Egyptian Journal of Rabbit Science, 32 (2): 181 -199(2022)

IMPACT OF BEE VENOM AND OXYTETRACYCLINE ON BLOOD PARAMETERS, ANTIOXIDANT, IMMUNITY STATUS AND BACTERIAL COUNT OF WEANING RABBITS

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ABSTRACT:
The present study aimed to compare the effects of bee venom (BV) and Oxytetracycline (OXY) supplementation on blood biochemical analysis, antioxidant, immunity status and bacterial count of weaning rabbits. Sixty Californian male rabbits at 35 days of age with average body weight of 589±90 g *were* randomly *divided into five equal* groups *(12 for each)*; *1st group (control) was given water (placebo), 2nd group (OXY; 1g/l water), 3rd, 4th, and 5th groups were received BV at (2, 4 and 8 mg/kg body weigh/day, respectively). Results indicated that weaning rabbits treated with OXY and BV had significant increases of total plasma protein (TP) and globulin (Glo) while decreasing AST and ALT, except for OXY group rise of ALT compared to control group. Rabbits treated with OXY or BV had a significantly declined tri-glycerids (TG), total cholesterol (TC) and very low-density lipoprotein (VLDL-c), while all treatment records were insignificant for high-density lipoprotein (HDL-c) and low-density lipoprotein (LDL-c) compared to control group. Groups treated with BV showed increase of IgG, total antioxidant capacity (TAC), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). Group treated with 2 mg BV/kg body weight/day had a decreased total bacterial count (TBC), salmonellae, E. coli, Proteus and Clostridia.*
Conclusively, *it could be recommended the use levels of BV (2 mg BV/kg body weight/day) to improve the biochemical, immunological and antioxidative responses and decrease pathogenic bacteria in hindgut of weaning rabbits.*

Key words: Antioxidant, bee venom, immunity, oxytetracycline, rabbit.

INTRODUCTION

Bee venom (BV) is an important product of the honey bee, and it has been used to treat a variety number of diseases (**Hegazi, 2012**). The honey BV is a white liquid with a strong, bitter taste. One of the essential chemicals produced by honey bee *(Apismellifera)* is apitoxin. Low molecular polypeptides and enzymes account for the majority of whole honey bee venom. Mast-cell-degranulating peptides, apamin, adolapin, and melittin are forms of peptides. The enzymes are hyaluronidase, phospholipase A_2, D-glucosidase, lysophospholipase-acetylamino-deosiglucosidase, arylamidase, and phosphomonoesterase acid esterase. Esterase is among the enzymes. Furthermore, the BV includes physiologically active amines such as histamine and adrenaline, and non-peptide drivaties with diverse pharmacological effects, as reported by Dong *et al.,* (2007). It is believed to be one of the best ways to experience a new component that could be utilized in medicine and biochemistry **(**Moreno and Ernest, 2015). Bee venum has anti-cancer effects and can protect the liver **(**Lim *et al.,* 2015**).**

The effect of BV on estimating TP, Alb and Glo concentration in serum, and liver enzyme activity has also been established as (ALT and AST) in blood serum **(**Hassan and Raghad, 2021**).** Due to the prevalence of melitin in BV, it bears the responsibility to regulate alterations in cell membranes by influencing the interactions of lipoproteins that enter into the development of these membranes **(**Bollinger *et al.,* 2004). Honey BV has often been used as a pain reliever and therapy for inflammatory diseases Yoon *et al.,* (2013). Furthermore, considering apamin and phospholipase A_2 in BV have a powerful immunoregulatory function, so that BV treatment could be effective in multiple immune diseases **(**Castro *et al.,* 2005**).** Moreover, in the initial stages, BV supplementation on drinking water had a massive influence on broiler performance. Han *et al*., (2010) suggested that tetracycline residues may be present in edible animal products due to extensive and improper use, which can be dangerous to human health and can provoke allergic reactions. Furthermore, low-dose antibiotics in products taken for long periods of time can spread drug-resistant microorganisms **(**Yu *et al.,* 2011**).**

Tetracycline antibiotic residues may be present in edible animal products as a result of extensive and improper use, which can be dangerous to human health and can provoke allergic reactions. Furthermore, low-dose antibiotics in products taken for long periods of time can lead to the spread of drug-resistant microorganisms **(**Yu *et al*., 2011**).**

The goal of this research will be how BV and OXY supplementations

effect on biochemical blood analysis, antioxidant, immunity status and bacterial count of weaning rabbits.

