

Research Article

Evaluation of the effectiveness of levofloxacin detrimental effects on liver tissues and biochemical markers in male white rats using aqueous ginger extract (*Zingiber officinale* Rosce)

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Abstract:

The order to lessen the effects of the antibiotic levofloxacin on male white rats weighing 150–200 g, the study sought to ascertain how well secondary chemicals in the aqueous ginger extract worked. A total of a Thirty dult rats include six equal groups, G 1 as e control. G 2, 3, 4, 5, 6 was dosed with (levofloxacin 16 mg/kg , ginger extract 100 mg/kg + 16 mg/kg , extract ginger 300 mg/kg + 16 mg/kg, extract ginger 100 mg/kg , extract ginger 300 mg/kg) respectively, statistical of results explained a significant $p \leq 0.05$ with liver weight when comparing the antibiotic treated rats with the control group and other experimental groups. Not significant was showed between groups treated with ginger at concentrations of 100 and 300 mg/kg when compared with others.

Biochemical parameters represented by liver enzymes ALT, AST, and GGT a significant $p \leq 0.05$ with treated with levofloxacin, while groups treated with ginger extract did not show any significant difference. As for the histopathological changes, microscopic examination revealed several histopathological changes livers of male rats given levofloxacin treatment compared with control and other groups. However, the histological sections livers treated with the antibiotic + ginger extract at concentrations of 100 and 300 mg/kg did not show histopathological changes, thereby, conclude that aqueous ginger extract at a concentration of 300 mg/kg contributes significantly to minimizing liver damage and preserving the integrity of liver enzymes and cell membranes, whereas 100 mg/kg of ginger extract resulted in very slight cellular alterations.

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Introduction

Levofloxacin (LFX) is a wide spectrum antibiotic from fluoroquinolones and is the S-isomer of ofloxacin, Its antibacterial activity against G⁺ve, G⁻ve and anaerobic bacteria is about twice that of ofloxacin when rapidly absorbed orally, It has a high concentration in tissues and fluids its Age, gender, and ethnicity have little effect on pharmacokinetics; however, variations in body mass and renal function do, It is widely used today in both human and veterinary applications as an

antibacterial agent [1]. It is often used to treat vaginal and respiratory tract bacterial infections especially when used for prolonged periods and at high doses Side effects commonly manifested include gastrointestinal and neurological disorders significantly affecting the skin [2].

Some studies have confirmed that taking levofloxacin in high doses induces hepatic and renal toxicity by affecting organ tissues and causing inflammation that generates reactive oxygen species (ROS) in the mitochondria which area associated with epatictoxicity [3].

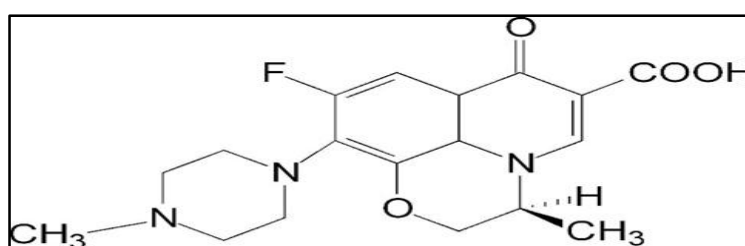


Figure (1): The chemical structure of levofloxacin [4].

Currently, the use of alternative medicine such as medicinal herbs is preferred in treating chronic diseases because they have fewer side effects than chemical drugs and are less expensive Medicinal plants are beneficial for treating many diseases by producing secondary metabolic compounds such as proteins, alkaloids, steroids, flavonoids, phenolic compounds, vitamins, and others [6].

These compounds possess potential antioxidant capabilities to reduce oxidative damage caused by free radicals, Gingers medicinal plants which contain secondary components like flavonoids and polyphenols, which have the ability to inhibit free radicals, Ginger has a long history in traditional Chinese

medicinedating back 2000 years [7].

To treat many diseases represented by conditions such as headaches, toothaches, nausea, rheumatism, improving blood circulation and colds, it is attributed to its medicinal properties due to its secondary components, which include essential oils and pungent compounds like Gingerols, Shagoals, and Zingibere Zingerone, Gingerdiol and Zingibrene which have antioxidant properties[8], some studies have shown ginger has a protective effect on DNA against hydrogen peroxide damage and may reduce oxygen radicals andit can be usedasan antioxidants [9].

