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Clinicopathological Studies on Neem and Ginger Effects as Feed Additives in Normal and *E. coli* Infected Weaned Rabbits

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Abstract

The present study was performed to investigate the clinicopathological effects of neem and ginger as feed additives. One hundred and twenty weaned White New Zealand rabbits were divided into 6 equal groups. Group (1) kept as control. Groups (2 and 5) received ration contained neem leaves daily (5% of diet). Groups (3 and 6) received ration contained ginger powder daily (2% of diet). Groups (4, 5 and 6) were experimentally infected by *E. coli* (O103 once orally with a dose of 3 ml of suspension containing $3x10^7$ CFU at the end of the 4^{th} week of experiment. The results revealed normal parameters in none infected as well as neem and ginger treated groups (1, 2 and 3). However a significant decrease in the serum total protein, albumin, globulin and catalase levels (CAT) on the 1^{st}, 3^{rd} and 15^{th} day PI was observed in infected non treated animals (Group 4). On the other hand a significant increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), malondialdehyde level (MDA), phagocytic percentage and phagocytic index were observed in the same group. In Groups 5 and 6; animals showed a significant increase in total protein, albumin, globulin, CAT and a significant decrease in the other parameters comparing with the infected group. It could be concluded that both neem and ginger can be used as feed additives in rabbit ration to enhance hepatic, renal and antioxidant activities beside cell mediated immunity .Moreover, Neem was better than ginger in amelioration of the harmful effects of *E. coli* infection .

Keywords: Antibacterial, Immunostimulant, Neem, Ginger, Antioxidant

Introduction

There is a worldwide trend towards the use of natural additives in food as spices and herbal medicine Neem and ginger are important members of herbal medicine [1,2]. Both of them have compounds of many biological activities as hepato and renal protective effects in addition to anti-oxidant and immunostimulant properties [2,3].

The effect of dietary neem leaves meal on serum biochemical parameters was investigated by Obikaonu *et al.* [4]. The AST, ALT and ALP levels were decreasing by increasing neem leaves percent in diet comparing with the control. Mukherjee *et al.* [5] found that the administration of oral mixture of leaves and seed extract at 10% concentration for 6 weeks in rodent caused specific activation of T-lymphocytes and phagocytic cells. Biswas *et al*. [1] found an increase in catalase activity (CAT) while malondialdhyde level (MDA) was decreased. Lebda *et al*. [6] studied the effect of different ginger treatments on hepatic oxidative stressed male New Zealand rabbits. The results revealed that AST, ALT, ALP and urea were decreased with increased creatinine level comparing with control. Onu and Aja [7] recorded a significantly decreased MDA level with increased CAT activity using ginger (0.25% of diet) on weaned rabbits as supplement for 10 weeks. Oral ginger administration as feed additives stimulated phagocytic activity [8].

Escherichia coli is one of the most important etiological agents of enteritis and losses in rabbit industry [9] The most pathogenic

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serotypes inducing high mortalities are (O109:H2), with neonatal diarrhea, (O103:H2) weanling diarrhea, O123 and O132 [10, 11].

This work aimed to study hepatic and renal protective effects as well as antioxidants and immunological effects of neem leaves and ginger rhizomes on normal and *E. coli* experimentally infected rabbits.

Material and Methods

Experimental Design

One hundred and twenty weaned white New zealand rabbits apparently healthy were obtained from a private farm near Menia Elkameh, Sharkia Governorate . The basal and balanced growing ration was given to animals. The rabbits were divided into 6 equal groups.Group 1 was kept as control. Groups (2 and 5) received neem leaves powder as 5% of diet [12]. Groups (3 and 6) received ginger powder 2% of diet daily for 6 weeks [6]. Groups (4, 5 and 6) were experimentally infected rabbits by *E. coli* with of O103 strain once orally with a dose of 3 ml of suspension containing $3x10^7$ CFU [13] at the end of the 4^{th} week of experiment. The animals were observed for clinical examination daily along the experiment.

Feed additives

Neem, fresh matured neem leaves were harvested from garden in El-Asher Men Ramadan City. The samples were identified in Botany Department, Faculty of Science, Zagazig University. The leaves were cleaned, dried in shaded place and powdered. The powder was added to ration as 5% of diet [12].

Ginger rhizomes were collected from local markets as dry rhizomes then were ground well till became fine powder and added to ration as 2 % of diet [6].