MATERIALS AND METHODS

Housing and management:

From January till April 2020 (winter season), this study was carried out at a private rabbitry farm located in Qalubia governorate, Egypt. It aimed to study the impacts of Bee venom (BV) and Oxytetracycline (OXY) supplementations on the blood parameters of Californian growing rabbit males. Sixty male growing Californian rabbits aged 35 day old within average body weight of 589±9.90 g were randomly distributed into five equal treatments (12 for each). Rabbits were housed in wire galvanized batteries approximately 60×55×40 cm in a naturally ventilated house. Each cage was supplied with stainless steel nipples for drinking and feeders that permitted each rabbit's individual feed intake to be recorded. The temperature ranged from 18 to 25°C, with a relative humidity of 45–58% and a light photo time of 16 hours of light and 8 hours of darkness. Feed and water were available for free (*ad libitum*). All rabbits were kept in the same managerial conditions and were individually weighed and kept in the managerial conditions.

They were healthy, hygienic, and clinically free of external and internal parasites, and feed intake was recorded weekly during the experimental period. The basal diet was formulated and pelleted to cover the nutrient requirements of rabbits according to NRC (1977) as shown in Table 1.

Chemical analysis of Bee venom:

Bee venome (BV) samples were collected from apis mellifera carnica kept at the Plant Protection Research Institute, Agriculture Research Centre, Egypt. The product recorded and analyzed according to Hind *et al.,* (2018). It contains, Protease, phospholipase A_2 and Hyaluronidase activity were appreciated knowing by Hind *et al.,* (2018) in Egypt.

Doses: BV were given orally in drinking water 2, 4, and 8 mg/kg BW/daily/7wk; dose calculated according to Ahmed *et al.,* (2019). Oxytetracycline,OXY(20%) Produced by the Arab Co. Pharmaceutical products, Egypt.

Experimental groups were distributing as follow:

Group 1: basal diet and served as control **(C).**
Group 2: basal diet+1g/l water Oxytetracycline (20%) (**OXY**).
Group 3: basal diet + 2 mg/kg BW/day **(BV1**).
Group4: basal diet + 4 mg/kg BW/day **(BV2).**
Group 5: basal diet +8 mg/kg BW/day **(BV3**).

Table 1. Composition and chemical analysis of basal diet

Ingredients	%
Yellow corn	6.22
Soybean meal, 44%	15.00
Wheat bran	23.33
Barley	15.00
Alfalfa hay	30.12
Ground limestone	1.00
Hay	7.33
Dicalcium phosphate	1.20
Sodium chloride	0.50
Vit. + min. premix*	0.30
Total	100
Calculated analysis	
Crude protein, %	18.0
Crude fiber, %	14.0
Ether extract, %	3.0
Digestible energy (kcal/kg diet)	2560

*Each 3 kg of premix contains: Vit. A: 12,000,000 IU; Vit. D_3: 3,000,000 IU; Vit. E: 10.0 mg; Vit. K_3: 3.0 mg; Vit. B_1: 200 mg: Vit. B_2: 5.0 mg Vit. B_6: 3.0 mg: Vit. B_{12}: 15.0 mg; Biotin: 50.0 mg; Folic acid: 1.0 mg; Nicotinic acid: 35.0 mg: Pantothenic acid: 10.0 mg; Mn: 80 g; Cu: 8.8 g; Zn: 50 g; Fe: 35 g; I: 1 g; Co: 0.15g and Se: 0.3g, FAs: Fatty acids.

Blood samples:

At the end of the experiment (14 weeks of age), 5 blood samples (5 ml each) were withdrawn from marginal ear vein for each treatment group in the morning before receiving feed and water, using sterile disposal needles. Blood samples were centrifuged at 3000 rpm for 15 minutes to obtain clear blood plasma, then stored at -20 ^{o}C until the biochemical blood were analyzed.

Biochemical analysis:

Total plasma protein (TP), and albumin (Alb) were measured and globulin (Glo) was calculated. Tri-glycerides (TG); cholesterol, AST, ALT, high-density lipoprotein (HDL-c), very low- density lipoprotein (VLDL-c); IgG; IgM; SOD; CAT; GPx; TAC and MDA were determined**,** however, low-density lipoprotein (LDL-c) were calculated using the formula:

LDL-c, (mg/dl) = Total cholesterol–{HDL-c+ (TG/5)}, which explained by William *et al.*, (1972).

