levels than other groups, although there were nonsignificant differences between groups 6, 5, 4, and group 1 (Table 10).

Table 9: Effects of CNPs supplementation and *E.coli* infection on serum antioxidant enzymes

Group	SOD (U/L)		CAT (U/L)	
	1st wk pc*	At the end of the experiment	1st wk pc*	At the end of the experiment
G1	4289± 53.67[c]	4289± 53.67[c]	336.7± 4.80[b]	336.7± 4.80[b]
G2	1368± 214.20[f]	3563± 218.10[d]	250.2± 11.75[c]	135.7± 18.95[d]
G3	6208± 232.90[a]	6208± 232.90[a]	443.8± 3.43[a]	443.8± 3.43[a]
G4	3357± 85.07[d]	3607± 184.50[d]	274.9± 10.67[c]	235.9± 2.86[c]
G5	2747± 239.30[e]	4274± 39.37[c]	353.5± 16.77[b]	251.6± 13.49[c]
G6	5086± 38.00[b]	5403± 212.90[b]	439.5± 29.71[a]	426.9± 21.78[a]

The values are expressed as a mean value ± standard error. At (P < 0.05, means with various letters in the same column differ significantly), pc* (post-infection).

Table 10: Effects of CNPs supplementation and *E.coli* infection on liver enzymes

Group	ALT (U/L)		AST (U/L)	
	1st wk pc*	At the end of the experiment	1st wk pc*	At the end of the experiment
G1	47.00± 3.05[c]	47.00± 3.05[c]	30.33± 2.60[c]	34.67± 3.18[b]
G2	79.33± 11.84[a]	77.67± 3.84[a]	51.33± 13.54[a]	49.67± 2.33[a]
G3	53.67± 6.88[c]	53.67± 6.88[cb]	22.00± 1.15[d]	30.33± 0.66[b]
G4	55.00± 1.73[c]	50.67± 1.76[c]	33.33± 2.72[c]	49.00± 8.327[a]
G5	63.00± 2.64[b]	56.00± 5.50[b]	46.67± 1.85[b]	49.67± 2.33[a]
G6	53.67± 6.96[c]	50.67± 2.96[c]	32.67± 1.45[c]	46.67± 1.85[a]

The values are expressed as a mean value ± standard error. At (P < 0.05, means with various letters in the same column differ significantly), pc* (post-infection).

Effects of CNPs supplementation and *E.coli* infection on kidney function

A significantly higher creatinine and urea level in group 2 than in the other groups, while groups 3 and 6 showed significantly lower urea, creatinine, and uric acid levels than others, although there were nonsignificant differences between groups 4, 5, and group 1 (Table 11).

Table 11: Effects of CNPs supplementation and *E.coli* infection on kidney function

Group	Urea (mg/dL)		Creatinine (mg/dL)		Uric acid (mg/dL)	
	1st wk pc*	At the end of experiment	1st wk pc*	At the end of experiment	1st wk pc*	The end of experiment
G1	39.33± 2.90[a]	39.33± 2.90	1.50± 0.098[b]	1.50± 0.098	0.55 ± 0.02[b]	0.55 ± 0.02[a]
G2	45.33± 2.02[a]	39.33± 1.76	2.01± 0.05[a]	1.57± 0.08	1.23± 0.08[a]	0.40± 0.11[a]
G3	32.67± 1.45[b]	38.00± 5.29	1.29± 0.02[c]	1.29± 0.02	0.36± 0.21[c]	0.13± 0.03[b]
G4	39.00± 2.08[a]	43.33± 4.37	1.60± 0.33[b]	1.57± 0.06	1.00± 0.05[a]	0.36± 0.21[a]
G5	43.67± 2.33[a]	43.67± 2.33	1.80± 0.15[b]	1.55± 0.17	0.86± 0.14[b]	0.36± 0.21[a]
G6	33.67± 0.66[b]	41.33 ± 1.76	1.34± 0.03[c]	1.4± 0.03	0.60± 0.11[b]	0.26± 0.03[a]

The values are expressed as a mean value ± standard error. At (P < 0.05, means with various letters in the same column differ significantly), pc* (post-infection).

Effects of CNPs supplementation and *E.coli* infection on total protein, albumin and globulin

According to Table 12, total protein, albumin, and globulin were non-significantly increased in group 3, while total protein and albumin were significantly decreased in group 2.