Materials and methods

1-Preparation of the laboratory animals of study: The experiment was conducted at the Animal House, Department of Biology, College of Science, Universityof kufafor a period of 30 days, Thirty male white rats, weighing between 150 and 200 grams, were used. The male rats were placed in plastic cages lined with sawdust. Good conditions of light and darkness were provided over a 24-

hour period, along with ventilation and 22-28°C, supplied with distilled water , nutrition material in sufficient quantities and continuously until the end of the experiment. Animals were weighed prior to dosing, and individual doses were calculated daily based on body weight using the formula: Dose (mg) = body weight (kg) × required dose per kg. forweightvariationduringthe30-dayexperiment [10].

2-Choosingtheplant

A: Buyingtheplantanddrying

Ginger roots were purchased from the markets, washed and allowed to air dry at room temperature in a well-ventilated area free from

B: Preparation of the aqueous extract

The researcher (11) adopted the method for preparing the hot water extract from ginger tubers, 20 grams of dried ginger powder and 200 milliliters of boiled distilled water are combined for extraction, then the mixture is put in an electric blender and blended for 15 minutes. The solution is then covered and filtered through three layers of gauze and allowed to sit at room temperature for 24 hours.

The mixture is then filtered using Watman filter paper (No.1) to remove the residue. Then, the filtrate is taken and placed in a centrifuge at 3000 RPM for 10 minutes to separate the sediment and obtain a pure extract.

The filtrate is placed in glass containers and the extract is dried in an electric oven at a

3-Experimental groups

G1: Dosed with distilled water and left for a month

G2: Received the antibiotic levofloxacin orally as 16 mg/kg of body weight.

G3: Administered orally with an aqueous ginger extract at a concentration of 100 mg/kg + levofloxacin as 16 mg/kg.

4-Bloodsamplecollection

After 30-day experiment, animals were fasted for 24 hours, then their weights were recorded, and the treated animals were sacrificed. Blood was drawn (3-5 ml) via a method called heart puncture. Samples were

5- valuationofbiochemicalbloodparameters

The effectiveness of liver enzymes (ALT, AST, ALP) in serum was evaluated according to method [12], which used kits and reagents

6- Anatomical study

The animals were dissected by making a longitudinal incision in the abdomen of the laboratory animal from the posterior region to the anterior region. After removing the external parts of the body represented by the skin, the rat's liver was extracted and placed in

moisture. An electric grinder was used to process the dried ginger roots, and the finely ground powder was there after kept out of direct sunlight in sealed glass jars, then warm up till needed.

temperature of 40-45°C. The extract is left to dry, then the dry powder is collected in an opaque bottle and until use, followed stored in the refrigerator by the preparation of the original solution of the aqueous extract.

C: Preparation of levofloxacin

The antibiotic levofloxacin is used in the form of tablets with an active ingredient concentration of 500 mg per tablet. It was dissolved in 50 ml of D.W. to create a suspension with a concentration of 16 mg/50 ml, orally administered as dose of 16 mg/kg of the animal's weight daily, after weighing the animal in advance to calculate the dose and The antibiotic was administered orally once daily for 30 days using oral gavag

G4: Administered with an aqueous ginger extract orally as 300 mg/kg + levofloxacin as 16 mg/kg.

G5: This group was administered an oral aqueous ginger extract as 100 mg/kg.

G6: This group was administered an oral aqueous ginger extract as 300 mg/kg.

placed in gel tubes and left at room temperature (25°C) for 30 minutes before centrifugation at 3000 rpm for 15 minutes. The resulting serum was transferred to Eppendorf tubes and stored at -20°C until biochemical analysis

prepared by Randox La – France Company, Furthermore, the absorbance readings (546, 546, 540 nm) were measured sequentially using a spectrophotometer.

a physiological solution to prevent the organs from drying out. The fat tissues were removed, and then it was dried with sterile filter paper. The liver was then weighed on a sensitive scale and placed in a 10% formalin solution for the purpose of preparing tissue sections [13,14].

7-Statistical analysis

All data were statistically analyzed using one-way Analysis of Variance (ANOVA) to determine significant differences among the experimental groups. The experimental design

followed a Completely Randomized Design (CRD). Comparisons between means were performed using the Least Significant Difference (LSD) test at a significance level of $p < 0.05$ [15].