Bacterial count:

After slautring of rabbit (at 14 weeks of age) total anaerobic bacterial count, Escherichia coli (*E.coli*) and lactobacilli bacteria count were estimated in caecum contents, caecum pH was measured by using pH meter infiltrating caecum content. Ammonia nitrogen concentration was determined as described by Conway (1958).

Statistical analysis:

All data were subjected to analysis of variance as described in SAS Program (SAS, 2002). The significant means differences among groups were separated by Duncan's Multiple Rang Test (Duncan, 1955).

RESULTS AND DISCUSSION

Biochemical analysis of BV:

There are about 60 components in BV that can be recognized, with melittin being the most prevalent (Damianoglou *et al.*, 2010). BV contains several components such as enzymes, proteins, peptides, and many more minor compounds (amino acids, catecholamine's, sugars, and minerals (Park *et al.*, 2011). The essential features are proteins and peptides. The mean values of enzymes and more minor compounds were found in the venoms of most stinging insects, including honey bees. Different stinging insect's venom has different biological actions. Table 2 shows the results according to the methods of analysis according to Teoh *et al.*, (2017) and Mammadova and Topchiyeva (2017).

Table 2. The major enzymes component activity of the Egyptian honey bee venom extracted by using two methods.

Methods	**Honey bee venom analysis**			
	Melittin analysis %	**Protease (U/mg)**	**Hyaluronidase (U/mg)**	**Phospholipase A_2 activity (U/mg)**
Manual method	46.71	32,08	99.37	102.77
Electric method	67.44	135.08	129.81	222.38
SEM	**0.24**	**0.37**	**0.28**	**0.38**

Effect of OXY and BV on biochemical blood analysis:

Data in Table 3 indicated that treating weaning rabbits with OXY and BV induced significant increases in TP and Glo while decreasing AST and ALT, except for OXY group which demonstrated a rise in ALT compared to control. On the other hand, all treatment records were insignificant for Alb

Table 3. Effect of OXY and BV delivered orally in drinking water on blood parameters of growing rabbits (14 weeks of age).

Items	Treatment groups					SEM	P-value
	C	OXY	BV1	BV2	BV3		
TP (g/dL)	5.50 ^{c}	6.50 ^{b}	6.93 ^{ab}	7.20 ^{a}	7.19 ^{a}	0.081	0.0001
Alb (g/dl)	4.10	3.40	3.90	4.10	3.75	0.146	0.316
Glo (g/dl)	1.40 ^{b}	3.10 ^{a}	3.03 ^{a}	3.10 ^{a}	3.44 ^{a}	0.156	0.0038
AST (U/L)	35.99 ^{a}	27.90 ^{b}	23.90 ^{b}	23.93 ^{b}	24.50 ^{b}	0.649	0.0001
ALT (U/L)	42.08 ^{a}	39.98 ^{a}	26.67 ^{b}	24.08 ^{b}	23.00 ^{b}	0.350	0.002

$^{a\text{-}b\text{-}c}$: Values in the same row with different superscripts differ significantly ($P \leq 0.05$).
C : Control; OXY : Oxytetraccline 1gm/litter water; BV1: 2 mg bee venom/kg BW/day; BV2: 4 mg bee venom/kg BW/day; BV3: 8 mg bee venom/kg BW/day; TP: total protein; Alb: albumin; Glo: globulin; AST: aspartate aminotransferase activities; ALT: alanine aminotransferase activities.

compared to the control group. Our findings showed that rabbits provided with BV and OXY had a high significant decrease in AST and ALT levels, which agrees with the observations of Hassan *et al.,* (2019) who revealed that after oral administration of BV to rats, a significant decrease in serum ALT, AST and Alb activities when compared to control, as it was discovered that BV seems to have a hepato-protective effect, which could have been explained by the reduction of elevated hepatic nuclear factor kappa B (NF-kB) expression in the liver. Other investigations have shown that BV has a potent hepatoprotective benefit by suppressing the release of pro-inflammatory cytokines and diminishing increased serum aminotransferase enzymes in different models of induced liver damage (Park *et al.,* 2010). Ali and Mohanny (2014) found no significant differences in AST and ALT, TP, Alb, Glo, or Alb/Glo ratio in injected checks with BV. On the other hand, ALT and AST are indicators for liver integrity and function according to Zafar *et al.,* (2009). Due to the presence of phospholipase A_2, the second most prevalent component of BV treated rats showed a significant reduction in ALT and AST activity compared to untreated rats (Zahran *et al.,* 2021). Also, Kim *et al.,* (2014) recorded that bee venom decreases aminotransferase enzymes and inhibits the release of pro-inflammatory cytokines, which has been related to hepatic damage.