Pathogenic *E. coli* O103 was obtained from Animal Health Research Institute, Dokki, Giza, Egypt and was used for infection.

Blood samples

Blood samples were collected from ear vein on the 1^{st}, 3^{rd} and 15^{th} day PI. The first sample was collected on heparin for phagocytic activity determination [13] and the second one was collected for serum biochemical analysis AST, ALT [14] ALP [15] total protein [16] albumin [17] globulin was calculated, urea [18] and creatinine [19].

Antioxidant activities

Catalase activities and MDA levels were calorimetrically determined using Kits of Bio Diagnostics [20].

Phagocytic activity

The Phagocytic percent and index were evaluated according to Wilkinson [21]. The phagocytic percent is the total number of phagocytic cells at any stage of phagocytosis in 100 mononuclear phagocytic cells. Phagocytic index (PI) is the number of *C. Albicans* ingested by 100 phagocytic cells.

Statistical analysis

The obtained data were statistically analyzed by F-test [22] using MSTAT-C computer program.

Results and Discussion

Neem and ginger are important members of herbal medicine [1, 2]. Both of them have biological activities as hepato and renal protective in addition to anti-oxidant and immunostimulant properties [2, 3].

The use of neem or ginger as feed additives in rabbit ration with a percent of 5% and 2% respectively were investigated for their beneficial impact on rabbit biochemical and immunological properties as well as their antibacterial efficacy.

Our results revealed that Groups (2 and 3) treated non infected animals showed no significant changes in AST, ALT and ALP hepatic enzymes all over the experimental periods compared to control group (Tables 1, 2). This may be due to that neem leaves meal or ginger are safe and has no deleterious effect on the liver and these results confirmed histopathologically where there is no pathological lesions in the hepatic tissues. These results are in agreement with Haque *et al*. [23] and Ogbuewu *et al*. [12] who stated that AST and ALT were non significantly changed in neem and ginger treated groups comparing with the control .

Table (1): Effect of Neem and Ginger on hepatic enzymes and proteinogram in infected and normal rabbits through 15 days PI (mean ± SE)

Hepatic enzymes

Parameter	AST (U/L)			ALT (U/L)			ALP (U/L)		
Time / Group	1st day PI	3rd Day PI	15th day PI	1st day PI	3rd day PI	15th day PI	1st day PI	3rd day PI	15th day PI
GP (1) Control	40.20 ±0.374^{d}	40.40 ±0.509^{d}	41.00 ±0.447^{d}	40.60 ± 0.24^{d}	42.00 ± 0.31^{c}	44.00 ± 0.44^{c}	35.00 ±0.44^{de}	35.80 ±0.37^{de}	40.00 ±0.54^{d}
GP (2) Neem	39.60 ±0.509^{d}	39.40 ±1.122^{d}	38.00 ±0.836^{d}	41.60 ± 0.50^{d}	41.00 ± 0.37^{c}	40.00 ± 0.44^{c}	33.20 ±2.37^{d}	34.20 ±0.37^{de}	37.40 ±0.24^{d}
GP (3) Ginger	40.40 ±0.244^{d}	39.20 ±0.37^{d}	39.40 ±0.244^{d}	38.20 ±0.37^{d}	40.40 ± 0.40^{c}	41.20 ± 0.37^{c}	35.40 ±0.24^{de}	35.00 ±0.31^{de}	39.00 ±0.31^{d}
GP (4) E. coli	67.40 ±1.029^{a}	90.60 ±0.871^{a}	60.60 ±1.691^{a}	58.60 ± 1.02^{a}	80.00 ± 0.89^{a}	60.20 ± 1.28^{a}	57.20 ±1.11^{c}	88.60 ±0.60^{a}	60.20 ±1.31^{c}
GP (5) Neem + E. coli	50.60 ±0.40^{c}	68.20 ±0.86^{c}	44.20 ±0.969^{c}	49.00 ± 0.44^{b}	64.40 ± 1.12^{b}	48.50 ± 0.50^{b}	48.20 ±8.06^{d}	76.20 ±0.58^{b}	49.40 ± 1.4^{d}
GP (6) Ginger + E.coli	55.60 ±1.50^{b}	74.80 ±0.91^{b}	50.20 ±0.583^{b}	45.80 ±1.8^{c}	60.20 ±1.2 8^{b}	50.10 ± 1.31^{b}	52.4 ±206^{cd}	78.2 ± 0.91^{b}	51.6 ±0.24^{cd}
F-test	*	*	*	*	*	*	*	*	*