Results

1- Levofloxacin treatment with ginger extract was effected on the relative liver weight of male white rats at doses (100 , 300) mg/kg.

Results of the statistical analysis of a significant increase $p < 0.05$ in liver weight in the group deal with levofloxacin ($0.106 \pm 0.0012a$) compared to control. Statistical analysis showed increase significant $p < 0.05$ with ginger extract concentration 300mg/kg ($0.055 \pm 0.002b$) compared to control. However, the statistical analysis did not show a significant effect $p > 0.05$ on liver weight in the groups treated with ginger extract concentrations of 300mg/kg and 100mg/kg + levofloxacin compared to control, as in table (1).

2 - Effect of levofloxacin treatment and aqueous ginger extract at doses (100-300) mg/kg on the liver enzyme activity of male white rats.

Statistical analysis of results were indicated that the group administered levofloxacin was increase significant $P < 0.05$ at activity of alanine aminotransferase (ALT) enzyme, which 366.4 ± 87.5 a units/liter compared to control, which had ($61 \pm 12.7c$ units/liter), while the groups treated with ginger extract

100 mg/kg, ginger extract 300 mg/kg, levofloxacin + ginger extract at concentrations (300 and 100) mg/kg and mg/kg not significant differences $P > 0.05$ in ALT enzyme activity when compared to control and among the other groups, as in the table below (1).

The results indicated that the group treated with levofloxacin (LFX) increase a significant $P < 0.05$ in activity of the aspartate aminotransferase (AST) enzyme, which 473.6 ± 63.2 a units/liter compared to control ($109.7 \pm 12.7c$ units/liter) and other groups. Meanwhile, groups treated with ginger extract at (100 mg/kg, 300 mg/kg) , levofloxacin + ginger extract at (100 mg/kg, 300 mg/kg) didn't appeared any significant differences in AST enzyme activity when compared with control and each other, as shown in the table (1).

Results revealed a decrease significant ($P < 0.05$) in activity of gamma-glutamyl transferase enzyme in group treated with the ginger extract at 300 mg/kg, amounting to ($80.2 \pm 5.24d$ units/liter) compared to control. However, other groups: the ginger extract at 100 mg/kg, the levofloxacin + ginger extract at (100 mg/kg, 300 mg/kg), didn't show any significant differences ($P > 0.05$) in GGT enzyme activity when compared with control and other groups, as in table (1).

Table (1): It shows the effect of the antibiotic LFX and the aqueous ginger extract on the relative liver weight and liver enzyme activity.

Liver enzyme activity (units/liter)				
GGT	AST	ALT	The relative weight of the liver	Experimental groups
135.4±8.4c	109.7±12.7c	61 ±12.7 c	0.032±0.0005cd	Control group
311.4±38.6a	473.6±63.2 a	366.4±87.5 a	0.106±0.0012a	Levofloxacin at 100 mg/kg
96.8±5.08cd	98.4±11.2c	68.6±8.09c	0.034±0.0014cd	Group of ginger extract at 100 mg/kg
80.2±5.24d	77.4±7.11c	58.8±2.1c	0.055±0.002b	Ginger extract group at 300 mg/kg
126.7±6.08cd	113.4±3.66c	63±8.06c	0.035±0.005cd	Levofloxacin group + ginger extract at 100 mg/kg
123.9 ±9.3cd	107.2±3.01c	75.6±8.44c	0.033±0.004b	Levofloxacin group + ginger extract at 300 mg/kg
48.12	84.5	85.2	0.0040	LSD

The values represent the mean ± standard error of seven replicates. Different letters between any two means indicate significant differences at 0.05 significance ($P < 0.05$).

2- Histological changes

2:1: The effect of levofloxacin and ginger extract on liver tissues at doses (100 and 300) mg/kg



Image (2-2): A section of the liver tissue of a male rat from the group dosed with levofloxacin 16 mg/kg. Stained: Hematoxylin-Eosin: Magnification (400 X).