Table 12: Effects of CNPs supplementation and *E.coli* infection on total protein, albumin and globulin

Group	Total protein(g/L)		Albumin (g/dL)		Globulin (g/dL)	
	1st wk pc*	At the end of the experiment	1st wk pc*	At the end of the experiment	1st wk pc*	At the end of the experiment
G1	7.56± 0.37 a	7.56± 0.37	3.30± 0.06 a	3.30± 0.06	4.26± 0.34	4.26± 0.34
G2	6.40± 0.15 b	6.90± 0.26	2.51± 0.17 b	3.26± 0.04	3.88± 0.32	3.90± 0.09
G3	8.13± 0.20 a	7.36± 0.26	3.34± 0.25 a	3.34± 0.25	5.05± 0.27	4.02± 0.26
G4	7.30± 0.11 a	7.16± 0.08	3.03± 0.04 a	3.10± 0.05	4.26± 0.10	3.80± 0.23
G5	7.23± 0.13 a	7.10± 0.72	2.67± 0.09 a	2.93± 0.26	4.02± 0.26	4.16± 0.46
G6	7.36± 0.26 a	7.36± 0.38	3.08± 0.09 a	3.42± 0.04	4.55± 0.21	3.94± 0.33

The values are expressed as a mean value ± standard error. At (P < 0.05, means with various letters in the same column differ significantly), pc* (post-infection).

Histopathological findings

1. Liver

The liver tissues of untreated control rabbits displayed a normal portal area and normal hepatic parenchyma of the central vein with radiating hepatic cords **(Fig. 2A)**. Conversely, the liver tissues of rabbits infected with *E. coli* displayed distinct focal areas of coagulative necrosis along with the infiltration of mononuclear cells **(Fig. 2B)**. However, the hepatic tissues of rabbits fed CNPs exhibited normal structure **(Fig. 2C)**. The normal histology of rabbits infected with *E. coli* and given CNPs was moderately restored, showing hepatocyte vacuolar degeneration accompanied by focal infiltration of perivascular mononuclear cells and sinusoidal cell activation **(Fig. 2D)**. On the other hand, the hepatic parenchyma of the *E. coli*-infected rabbits treated with streptomycin showed notable improvement. **(Fig. 2E)**, although hyperemia was observed in some areas of the hepatic parenchyma. Amazingly, the normal hepatic structure was restored in infected rabbits exposed to CNPs and streptomycin without cytoplasmic vacuolation, cellular infiltration, or necrotic changes. **(Fig. 2F)**.

2. Kidney

The glomeruli and renal tubules of the kidneys of the control rabbits had normal histological appearances **(Fig. 3A)**. On the other hand, rabbits infected with *E. coli* exhibited marked interstitial nephritis, including focal tubular necrosis and inflammatory infiltrates, mainly macrophages, lymphocytes, and some heterophils **(Fig. 3B)**. However, rabbits fed a diet containing CNPs had kidneys with a normal structure **(Fig. 3C)**. A moderate reduction in renal histological alterations was noted in *E. coli*-infected rabbits given CNPs **(Fig. 3D),** except for small focal areas of interstitial nephritis, vacuolar degeneration of renal tubules, and mild congestion of glomerular capillaries and inter-tubular blood vessels. Streptomycin-treated Rabbits with *E. coli* infection exhibited minor renal alterations, including congested glomerular capillaries and mild renal epithelial vacuolar degeneration with pyknotic nuclei **(Fig. 3E)**. Remarkably, renal parenchyma was significantly restored in *E. coli*-infected rabbits given a combination of streptomycin and CNPs **(Fig. 3F)**.

3. Lung

The pulmonary tissues of untreated control rabbits showed normal alveoli with thin-walled interalveolar septa. **(Fig. 4A)**. Conversely, the lungs of the rabbits in the *E. coli* infection group exhibited features of interstitial pneumonia, including thickening of the interalveolar septa with infiltrating mononuclear cells and blood vessel congestion. **(Fig. 4B)**. Rabbits fed a diet containing CNPs displayed normal

lung histology, except for those with mild focal pulmonary emphysema, which was in line with the findings of the control group **(Fig. 4C)**. The features of interstitial pneumonia were slightly ameliorated in *E. coli*-infected rabbits supplemented with CNPs **(Fig. 4D)**. This amelioration was enhanced in *E. coli*-infected rabbits treated with streptomycin with a moderate degree of interstitial pneumonia **(Fig. 4E)**. A significant improvement was observed in the *E. coli*- infected group treated with a combination of streptomycin and CNPs, which exhibited minute focal areas of interalveolar thickening **(Fig. 4F)**.