Proteinogram

Parameter	Total protein (g/dL)			Albumin (g/dL)			Globulins (g/dL)		
Time / Group	1st day PI	3rd day PI	15th day PI	1st day PI	3rd day PI	15th day PI	1st day PI	3rd day PI	15th day PI
GP (1) Control	6.60 ±0.04	6.62 ±0.05^{a}	6.60 ±0.06^{a}	3.34 ±0.02	3.34 ±0.02^{a}	3.34 ±0.02^{a}	3.26 ±0.024	3.28 ± 0.03^{a}	3.26 ±0.04^{a}
GP (2) Neem	6.58 ±0.04	6.62 ±0.03^{a}	6.76 ± 0.02^{a}	3.34 ±0.024	3.34 ±0.02^{a}	3.40 ±0.04^{a}	3.24 ±0.024	3.28 ±0.02^{a}	3.36 ±0.02^{a}
GP (3) Ginger	6.58 ± 0.03	6.56 ±0.04^{a}	6.70 ±0.04^{a}	3.32 ±0.024	3.32 ±0.02^{a}	3.36 ±0.02^{a}	3.26 ± 0.05	3.24 ±0.02^{ab}	3.32 ±0.03^{a}
GP (4) E. coli	6.36 ± 0.15	4.76 ±0.07^{d}	5.82 ±0.09^{c}	3.30 ± 0.15	2.70 ±0.10^{c}	2.98 ±0.03^{b}	3.06 ± 0.18	2.06 ±0.07^{c}	2.86 ±0.12^{b}
GP (5) Neem + E. coli	6.70 ± 0.07	6.30 ±0.15^{b}	6.76 ±0.06^{a}	3.36 ± 0.02	2.96 ±0.02^{b}	3.48 ± 0.04^{a}	3.34 ± 0.07	3.34 ±0.16^{a}	3.28 ±0.03^{a}
GP (6) Ginger +E. coli	6.72 ± 0.07	5.86 ±0.07^{b}	6.40 ±0.08^{a}	3.46 ± 0.08	2.88 ±0.08^{b}	3.30 ±0.08^{a}	3.26 ± 0.12	2.98 ±0.13^{b}	3.10 ±0.03^{a}
F-test	N.S	*	*	N.S.	*	*	N.S.	*	*

N.S.: non significant *: Significant at 0.05 probability PI: post infection

However, The increase in serum ALT, AST and ALP activities was observed in group (4) which may be attributed to the damaging effect of E. coli (lipopolysaccharide) on the liver and increased cell membrane permeability [24-25]. This confirmed pathologically (Figure1A and B) which showed severe congestion of the hepatic blood vessels, hydropic degeneration and coagulative necrosis of the hepatocytes with pyknotic and karyolitic nuclei .The significant decrease in the hepatic enzymes in groups (5 and 6) comparing with group (4) may be due to administration of neem and ginger which contain hepatoprotective and antibacterial active principals [26,27]. This was confirmed pathologically (Figure 1C) and was manifested by as reduced degenerative changes in hepatocytes. Ginger has hepatoprotective effect and repair the damaged hepatic tissue [28,29]. Decreasing in proteinogram in group (4) may be due to E coli effects on liver and kidney [9]. Serum total protein, albumin and globulin levels were increased in groups (5

and 6) on the (3^{rd} and 15^{th}) day post infection comparing with infected group [29,30].

A significant increase in urea and creatinine (Table 2) was found in group (4). *E. coli* infection (lipopolysaccharide) caused damage in renal tissue [9,25,31]. This was confirmed pathologically (Figure 1D) with multiple cystic dilatations of renal tubules with hyaline and cellular casts. Renal protective and antibacterial effects of neem and ginger ameliorated the elevation in urea and creatinine levels in groups 5 and 6. Similar results were obtained previously by lebda *et al*. [6] and Ezz-Din *et al*. [32]. Also this may be due to polyphenols and flavenoids present in ginger that remove waste products from plasma [6].

In respect to antioxidant activity, Groups (2 and 3) showed a significant increase in CAT and a significant decrease in MDA on the 1^{st}, 3^{rd} and 15^{th} day PI (Table 3). It could be explained by the antioxidant effects of neem that may increase the synthesis of antioxidant molecules as mentioned previously by Dkhill *et al*. [33]. Also, this may be due to ginger contains antioxidants that act as a free radical scavenger. A significant decrease in CAT and increase MDA was recorded in group (4) which may be attributed to lipopolysaccharide [34,35]. Groups (5 and 6) showed a significant increase in CAT and decrease in MDA level in comparison to infected group. This may be attributed to scavenging effects of neem [33, 36] and ginger [37] among free radicals and so relieving oxidative stress of *E. coli* infection.