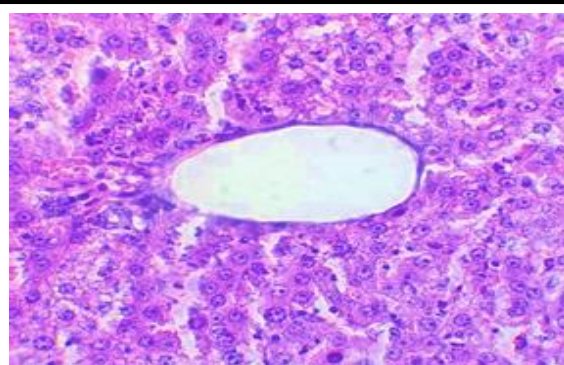


Image (1-2): Section of the liver tissue of a male rat from the control group. Stained: Hematoxylin-Eosin, magnification power (X400).

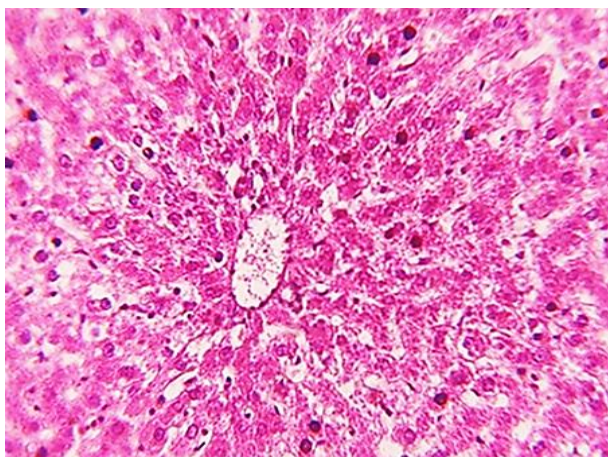


Image (2-4): Section of the liver tissue of a male rat from the group administered with 100 mg/kg of aqueous ginger extract. Stained: Hematoxylin-Eosin: Magnification power (X400).

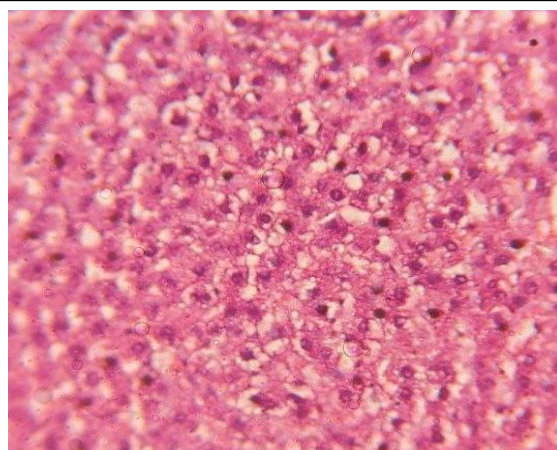


Image (2-3): Section of the liver tissue of a male rat from the group administered with 100 mg/kg of aqueous extract ginger. Stained: Hematoxylin-Eosin: Magnificationpower(X400).

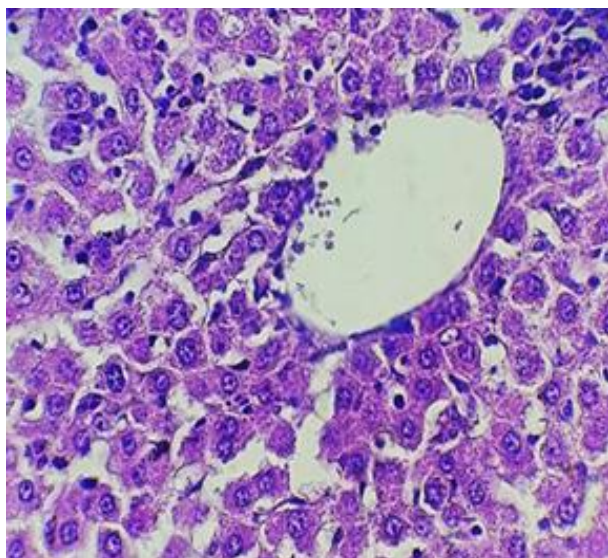


Image (2-6): A section of the liver tissue from a male rat in the group administered levofloxacin 16 mg/kg with ginger aqueous extract 300 mg/kg. Stained: Hematoxylin-Eosin: Magnification power (0X40).