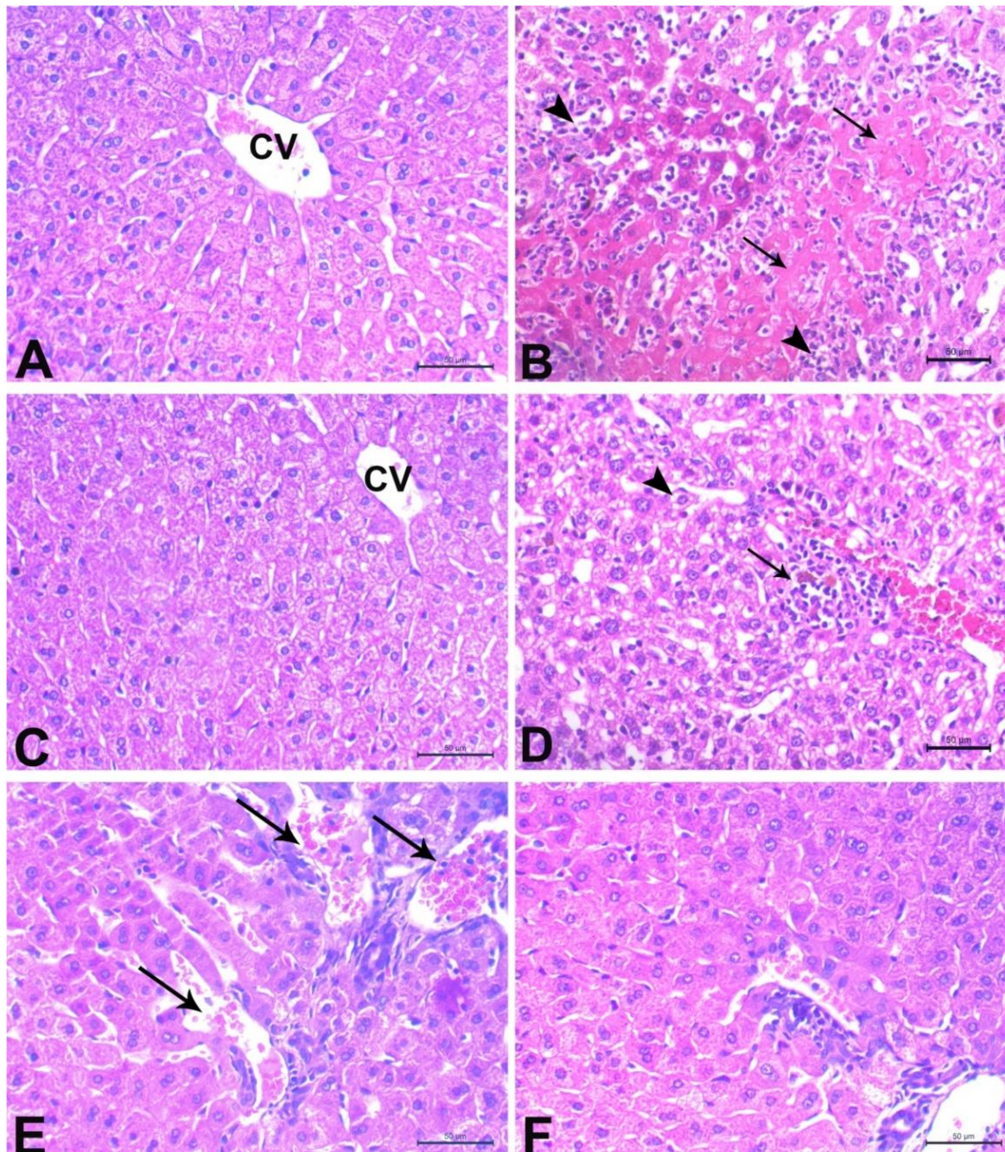

Fig. 2: Histopathological findings of the liver of rabbits in different experimental groups. **(A):** The control group displayed normal hepatic parenchyma of the central vein (CV) with radiating hepatic cords. **(B)**: *E. coli*-infected rabbits showing coagulative necrosis *(arrows)* accompanied by mononuclear cell infiltration of *(arrowheads).* **(C):** Rabbits received a diet supplemented with CNPs exhibiting normal hepatic architecture of the central vein (CV) and hepatocyte cords. **(D):** *E. coli*-infected rabbits supplemented with CNPs demonstrating mild vacuolar hepatic degeneration *(arrowhead)* with focal perivascular mononuclear cell infiltration *(arrow)*. **(E):** *E. coli*-infected rabbits treated with streptomycin showing dilated hyperemic sinusoids *(arrows)*. **(F):** *E. coli*-infected rabbits treated with a combination of CNPs and streptomycin show*ed* normal hepatic architecture. *All are H&E stained (x200), bar = 50 µm.*

