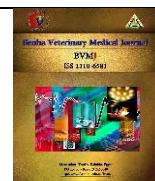




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### Original Paper

## In Vivo synergistic effect of curcumin in combination with marbofloxacin against *E coli* infection in rats

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### ABSTRACT

This study aimed to evaluate the potential synergistic effect of curcumin in combination with marbofloxacin against *E coli* infection in rats. Twenty-five male rats were segregated equally into five groups of Wister albino rats; Group (1) acted as the control group (normal saline only, 0.2 ml); Group (2) was given *E. Coli*. Group (3) included rats infected with *E. coli*, and were administered an oral dose of marbofloxacin (5 mg/kg b.wt) for 5 days; Group (4) also administered the same oral dose of marbofloxacin daily for 5 days. . Group (5) rats were treated to *E. coli* by a single intraperitoneal injection of 2 ml of ( $1 \times 10^9$ ) of colony forming units/ml. Following that, rats were received oral dosages of both marbofloxacin and curcumin (20 mg/kg b.wt) Serum biochemical analysis revealed that in marbofloxacin treated group, albumin levels were significantly ( $P < 0.05$ ) decreased mean while transaminases (ALT and AST), alkaline phosphatase (ALP), total bilirubin, triglycerides, and cholesterol were significantly increased during marbofloxacin treatment. On the other hand, rats treated with marbofloxacin and curcumin showed noticeably decreased levels of triglycerides, cholesterol, and transaminases (ALT and AST), and significantly increased levels of albumin compared to rats that received marbofloxacin only. Histopathological examinations of liver tissue revealed severe liver damage in *E.coli* infected rats and counteracted by marbofloxacin and more treated through curcumin combination. In conclusion, the administration of curcumin in combination with marbofloxacin had a potential synergistic effect on the liver damage caused by *E. coli* infection in rats.

## 1. INTRODUCTION

A class of medications known as the broad spectrum, systemic antibacterial fluoroquinolones has been used extensively to treat respiratory and urinary tract infections. Fluoroquinolones have an effect on a wide range of aerobic Gram-positive and Gram-negative organisms. *Streptococcus pneumoniae* and *viridans*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Nocardia species*, and *Staphylococci* whether or whether they produce penicillinase are examples of gram-positive bacteria. Gram negative bacteria include *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Vibrio species*, and *Neisseria meningitides* (Elgendy et al., 2023). The mechanism of action of fluoroquinolones is believed to be through inhibition of type II DNA topoisomerases, or gyrases, which are essential for bacterial mRNA transcription and DNA replication (Moseley et al., 2013). The fluoroquinolones that are currently easily accessible in the United States include ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. These medications are readily absorbed, well tolerated, and rarely cause negative side effects when taken orally. The removal of several quinolones and fluoroquinolones, including temafloxacin (1992), gatifloxacin (2006), and trovafloxacin (1999), occurred in response to unprompted concerns of substantial adverse effects, including hepatotoxicity. Based on calculations, idiosyncratic liver harm in exposed persons appears to occur seldom with current fluoroquinolones (1:100,000). The idiosyncratic

liver injury caused by fluoroquinolones may be a "class" effect; the injury pattern is the same, with acute and often severe hepatocellular injury happening 1-4 weeks after the treatment starts (Elgendy et al., 2023). The two fluoroquinolones that are most often used and have been linked to liver damage are ciprofloxacin and levofloxacin. Liver enzymes mildly increase in 1% to 3% of patients using ciprofloxacin, norfloxacin, or ofloxacin (MacDougall et al., 2018).

As a second-generation fluoroquinolone, levofloxacin has a notable post-antibiotic impact and is a broad-spectrum, concentration-dependent bactericidal antibiotic (Rusu etL., 2023). It works by blocking the activity of bacterial DNA-gyrase, which stops DNA synthesis and supercoiling (Collin et al., 2011). It is equally effective against a variety of Gram-positive and Gram-negative bacteria as fluoroquinolones in terms of antibacterial activity (Lungu et al., 2022) , Orally administered marbofloxacin is quickly and effectively absorbed. Similar to other fluoroquinolones, ribofloxacin can accumulate to high amounts in a variety of tissues' cells, In addition to being present in breast milk and crossing the placenta, it is also discovered in trace amounts in the cerebral spinal fluid, marbofloxacin is excreted unaltered in urine and bile/feeces, with the liver only processing a little portion of it (Pallo-Zimmerman et al., 2010). It is well known that the quinolone class of drugs has been shown to induce arthropathy in young animals of various species, including juvenile rats, along with additional symptoms such as

