JOURNAL of QASSIM UNIVERSITY FOR SCIENCE
© 2023 Qassim University [E-ISSN: 1658-9610]
Vol. 2, Issue 1, pp 147-160 (July 2023)
JQUS

The ameliorating effect of camel milk against liver toxicity induced by levofloxacin in male albino rats

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Abstract:

-***Background:*** Levofloxacin (Levo) is an antibiotic originating from the second generation of fluoroquinolones. It is used to treat infections of the respiratory tract, urinary tract, and genital tract. In spite of its great potency in the treatment of many diseases it has many side effects such as hepatotoxicity & renal toxicity.

- *Objectives:* The current study aimed to examine the therapeutic potential of camel milk to attenuate the liver toxicity of levofloxacin on some biochemical parameters in male albino rats.

- *Methodology:* The study investigated the effect of a dose (100 mg/kg) of levofloxacin for 10 days and evaluation of treatment with camel milk (5 ml/rat/day) for 15 days, on biochemical parameters: Glutamate-oxaloacetate (GOT), Glutamate pyruvate transaminase (GPT), total bilirubin (T.BIL), direct bilirubin(D.BIL), indirect bilirubin(Ind.BIL), Glucose, values were assessed.40 albino male rats weighing between (150 -180 g) were divided into four groups, including ten in each group, as follows: **G1**: regular rodent food and water are given to the control group. **G2:** CM (5ml/rat/day) for 15 days in drinking bottles. **G3**: oral administration of LFX through gastric tube (100mg/kg body wt.) for 10 days. **G4:** oral administration of LFX (100mg/kg body wt.) for 10 days, followed by CM (5ml/rat/day) for 15 days in drinking bottles.

- ***Results:*** The activities of transaminases (GOT), (GPT), levels of:(T.BIL), (D.BIL), and (Ind.BIL), in **G3**:(LFX-group) significantly increased($p \leq 0.01$) by (42.4%,64.5%,151.4%,154.4%,148.8%) respectively after treatment with the antibiotic levofloxacin (LFX) at a dosage of (100 mg/kg/B wt) for 10 days. Additionally, there was a notable drop in serum glucose level ($p \leq 0.01$) by (-28.9%) in comparison to the control group of the above. While treatment with camel milk (5 ml / rat / day) for 15 days in **G2**: (CM-group) did not result in any significant difference ($p < 0.01$) in the above parameters compared to the control group. Oral administration of **G4**:(CM+LFX/group) for 15 consecutive days showed a less significant decrease ($p \leq 0.01$) in the activities of (GOT), (GPT) (-7.6%, -13.6%) respectively. While the results of (T.BIL), (D.BIL) and (Ind.BIL) showed a significant improvement by (-33.3%, -28%, -35.6%) respectively. And a significant increase ($p \leq 0.01$) by (17.6%) in the values of glucose compared to the group treated with levofloxacin.

- ***Conclusion:*** The study's findings support the use of camel milk as an external antioxidant supplement to lessen the toxicity of levofloxacin.

Key Words: Fluoroquinolones, levofloxacin, glucose, camel milk, liver functions.

1. Introduction:

Fluoroquinolones (FQs) are nalidixic acid derivatives that have bactericidal activity against both gram-positive and gram-negative bacteria [1].

It is one of the most often used antibiotics, particularly for treating infections [2]. Levofloxacin (LFX) is a fluoroquinolone derivative of the second generation that is used to treat respiratory, urinary tract, genital, and skin infections [3-4]. The drug is also known by trade names: Volfan,Levox,Tavanic and Levaquin[1]. The duration of treatment ranges from 7-14 days, depending on the type and severity of the infection [5].

The Committee for Medicinal Products for Human Use (CMPH) confirmed on November 15, 2018, that the use of fluoroquinolone antibiotics should be limited in cases such as treating infections that may improve without treatment, treating non-bacterial infections, and treating recurrent lower urinary tract infection [6].