The presence of phospholipase A_2 in bee venom, which has antioxidant, anti-inflammatory and hepato-protective effects was attributed to the improvement in TP, Alb and Glo (Zahran *et al.,* 2021). Baeg-Young *et al.,* (2011) reported that there were no differences in plasma biochemical components including AST, ALT, alkaline phosphate (ALP), TP, Alb, Glo, and

total bilirubin in calves treated with bee venom. Finally, Alaa Elkomy *et al.,* (2021) recorded a significant reduction in both AST and ALT activities in treating rabbits with BV.

Regarding OXY, Ayana *et al.,* (2016) recorded that TP and transaminases were decreased with the group treated with OXY compared to the control group**.** In contrast, Shabana *et al.,* (2012) recorded that albino rats consuming a diet supplemented with OXY showed significantly increased of AST, ALT, bilirubin, urea, creatinine, and gamma-globulin levels in the serum. The significant elevation in the levels of ALT and AST in the serum of OXY-administrated rats in study in accordance with the results of Santhosh *et al.,* (2006). Elevated levels of these enzymes in the serum are presumptive markers of drug-induced necrotic lesions in the hepatocytes (Amr and Alaa, 2005). The same result was obtained by Jayanthi and Subash (2010), who detected significantly increased serum AST, ALT, ALP, and LDL in rats that orally consumed OXY compared to the control group. On the other hand, Janbaz *et al.,* (2004) explained the increased liver enzyme activities level after oxytetracycline treatment because led are the most sensitive markers for diagnosing hepatic damage because they are cytoplasmic in location and released into the circulation after cellular damage.

Effect of OXY and BV on lipid profile:

The effect of OXY and BV on the lipid profile of weaning rabbit displayed in Table 4 indicated that the treated rabbits had a significantly declined TG, TC, LDL-c and VLDL-c, while all treatment records were significant increased HDL-c in compared to the control group.

Table 4: Effect of OXY and BV delivered orally in drinking water on the lipid profile of growing rabbits (14 weeks of age)

Items	Treatments					SEM	P-value
	C	OXY	BV1	BV2	BV3		
TG (mg/dL)	157.50^{a}	110.33^{b}	90.00^{bc}	90.33^{c}	92.00^{c}	2.481	0.0001
TC (mg/dL)	80.33^{a}	73.00^{b}	65.33^{c}	64.67^{c}	65.33^{c}	0.798	0.0001
HDL-c (mg/dL)	34.68^{b}	40.07^{a}	41.97^{a}	42.33^{a}	42.33^{a}	1.144	0.0422
LDL-c (mg/dL)	14.18^{a}	10.87^{b}	5.36^{c}	4.27^{c}	4.60^{c}	1.537	0.0511
VLDL-c (mg/dL)	31.50^{a}	22.07^{b}	18.00^{bc}	18.07^{c}	18.40^{c}	0.496	0.0001

$^{a\text{-}b\text{-}c}$: Values in the same row with different superscripts differ significantly ($P \leq 0.05$).

C : Control; OXY : Oxytetraccline 1gm/litter water; BV1: 2 mg bee venom/kg BW/day; BV2: 4 mg bee venom/kg BW/day; BV3: 8 mg bee venom/kg BW/day; TG: triglycerides; TC: total cholesterol; HDL-c: high density lipoprotein; LDL-c: low density lipoprotein; VLDL-c: very low density lipoprotein.

