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RESEARCH ARTICLE

ANTI-INFLAMMATORY, IMMUNOMODULATORY AND ANTIOXIDANT EFFECTS OF LYCOPENE AND VITAMIN E IN *E. COLI* INFECTED BROILERS.

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Abstract

The present study was conducted to evaluate the effect of lycopene in comparison with vitamin E on some inflammatory, immunological, oxidative and biochemical markers in broiler chicks experimentally infected with *Escherichia coli*. A total of 120 one day old broilers were used and divided equally into 6 groups. Group (1) was fed on the commerciall basal diet without any additives. Group (2): was fed on commercial basal diet plus lycopene (200mg/kg diet). Group (3): was fed on commercial basal diet plus vitamin E (200mg/kg). Group (4): was fed the commercial basal diet and challenged with *E. coli O78* at 3 weeks old. Group (5): was fed on commercial basal diet plus lycopene and challenged with *E.coli O78* at 3 weeks old. Group (6): was fed on commercial basal diet plus vitamin E and challenged with *E.coli* at 3 weeks old. Clinical signs and mortality were recorded. Some inflammatory, immunological and oxidative marker in addition to some serum biochemical parameters were measured. Infected non-treated group showed significant increases in serum C-reactive protein, haptoglobin, interleukin-1β and interleukin 10 and significant decreases in phagocytic activity and index when compared to control one. Liver malondihyde level showed a significant increase meanwhile, glutathione peroxidase, catalase and superoxide dismutase were significantly decreased in the same group. Results of aspartate transaminase, gamma glutamyle transpeptidase, uric acid, creatinine and total cholesterol revealed significant increases in infected non treated birds. Treatment with lycopene or vitamin E partially protect against the destructive effect of *E. coli* infection via modulation of the above mentioned parameters with more improvement in case of lycopene treatment.

Introduction:-

Poultry industry suffers great losses annually due to infectious diseases. Amongst these infections, *Escherichia coli* (*E. coli*) infection which causes a large number of conditions in the chicken such as pericarditis, perihepatitis, air

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sacculitis, peritonitis, salpingitis, omphalitis, colisepticaemia, coligranuloma etc **(Saif et al., 2003).** In the last few years, there has been an exponential growth in the field of herbal medicine, and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects **(Modak et al., 2007).** The chemical diversity, structural complexity, lack of substantial toxic effects, and broad spectrum of antiviral and antibacterial activity of these natural products make them ideal candidates for new therapeutics **(Mukhtar et al., 2008).** Lycopene (LYC) is a bright red carotenoid pigment found in red fruits and vegetables such as tomato and watermelon. It has a potent antioxidant, antiinflammatory, immunostimulant and anticancer properties **(Bayramoglu et al., 2015)**. LYC because of its high number of conjugated double bonds, has been declared to exhibit higher singlet oxygen quenching ability compared to β-carotene or α-tocopherol and to act as a potent antioxidant, preventing the oxidative damage of critical biomolecules including lipids, proteins and DNA **(Palozza et al., 2010)**. LYC, as an antioxidant, reduces oxidative stress and plays a significant role in many health concerns, including cardiovascular disease, diabetes, cancer, osteoporosis, liver disease, cataracts, and male infertility **(Selvan et al., 2011)**. Vitamine E (VE), a fat-soluble vitamin, has immunostimulant effects as well as antioxidant properties **(Khan et al., 2012)**. Studies have shown that broiler feed supplemented with VE can prevent losses due to infections by *E. coli*, enhance phagocytic activities of macrophages **(Konjufca et al., 2004)**, and improve cellular and humoral immune responses **(Leshchinsky and Klasing, 2001)**. Consequently, the aim of the present work was to study the anti-inflammatory, antioxidative and immunomodulatory effects of LYC comparing with VE in healthy and *E. coli* experimentally infected broilers.

Materials and methods:

Experimental chicks and treatments:

One hundred and twenty-one day old chicks (avian48) were obtained from fat hens company. Tanta, Egypt. Chicks were housed in previously disinfected rooms and were divided into six equal groups reared for 35 days as the following:

Group 1 (Gp 1): chicks maintained without any treatment all over the experimental period and fed on commercial basal diet (control negative).