LFX has been demonstrated to disrupt the equilibrium of oxidants and antioxidants [3]. After 7-14 days of exposure, the adverse effects included hepatotoxicity and renal toxicity [1-2 ,7]. When antioxidant mechanisms are overwhelmed by reactive oxygen species due to medication toxicity, exogenous

antioxidant supplementation protects against oxidative damage is an effective external antioxidant supplement that may be used to reduce oxidative stress caused by a variety of ailments [4]. Camel milk is high in antioxidants, including lactoferrin, and contains a variety biologically active proteins, including lactoperoxidase, which has antibacterial and immunodeficiency properties [8-10]. It has demonstrated beneficial effects against drug-induced hepatic and renal damage in general [10-13]. Thus, the aim of the current study to Examine the therapeutic potential of camel milk to attenuate to reduce the toxicity of levofloxacin on some enzyme parameters in male albino rats.

2. Materials and Methods:

2.1. Animal and Dose Preparation:

2.1.1. Animal:

40male albino rats weighing (150-180g) were purchased from the animal house faculty of Science at King Saud University in Riyadh. They were housed in the postgraduate laboratory's animal house at Qassim University's biology department. All rats were kept in cages for one week of seven rats each at room temperature of (24-25°C), humidity of 50-60%, and light/dark cycle of 8/16 h, respectively, for adaptation to laboratory settings. Standard rat pellets and tap water were always accessible.

2.1.2. LFX:

(LFX) dose utilized in this study was calculated from the maximal therapeutic dose in humans using [14]. Sanofi-Aventis Arabia produced levofloxacin (LFX) (500 mg), which was bought from the drug world pharmacy in Qassim. In 0.1ml of distilled water, the appropriate dosage concentration of levofloxacin 500mg tablet was dissolved.The tablets were crushed each time they were used to make and store treatments in sealed sterile bottles.

2.1.3.CM samples source:

Fresh milk camel was brought from modern breeding farms in Qassim. Camel milk was collected daily for 28 days in sterile bottles and stored in cool boxes until used.

2.2. Experimental Design:

The animals were randomly parted into four groups with ten animals in each group:

- **1.Control group (n=10):** fed a normal diet and water.

- **2.LFX- group(n=10):** received LFX only at dose (100mg/kg body wt.) once a day for 10 days orally by gastric tube [15].
- **3. CM group(n=10):** received CM only orally (5ml/rat/day) for 15 successive days in drinking bottles [15].
- **4.LFX+CM group(n=10):** LFX (100mg/kg body wt.) received orally by gastric tube for 10 days [16] then followed with fresh CM in drinking bottles (5ml/rat/day) daily for 15 days [16]**.**

At the end of the study, rats fastened for 24 hours then blood was drawn from the animals by cervical dislocation after anasethia. Sera separated and kept at -80C umtil used.

2.3. Analytical procedure:

2.3.1. Estimation of biochemical parameters:

Serum values of GOT, GPT, (T.BIL), (D.BIL), and (Ind.BIL) were estimated by using "Human kits" that were purchased from Ejadah Medical Company, for scientific medical materials, chemical and laboratory and hospital equipment, Riyadh according to previous methods [17-18]. By using a spectrophotometer device Agilent spectrophotometer (UV /Visible) Cary 60.

2.4. Statistics:

Comparisons between means were carried out using one way analysis of variance (ANOVA) followed by post hock (Tukey)and the Statistical Analysis System's General Linear Model Procedure (SAS 1982). Multiple comparisons test at $P \leq 0.05$ according to previous [19]. This was carried out using Statistical Analysis System (SAS) program software; copyright©1998 by SAS institute Inc., Cary, NC, USA.