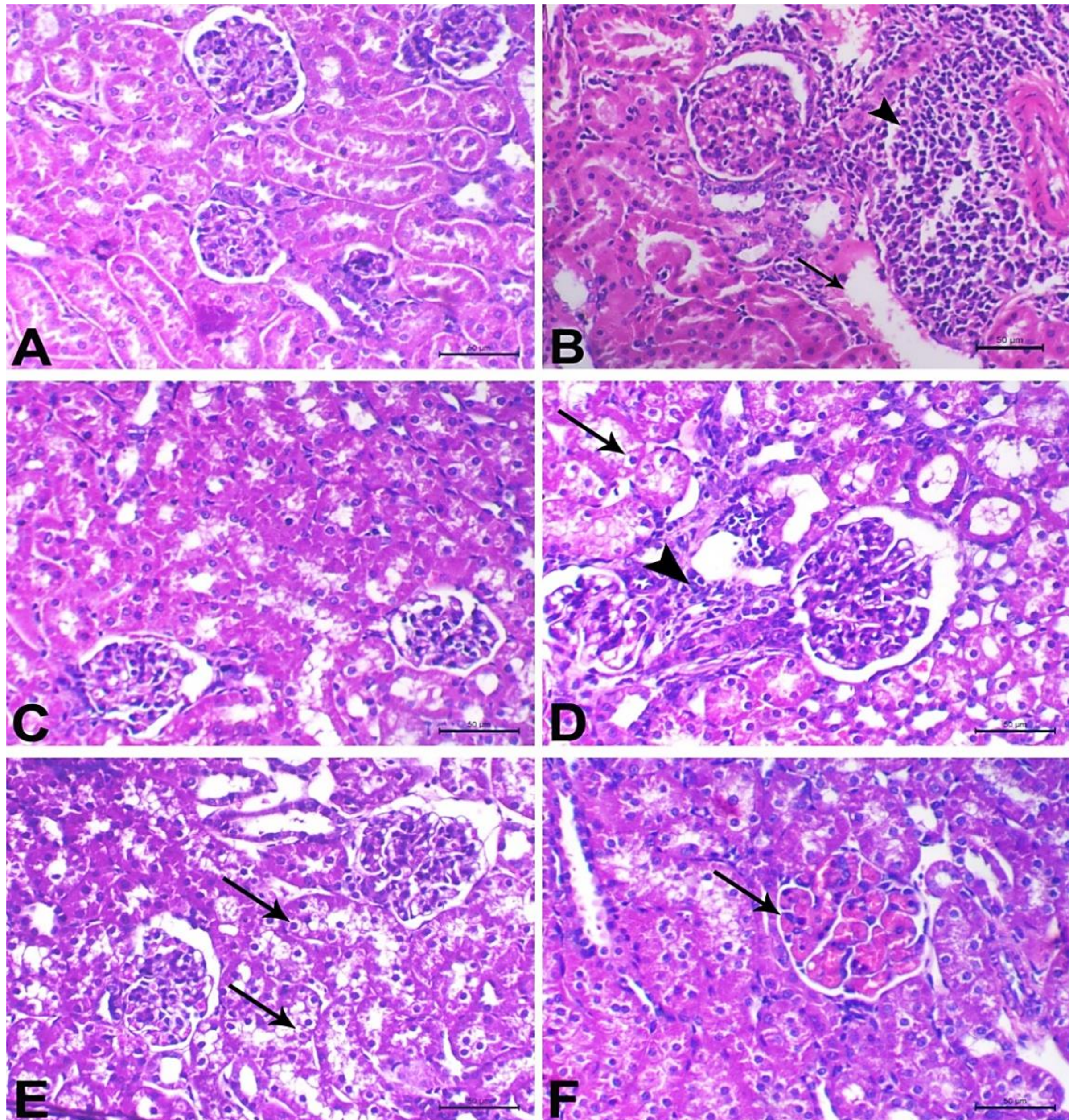

Fig. 3: Histopathological findings of the kidney of rabbits in different experimental groups.

(A): The control group showed normal renal parenchyma of the glomeruli and renal tubules. (**B**): The kidneys of rabbits infected with *E. coli* showing interstitial nephritis associated with tubular degenerative changes *(arrow)* with mononuclear cell infiltration *(arrowhead).* **(C):** The rabbits received a diet supplemented with CNP and exhibited normal renal histology. **(D):** Kidneys of infected rabbits supplemented with CNPs displaying vacuolar degeneration of the renal tubular epithelium with pyknotic nuclei *(arrow)* accompanied by small focal mononuclear cell infiltration *(arrowhead).* **(E):** The kidneys of infected rabbits treated with streptomycin showed mild vacuolar degeneration of the tubular epithelium *(arrows).* **(F):** The kidneys of infected rabbits treated with a combination of CNPs and streptomycin show normal renal parenchyma with slight congestion of the glomerular tuft *(arrow). All are H&E stained (x200), bar = 50 µm.*