Gp 2: were fed on commercial basal diet plus LYC (50 mg LYC tablets, purclinica. Company. England) at a dose of 200 mg/kg diet **(Sahin et al., 2008)** all over the experimental period.

Gp 3: were fed on commercial basal diet plus VE (400 mg synthetic VE capsules produced by Pharco pharmaceuticals Co. Egypt) from the first day to the end of experiment at a dose of 200 mg/kg diet **(Niu et al., 2009)**.

Gp 4: were fed on commercial basal diet and challenged with 0.3 ml of broth culture containing $3.6x10^8$ CFU *E. coli* O78/ml by imtramuscular (IM) route at 3 weeks old (control positive) **(Madian et al ., 2008)**.

Gp 5: were fed on commercial basal diet plus LYC from first day to the end of experiment at a dose of 200 mg/kg diet and challenged with *E. coli O78* as in gp (4).

Gp 6: were fed on commercial basal diet plus VE from first day to the end of experiment at a dose of 200 mg/kg diet and challenged with *E. coli O78* as in gp (4).

Sampling:

First blood sample were collected in a plain tube from wing vein of 5 chicks in each group 4 days post infection (PI) and 2 weeks PI then centrifuged at 3000 rpm for 20 minute to obtain clear serum to be used for estimation of inflammatory markers and biochemical parameters. A nother blood sample was taken on sodium citrate tube for estimation of phagocytic activity and index. Also liver specimens were taken from the same birds for estimation of oxidative markers.

Serum inflammatory markers determination:

Serum c-reactive protein (CRP) was determined using chicken CRP ELISA kits of MBS. USA. Serum haptoglobin was determined using ELISA kits of Abbexa Ltd., Cambridge Science Park, Cambridge. UK. Meanwhile interleukin **(**IL1-β) and IL 10 were determined by sandwich ELISA using ELISA kits of MBS. USA

Determination of Phagocytic activity and phagocytic index:
These parameters were determined according to **Kawahara et al., (1991).**

Oxidative markers:
Tissue level of malondihyde (MDA), glutathione peroxidase (GPX), catalase (CAT) and super oxide dismutase (SOD) were estimated using Commercial diagnostic kits obtained from Bio diagnostic. Co. (Egypt. Giza).

Serum biochemical estimations:
Commercial diagnostic kits used for determination of aspartate transaminase (AST), gamma glutamyle transpeptidase (GGT), uric acid, creatinine, total cholesterol (TC) were obtained from Bio.Med. Company Egypt.

Statistical analysis:
Statistical analyses were performed by **SPSS 19.0. Chicago. USA**. Difference among the control and exposed groups were tested by one way analysis of variance (ANOVA) followed by Tukey Post-hoc test for multiple comparison. All the values were expressed as mean± S.E. The signifcance levels were defined as $P < 0.05$.

Results:-

Clinical signs:
Experimentally infected non-treated chickens (gp4) showed clinical signs 3days PI represented by anorexia, dullness, depression, ruffled feather, diarrhea with pesty vent followed by respiratory signs (cough, sneezing, gasping and nasal discharge) at the fourth day. Symptoms were milder and mortalities was lower (10% versus 15%) in treated infected groups (5 and 6) than these in non treated infected one (gp4).

Serum inflammatory markers:
In table (1): LYC treated non infected group when compared to control one showed a significant decrease in CRP and haptoglobin 4 days and 2 weeks PI as well as significantly decreased IL-1β only 2 weeks PI and significantly increased IL-10 at both collections. VE treated group showed non significant changes in all above mentioned parameters when compared to negative control group. A significant increase in CRP and haptoglobin was observed in *E. coli* infected non treated group 4 days and 2 weeks PI in addition to significant increases in both IL-1β and IL-10 only 4 days PI when compared to negative control group. LYC treated *E. coli* infected group comparing to infected non treated group had significantly decreased CRP and haptoglobin 4 days and 2 weeks PI and a significant decrease in IL-1β only 4 days PI and a significant increase in IL-10 at both collections. VE treated infected group comparing to infected non treated group had significantly decreased CRP only 4 days PI and significantly decreased haptoglobin at both collections. Also non significant changes in IL-1β and IL-10 were noticed. More improved picture was observed in lycopene treated group than VE treated one.