3. Results and discussion:

The obtained data in table 1 & figure 1 showed that oral treatment of healthy adult male rats with camel milk (5ml/rat/day) orally for 15 successive days in drinking bottles did not deteriorate ($p < 0.01$) **GOT** activity when this group compared to the corresponding value of the control animal group (65.2 Vs 64.6). In contrast, oral administration of male albino rats with therapeutic dose of levofloxacin by gastric tube (100mg/kg body wt.) for ten days resulted in a more significant ($p \leq 0.01$) increase (42.4 %) in the value of serum **GOT** activity (92 Vs 64.6) when was compared to the control animal group. Interestingly, the oral administration of camel milk to the levofloxacin- treated rats for 15 consecutive days revealed a less significant ($p \leq 0.01$) decline (-7.6%) in the elevated values of **GOT** (85 Vs 92) in comparison to LFX-treated animals 'group **(Table 1 and Figure 1).**

While the oral treatment of normal adult male rats with camel milk (5ml/rat/day) orally for 15 successive days in drinking bottles did not deteriorate ($p< 0.01$) **GPT** activity when this group compared to the corresponding value of the control animal group (33.4Vs 33.2). In the contrary, oral administration of male albino rats with therapeutic dose of levofloxacin by gastric tube (100mg/kg body wt.) for ten days resulted in a more significant ($p\leq0.01$) rise (64.5 %) in the value of serum **GPT** activity (54.6 Vs 33.2) when was compared to the control animal group. While the oral administration of camel milk to the levofloxacin-treated animals for 15 consecutive days exhibited a less significant ($p\leq0.01$) decline (-13.6%) in the elevated values of **GPT** (47.2 Vs 54.6) in comparison to LFX-treated animals 'group **(Table 1 and Figure 2).**

The results of the current study on the toxicity of levofloxacin are consistent with the criteria for a significant increase in GOT and GPT levels [7,20-21]. In contrast, a study found a significant increase ($P \leq0.05$) after oral administration of two doses of Levo after only 4 weeks of treatment, but no significant difference after 2 weeks [22].On the other hand, a study revealed a decrease in GOT levels at a dose of LFX on days 7 and 14 of the study, Which contradicts the study result [23].GOT and GPT are enzymes that are essential for liver function and integrity, and they are released into circulation when an organ such as the liver is injured, LFX may increase the activity of these enzymes owing to their release in reaction to tissue damage caused by blood cells being destroyed as is usual and expected leukocytes, liver cells, red blood cells, and other types of cells [20]. The findings of our investigation support the same effects of camel milk on the substantial decreasing impact in levofloxacin-treated rats as well as the findings of non-significant differences for camel milk-treated rats on the parameters of GOT and GPT [12-13,24-25]. The results could be related to Characteristics of camel milk:Casein, LAB, active peptides, and whey proteins, notably lactoferrin, are the primary components of camel milk that include antioxidant characteristics. As an antioxidant, it lowers the oxidative stress associated with many illnesses [8,10].

The oral treatment of normal adult male albino rats with camel milk (5ml/rat/day) orally for 15 successive days in drinking bottles did not induce any significant change ($p< 0.01$) in the levels of serum **T. Bilirubin** when values of this group compared to the corresponding value of the control animal group (1.04 Vs 1.05). While the oral injection of male albino rats with therapeutic dose of levofloxacin by gastric tube (100mg/kg body wt.) for ten days resulted in a more significant ($p\leq0.01$) elevation (151.4 %) in the values of serum **T. Bilirubin** (2.64 Vs 1.05) when was compared to the control animal group. While the oral treatment of camel milk to the levofloxacin-treated animals for 15 consecutive days declared significant ($p\leq0.01$) improvement (-33.3%) in the elevated values of serum **T. Bilirubin** (1.76 Vs 2.64) in comparison to LFX-treated animals 'group **(Table 1 and Figure 3).**

The oral treatment of control adult male albino rats with camel milk (5ml/rat/day) orally for 15 successive days in drinking bottles did not reveal any significant change ($p< 0.01$) in the levels of serum **D. Bilirubin** when values of this group compared to the corresponding value of the control animal group (0.321 Vs 0.320). While the oral treatment of male albino rats with therapeutic dose of levofloxacin by gastric tube (100mg/kg body wt.) for ten days resulted in a more significant ($p\leq0.01$) increase (154.4 %) in the values of serum **D. Bilirubin** (0.814 Vs 0.320) when was compared to the values of control animal group. While the oral treatment of camel milk to the levofloxacin-treated animals for 15 consecutive days declared significant ($p\leq0.01$) improvement (-28%) in the elevated values of serum **D. Bilirubin** (0.586 Vs 0.814) in comparison to LFX-treated animals 'group **(Table 1 and Figure 4**).