The present results are in agreement with those obtained by Yakout *et al.,* (2019) and Ivas *et al.,* (2014) who stated that treating white male albino rats with BV decreased serum TG, TC, and LDL-c. These results suggest that BV is effective in improving biochemical blood parameters and, decrease of the serum cholesterol level under the effect of BV. Two plasmatic enzymes modify the lipoproteins HDL, LDL and VLDL: lecithin-cholesterol acetyltransferase, A_2 phospholipasic activity, and lipoprotein lipase. The action specificity of those two enzymes is the key to understanding lipid metabolism. At the same time, the A_2 phospholipases in venoms were demonstrated to have an enzymatic activity three times higher than that of the plasmatic lecithin-cholesterol acetyltransferase ***(***Ivas *et al.,* 2014***).*** The free cholesterol in HDL is esterified by phospholipase activity ***(***Guillaume et al., 2006***)***. However, the partial lysis of the membranary phosphatidylcholine in adipocytes by A_2 phosphofolipase in venom affords the binding of a greater number of insulin molecules, promoting an increase in glucose transport as well as an acceleration of taking the lipids in the adipose tissue **(**Ivas *et al.,* 2014**).** These effects, generated by the A_2 phospholipase in the BV, could explain the hypocholesterolemic and hypotriglyceridemic effects that are unanimously accepted and made evident in the present study with both low and high venom doses. Another study by Khulan *et al.,* (2015) recorded that treating rats with BV led to reduced values of blood cholesterol and LDL-c while increasing HDL levels. Gupta and Sharma (2010) recorded that BV-treated rats showed a significant decrease in TC and TG levels and increase in plasma HDL level; this is also compatible with Khulan *et al.,* (2015) who conducted his experiment on rabbits. Also, Zainab and Ahmed (2019) recorded that injected mature male albino rats with BV had a significant decrease in TC, TG, and LDL and a significant increase in HDL levels compared to the control group.

Regarding OXY, Ayana *et al.,* (2016) recorded that supplemented diet for broiler chickens did not deviate from indices TG, cholesterol levels in the control and treated groups. In contrast to our results**,** Shabana *et al.,* **(2012)** who recorded that serum of male albino rats utilized diet supplemented with tetracycline increased significantly TG, LDL-c, whereas the level of HDL-c was significantly decreased in the serum; these results are in agreement with those reported by Santhosh *et al.,* (2006). Also, TG was significantly increased in the serum of the animals treated with oxytetracycline (Stenberg, 1976). Machado *et al.,* (2003) explain the increased TG by saying that the organelles that changed in the presence of tetracycline were mainly mitochondria. The beta-oxidation enzyme is inhibited, resulting in an accumulation of triglycerides inside the cytoplasm

(Machado *et al.,* 2003)**.** They suggest that hypertriglyceridemia may be due to the increased release of lipoproteins into the circulation.

Effect of OXY and BV on immunity and antioxidant status:

Table 5 summarized the effects of treatment of weaning rabbits with OXY and BV on immune and antioxidant status. The results showed a highly significante increases for BV on IgG, while, OXY led to a decrease for IgG. The concentration of IgM numerically increased in all groups BV, but the group OXY showed decreased IgM compared with the other treatments and control groups.

The predent results are identical with Alaa Elkomy *et al.,* (2021) who revealed a significant increase in immune response IgG, IgM and IgA levels with BV groups compared to the control group. Results documented that BV could be used in rabbit farming as an effective and safe alternative to improve immune response and health. Also, El-Hanoun *et al.,* (2020) mentioned that treating V-line buck rabbits with BV resulted in a significant increase in IgA and IgM. These results revealed that BV had a significant positive impact on raising immune status.

In the study of Bock-Gie *et al.,* (2013) who showed that the increase in final body weight following BV spray conduct was more pronounced in broiler chicks infected with a low lethal dose of *S. Gallinarum* bacteria. These results suggest that administering BV by spray could help improve growth performance in the absence of infection and in environments with a risk of exposure to contaminating pathogens, such as traditional farms. Antibody production against formalin-killed S. gallinarum bacteria increased significantly in the BV-sprayed group compared to untreated group. This result was similar to a previous report that acupuncture (injection) with honey bee stings improved antibody production against the classical swine fever virus vaccine, the mycoplasma hyoponeumoniae vaccine, and the atrophic rhinitis vaccine in pigs (Kwon and Lee, 2001). As a result, it suggests that humoral immunity was enhanced improved by administering HBV to broiler chicks, as the antibody titer is a humoral immunity indicator, Yang *et al.,* (2008).