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articular cartilage erosions in weight-bearing joints (Kashida and Kato 1997). However, the evidence of abnormal cartilage appears to be dose-related. It's also important to keep in mind that fluoroquinolone use has not been recommended as a first line of treatment for pregnant, lactating, or juvenile rats (less than 4 months old) due to the possibility of cartilage deformities (Egerbacher et al., 2000). *E. coli* is a major contributor to neonatal calve diarrhea (NCD) and a costly danger to the world's dairy and livestock industries (Lorenz et al., 2006). Newborns (9–10 days old) with colibacillosis typically have watery, white, or yellowish diarrhea, a rapid onset, and a high mortality rate. After giving birth, affected calves usually experience diarrhea for 36–72 hours before passing out in two to three days (Radostits et al., 2007).

*Curcuma longa* Linn (Zingiberaceae) rhizome is the source of curcumin (diferuloylmethane), the yellow-colored component of turmeric (Raviella et al., 2020). Curcumin has anti-inflammatory, immunomodulatory, and antiatherogenic qualities. It is a potent inhibitor of many enzymes that generate reactive oxygen species. In traditional herbal therapy, it has been used to treat inflammatory disorders and liver problems (Stickel et al., 2007). Curcumin efficiently scavenges reactive oxygen species, including hydroxyl and superoxide anion radicals (Borra et al., 2014). It has also been reported to stop erythrocyte lipid peroxidation. Furthermore, curcumin protected the lungs of rats against lung damage brought on by paraquat and myocardial ischemia brought on by the generation of free radicals (Otuochere et al., 2014).

This study aimed to investigate the protective activity of curcumin and marbofloxacin combinations in *E. coli*-infected rats.

## 2. MATERIAL AND METHODS

### Approval Ethics

The Research Ethical Committee, Faculty of Veterinary Medicine, Benha University approved this study (Approval No BUFVTM 02-03-24).

### 2.1. Chemicals

Wisdom Pharmaceutical Co., Ltd. was the Chinese provider of pure powder marbofloxacin. Fluka Co. produced curcumin (purity~ 99%), which was purchased from El-Gomhouria Co. for Chemical Trading, Medicine, and Medical Appliances, Egypt. The Animal Health Research Institute provided *E. coli*, while Biodiagnostic Co. provided the analytical kits.

### 2.2. Experimental design

Twenty-five male Wister Albino rats, weighing between 185 and 200 grams, were obtained from Animal House, Faculty of Veterinary Medicine, Benha University. Rats were kept in constant environmental and nutritional circumstances for the duration of the trial. Before the trial started, the animals had fifteen days for adaptation. Twenty-five male rats were randomly divided into five main groups including five rats each:

Group 1: rats were given an oral dose of 0.2 milliliters of saline as a control.

Group 2: rats were administered a single intraperitoneal injection of *E. Coli* 2 ml of ( $1 \times 10^9$ ) of colony forming unit/ml (Radwan et al., 2021).

Group 3: rats were administered an oral course of marbofloxacin (5 mg/kg b.wt) (Chauhan et al., 2019) for five

days after receiving a single intraperitoneal injection of *E. coli* 2 ml of ( $1 \times 10^9$ ) colony forming units/ml].

Group 4: rats were given oral marbofloxacin (5 mg/kg b.wt) for five days.

Group 5: rats were treated to *E. coli* by a single intraperitoneal injection of 2 ml of ( $1 \times 10^9$ ) of colony forming units/ml. Following that, rats were received oral dosages of both marbofloxacin and curcumin (20 mg/kg b.wt) for a consecutive five days (Ashleigh et al., 2018).

### 2.3. Blood sampling

Blood samples were taken from each group on the first, seventh, and fourteen-days post-therapy. For hematological and biochemical examinations, two blood samples were taken from the median canthus of each set of rats' eyes. The first blood sample was taken to separate the clear serum for biochemical analysis without the use of an anticoagulant.