The oral administration of camel milk (5ml/rat/day) orally for 15 successive days in drinking bottles to the healthy male albino rats did not reveal any significant change ($p< 0.01$) in the levels of serum **Ind. Bilirubin** when values of this group compared to the corresponding value of the control animal group (0.724 Vs 0.730). While the oral injection of male albino rats with therapeutic dose of levofloxacin by gastric tube (100mg/kg body wt.) for ten days resulted in a more significant ($p\leq0.01$) increase (148.8 %) in the values of serum **Ind. Bilirubin** (1.816 Vs 0.3730) when was compared to the values of control animal group. While the oral administration of camel milk to the levofloxacin-treated animals for 15 consecutive days showed significant ($p\leq0.01$) improvement (-35.6%) in the elevated values of serum **Ind. Bilirubin** (1.17 Vs 1.816) in comparison to LFX-treated animals 'group **(Table 1 and Figure 5).**

The effects of levofloxacin in significantly increasing bilirubin levels are consistent with[7,20,23]and this is may be related to hepatic disorders: necrosis, gallbladder, nucleus hypertrophy & decreased ability of hepatocytes to absorb drugs due to inflammation or hepatic cirrhosis[7,23].As a result, both cases of metabolic dysfunction and excessive bilirubin production Due to flaws in its absorption, storage, and excretion in liver, result in a rise in serum unconjugated bilirubin[26].

The treated CM in our study showed a decrease in bilirubin levels agree with the results [12,24-25], which may indicate an improvement in liver function; the toxicity was reduced and the parameters were maintained close to control in both groups may be due to the higher levels of C, B2, and E vitamins in CM[25], the results of the effect of both groups CM and CM+LFX-treated animal on bilirubin parameters are consistent with studies that revealed a significant decrease in bilirubin after combined treatment with different substances with camel milk[24-25].

The oral administration of camel milk (5ml/rat/day) orally for 15 successive days in drinking bottles to the healthy male albino rats did not reveal any significant change ($p\leq 0.01$) in the levels of serum **glucose** when values of this group compared to the corresponding value of the control animal group (105 Vs 105.2). While the oral injection of male albino rats with theracomparedof levofloxacin by gastric tube

(100mg/kg body wt.) for ten days resulted in a more significant ($p \leq 0.01$) decline (-28.9 %) in the values of serum **glucose** (74.8 Vs 105.2) when was compared to the values of control animal group. While the oral administration of camel milk to the levofloxacin-treated animals for 15 consecutive days showed significant ($p \leq 0.01$) rise (17.6%) in the elevated values of serum **glucose** (88 Vs 74.8) in comparison to LFX-treated animals 'group **(Table 2 and Figure 6).**

The results in this study are consistent with the results of previous studies that revealed a significant glucose-lowering effect as a result of levofloxacin [2,27], Contrarily, the research found that those who used Levo experienced hypoglycemia as a rare side effect (0.1%) [27].On the other hand, hyperglycemia was more prevalent than hypoglycemia although the study revealed that other elements, such as stress factors and the concurrent use of steroid medications, also had a role in these elevated levels with Levo therapy [4]. This is in line with another study, which found that a dosage of LFX raised blood glucose levels on day 14 of the experiment—the drop, however, happened on day 7 [29]. Levofloxacin causes a disturbance in the structure of cell membranes, which is indicative of oxidative stress [28], thus the effect of LFX on glucose deficiency may be attributed to levofloxacin's blocking of ATP-sensitive potassium channels in pancreatic beta cells, which depolarizes the beta cell membrane and causes the opening of calcium-dependent channels. On excretion and insulin release, which causes hypoglycemia [27].

Based on the considerable reduction in glucose levels caused by CM in rats given LFX treatment, which supports [13,30]. And what explains the results of the significant effect of camel milk on animals treated with levofloxacin, and the lack of significant differences in animals treated with camel milk only in this study, it was discovered that some camel milk proteins had an amino acid sequence that is high in half-cysteine and comparable to the peptides in the insulin family, therefore, the presence of insulin-like molecules in camel milk and the concentration of immunoglobulins in the cell may be responsible for the findings of this study on glucose parameters [29].