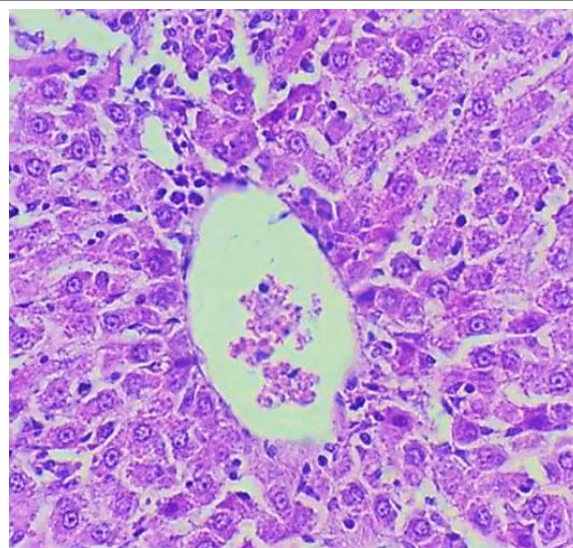


Image (2-5): A section of the liver tissue of a male rat from the group treated with levofloxacin 16 mg/kg with 100 mg/kg of aqueous ginger extract. Stained: Hematoxylin-Eosin: Magnification

Discussion

1 -The levofloxacin treatment and ginger extract were effected on relative liver weight of male white rats at (100 and 300) mg/kg.

Fluoroquinolones were among the most commonly used antibiotics by doctors worldwide. Levofloxacin, one of the fluoroquinolones, is used therapeutically in many countries; however, its long-term use can cause liver dysfunction. The effect of levofloxacin (16 mg/kg body weight daily for one month) on liver functions in male rats, statistically analysis appeared: a significant increase ($p < 0.05$) in liver weight in the group treated with levofloxacin. The current study was consistent with the study by [16], and colleagues, where chickens were administered levofloxacin at 20 mg/kg body weight period 28 consecutive days. Researchers demonstrated that levofloxacin significantly affects liver weight and function, indicating that levofloxacin causes hepatotoxicity, This leads to an increase in liver weight and elevated enzyme levels. The reason is that the receptors responsible for mass are affected by metabolism, and the effect of this type of antibiotic is cumulative, showing its toxicity over a long period, This impacts the weight of the liver and kidneys, relies on the weight of the body and organs depends on the therapeutic dose and the duration of administration to show toxic changes in liver weight, consequently producing reactive oxygen species and the toxic mechanism of oxidative stress, as confirmed by [17].

Statistical analysis explained a significant increase ($P < 0.05$) in group treated with a 300 mg/kg of ginger extract compared to the other groups. This may be attributed to main active component in root of ginger, which is ginger oil and the influential phenolic compounds such as gingerol, a very potent anti-inflammatory compound. It appears that ginger stabilizes the hormones of adipose tissue, plasma, lipases, and fat levels in mice, as confirmed by the study of [18], While the groups treated with levofloxacin + ginger extract at (100 and 300) mg/kg did not show

any effects, this is attributed to the presence of chemical compounds such as polyphenols, vitamin C, vitamin B, beta-carotene, flavonoids, and tannins. These components are effective and have antioxidant activity that works to inhibit free radicals, hydroxyl radicals, and superoxide radicals, which protect cell membrane lipids from the harmful oxidative effects caused by the oxidative stress generated by the antibiotic levofloxacin when taken for a long period. This was confirmed by [19].

2-The effect of levofloxacin treatment and ginger extract as activity of liver enzymes male white rats at (100-300) mg/kg.

Levofloxacin, an antibiotic from the fluoroquinolone class, is associated with hepatotoxicity as evidenced by elevated liver enzymes and tissue damage. Previous research indicates that levofloxacin can significantly increase liver enzymes such as AST and ALT, especially when high doses are taken, indicating potential liver toxicity. This was noted by researcher [15] and colleagues, and their study aligned with the current study's results. Elevated liver enzyme levels indicate liver damage caused by the use of antibiotics, including levofloxacin, which damages DNA structure, as proven by researcher [20].

While liver enzymes did not show any significant changes when male rats were administered levofloxacin + ginger extract at 100 and 300 mg/kg body weight, this indicates the therapeutic role of ginger in maintaining liver enzyme activity, particularly the 300 mg/kg. This is attributed to the presence of active antioxidant compounds in ginger, represented by phenols, flavonoids, terpenes, and vitamins A, B, C, and E, as well as minerals like zinc (Zn), selenium (Se), and calcium (Ca). Their presence in ginger leads to a significant reduction in lipid peroxidation by detect activity of antioxidant enzymes such as catalase, which play a role in inhibiting oxidative stress caused by free radicals generated from antibiotic effects, thereby reducing DNA damage [21].