### 2.4. Serum biochemical analysis

Serum was collected by centrifugation at 3000 RPM for 15 minutes. Separated serum was kept in deep freeze at -20 °C until utilized for serum biochemical analysis. According to (Egerbacher et al., 2000), a spectrophotometer and specific kits from the Biodiagnostic company were used to determine serum ALT and AST colorimetric ally. A kit from (Biodiagnostic Co.) was used to assay serum alkaline phosphatase in compliance with (Chairman et al., 1983). Colorimetric measurements of serum albumin were performed in compliance with (Doumas et al., 1981). Triglycerides and cholesterol were estimated in compliance with (Rifal et al., 1999). Total bilirubin was measured by kits from Biodiagnostic company in compliance with Hargreaves (1965).

### 2.5. Histopathological studies

Tissue specimens were taken from the livers of rats in different groups. These specimens were fixed in 10% formol saline for 24 hours. A tissue paraffin sections were routinely prepared, and stained with hematoxylin and eosin (Bancroft and Gamble, 2008).

### 2.6. Statistical analysis data

Statistical analysis was carried out using the Statistical Package for Social Science Released (2009). The means were compared using a one-way ANOVA, and Duncan's multiple range test was then performed Duncan (1955). A significance level of  $P \leq 0.05$  was considered.

## 3. RESULTS

### 3.1. Biochemical findings

Oral administration of a therapeutic dose of marbofloxacin (5 mg/kg body weight for 5 consecutive days) Led to a significant increase in AST, ALT, ALP and total bilirubin and decrease in albumin levels in non-infected rats treated with marbofloxacin (group 4) and infected rats with *E. Coli* either treated with marbofloxacin or non-treated (group 2 and 3) when compared with non-infected, non-treated rats (group 1) at (1, 7, and 14 days) post-treatment. While, there was a significant decrease of AST, ALT, ALP, and total albumin and increase in albumin level in infected rats with *E. Coli*, treated with marbofloxacin and curcumin (group 5) when compared with non-infected rats treated with marbofloxacin (group 4) and infected rats with *E. Coli* either treated with marbofloxacin or non-treated (group 2 and 3) and the result return to normal values as in non-infected, non-treated group (control group) (fig. 1 & 2).

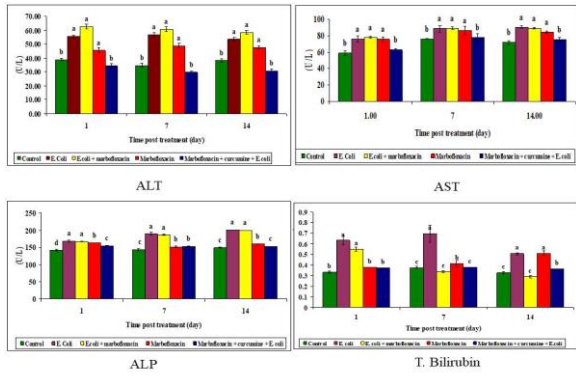


Figure (1): The effect of marbofloxacin alone and in combination with curcumin on the levels of ALT, AST, ALP, and total bilirubin in both healthy and experimentally infected rats with *E. coli*.

In both healthy and experimentally infected rats with *E. coli*, oral administration of a therapeutic dose of marbofloxacin (5 mg/kg body weight for 5 consecutive days) At 1<sup>st</sup>, 7<sup>th</sup>, 14<sup>th</sup> days post treatment there was a significant increase in serum cholesterol triglycerides levels in all groups non infected treated with marbofloxacin (group 4), non-treated infected with *E. Coli* (group 2) and infected with *E. Coli* treated with marbofloxacin (group 3) when compared with non-infected non treated group (control group). Otherwise, Infected rats treated with marbofloxacin and protected with curcumin showed a significant decrease in serum cholesterol and triglycerides levels when compared with other groups non-treated infected with *E. Coli*, non-infected treated with marbofloxacin or infected and treated with marbofloxacin and the result return to normal values as in non-infected, non-treated group (control group).

When curcumin and marbofloxacin were administrated together, there was a considerable decrease in these previous lipid profile indicators (fig. 2).