Table (1): Effect of oral administration of Camel milk on serum liver function of Levofloxacin-treated group (M ±SE).

Parameters / Groups		GOT [U/L]	GPT [U/L]	T. Bili (mg/dL)	D. Bili (mg/dL)	Ind. Bili (mg/dL)
Control	M ±SE	64.6±0.4^{A}	33.2±0.8^{A}	1.05±0.01^{A}	0.320±0.01^{A}	0.730±0.02^{A}
CM	M ±SE	65.2±0.8^{A}	33.4±0.4^{A}	1.04±0.01^{A}	0.321±0.01^{A}	0.724±0.01^{A}
CM	% Change A	0.93 %	0.6%	-1%	0.3%	-0.8%
LFX	M ±SE	92±0.7^{B}	54.6±0.7^{B}	2.64±0.07^{B}	0.814±0.04^{B}	1.816±0.07^{B}
LFX	% Change A	42.4 %	64.5%	151.4 %	154.4%	148.8%

LFX+CM	M ± SE	85±0.3 c	47.2±0.6 c	1.76±0.7 c	0.586±0.1 C	1.17±0.05 c
	% Change B	-7.6%	-13.6%	-33.3%	-28%	-35.6%

Data are presented as mean ± standard error of mean. Data were subjected to one-way ANOVA followed by Duncan post hoc test at p≤0.01. Within the same column, means with different superscript letters are significantly different. CM (camel milk) & LFX (levofloxacin).

Table (2): Effect of oral administration of Camel milk on serum glucose level(mg\dL) of Levofloxacin-treated group (M ±SE).

Groups / Parameters	Control	CM	LFX	LFX+C M
M ±SE	105.2±0.9 A	105±0.7 A	74.8±1.1 B	88±0.7 C
% Change A	--------	-0.2%	-28.9%	----
% Change B	----	----	------	17.6

Data are presented as mean ± standard error of mean. Data were subjected to one-way ANOVA followed by Duncan post hoc test at p≤0.01. Within the same column, means with different superscript letters are significantly different. CM (camel milk), LFX (levofloxacin).

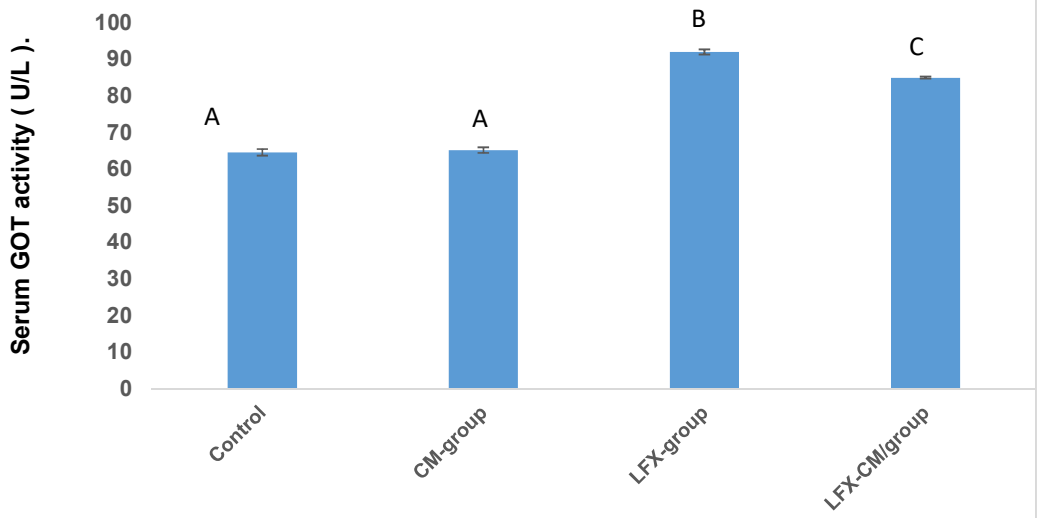

Fig.1:Means of serum GOT activity (U/L) of adult male albino rat *Rattus norvegicus*.