Phagocytic activity and index:
Table (2) revealed non significant changes in LYC and VE treated groups (gps 2 and 3) comparing to negative control group 4 days and 2 weeks PI except a significant increase in phagocytic activity in LYC treated group 4 days PI. On the other hand the infected non treated group (gp 4) when compared to control group showed non significant changes in these parameters 4 days PI turned to significant decreases at 2 weeks PI. LYC treated *E. coli* infected group (gp5) when compared to infected non treated group (gp 4) revealed a statistical increase in phagocytic activity and phagocytic index 2 weeks PI (normalization toward control). VE treated *E. coli* infected group (gp 6) when compared to infected non treated group (gp 4) had a significantly increased phagocytic activity and non significantly increased phagocytic index.

Oxidative markers:
Table (3) showed a significant decrease in the liver MDA and a significant increase in liver CAT, GPX and SOD in treated groups (2 and 3) 4 days and 2 weeks PI while *E.coli* infected non treated group (gp4) showed a significant increase in MDA and a significant decrease in CAT at both collections in addition to non significant changes GPX and SOD 4 days PI turned to a significant decrease 2 weeks PI when compared to negative control group. Concerning to LYC treated *E.coli* infected group (gp5) comparing to *E coli* infected non treated group (gp 4) showed a significant decrease in MDA and a significant increase in CAT, GPX and SOD at both collections while VE treated *E.coli* infected group (6) had a significant decrease in MDA and a significant increase in CAT 4 days and 2 weeks PI as well as non significant increase in GPX and SOD 4 days PI turned to a significant increase 2 weeks PI. More prominent antioxidant effect was in LYC treated group than VE treated one.

Serum biochemical parameters:
As in table (4) serum AST, GGT, uric acid, creatinine and TC revealed non significant changes in treated groups (2 and 3) at both collections while *E.coli* infected non treated group (gp4) showed a significant increase serum AST, GGT uric acid and TC at both collections and a significant increase in serum creatinine at the second collection only when compared to control group. LYC treated *E.coli* infected group (gp5) when compared to *E coli* infected non treated group (gp4) represented a significant decrease in serum AST and GGT at both collections and non significant changes in TC and creatinine at first collection turned to a significant decrease at second collection while uric acid revealed non significant changes at both collections (but not statistically differ from control at second collection). VE treated *E.coli* infected group (gp 6) showed non significant changes in all above mentioned parameters except AST at second collection and GGT at both collections revealed significant decreases when compared to *E coli* infected non treated group (gp 4). LYC treated birds showed more prominent improvements in biochemical parameters than VE treated ones.

Discussion:-

The *E. coli* infected chicks showed anorexia, ruffled feathers, dullness, depression and diarrhea with pasted vent at 3 days PI followed by respiratory signs in the form of rhinitis, sneezing, cough, wet eyes and nasal discharge at fourth day. Similar clinical signs were reported by **Abd El-Tawab et al., (2015) and Abd-Allah et al., (2018)**. Chickens feed LYC or VE in diet and experimentally challenged with *E. coli* developed less response in the form of clinical signs and mortalities in comparison to infected non treated birds, this may be attributable to LYC-induced bacterial cell death, including OH accumulation, double-strand DNA breaks and cell division arrest (**Lee and Lee, 2014)** while in VE supplemented group may be associated to the anti-inflammatory and antioxidant activities in tissues that modulate the immune function reducing bacterial colonization **(Gay et al., 2004).**