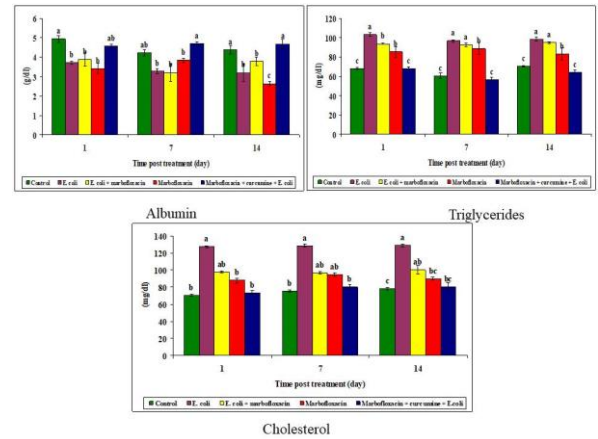
### 3.2. Histopathological findings

The histopathological analyses of the liver confirmed the observed Serum biochemical findings (Figures 3). The majority of the liver sections of the control rats had normal hepatic cells, portal regions, and central veins. However, the examined liver of rats infected with *E coli* showed signs of severe liver congestion, including hepatic cell necrosis, granular and vacuolar degeneration.

In the portal sites, congested portal blood arteries, proliferation of the bile duct epithelium with newly formed bile ductules, and portal edema were also found. The tissue sections of the liver from the Marbofloxacin control group only revealed degenerative alterations, in a few hepatocytes. Almost hepatocytes were more or less normal. Rats treated with Marbofloxacin and infected with *E. Coli* showed good repair of hepatic parenchymal cells in their livers, with only slight central vein congestion and mild necrobiotic changes of scattered hepatic cells. In the portal sites, there was bile duct congestion along with significant edema. Examination of the livers of rats treated with Curcumin and Marbofloxacin after contracting an *E. coli* infection showed slight portal edema, hepatic sinusoidal dilatation, portal congestion, with the presence of a few apoptotic cells and mild necrobiotic alterations of the hepatic cells. The majority of the liver sections of the control rats had normal hepatic cells, portal regions, and central veins. However, the examined liver of rats infected with *E coli* showed signs of severe liver congestion, including hepatic cell necrosis, granular and vacuolar degeneration. In the portal sites, congested portal blood arteries, proliferation of the bile duct epithelium with newly formed bile ductules, and portal edema were also found.

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Figure (2): The effect of marbofloxacin alone and in combination with



curcumin on albumin, triglycerides, and cholesterol levels of healthy and experimentally infected rats with *E. coli*.

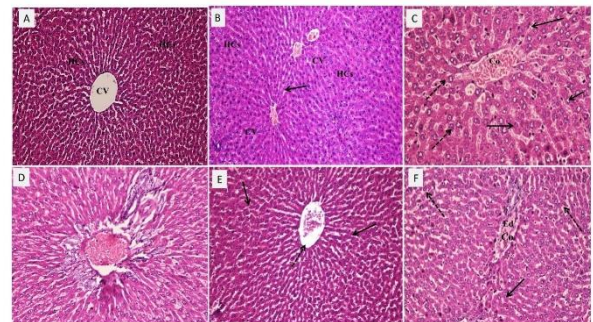


Figure (3): shows the histopathological investigation of the liver in different groups as follows; A (Control negative group: Liver of rat in control group showing normal hepatic cells (HCs) and central vein (CV). Group B (Marbofloxacin treated rats): Rat liver administered with Marbofloxacin showing normal hepatic cells (HCs), normal portal region (arrow), and normal central vein (CV). Group C: infected control positive group: Rat liver infected with *E. Coli* displaying considerable congestion of the hepatic sinusoids (arrow) and central vein (Co), as well as noticeable hepatic cell necrosis and degeneration (dashed arrow and short arrow, respectively). Group D: *E. Coli*-infected rat treated with Marbofloxacin; Showed excellent recovery of the hepatic parenchymal cells, with only slight central venous congestion (dashed arrow) and mild necrobiotic alterations (arrow) of scattered hepatic cells. Group E & F *E. Coli* and treated with Curcumin and Marbofloxacin demonstrated rat liver infected with *E. Coli* and treated with Curcumin and Marbofloxacin demonstrating a few apoptotic cells (arrow), and mild necrobiotic alterations of the hepatic cells. (H&E, X200).