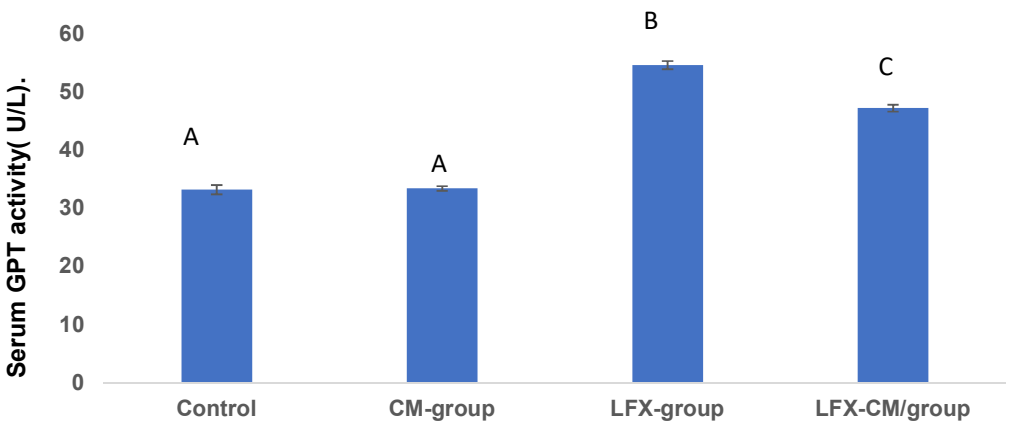

Fig.2:Means of serum GPT activity (U/L) of adult male albino rats *Rattus norvegicus*.

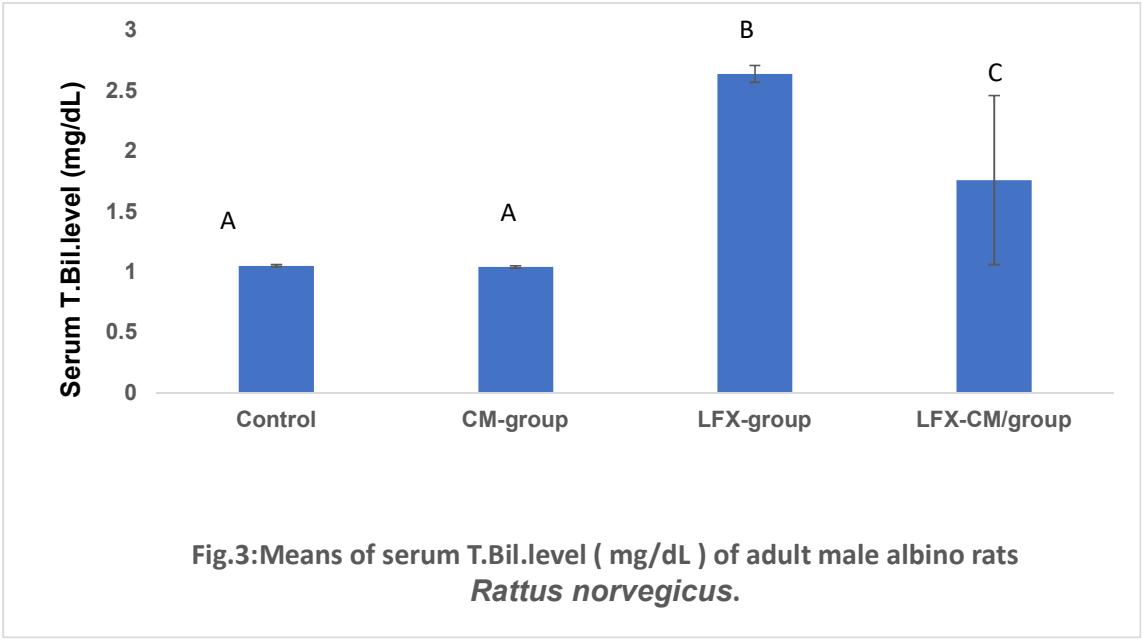

Fig.3:Means of serum T.Bil.level (mg/dL) of adult male albino rats *Rattus norvegicus*.