Regarding OXY on immunity, Stetsenko *et al.,* (1976) reported that rabbits consuming tetracycline caused significant changes in both the central and peripheral immune organs. In the system of immunogenesis, two parameters in the development of the reaction were observed: (1) stimulation, transformation, and differentiation of immune-competent cells; and (2) cell destruction, especially by converting and proliferating cells. This caused the immune system to be diminished, aggravated if the treatment was used for a long time and at higher doses. Karput (1976)

Table 5. Effect of OXY and BV delivered orally in drinking water on the immune response and antioxidant status of growing rabbits (14 weeks of age)

Items	Treatment groups					SEM	P-value
	C	OXY	BV1	BV2	BV3		
IgG (mg/dl)	475 ^{bc}	415 ^{cd}	645 ^{a}	525 ^{b}	331^{d}	40.81	0.0001
IgM (mg/dl)	39.00	35.00	43.00	53.00	40.00	4.209	0.065
TAC, (µmol/ml)	1.91^{c}	0.54^{d}	2.42^{b}	2.68^{b}	3.01^{a}	0.028	0.0001
SOD (IU/ml)	6.38^{b}	3.43^{c}	7.32^{a}	8.41^{a}	7.8^{a}	0.54	0.0001
CAT(IU/ml)	71.16^{b}	48.65^{c}	87.75^{a}	83.43^{a}	89.77^{a}	3.134	0.0004
GPx (IU/ml)	6.09^{b}	2.23^{c}	7.84^{a}	8.12a	8.56^{a}	1.05	0.003
MDA (nmol/ml)	0.42^{b}	0.56^{a}	0.33^{c}	0.28^{c}	0.29^{c}	0.04	0.0001

$^{a-b-c}$: Values in the same row with different superscripts differ significantly ($P \leq 0.05$).

C : Control; OXY : Oxytetraccline 1gm/litter water; BV1: 2 mg bee venom/kg BW/day; BV2: 4 mg bee venom/kg BW/day; BV3: 8 mg bee venom/kg BW/day; IgG: immunoglobulin G; IgM: immunoglobulin M; TAC: total antioxidant capacity; SOD: superoxide dismutase; CAT: catalase; GPx: glutathione peroxidase; MDA: malondialdehyde.

found that oxytetracycline and tetracycline administered to the animals formed complexes with the proteins, especially with albumins and gamma-globulins. Immunomorphological changes accompanied by the formation of antibodies to the antibiotics were found in the blood-lymphoid system after repeated parental administration of the tetracyclines. The use of tetracyclines during the induction stage of immunogenesis had a pronounced inhibitory effect on the development of immunity. Based on the tetracycline capacity for binding with immunoglobulins by the lymphocytes, it is possible to suppose that the inhibitory effect of the antibiotics on immunogenesis was connected with their blocking the receptors of T- and B-lymphocytes. At the same observation, Slavcheva (1976) discovered tetracycline's effect on plate- and rosette-forming cell proliferation in the spleen. It was found that tetracycline acted as an inhibitor of immunogenesis. When they were administered simultaneously, their inhibiting effect decreased. The inhibiting effect of the antibiotic was more pronounced concerning the plate-forming cells than for the rosette-forming cells. The inhibiting effect of the antibiotic was lower in the mesenterial lymph nodes than in the spleen. According to Challem (1996), some antibiotics prevented WBCs from attacking and fighting bacteria, with tetracycline-class treatments the biggest culprits. Other research corroborates tetracycline's negative impact on immunological response. Banck and Forsgreen (1979) investigated the effect of antibiotics on lymphocyte function suppression *in vitro*. They led to the realization that

doxycycline reduced the mitogenic response of both B- and T-cells. According to these researchers, tetracyclines inhibit protein synthesis, which explains why they have a deleterious influence on antibody formation (Korkelia, 1971).

Effect of OXY and BV on antioxidant capacity:

Treated rabbits with BV showed significantly ($P \leq 0.05$) increased TAC, SOD, CAT, and GPx. In contrast, groups supplemented with OXY had the lowest value of all antioxidant parameters and a high level of MDA, groups treated with BV showed a high level of all measured parameters of antioxidant and the lowest level of MDA.