Our study revealed that serum CRP and haptoglobin were significantly decreased in LYC treated group (gp2) and non significantly changed in VE treated group (gp3) while significant increases in these parameters were observed in *E. coli* infected non treated group (gp4) when compared to control group 4 days and 2 weeks PI. Similar to our results **Penaililloa et al., (2016)** recorded a significant increase in CRP level in rabbits treated with low doses of *E. coli* lipopolysaccharide (LPS). Also **Dishlyanova et al., (2009)** recorded a significant increase in haptoglobin in rabbits with experimentally induced *E. coli* infection. Increased CRP and haptoglobin during infection occur in response to monocytic mediators such as IL-1 and IL-6 **(Kingsley and Jones, 2008).** LYC treated infected group (gp5) had significantly decreased CRP and haptoglobin comparing to infected non treated group (gp4). Our results come in agreement with **Bala et al., (2015)** who found that LYC treatment (5 mg/kg and 10 mg/kg p.o.) attenuates scopolamine induced increase in CRP levels in mice thus proving its anti-inflammatory potential. This decrease may be due to the anti inflammatory effect of LYC which inhibits LPS-induced COX-2 expression **(Lin et al., 2014)**, also inhibits the release of TNF-α and stimulates IL-10 production **(Hazewindus et al., 2012).** VE treated infected group (gp6) had significantly decreased CRP 4 days PI turned to non significant decrease at 2 weeks while haptoglobin was significantly decreased at both collections comparing to infected non treated group gp(4). Similarly **Devaraj et al., (2007)** recorded lowered CRP concentration in patients with coronary artery disease supplemented with α-tocopherol compared to placebo. This anti-inflammatory effect may be attributed to that VE supplementation can decrease the release of IL-1β from monocytes. IL-1β in turn may elevate the IL-6 level **(Singh et al., 2005).** Also V E has been shown to inhibit COX-2, the enzyme involved in inflammatory reactions **(Nazrunet al., 2012).**

Regarding to cytokines our study revealed that LYC treatment significantly decreased IL-1β at 2 weeks PI and significantly increased IL-10 4 days and 2 weeks PI while VE treatment had non-significant effect on both IL-1β and IL-10. On the other hand a significant increase in both IL-1β and IL-10 4 days PI turned to non significant increase after 2 weeks was observed in *E. coli* infected non treated birds comparing to control ones. Similar results were obtained by **Abd-Allah et al., (2018**) who reported a significant increase in IL-1β in *E. coli* experimentally infected birds. Also **Fayyaz et al., (2018)** observed a significant increase in IL-10 during *E.coli* infection in experimental rabbits. These changes may be attributed to that cytokines are very important in the host defense system, and play a critical role in protection against bacterial infections **(Mariathasan and Monack, 2007).** LYC treated infected group (gp5) comparing to *E. coli* infected non treated one showed a significant decrease in IL-1β 4 days PI and a significant increase in IL-10 4 days and 2 weeks PI. Our results come in agreement with **Sezen et al., (2016)** who found that LYC treatment significantly decreased the melatonin induced tissue proinflammatory cytokines such as tumor necrosis factor alpha and IL-1β in Sprague-Dawley adult male rats. In addition **Luo and Wu, (2011)** found that LYC treatment led to significant increases in blood IL-10 level in rats with gastric cancer. The proposed mechanisms of anti inflammatory effect of lycopene are associated with inhibition of macrophage

migration and reduction of Jun N-terminal kinase (JNK) and NF-κB signaling pathways with reduction of dendritic cells maturation and suppression of pro-inflammatory cytokines **(Feng et al., 2010** and **Marcotorchino et al., 2012).** On the other hand VE treated infected group comparing to infected non treated one showed non significant changes in both IL-1β and IL-10. Our results are in consistence with **Norazlina et al., (2004)** who found that alpha tocopherol had no significant effects on nicotine-induced elevation of IL-1 and IL-6 in rats. Also **Kaiser et al., (2012)** who found that dietary VE 220.00 IU/kg of diet, did not affect LPS-induced increase in IL-10 mRNA expression in broiler chicks.