Groups (2, 3, 5 and 6) showed a significant increase in phagocytic percent and index all over the experimental period (Table 4). This may be due to neem increase nonspecific immune response [36,38]. Ginger stimulated phagocytic activity as described by Ajith *et al*., and Mallikarjuna *et al*. [39,40]. Phagocytic percent and index were significantly increased in group (4). This may be referred to immune response against *E. coli* as explained by Eisa and Alam [41, 42]. Leukocytosis, neutrophilia and monocytosis were found in groups 4, 5, and 6 on 1^{st} day PI. Neutrophilia and monocytosis were still present on 3^{rd} day. Lymphopenia was found in the same groups on the 1^{st} and 3^{rd} day PI. These changes may be due to the acute defense mechanism against bacterial infection as recorded by Edrees *et al.*, and El-Boushy *et al.* [9,25]. A significant decrease in TLC was found in group 4 on the 3^{rd} and 15^{th} day PI. The changes in leukogram may be due to immunodepresant effect of *E. coli* infection as stated by many authors [31,41,43,44].

Conclusion

It could be concluded that neem (5% of diet) and ginger (2% of diet) enhanced hepatic, renal and antioxidant activities of rabbits. Also, they acted as immune stimulant and ameliorated the harmful effects of *E. coli* infection. Moreover, neem effects were stronger than ginger effects.

Table (2): Effect of Neem and Ginger on Serum urea and creatinine in infected and normal rabbits through 15 days PI (mean ± SE)

Parameter	Serum urea (mg/dL)			Serum creatinine (mg/dL)		
Time / Group	1st day PI	3rd day PI	15th day PI	1st day PI	3rd day PI	15th day PI
GP (1) Control	17.30 ± 0.104 b	17.17 ± 0.100d	17.63 ± 0.163c	1.26 ± 0.014b	1.24 ± 0.009d	1.27 ± 0.011d
GP (2) Neem	17.16 ± 0.094 b	17.68 ± 0.554d	17.39 ± 0.140c	1.25 ± 0.005 b	1.27 ± 0.006cd	1.28 ± 0.0096cd
GP (3) Ginger	17.36 ± 0.066 b	17.30 ± 0.074d	17.88 ±0.112c	1.28 ± 0.008 b	1.30 ± 0.007cd	1.30 ± 0.009cd
GP (4) E. coli	19.0 ± 0.447a	26.80 ± 0.622a	24.60 ± 0.484a	1.46 ± 0.050a	1.88 ± 0.014a	1.42 ± 0.031a
GP (5) Neem + E. coli	17.39 ± 0.191 b	19.75 ± 0.139c	17.40 ± 0.155c	1.25 ± 0.007b	1.67 ± 0.021b	1.34 ± 0.008b
GP (6) Ginger + E. coli	17.88 ± 0.333 b	21.89 ± 0.150b	18.78 ± 0.092bc	1.28 ± 0.008b	1.70 ± 0.020b	1.37 ± 0.010b
F-test	*	*	*	*	*	*

*=significant at 0.05 probability. PI: post infection

Table (3): Effect of Neem and Ginger on antioxidant activities of liver tissues of infected and normal rabbits Through 15 days PI (mean ± SE)

Parameter	Catalase (Mu/mg)			MDA (nmol/mg)		
Time / Group	1st day PI	3rd day PI	15th Day PI	1st day PI	3rd day PI	15th Day PI
GP (1) Control	1. 36 ± 0.058b	1.36 ±0.066b	1.37 ± 0.059b	1.53 ± 0.008d	1.53 ± 0.007d	1.42 ± 0.007b
GP (2) Neem	1.53 ± 0.056a	1.60 ± 0.046a	1.80± 0.038a	1.35 ± 0.006e	1.30 ± 0.005f	1.00 ± 0.20c
GP (3) Ginger	1.49 ± 0.032a	1.50 ± 0.023a	1.70 ± 0.049a	1.40 ± 0.005f	1.35 ± 0.006f	1.10 ± 0.007c
GP (4) E. coli	0.78 ± 0.048d	0.71 ± 0.031d	1.206 ± 0.062c	1.93 ± 0.020a	2.20 ± 0.36a	1.78 ± 0.008a
GP (5) Neem + E. coli	1.13 ± 0.050c	1.178 ± 0.018c	1.35 ± 0.024b	1.75 ± 0.012bc	1.90 ± 0.003bc	1.44 ± 0.006b
GP (6) Ginger + E. coli	1.10 ± 0.007c	1.134 ± 0.017c	1.33 ± 0.024b	1.81 ± 0.06b	1.73 ± 0.006bc	1.45 ± 0.010b
F-test	*	*	*	*	*	*