## 4- DISCUSSION

The effects of marbofloxacin on liver function were evaluated using a 5-day oral regimen at a therapeutic dose of 5 mg/kg body weight. The levels of AST, ALT, ALP, and total bilirubin, were significantly increased while serum albumin was significantly decreased in both experimentally and normally infected rats with *E. coli*, indicating acute

hepatic hepatotoxicity. The results were consistent with the findings of Orman et al. (2011), Mousa et al. (2011), and El-sayed et al. (2019). After administering marbofloxacin, a significant increase in liver enzyme activity, which could be a sign of hepatic damage (Mousa et al., 2011). In addition, Orman et al. (2011) reported a steady increase in the serum alkaline phosphatase. However, EL. Sayed et al. (2019) discovered that the marbofloxacin-treated group significantly underwent reductions in total protein, and albumin content when compared to the control group. In twenty male Wistar rats, Olayinka et al. (2015) observed that the administration of levofloxacin, a member of the fluoroquinolones group, at different doses (5, 10, and 20 mg/kg/b.w.) for seven days significantly increased the plasma activities of ALP, ALT, and AST, when compared to the control.

Additionally, in the present study total bilirubin levels in the marbofloxacin treated groups were significantly higher than those in the control groups. In comparison to the control group, also in treated groups a significant increase in plasma total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides was recorded. According to Mousa et al. (2011) revealed increased levels of alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase in marbofloxacin treated group.

The oral treatment of 20 mg/kg body weight curcumin and 5 mg/kg body weight marbofloxacin for 5 days resulted in a notable decrease in serum levels of alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase, indicating a protective effect on hepatocytes in rats infected with *E. coli*. The marbofloxacin-treated *E. coli*-infected rats showed a substantial decrease in their levels of cholesterol and triglycerides and an increase in albumin at days 1, 7, and 14 post-treatment as compared to the non-infected rats. Girish & Pradhan (2012) found that curcumin can be used as an active phytochemical to prevent toxic liver injury by three different mechanisms: lowering lipid peroxidation, increasing the antioxidant defense system, or stimulating hepatocyte regeneration. These results show that curcumin protects the liver from the hepatotoxic effects of cisplatin. Moreover, Otuechere et al. (2014) proposed that curcumin shielded rats receiving propanil from liver damage. The results of this study showed that AST and ALT activities were elevated by propanil injection. Lipid peroxidation has also been proposed as a potential factor in the process of hepatic development.

In the present study, the group using marbofloxacin had significantly higher levels of triglycerides and cholesterol than the group taking curcumin, and these results come in agreement with the study done by Hamdy et al. (2023) investigating the protective effect of curcumin against liver injury and recorded a significant decrease in levels of ALT, AST, ALP, cholesterol, and triglycerides in curcumin-treated groups.

Microscopic examination of the majority of liver sections in the control group revealed that the livers contained normal hepatic cells, portal regions, and central veins, which is consistent with the biochemical results. In this study tissue sections of the liver of the Marbofloxacin control group showed near to normal histological appearance, only degenerative changes of few hepatocytes was noticed. This is consistent with a study by Al-shawi (2012) that showed the administration of therapeutic doses of ciprofloxacin causes histopathological changes in the liver, such as degenerative changes and necrosis, as well as a study by Abdullah et al. (2021) that showed the effect of levofloxacin of some body tissue, such as the liver, showing congestion of blood vessels in the portal area and central veins with

inflammatory cells infiltrating. In this study the rats infected with *E. coli* showed signs of severe liver congestion, including hepatic cell necrosis, granular and vacuolar degeneration, and substantial congestion of the hepatic sinusoidal and central veins.

The histological picture of the liver of the *E. coli*-infected rats treated with Marbofloxacin and curcumin, on the other hand, showed the ameliorative effect of curcumin. These results come in agreement with Adikwu (2012) who mentioned in their study fluoroquinolones Reported Hepatotoxicity that liver biopsy revealed extensive hepatocellular necrosis involving zones 3 and 2 of hepatic acini and a mixed inflammatory infiltration containing abundant eosinophils. The liver architecture was nearly normal, and the animals treated with curcumin demonstrated a significant improvement in liver picture. These findings are consistent with the findings of Girish & Pradhan (2012), Basol et al., (2018), Tokaç et al., (2013), Kim et al., (2016). These data showed a strong correlation with the biochemical results, providing convincing proof that curcumin administration improved both the hepatic architecture and liver function.

## 5. CONCLUSIONS

It could be concluded that the *E. coli* infection was associated with severe liver damage and co-administration of curcumin with marbofloxacin had a potential synergistic effect of this hepatic injury in rats.

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