About our results of phagocytic activity and phagocytic index a significant increase in phagocytic activity was observed in LYC treated group (gp2) comparing to negative control group at first collection. On the other hand, infected non treated group (gp 4) when compared to control group showed non-significant changes in these parameters 4 days PI turned to significant decreases 2 weeks PI. Our results come in agreement with **Abd-El-Tawab et al., (2015).** These changes may be attributed to *E. coli* infection that causes impairment of polymorph nuclear leukocytes function decreasing its phagocytic activity and resulted in in effective opsonization **(Van Dijk et al., 1980)**. LYC treated *E. coli* infected group (gp 5) when compared to infected non treated group (gp 4) revealed a statistical increase in phagocytic activity and phagocytic index 2 weeks PI. Our results coincide with **Yonar, (2012)** who recorded that LYC treatment associated with a significant increase in the oxy tetracyclin-suppressed phagocytic activity in rainbow trout. Improvements in immunological parameters may be due to immunostimulant effect of LYC which stimulates the immune system acting against the oxidative damage of the lymphocytes' DNA **(Palabiyik et al., 2013).** It stimulates lymphocytes by increasing the production of IL-2 and interferon-gamma (INF-γ), a potent activator of T lymphocytes **(Yuksek et al., 2013).** In addition it stimulates the communication between cells and raises the immune response **(Olson et al., 2008).** VE treated *E. coli* infected group (gp 6) when compared to infected non treated group (gp 4) had a significantly increased phagocytic activity and non-significantly increased phagocytic index. Our results come in harmony with **Konjufca et al., (2004)** who found that VE supplementation (110 and 220 mg/kg feed) increased the phagocytosis in three weeks old broilers compared with age-matched controls. This improvement reflects the immunomodulatory effect of VE as the process of phagocytosis by macrophages is a membrane-mediated phenomenon, maintained by the availability of higher levels of VE which down-regulates the prostaglandins synthesis which are known to be immunosuppressive **(Qureshi et al., 2000).**

For oxidative markers LYC and VE treatment led to a significant decrease in liver MDA and a significant increase in liver CAT, GPX and SOD. These results come in consistence with **Mezbani et al., (2019)** who observed that inclusion of LYC (100 mg/kg) in broiler diet caused a significant decrease in MDA concentration and elevated CAT and GPx activities in the serum comparing with the control birds. Also **Li et al., (2014)** recorded a significant decrease in MDA and a significant increase in GPx, CAT and SOD in VE supplemented juvenile grass carp. Infected non treated group (gp4) when compared to control group had a significant increase in MDA and a significant decrease in CAT while GPX and SOD showed a significant decrease**.** Our findings come in harmony with **Abd-Allah et al., (2018**) and **EL-Kilany et al., (2018)**. On the other hand **Jiang et al., (2017)** recorded that *E. coli* challenge in pigglets didn't influenced antioxidative enzymes (superoxide dismutase and GPX). Difference may attributed to species. These changes may be due to that infection with *E. coli* and its bacterial LPS (endotoxin) induces extensive damage to a variety of organs, including liver with production of reactive oxygen intermediates and a resultant rise in lipid peroxidation **(Kono et al., 2013).** The excessive ROS would break the balance between ROS production and antioxidant defenses leading to exhaustion and depletion of antioxidant enzymes **(Eraslan et al., 2007).** LYC and VE treated *E. coli* infected groups (5 and 6) when compared to *E. coli* infected non treated group (gp 4) showed a significant decrease in MDA and a significant increase in CAT, GPX and SOD. Our findings agreed with **Sahin et al., (2016)** who found that increasing dietary LYC level (20, 50 and 100 mg/kg diet) linearly increased serum activities of SOD and GSH-Px and decreased MDA concentration in heat stressed broilers. Moreover **Jena et al., (2013)** recorded that VE supplementation to broiler breeder hens during summer (250 mg or 500 mg/kg) for a period of 8 weeks significantly lowered MDA level and increased the activities of SOD and CAT. LYC induced changes may be attributed to its potent antioxidant effects related to higher singlet oxygen quenching ability which is twice as high as that of β-carotene and 10 times higher than that of α-tocopherol. It scavenges the free radicals via three different mechanisms: adduct formation, electron transfer, and hydrogen atom transfer **(El-Agamey et al., 2004).** Consequently LYC prevents lipid peroxidation and DNA damage simultaneously, it induces enzymes of the cellular antioxidant defense systems by activating the antioxidant response element transcription **(Kelkel et al., 2011).** VE induced changes may be resulted from its antioxidant effect donating hydroxyl group on its ring structure to free radicals, preventing lipid peroxidation thereby prolonging the biological life of

polyunsaturated fatty acids in the cell membranes by slowing the formation of free radicals and hyper-peroxides **(Traber and Atkinson, 2007)**.