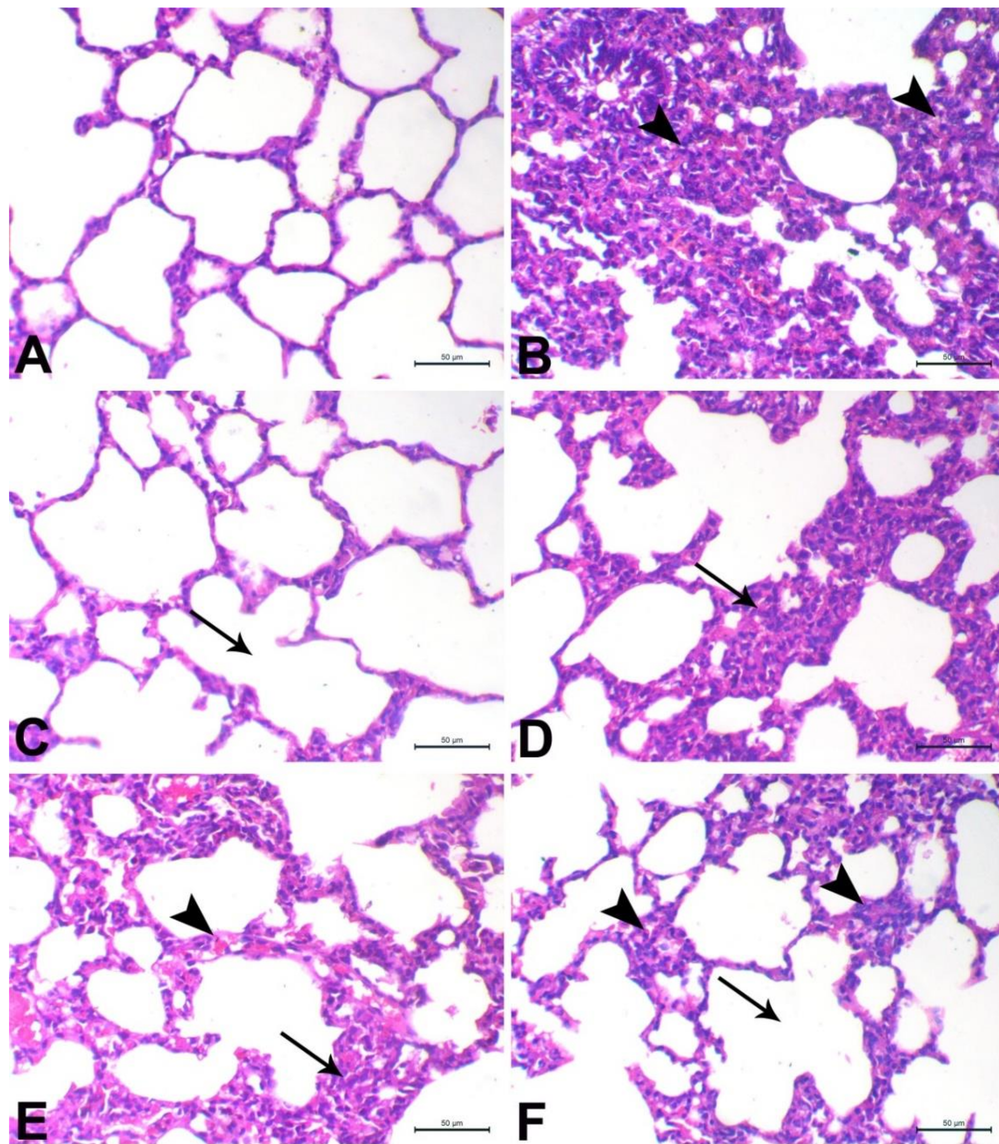

Fig.4: Histopathological findings of the rabbit's lung in different experimental groups. **(A):** The lungs of the control group showed normal alveoli and interalveolar tissues. **(B)**: Infected group with *E. coli* demonstrating marked interstitial pneumonia with thickened interalveolar septa with infiltrating mononuclear cells *(arrowheads).* **(C):** CNP-supplemented group showing normal air spaces *(arrow)*. **(D):** The *E. coli* infected-group supplemented with CNPs exhibited moderately thickened interalveolar septa *(arrow)*. **(E):** *E. coli*-infected rabbits treated with streptomycin exhibited mild thickening of the interalveolar septa with infiltrating mononuclear cells (arrow) and congested interalveolar capillaries *(arrowhead)*. **(F):** The *E. coli* infected group treated with a combination of CNPs and streptomycin displayed minute focal interalveolar thickening *(arrowheads)* with mild emphysema *(arrow). All are H&E stained (x200), bar = 50 µm.*

DISCUSSION

One of Egypt's most significant animal industries is the raising of rabbits. (Saif-Eldin *et al*., 1994). According to Hong *et al.* (2017), a rabbit farm had a high mortality rate of 24%, and isolates of diarrheagenic *E. coli* were responsible for 75% of these deaths. The current investigation aimed to separate diarrheagenic *E.coli* from rabbits. Out of 100 fecal samples, 59 had *E. coli*, representing a 59% prevalence rate. These outcomes matched those reported by El-Masry and Tamam (2021).

The putative *E. coli* isolates, Gram staining, culture traits, and biochemical test results agreed with those of Edward and Ewing (1972) and El-Masry and Tamam (2021). Additionally, Singh and Gupta (1996) mentioned that the ability of virulent *E. coli* isolates to interact with Congo red can be used to identify them. The results of the Congo red dye binding test, which was used to assess the in vitro pathogenicity of the suspected *E. coli*, were consistent with the findings of Berkhoff and Vinal (1986), who reported a substantial correlation between the virulence of *E. coli* in chickens and its expression of the CR phenotype. Additionally, the results agreed with those of El-Masry and Tamam (2021), who reported that 8 out of 27 isolates (29.63%) produced positive results and had tiny and dark red colonies.

Our results demonstrated that polymerase chain reaction (PCR) was implemented to identify the three virulence genes, *tsh*, *astA*, and *hlyA*, as well as the *phoA* gene of *E. coli*, which generates a band at 720 bp. According to the data, nine isolates out of ten tested (90%) carried the *tsh* gene, resulting in products at 620 bp. These results were in agreement with those of Walaa and Lamyaa (2016), who reported that all detected *E. coli* serogroups isolated from nursing rabbits expressed the *tsh* gene, and disagreed with those published by Eid *et al.* (2017), who reported that the *tsh* gene was expressed in only one of five isolates. Furthermore, our results showed that *hlyA* was detected in two out of ten isolates.