The present results were in harmony with those obtained by **Yakout *et al.*, (2019)** who revealed that the treatment with BV recorded increasing catalase (CAT), glutathione peroxidase (GSH-px), and superoxide dismutase (SOD) and diminished MDA. On the other hand, **Hegazi (2012)** stated that BV treatment is a potent antioxidant that leads to a decline in the levels of reactive oxygen species (ROS) and decreased MDA. Also, Rekka *et al.,* (1990) mentioned that BV antioxidant powerful capacity to inhibit the lipid peroxidation process and to increase superoxide dismutase (SOD) activity (Han *et al.,* 2010). Same result obtained by Hegazi (2012) stated that BV therapy is a potent antioxidant which led to a decrease in the levels of reactive oxygen species (ROS), which may be associated with the observations of BV affecting increasing glutathione, superoxide dismutase (SOD) and catalase. Salman *et al.,* (2015). Also**,** Hassan *et al., (*2019) noted that treating rats with BV resulted in a significant decrease in MDA while a significant increase in TAC, GSH content, and CAT activity. Also, Alaa-Elkomy *et al.,* (2021) mentioned a significant increase in antioxidative enzymes such as TAC, GST and GPx and a decrease in MDA and thiobarbituric acid reactive substances in BV groups compared to the control group. The same results obtained by El-Hanoun *et al.,* (2020) who recorded significantly higher antioxidant indices of TAC, GST, and GSH in BV male rabbit groups compared to the control group. In contrast, Denk *et al.,* (2021) recorded that injecting rat with bee venom (apitoxin) increased MDA and carbonated protein (PCO), and decreased GSH levels significantly.

The present results were similarly with Jayanthi and Subash (2010) who discovered that the levels of enzymatic antioxidants, namely SOD, CAT, and GPx, were significantly reduced in rats that consumed oxytetracycline orally. Also, Abdel-Daim and Ghazy (2015) recorded that OXY treatment elevated lipid peroxidation through raising hepatic and renal MDA values, decreasing hepatic and renal enzymatic SOD and CAT as well as non-enzymatic GSH antioxidant concentration. At the same time, hepatic and renal TAC was also reduced. On the other hand, all of these effects play a significant role in OTC-

induced hepato-renal oxidative damage and toxicity, which is generated by the excessive generation of free radicals, which have also been shown to damage a variety of biological molecules, including lipids, and promote lipid peroxidation. The activities of enzymes involved in glutathione pathways were also altered in the OTC-treated group, indicating that oxidative stress plays an important role in OTC-induced hepatorenal damage. These findings are in agreement with Saleem *et al.,* (2015) who pointed to the role of reactive oxygen species (ROS) in OTC-mediated damage and toxicity, the same observation obtained by Asha *et al.,* (2007) who revealed that antioxidant enzymes including such superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase were unaffected or slightly reduced in the liver of rats after treatment with tetracycline at 50 mg/kg-1, but their concentration was significantly reduced in rats treated with 200 mg/kg-1.

Effect of OXY and BV on bacterial count:

Apis mellifera venom (BV) is composed of a complex mix of active peptides, enzymes, and amines (**Hider, 1988)**. Mellitine, a major component of bee venom has greater antimicrobial activity against gram-positive than against gram-negative bacteria. Furthermore, BV has been shown to have a variety of effects on different types of cells, including antibacterial, antiviral, and anti-inflammatory effects (Hossein *et al.,* 2016).

The present examination showed that the antibacterial activity of BV at the three concentrations against TBC**,** Salmonella, E. coli, Proteus, and Clostridia was more significant than that of the standard antibiotic oxytetracycline at 1 gm. /litter of drinking water. However, the antibacterial activities of BV against Salmonella at the concentrations BV1 and E.coli in BV3 were less than those of the standard antibiotic oxytetracycline at 1 gm. /litter of drinking water (Table, 6). The present results are in agreement with Hossein *et al.,* (2016) who reported that BV has been confirmed to have antibacterial effects against gram-positive bacteria. Furthermore, BV inhibited the growth and survival of specific bacterial strains, and we conclude that BV may be an effective complementary antimicrobial factor for use against specific pathogenic bacteria. Also, Ortel and Markwardt (1955) measured the zones of inhibition, the bacteria's relative sensitivities being qualitatively estimated. They discovered that gram-positive bacteria were more sensitive to lower BV concentrations than gram-negative bacteria. Interestingly, Lariviere and Melzack (1996) noted that the antibacterial effect of BV may be due to the presence of peptides, enzymes, biologically active amines, and non-peptide components, and that these compounds may interact with specific molecules of bacteria. Phospholipase A_2 (PLA2) has been reported to have an antibacterial effect by Permual *et al.,* (2007).