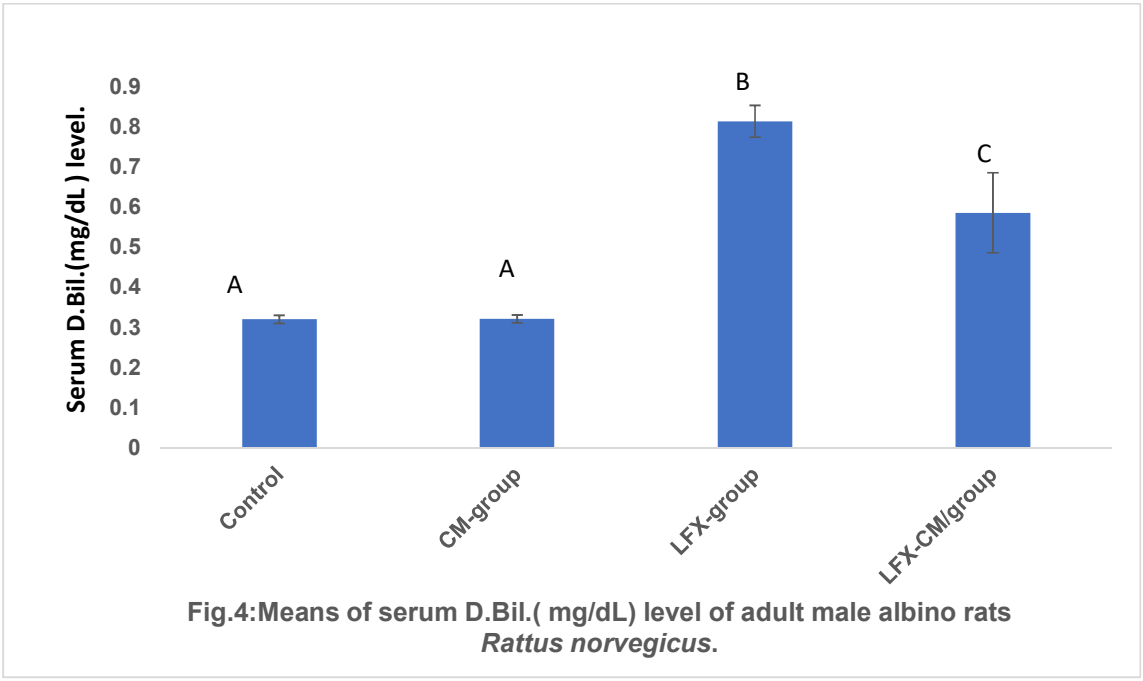

Fig.4:Means of serum D.Bil.(mg/dL) level of adult male albino rats *Rattus norvegicus*.