*=significant at 0.05 probability. PI: post infection

Table (4): Effect of Neem and Ginger on phagocytic % and phagocytic index in infected and normal rabbits through 15 days PI (mean ± SE)

Parameter	Phagocytic %			Phagocytic index		
Time / Group	1st day PI	3rd day PI	15th day PI	1st day PI	3rd day PI	15th day PI
GP (1) Control	63.04 ± 0.09^{f}	62.12± 0.14^{d}	64.18± 0.177^{b}	2.38± 0.037^{e}	2.46± 0.050^{e}	2.46± 0.050^{c}
GP (2) Neem	70.44± 0.15^{cd}	70.26± 0.18^{c}	73.24± 0.172^{a}	3.06± 0.092^{c}	3.09± 0.060^{c}	3.55± 0.063^{a}
GP (3) Ginger	65.92± 0.23^{e}	70.94± 0.21^{c}	71.18± .139^{a}	2.56± 0.050^{d}	2.66± 0.092^{d}	2.74± 0.067^{b}
GP (4) *E. coli*	80.60± 0.68^{b}	74.34± 0.22^{ab}	62.70± 0.234^{c}	2.86± 0.050^{c}	3.46± 0.074^{b}	2.40± 0.141^{b}
GP (5) N + *E. coli*	86.66± 0.20^{a}	75.10± 0.24^{a}	64.10± 0.264^{b}	4.62± 0.073^{a}	3.82± 0.058^{a}	3.02± 0.058^{a}
GP (6) G + *E. coli*	83.64± 0.22^{b}	74.44±0.24^{a}	63.14± 0.163^{b}	4.34± 0.050^{b}	3.58± 0.037^{b}	2.69± 0.124^{b}
F-test	*	*	*	*	*	*