Most the *E.coli* isolates in our study were sensitive to amikacin, ampicillin, streptomycin, and cefoxitin. These outcomes were almost identical to those reported by Xiaonan *et al.* (2018), who reported that imipenem, ceftriaxone, and ceftazidime were effective against all *E. coli* strains. Additionally, our findings showed that the *E. coli* isolates were resistant to doxycycline and sulfamethoxazole/ trimethoprim. These findings aligned with those of Sabry and Mohamed (2009), who discovered that rabbit *E. coli* strains exhibited resistance to tetracycline and sulfamethoxazole. Additionally, the findings were in line with those of Chuong *et al.* (2021), who reported that isolates of *E. coli* were resistant to 100% doxycycline, 95.46% sulfamethoxazole, and 86.37% neomycin. Since rabbits are more susceptible to beta-lactams, we could not utilize cefoxitin or ampicillin in our experiment and had to use streptomycin in the drinking water.

On the third day post-infection, the *E. coli*-infected rabbits in this study displayed symptoms such as anorexia, dullness, abdominal distension, and brown, watery diarrhea. All internal organs were enlarged; pericarditis, enteritis, and petechial bleeding on the intestinal wall were observed during the examination of deceased rabbits. These findings are consistent with earlier reports (Licois 2004; Ismail *et al.,* 2017; Abdallah *et al.,* 2023).

Cinnamaldehyde is linked to the antibacterial properties of cinnamon (Zhou *et al.,* 2007). According to Gill and Holley (2004), the impact of membrane permeability and the suppression of glucose uptake or utilization are two potential pathways for the antibacterial activity of cinnamon aldehyde. Additionally, Abd El-Hack *et al.* (2020) noted that the primary active components of cinnamon are eugenol and cinnamaldehyde, both of which have additive or synergistic qualities. These elements work together to facilitate the entry of cinnamaldehyde into the phospholipid bilayer of bacterial cells and walls, making it easier to bind to proteins. This prevents proteins from performing their regular functions, resulting in cytoplasmic coagulation, denaturation of proteins and enzymes, and loss of

metabolites and ions (Burt, 2004). Research indicates that the presence of cinnamon oil can suppress the growth of bacteria (Wang *et al.,* 2018).

According to Pereira *et al.* (2021), cinnamaldehyde has significant anti-adhesive properties against pathogenic *E. coli*, and CNPs help to inhibit or decrease *E. coli* infection. In our research, the re-isolation rate of *E. coli* was lower in the groups treated with CNPs and antibiotics together and in the groups treated with CNPs or antibiotics alone than in the non-treated groups.

In our study there were significant ($p < 0.05$) differences between the groups of growing rabbits fed a diet containing CNPs and the control group in growth performance parameters (body weight, weight gain, feed intake, feed conversion ratio, and feed efficiency). All animals fed CNPs showed the highest body weight, weight gain, and feed conversion ratio, while the control groups, 1 and 2, showed the lowest final body weight and weight gain. Furthermore, when comparing growing rabbits provided a diet containing CNPs to those fed on a diet without CNPs, the best feed conversion ratio was observed in that fed diet with CNPs. Agreeing with the findings of our study, *El-Kholy et al.* (2012) and Zeweil *et al.* (2016 a) reported that growing rabbits fed diets supplemented with cinnamon had significantly superior final body weights, weight gains, feed conversion ratios, and feed efficiency at performance than control groups. In this study the feed intake of growing rabbits supplemented with CNPs remained the same as that of the control group; these results were similar to Naderi *et al.* (2014) and Mohamed *et al.* (2023). The data indicating that the CNP-supplemented diets improved the growth performance of the rabbits may also have resulted from the presence of the bioactive ingredient (cinnamaldehyde), which increases feed utilization and enhances growth (Zeweil *et al.,* 2016 a).

Red blood cell counts and hemoglobin levels did not differ significantly between the groups; however, WBC counts increased in group 3, which was fed CNPs and a basal diet, and decreased in group 2, which was inoculated with *E. coli*. But there were nonsignificant differences between groups 4, 5, 6, and group 1. The normal RBCs supported these findings and clarified that there was neither hemolytic anemia nor erythrogenesis depression. The fact that all of the experimental rabbits had normal hemoglobin concentrations suggests that the added feed ingredients support the formation of hemoglobin. In contrast, Zeweil *et al.* (2016 a) reported that cinnamon significantly increased RBCs and hemoglobin but, similar to our study, significantly increased WBCs, which is in agreement with the findings of Baghban *et al.* (2016), who demonstrated that cinnamon did not alter red blood cell count or hemoglobin.