Table 6. Effect of OXY and BV delivered orally in drinking water on bacterial count on caecum of growing male Californian rabbits (14 weeks of age)

Items	Treatment groups					SEM	P-value
	C	OXY	BV1	BV2	BV3		
T.B.C., 10^6/Cm^3	3.00^{a}	2.5^{bc}	2.4^{c}	2.7^{ab}	2.85^{a}	0.08	0.001
Salm., 10^5/ Cm^3	0.72^{b}	0.53^{d}	0.63^{c}	0.81^{a}	0.73^{b}	0.21	0.001
E. coli, 10^5/ Cm^3	2.20^{b}	2.15^{b}	2.00^{b}	1.75^{c}	2.60^{a}	0.34	0.001
Proteus, 10^5/ Cm^3	1.21^{a}	0.54^{d}	0.96^{b}	0.57^{d}	0.86^{c}	0.09	0.001
Clostridia, 10^5/ Cm^3	1.85^{a}	1.75^{a}	1.50^{b}	1.45^{b}	1.55^{b}	0.05	0.001

$^{a\text{-}b\text{-}c}$: Values in the same row with different superscripts differ significantly (P≤0.05).
C : Control; OXY : Oxytetraccline 1gm/litter water; BV1: 2 mg bee venom/kg BW/day; BV2: 4 mg bee venom/kg BW/day; BV3: 8 mg bee venom/kg BW/day; T.B.C: total bacterial count; Salm.: salmonellae; E. coli: Escherichia coli.

Though BV contains PLA2, which may be responsible for its antibacterial properties, it also contains melittin, which may contribute to that antibacterial effect. On the other hand, several researchers have confirmed the antimicrobial activity of honey bee venom **(**Leandro *et al.*, 2015**),** particularly against Staphylococcus bacteria (Perumal *et al.*, 2007). At the same time, Giuliani *et al.*, (2008) revealed that melittin's antibacterial activity against gram-positive bacteria, particularly Staphylococcus aureus, is attributable to the fact that it may target the lipid bilayer of the object's membrane.

Conclusivly, from an economic point of view it could be recommended to use levels of BV (2 mg BV/kg BW/day) to improve the biochemical, immunological and antioxidative responses and decreased pathogenic bacteria in hindgut of weaning rabbits.

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تأثير سم النحل والأوكسى تتراسيكلين على خصائص الدم، حالة التأكسد والمناعة والعد البكتيرى فى الأرانب النامية

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إستخدم فى هذه الدراسة عدد ٦٠ أرنب ذكر كاليفورنيا عمر ٣٥ يوم بمتوسط وزن ٥٨٩ ± ٩ جم بشكل عشوائي إلى خمسة مجموعات متساوية. تم تغذية الأرانب في كل المجموعات على عليقة الأساسية. الأرانب فى المجموعات الثانية والثالثة والرابعة والخامسة قدم لها ماء شرب يحتوى على ١جم/أوكسيتتراسيكلين/ لتر ماء شرب أو ٢، ٤، ٨ مجم سم نحل لكل كجم وزن جسم حى على التوالى بينما تلقت المجموعة الأولى ماء عادى وحفظت للمقارنة. ويمكن تلخيص أهم النتائج على النحو التالي:

١- زاد تركيز كل من البروتين الكلى والجلوبيولين فى كل المجاميع المعامله سواء بالأوكسيتتراسيكلين أو سم النحل مقارنة بالكنترول.
٢- إنخفضت إنزيمات الكبد متمثلة فى (AST and ALT) للمجموعات المعاملة بسم النحل بينما لم ينخفض مستوى إنزيم ALT فى المجموعة المعاملة بالأوكسيتتراسيكلين مقارنة مع مجموعة الكنترول.
٣- لوحظ زيادة فى HDL-c وانخفاض LDL-c للمجموعات المعاملة بالأوكسيتتراسيكلين وسم النحل مقارنة مع مجموعة الكنترول.
٤- حدث تحسن فى حالة مضادات الأكسدة فى كل المجاميع المعاملة متمثلة فى TAC, SOD, CAT and GPX مقارنة بالكنترول.
٥- تحسنت الحالة المناعية فى كل المجاميع المعاملة متمثلة فى IgG مقارنة بالكنترول.
٦- المجموعة المعاملة ب ٢ مجم من سم النحل/كجم وزن جسم حى/ يوم لوحظ بها إنخفاض فى عدد البكتيريا الممرضة مقارنة بباقى المجاميع والكنترول

التوصية: استخدام سم النحل فى ماء الشرب لذكور الأرانب الكاليفورنيا النامية بمعدل ٢ مجم/كجم وزن جسم حى/ يوم أدى لزيادة مستوى بروتينات الدم وتحسن حالة الأكسدة والإستجابة المناعية، كما أدى لخفض أعداد البكتيريا الممرضة.