The results of AST and GGT indicated non-significant change in LYC and VE treated groups (2&3) compared with the control healthy group reflecting their safety usage with no harmful effect on the liver. Our results agreed with **Ibrahim and Banaee, (2014)** who found non significant changes in serum activities of AST in LYC and VE supplemented fish. The infected non-treated group showed a significant increase in the serum activities of AST and GGT when compared to the control one. These results come in agreement with **Suvarna et al., (2017)** and **Abd-Allah et al., (2018).** Higher hepatic enzyme activities could be due to altered hepatocytes' membrane permeability by the microorganism thus, the cell membrane losses its functional integrity resulting in cellular leakage of these enzymes to circulation **(Gahalain et al., 2011).** The LYC treated *E. coli* infected group (gp 5) denoted a significant decrease in serum AST and GGT values as compared with the infected non treated group (gp 4) 4 days and 2 weeks PI. Similar results were stated by **Sheik and Thiruvengadam, (2013)** who explored the protective role of LYC on liver during experimentally induced hepatitis by d-galactosamine/LPS in adult male Wister rats. The hepatic consolidating effect of LYC could be attributed to its ability for quenching of singlet oxygen and elimination of peroxyl radicals that was confirmed by the elevated antioxidant activities (liver SOD, GPx, and CAT) along with reduced MDA **(Abdel-Rahman et al., 2018).** In addition LYC decreases the adhesion molecules and pro-inflammatory cytokines and inhibites the leukocyte migration and genes involved in inflammation (**Vasconcelos et al., 2017).** VE treated *E. coli* infected group (gp 6) showed a significant decrease in serum AST 4 days and 2 weeks PI and GGT at 2 weeks only when compared to the infected non treated group (gp 4). Similar results were stated by **El-Desoky et al., (2012)** who mentioned that long-term treatment with VE (100mg/kg b.wt) significantly decreased the malathion induced elevations in AST and GGT activities in rats. In contrast to our results **Cinar et al., (2011)** stated that VE supplementation didn't affect the cadmium induced elevation in AST in broilers. Improvement may be attributed to antioxidant activities of VE which maintaining the cells integrity.

Uric acid and creatinine revealed non-significant changes in LYC and VE treated groups (2&3) compared with the control healthy group indicating their safety usage on the kidney. Safety usage of LYC and VE on the kidney also stated by **Ibrahim and Banaee, (2014).** Infected non-treated chicks displayed a significant increase in the levels of serum uric acid 4 days and 2 weeks PI and creatinine at 2 weeks only. These findings come in agreement with those of **Abd El-Ghany and Ismail, (2014)** and could be due to the effect of the microorganisms and it's toxin on the kidneys **(Abd-Allah et al., 2018))**. LYC treated infected group (gp5) when compared to infected non treated group (gp4) showed non significant changes in serum uric acid (but also not statistically differ from normal control values at second collection) beside a significant decrease in serum creatinine at 2 weeks PI. Decreased creatinine level by LYC treatment in hypercholesteremic rats was also documented by **Basuny et al., (2009)**. On contrary **Pektaş et al., (2014)** observed non significant improvement in serum creatinine in rats with renal ischemia when treated with LYC. Difference may be due to treatment regimen (4 mg/kg per day for 2 days) or species difference (rats). Improvement may be attributed to partial protective effect of LYC from oxidative renal damage by the organism and its endotoxin.VE treated infected group (gp 6) when compared to *E. coli* infected non treated group showed non significant changes in serum uric and creatinine. This agreed with results of **Biwas et al., (2018)** who found non significant decrease in serum urea and creatinine in aluminium phosphide toxicated rats treated with VE (1.5 mg/g)

Regarding to TC, our results showed that LYC and VE treated groups (2&3) revealed non significant changes while infected non treated group (gp 4) showed a significant increase in serum concentrations of TC 4 days and 2 weeks PI comparing to negative control birds. These results agreed with those of **Mekkawy, (2016)** and may be due to severe liver damage caused by bacteria that leading to inadequate cholesterol utilization as liver is responsible for biotransformation of cholesterol into bile acids**).** LYC treated infected group (gp 5) when compared to *E. coli* infected non treated group (gp 4) showed a significant decrease in serum TC at the second collections (reached to normal control limits). Our results come in the same side with **Abdel-Rahman et al., (2018)** who found normalization of TC in bisphenol intoxicated rats treated with 10 mg /kg lycopene for 30 days. The normalization of TC in our study may be due to the ability of LYC in protecting LDL from oxidation, to its role in inhibiting HMG-CoA reductase activity and to up-regulate LDL receptor activity in macrophages **(Heber and Lu, 2002).** VE treated infected group when compared to infected non treated one showed non significant change in serum TC at the two collections. Similar to our results **Leonard et al., (2007)** found that VE (400 IU for 8 weeks) didn't alter TC in hypercholesterolemic patients.