C: Control, N: Neem, G: Ginger

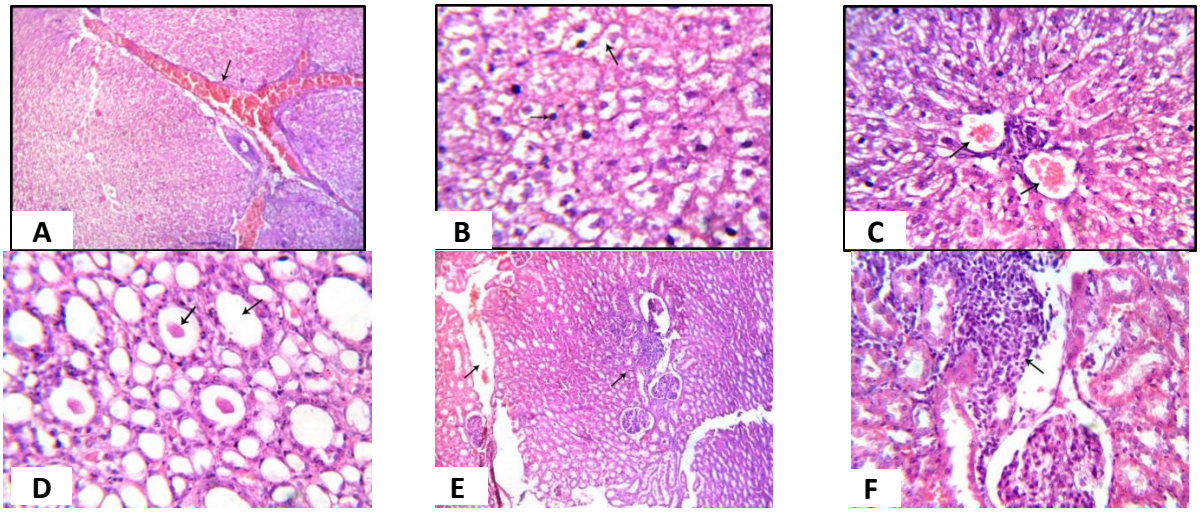

Figure 1: A) Liver (Group 4), 3 days PI showing severe congestion of the hepatic blood vessels (H&Ex130); B) Liver (Group 4), 3 days PI showing severe hydropic degeneration and coagulative necrosis of the hepatocytes with pyknotic and karyolitic nuclei (H&E x520); C) Liver (Group 5), on the 3rd day PI, showing congestion of the hepatic blood vessels together with mononuclear leukocytic cells infiltration (H&E x520); D) Kidney (Group 4), 3 days PI showing many cystic dilatations of some renal tubules with hyaline and cellular casts inside it (H&E x520); E) Kidney (Group 5), 3 days PI showing mild congestion of renal blood vessels in the renal cortex together with mononuclear leukocytic cell infiltration (H&E x300); F) Kidney (Group 6), 3 days PI showing mononuclear leukocytic cells infiltrating the renal cortex (H&E x 520).

Conflict of interest

None of the authors have any conflict of interest to declare.

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الملخص العربي

دراسات باثولوجية اكلينيكية على تأثيرالنيم والزنجبيل فى الأرانب السليمة والمعدية بالميكروب القولونى (بعد الفطام)

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اجريت هذه الدراسة لمعرفة تأثير النيم والزنجبيل على الأرانب السليمة والمعدية بالميكروب القولونى. اجرى هذا البحث على مائة وعشرون ارنب عمر شهر وتم تقسيمهم الى ٦ مجموعات متساوية وكانت مدة التجربة ٦ اسابيع. تم اعطاؤهم العليقة الاساسية مضاف اليها مسحوق اوراق النيم الجافة بنسبة ٥٪ من وزن العليقة للمجموعتين (٢ و٥) و بودرة الزنجبيل بنسبة ٢٪ من وزن العليقة للمجموعتين (٣ و٦) يوميا طوال فترة التجربة. تمت عدوى تجريبية بالميكروب القولونى (*E. coli* O103) عن طريق الفم جرعة واحدة ($3x10^7$ CFU) عند نهاية الاسبوع الرابع فى المجموعات (٤و٥و٦). اوضحت النتائج ان المجموعتين (٢،٣) كانت جميع قياساتهما مماثلة للمجموعة الضابطة (١) طوال فترة التجربة. اظهرت نتائج المجموعة الرابعة وجود نقص معنوى فى البروتين الكلى والزلال والجلوبيولين و معدل نشاط انزيم الكاتاليز. بينما وجد زيادة معنوية فى معدل انزيمات الكبد ومستوى البولينا والكرياتينين و مستوى المالونداي الدهايد والنشاط التبلعمى والقدرة القاتلة للخلايا وحيدة النواة. وأدى تناول النيم والزنجبيل الى تحسن نتائج المجموعتين (٥و٦) فى جميع القياسات مقارنة بالمجموعة الرابعة واقتربت من الطبيعى فى اليوم الخامس عشر. وجد ارتفاع معنوى فى عدد كرات الدم البيضاء نتيجة لزيادة العدد النوعى لخلايا النيتروفيل فى المجموعة ٤ فى اليوم الأول بينما استمر فى لليوم الثالث بعد العدوى فى المجموعتين ٥،٦. انخفض عدد كرات الدم البيضاء نتيجة لانخفاض عدد خلايا الليمفوسيت فى المجموعة ٤.انخفض عدد خلايا الليمفوسيت فى المجموعات ٤،٥،٦ فى اليومين الثالث والخامس عشر.وجد ارتفاع معنوى فى عدد كرات الدم البيضاء نتيجة لزيادة العدد النوعى لخلايا النيتروفيل فى المجموعة ٤ فى اليوم الأول بينما استمر فى لليوم الثالث بعد العدوى فى المجموعتين ٥،٦. انخفض عدد كرات الدم البيضاء نتيجة لانخفاض عدد خلايا الليمفوسيت فى المجموعة ٤. انخفض عدد خلايا الليمفوسيت فى المجموعات ٤،٥،٦ فى اليومين الثالث والخامس عشر. مما سبق يتضح ان اضافة النيم بنسبة (٥٪) والزنجبيل بنسبة (٢٪) الى العليقة له تاثير مضاد للميكروب القولونى كما أدى الى وتحسين كفاءة الكبد والكلى ومضاد للأكسدة ورفع الحالة المناعية.وكان النيم أقوى تأثيرا من الزنجبيل.