There were significantly decreased lymphocyte counts in group 2. Furthermore, group 2 had a notable increase in neutrophil counts, but group 1 and the other groups showed non-significant differences in neutrophil counts. However, the mixed cell count increased in the other groups to reach group 1, whereas it decreased in group 2. Our findings agreed with those of Abdel-Azeem (2019), who reported that supplementing with cinnamon improved the neutrophil/lymphocyte ratio. The increase in the percentage of the neutrophils in the group (2) and the corresponding decrease in the percentage of the neutrophils in the treated groups may indicate that the growing rabbits in group (2) were stressed. Additionally, CNPs have a protective impact by reducing the oxidative pathway of stress-related damage. Furthermore, including a CNPs supplement in the diet may help control

stress, making it a practical dietary approach for lowering the risk of stress.

SOD is a key defense mechanism against oxidative stress. It catalyzes the conversion of superoxide radicals to hydrogen peroxide and oxygen, increasing the body's ability to scavenge free radicals and reduce tissue or cell damage. Catalase (CAT) is another enzyme that catalyzes the breakdown of hydrogen peroxide into water and molecular oxygen. An antioxidant defense system is essential for shielding cells from oxidative damage caused by reactive oxygen species (ROS) (Owumi and Dim, 2019). The activities of the antioxidant enzymes (SOD and CAT) in the current study were significantly increased in groups 3 and 6. Following *E. coli* inoculation, the antioxidant enzymes (SOD and CAT) in groups 5 and 4 increased to reach group 1. These findings are similar to those of Abdel-Tawwab *et al.* (2018), who suggested that dietary CNPs exhibited antioxidant activity. In the present study, the serum levels of SOD and CAT were significantly lower in the *E. coli*-infected group than in the control group, suggesting oxidative stress, which accounts for the histological changes observed in the examined tissues. In contrast, in the infected groups treated with CNPs, there was a significant increase in the serum levels of SOD and CAT in groups 6, 5, and 4. This improvement was linked to the restoration of the histological structure of the liver, kidney, and lungs to normal levels; the group of rabbits that received both CNPs and streptomycin showed the greatest improvement compared to the other treatment groups. The main components of cinnamon, including phenols, terpenes, and cinnamaldehyde, are what give it its antioxidant properties and, consequently, lower lipid peroxidation (Qin *et al.,* 2010) and tissue damage. To the best of our knowledge, this is the first report on the protective effects of CNPs against pathological changes induced by *E. coli* infection in rabbits.

In this study, our results showed that liver enzyme levels (ALT and AST) were significantly increased in group 2, while they were significantly decreased in group 3, although there were nonsignificant differences between groups 6, 5, 4, and group 1. These findings suggest that CNPs have a hepatocyte protective effect. The levels of ALT and AST in the blood indicate the number of intracellular hepatic enzymes that permeate the bloodstream. Additionally, they function as indicators of hepatocyte injury (McGill, 2016). There was no evidence of liver damage in the groups that consumed cinnamon supplements, as indicated by the decrease in ALT and AST levels. Mammals and birds have shown altered liver metabolism in response to endotoxin therapy or a live bacterial challenge (Curtis and Butler, 1980).

Serum liver enzyme levels decreased in the experimental rabbits, especially those that received CNPs supplementation. These results were confirmed by the findings of El-Nomeary *et al.* (2020), who reported that cinnamon reduced serum GOT, and Kreydiyyeh *et al.* (2000), who reported that the active ingredients in cinnamon can penetrate intestinal cell membranes and inhibit Na+-K+-ATPase, which is the motor for numerous transport processes.

The current study showed that there were significantly higher serum creatinine and urea levels in group 2, while groups 3 and 6 showed significantly lower serum urea, creatinine, and uric acid levels, although there were nonsignificant differences between groups 4, 5, and group 1. These results indicated that CNPs don’t have any adverse effects on rabbit general health. These findings are comparable to those of El-Nomeary *et al.* (2020), who reported that cinnamon extract can considerably reduce blood urea and creatinine levels.

Cinnamaldehyde, an antioxidant and anti-inflammatory component found in cinnamon, is an active chemical in cinnamon that can improve kidney function.

In the present study, total protein, albumin, and globulin were non-significantly increased in group 3, while total protein and albumin were significantly decreased in group 2. Because the liver produces albumin and has a half-life of approximately two weeks, a drop in albumin levels could be caused by either decreased liver production or albumin loss from the kidney (nephropathy) or the gut (enteropathy). These findings are consistent with the findings of Al-Sayed *et al. (*2017), Abdel-Azeem and El-Kader (2022), who reported that albumin-based antibodies are major protein components of serum proteins generated in hepatic tissues. Total protein and globulin in plasma are also components of the immune system. Consequently, the results of the present investigation of blood total protein and globulin levels indicated that supplementation with CNPs may improve the humoral immune response. Liver function is substantially impacted by infection or sepsis (Kokosharov *et al.,* 1997), and liver degenerative alterations have been reported to be responsible for this decline. Additionally, Kokosharov (2006) reported a significant decrease in either the serum albumin or total protein concentration due to acute *S. gallinarium* infection.