Conclusion:-

It could be concluded that lycopene and vitamin E might be helpful in reducing the harmful effect of *E. coli* infection via their anti-inflammatory, immunomodulatory and antioxidant effects with higher improvement in case of lycopene treatment.

Table (1) Serum inflammatory markers (M±SE) in different groups 4 days and 2 weeks PI:

	Parameter / Group	CRP (pg/ml)	Haptoglobin (mg/dl)	IL-1β (ng/ml)	IL-10 (ng/ml)
4 days PI	Control	0.36^{b}± 0.007	149.5^{bc}± 0.95	17.56 ^{c}± 0.87	12.93^{c}± 0.39
	Lyc treated	0.32^{c}±0.005	143.0^{d}± 1.34	16.83 ^{c}± 0.55	20.60^{b}± 0.62
	VE treated	0.34^{bc}±0.004	144.1^{cd}± 1.29	19.83^{bc}± 0.96	13.20^{c}± 0.75
	Infected	0.40^{a}±0.009	169.12^{a}±1.37	24.40^{a}± 0.93	19.03^{b}± 0.55
	Lyc + infec	0.34^{bc}±0.010	152.96^{b}± 1.62	17.52^{c}± 0.73	23.97^{a}±1.11
	VE+ infec	0.35^{b}±0.008	157.44^{b}± 1.68	21.01^{ab}± 0.53	20.43^{b}±0.79
2 weeks PI	Control	0.55^{c}± 0.016	154.66^{cd}± 1.94	31.33^{a}± 0.66	14.17^{c}± 0.49
	Lyc treated	0.41^{d}± 0.006	146.18^{a}± 1.38	26.70 ^{b}± 0.83	17.73^{b}± 0.78
	VE treated	0.57^{c}± 0.011	148.32^{da}± 1.71	30.43^{a}±0.79	14.13^{c}± 0.55
	Infected	0.71^{a}±0.014	168.60^{a}± 0.72	33.03 ^{a}± 0.52	15.60^{bc}± 0.56
	Lyc + infec	0.64^{b}±0.006	155.44^{c}± 1.36	30.87^{a}± 0.72	23.00^{a}± 1.05
	VE+ infec	0.68^{ab}±0.008	161.28^{b}± 1.75	31.10^{a}± 1.05	18.60^{b} ±0.72

Table (2) Phagocytic activity and phagocytic index (M±SE) in different groups 4 days and 2 weeks PI:

	Parameter / Group	Phagocytic activity	Phagocytic index
4 days PI	Control	40.30^{b} ±0.89	0.29^{d}± 0.009
	Lyc treated	43.55^{a}± 0.81	0.49^{a}± 0.017
	VE treated	41.92^{ab}± 0.63	0.37^{b}± 0.00
	Infected	40.96^{ab}± 0.49	0.22^{e}± 0.012
	Lyc + infec	40.87^{ab} ±0.87	0.35^{bc}± 0.017
	VE+ infec	42.49^{ab}± 0.62	0.29^{cd}± 0.012
2 weeks PI	Control	44.70^{ab}± 0.57	1.76^{a}± 0.10
	Lyc treated	46.73^{a}± 1.04	1.83^{a}± 0.09
	VE treated	46.00^{ab} ±0.67	1.94^{a}± 0.11
	Infected	36.35^{c}± 0.89	1.28^{b}± 0.06
	Lyc + infec	44.12^{ab} ±0.92	1.72^{a}± 0.12
	VE+ infec	42.44^{b}± 0.86	1.59^{ab}± 0.09

Table (3) Liver oxidative markers (M±SE) in different groups 4 days and 2 weeks PI:

	Parameter / Group	MDA(nmol/g)	CAT (U/mg)	GPX (U/g)	SOD (U/mg)
4 days PI	Control	95.82^{c}±1.25	0.29^{d}± 0.009	41.77^{c}± 0.92	2.38^{bc}± 0.02
	Lyc treated	85.78^{d}± 1.19	0.49^{a}± 0.017	53.39^{a}± 1.44	4.39 ^{a}± 0.01
	VE treated	81.62^{d}± 1.22	0.37^{b}± 0.00	50.60^{ab}± 1.09	4.45 ^{a}± 0.01
	Infected	136.20^{a}± 2.32	0.22^{a}± 0.012	43.98^{c}± 1.62	1.76 ^{cd}± 0.02
	Lyc + infec	108.96^{b} ±0.97	0.35^{bc}± 0.017	50.78^{ab}± 1.77	2.72 ^{b}± 0.01
	VE+ infec	109.04^{b}± 1.8	0.29^{cd}± 0.012	44.80^{bc}± 1.73	2.08 ^{bc}± 0.01
2 weeks PI	Control	93.90^{bc} ±1.06	0.25^{d}± 0.006	49.34^{c}± 0.95	2.67^{b}± 0.17
	Lyc treated	77.00^{d}± 1.55	0.49^{a}± 0.005	78.37^{a}± 1.01	4.18^{a}± 0.16
	VE treated	77.43^{d}± 1.05	0.48^{a}± 0.004	58.90^{b}± 0.57	3.85 ^{a}± 0.13
	Infected	149.37^{a}± 1.19	0.18^{a}± 0.006	31.70^{d}± 0.71	1.17 ^{c}± 0.12
	Lyc + infec	98.63^{b}±0.87	0.37^{b}± 0.007	46.54^{c}± 1.16	23.70 ^{a}± 0.13
	VE+ infec	93.07^{c}± 0.87	0.29^{c}± 0.006	48.21^{c}± 1.03	2.98^{ab}± 0.11

Table (4) Some serum biochemical parameters (M±SE) in different groups 4 days and 2 weeks PI:

	Parameter / Group	AST (U/L)	GGT(U/L)	Uric acid (mg/dl)	Creatinine (mg/dl)	TC (mg/dl)
4 days PI	Control	53.59^{c} ± 1.1	8.16 ^{b}± 0.15	5.53^{b}± 0.08	0.792^{a}± 0.02	188.67^{b} ± 2.58
	Lyc treated	55.00^{c}± 0.836	8.01^{b}± 0.12	5.70^{ab}± 0.09	0.819 ^{a}± 0.01	185.31^{b} ± 2.55
	VE treated	54.65^{c} ± 1.45	8.06^{b} ± 0.15	5.77^{ab}± 0.09	0.824 ^{a}± 0.01	191.53^{b} ± 1.52
	Infected	79.45^{a} ± 0.809	9.11^{a} ± 0.18	5.93^{a}± 0.03	0.792 ^{a}± 0.02	210.79^{a} ± 1.91
	Lyc + infec	70.63^{b} ± 1.7	7.84^{b} ± 0.1	6.02^{a}± 0.11	0.831 ^{a}± 0.01	204.95^{a} ± 1.71
	VE+ infec	80.33^{a} ± 1.54	7.82^{b}± 0.23	5.97^{a}± 0.08	0.839 ^{a}± 0.01	211.76^{a} ± 0.61
2 weeks PI	Control	53.59^{c}±1.30	9.59^{d}± 0.15	5.37^{b}± 0.23	0.824^{b} ± 0.01	202.81^{c}± 1.63
	Lyc treated	51.06^{c}± 0.84	10.10^{d}± 0.19	5.43 ^{b}± 0.24	0.830^{abc}±0.004	201.24^{c}± 1.05
	VE treated	52.83^{c}± 1.30	10.80^{d}± 0.39	5.39 ^{b}± 0.20	0.842^{abc}±0.007	204.50^{bc}± 1.33
	Infected	78.86^{a}± 2.00	16.89^{a}± 0.29	6.27 ^{a}± 0.12	0.862^{a} ± 0.008	210.63^{a}± 1.54
	Lyc + infec	66.00^{b}±1.9	11.86^{c}± 0.44	6.14^{ab}± 0.10	0.828^{bc} ±0.005	203.07^{c}±0.74
	VE+ infec	69.2^{b}± 1.76	14.48^{b}± 0.16	5.76 ^{ab}± 0.14	0.844^{abc} ± 0.01	208.72^{ab}± 0.95

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