2- Histological changes

2:1: The effect of levofloxacin and ginger extract at 100 and 300 mg/kg on liver tissues

The histological examination results of the livers of male white rats treated with the antibiotic levofloxacin showed numerous histopathological changes, including hemorrhage with rupture within interstitial tissue of liver lobule, central vein dilation, hemorrhage within interstitial tissue of the liver lobule, infiltration of inflammatory cells around the central vein of the liver lobule, hemorrhage within the connective tissue of the liver lobule, necrosis, and apoptosis of liver cells. The microscopic examination results were consistent with the study by the researchers [22], which reported bleeding with the accumulation of inflammatory cells around the central vein, leading to dilation and congestion of the central vein [1]. The researcher [23] attributed the cause to the fact that the liver is the main organ responsible for the metabolism of drugs, chemicals, and toxic agents, making it a target for drug metabolic reactions and more susceptible to necrosis and inflammation of liver cells, as the researcher [24], and his colleagues indicated. This may be attributed to the formation of free radicals, which are oxidizing agents that contribute to mitochondrial damage, thereby inhibiting cellular respiration and reducing energy production by blocking the electron transport chain in the mitochondria. Free radicals cause oxidative stress by stimulating the oxidation of lipid molecules in cell membranes as well as other essential intracellular components such as nucleic acids and proteins, leading to apoptosis in other tissues. However, research indicates that liver damage caused by fluoroquinolone is primarily due to mitochondrial damage. These findings are consistent with those of researcher [25], and his colleagues, who studied cases of women who developed liver toxicity after 10 days of treatment with levofloxacin at a dose of 750 mg/day. This led to the appearance of pathological lesions resulting from widespread necrosis in liver cells and pyknosis, Infiltration of inflammatory cells was observed in the portal area. They believed that fluoroquinolone causes direct damage to DNA

gyrase in microorganisms and also affects, The mitochondrial DNA of mammals, which confirms that these histopathological changes in the liver are caused by prolonged and high-dose consumption of the antibiotic LFX, leading to persistent inflammation and elevated liver enzyme levels that indicate liver damage, as reported by the researcher [26].

While the microscopic sections of the groups treated with the antibiotic LFX and the ginger aqueous extract at 100 and 300 mg/kg body weight did not appear any histopathological changes, as infiltration of inflammatory cells was observed, the cells were closely packed and organized around the central vein of the liver. Results were consistent with the microscopic examination [27], and colleagues when studying the effect of the aqueous extract of *Moringa Oleifera* seeds against the damage caused by levofloxacin in the liver of male white rats. The histological examination of the liver in the group treated with the extract showed a nearly normal appearance of the central vein, alveolar spaces, and hepatocytes. This is attributed to the fact that ginger contains many phenolic, flavonoid, and vitamin compounds, including ascorbic acid and tocopherol, glycosides, tannins, and terpenoids that inhibit free radicals and reactive oxygen species (ROS), thereby reducing oxidative damage, preventing lipid peroxidation, and regenerating membrane-associated antioxidants. As researcher [28], and colleagues indicated, administering ginger as an initial treatment at 200 mg/kg body weight at 6 weeks restores antioxidant enzyme activities. This can be explained by the antioxidant compounds present in ginger, such as gingerols, shogaols, ketones, phenolic, and volatile oils. Additionally, researchers [29], The antioxidant activity of the aqueous ginger extract protects liver tissues from the harmful effects of drug-induced toxins. This is attributed to the compound 6-gingerol, the main component of ginger, which has an inhibitory effect on xanthine oxidase, the enzyme responsible for generating reactive oxygen species. The antioxidant activity in the ginger extract is explained by the results we obtained in our phytochemical study, which revealed high levels of polyphenols and lower

amounts of flavonoids, tannins, and other compounds. This was confirmed by the researcher [30].

Conclusions

The study results were appeared the aqueous extract of ginger, especially at 300 mg/kg, has protective effect against toxicity of liver

caused by levofloxacin. Where the extract contributed to improving biochemical indicators and protecting the hepatic tissue structure. It is recommended to use ginger extract as an adjunct to reduce the damage caused by certain antibiotics with hepatotoxic effects.

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