Histopathological analysis of the livers, kidneys, and lungs of rabbits experimentally infected with *E. coli* revealed architectural distortion, similar to the earlier reports of Azhar and Shahera (2014) and Lateef *et al.* (2018). Compared to those in the control group, the most common hepatic lesion was marked multifocal coagulative necrosis accompanied by infiltration of mononuclear cells (Abalaka *et al.,* 2017 and Abd El-Ghany *et al.,* 2022). Along with alveolar emphysema in the lungs interspersed with thickened interstitial septa, the kidneys also displayed focal interstitial nephritis according to Usman *et al.* (2022). Directly or indirectly, *E. coli* causes oxidative stress due to the increased generation of reactive oxygen species or the depletion of defense antioxidants combined with the production of endotoxin (Barreiros *et al.,* 2006). The cytotoxicity associated with oxidative stress derives from the free radicals caused by the oxidation of cellular constituents, including proteins, lipids, and DNA, leading to cell death (Valko *et al.,* 2006).

CONCLUSION

Based on the current study, CNPs may be an effective feed additive and a potential adjuvant to antibiotics for *E. coli* infections to attain maximum disease resistance. Because of their potent antibacterial activity, influence on growth performance, effects on the tissue structure, and antioxidant capacity, CNPs are a viable feed additive in rabbit diets. Additionally, this trial promotes the use of CNPs in combination with an appropriate amount of antibiotic (streptomycin) to fight disease and increase awareness about the overuse of antibiotics.

List of abbreviations

CNPs	Cinnamon nanoparticles
ALT	Alanine aminotransferases
AST	Aspartate aminotransferase
SOD	Super Oxide Dismutase
CAT	Catalase
RBCs	Red Blood Cells
WBCs	White Blood Cells
Hb	Hemoglobin

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Authorship contribution statement

All the authors worked together to complete this study. Methodology, formal analysis, writing (original draft), writing (review & editing), all authors wrote the initial and final drafts of the manuscript. All the authors have read and approved the final manuscript.

Declarations

Animal Welfare and Ethics Statement

The experimental methodology, protocols, and animal care used in the present study followed the relevant guidelines and regulations of the Animal Health Research Institute, Agriculture Research Center, Giza, Egypt.

Conflict of interest disclosure

The authors declare that they have no competing financial interests or personal relationships that could influence the work reported in this paper.

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تأثير جزيئات القرفة النانوية كإضافات علفية على أداء الأرانب ومناعتها وقدرتها المضادة للأكسدة ومقاومتها للإيشرشيا كولاى

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عبير محمد شحاته الكريدى ، ايمان توفيق السكرى ، شيماء الباز عبدالمحسن ،
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تم تقييد استخدام المضادات الحيوية في صناعة الدواجن ونتيجة لذلك، تم الاعتماد بشكل متزايد على الإضافات العلفية النباتية لتحقيق هذا الهدف، بالإضافة إلى فوائد أخرى. هدفت هذه الدراسة إلى فحص تأثير جزيئات القرفة النانونية على أداء نمو الأرانب، والمناعة، والكيمياء الحيوية في الدم، وأمراض الدم، وأنسجة الخلايا، والحماية من عدوي الإيشرشيا كولاى لذلك تم تقسيم ستين أرنبا نيوزيلندي أبيض سليم مفطوم عمر 35 يوم إلى ست مجموعات متساوية. تم الحصول على الأرانب من مزرعة خاصة بمحافظة كفرالشيخ وتأقلمت لمدة أسبوعين قبل بدء التجربة. تم تقسيم مجموعات الأرانب وفقا لإضافة القرفة النانونية إلى العلائق مع مضاد حيوي أو بدونه وعمل عدوى تجريبية , وفقًا لنتائجنا، أظهرت الأرانب التي تلقت القرفة النانونية تحسنا كبيرا في أداء النمو ونتائج إعادة عزل البكتريا والأعراض السريرية والصفة التشريحية. ادعمت جزيئات القرفة النانونية التأثيرات الواقية للكبد والكلى من خلال انخفاض انزيمات الكبد وزياده في مستوي البروتين الكلي والالبيومين, وعدد خلايا الدم البيضاء الكلية والخلايا الليمفاوية وانشطه الانزيمات المضادة للأكسدة. أظهرت التحاليل النسيجية أن مجموعة التحكم الإيجابية لديها تغيرات مرضية واضحة مثل التهاب الكلية الخلالي ونخر التخثر الكبدي والالتهاب الرئوي الخلالي مع تسلل الخلايا أحادية النواة. ومع ذلك، لوحظ التأثير الأفضل لمجموعة القرفة النانونية المعالجة بالاستربتومايسين حيث كانت التغيرات النسيجية أخف إلى متوسطة. في ظل الظروف التجريبية الحالية حسنت جزيئات القرفة النانونية أداء النمو ومضادات الاكسدة والحماية من العدوي التجريبية مع اقل تغيرات نسيجية.