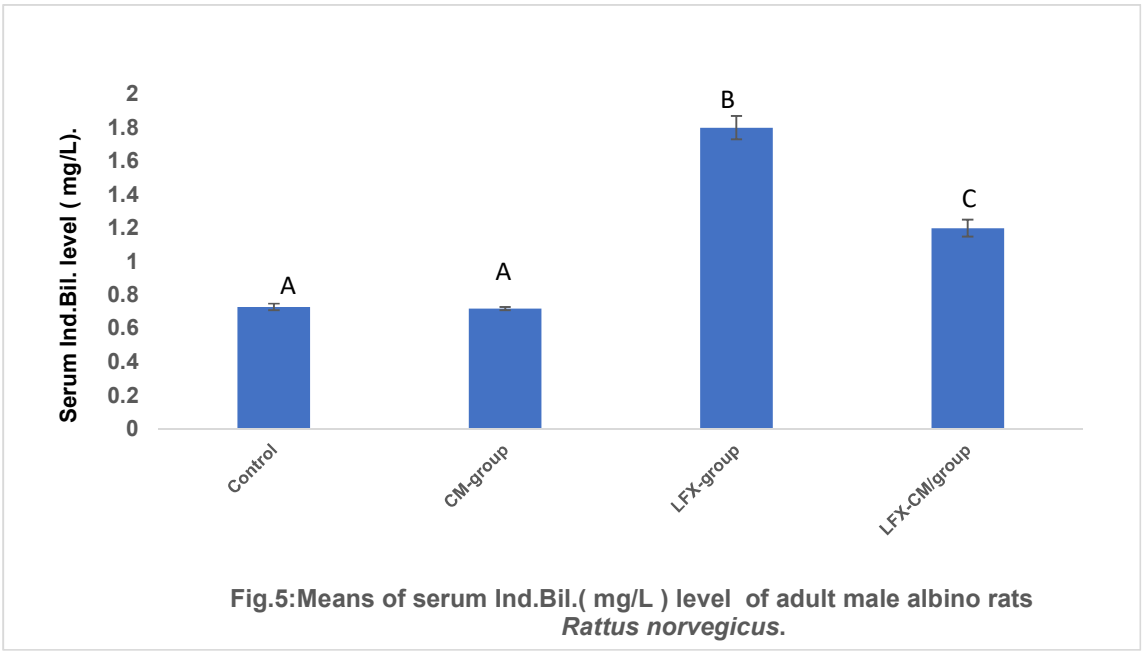

Fig.5:Means of serum Ind.Bil.(mg/L) level of adult male albino rats *Rattus norvegicus*.

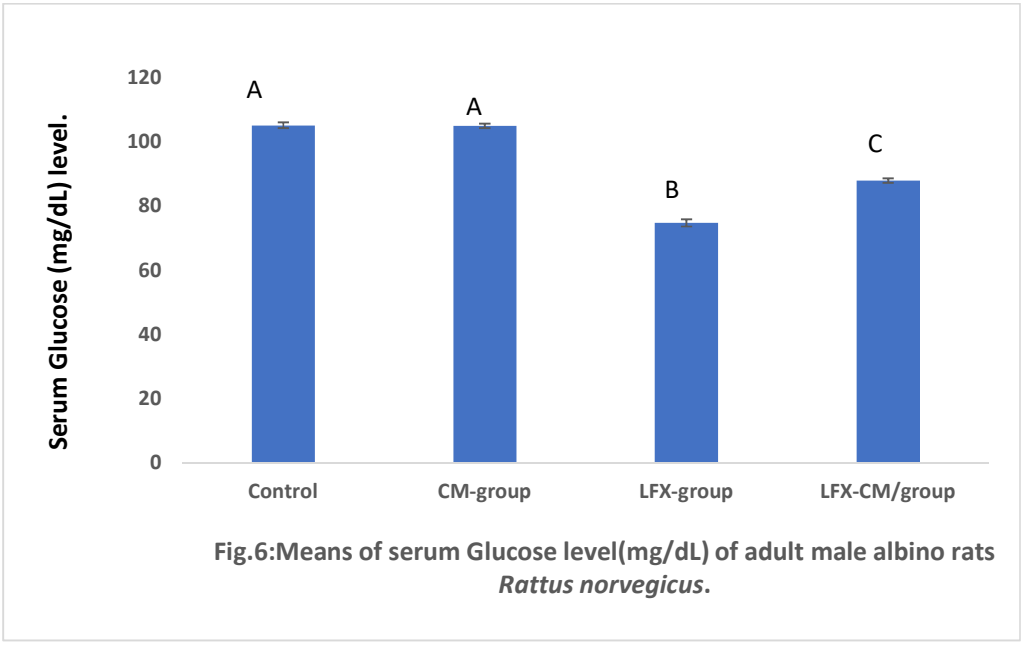

Fig.6:Means of serum Glucose level(mg/dL) of adult male albino rats *Rattus norvegicus*.

Conclusion:

Based on the findings, levofloxacin caused liver toxicity that was evidenced by increasing the values of liver function. Camel milk treatment for 15 days effectively reduced the toxic signs of oral

levofloxacin administration, suggesting that camel milk may be used as an external supplement to lessen LFX-induced toxicity.

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