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Research Article

Protective effect of cinnamon oil against ciprofloxacin toxicity on liver and kidney of male Wistar rats

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Abstract
Cinnamon zeylanicum is one of many herbal medications. This herb contains different materials like, cumarin, cinnamaldehyde and cinnamic acid. The plant plays a role as antiallergic, antiviral, antimicrobial, anti-inflammatory and antioxidant and other health conditions. This study focused on the therapeutic effect of cinnamon oil on hepatorenal toxicity induced by ciprofloxacin in male rats. Forty rats were housed in the animal house of the College of Pharmacy, University of Kerbala, Karbala city, Iraq. The animals were separated into four groups: Group 1. Control group (not taken drug nor cinnamon oil), Group 2. Ciprofloxacin group (drenched 250 mg/kg/day of ciprofloxacin for 30 days), Group 3. Cinnamon oil group (drenched 1ml/kg/day of cinnamon oil for 30 days) and Group 4. Cinnamon+ciprofloxacin group (drenched 1ml/kg/day of cinnamon + 250 mg/kg/day of ciprofloxacin for 30 days). Finally, 2ml of blood was collected from each rat and the serum was separated for estimating the biochemical parameters of the liver like, Aspartate transaminase (AST), alanine transaminase(ALT) and alkaline phosphatase(ALP) and the kidney (Creatinine, Urea and albumin) . The results proved that ciprofloxacin significantly elevates the parameters of the liver and kidney ($p \leq 0.05$). The results also proved the benefit of cinnamon oil in improving health by reducing the toxic effect of ciprofloxacin by lowering the elevated levels of (liver enzymes, creatinine, urea and albumin). The study showed that this oil reduced the toxic effect of ciprofloxacin on the kidney and liver.

Keywords: Cinnamon oil, Ciprofloxacin, Kidney toxicity, Liver toxicity

INTRODUCTION

Ciprofloxacin is a fluoroquinolone of the second generation, which has an antibacterial activity on a broad bacterial-spectrum. After oral administration, it easily penetrates the tissues (Papich, 1998 and Millanao *et al*., 2021). This drug is effective against a wide spectrum of bacteria such as gram negative and most gram-positive bacteria. It is also used to manage infections of the urinary tract, soft tissues, bones, respiratory tract, and gastrointestinal infections in humans (Sharma *et al.,* 2017 and Cao *et al.,* 2021). Some publications have documented hepatotoxicity related to ciprofloxacin in patients receiving a therapeutic dose of a drug. Ciprofloxacin-induced diarrhoea has been reported. The majority of patients have a high level of aspartate aminotransferase, alkaline phosphatase, alanine amino transferase and immune cells, which support hepatotoxicity. Biopsy of the liver indicated a heterogenous inflammatory infiltrate with continuous eosinophils penetrating the portal tracts (Hirsch and Landquist, 2009). Ciprofloxacin has been found, in animal studies, to tend to affect cardiotoxicity, one of these studies found that ciprofloxacin enhanced serum biochemical markers and caused substrate cardiotoxicity (Pispirigos and Kostantinos, 2001), another found that ciprofloxacin dose of more than 25 mg/kg for 7 days lead to cardiac toxicity (Saracoglu *et al.,* 2009), as well as Saad *et al.* (2021) found that ciprofloxacin caused alteration in electrocardiogram (ECG). The toxic side effects, contraindications, and sometimes diminutions in response after prolonged use of antibacterial drugs are encour-

aged to search for therapeutic herbal for safety, efficacy, and economy. Many herbal medications are known for their activity as antioxidant agents (Hadi *et al*., 2013).

Cinnamon is commonly used as a herbal medication. This plant usually grows in Asia and Australia. The medical benefits of this herb are linked to its active components. It is found from the analyses of cinnamon that it contains different materials like cumarin, cinamyldehyde and cinnamic acid (Lim and Ko, 2022). The plant has antiallergic, antiviral, antimicrobial, anti-inflammatory and antioxidant effects, as well as an effect on heart disease treatments and diabetes (Shen *et al*., 2012). Many recent studies have proved cinnamon's therapeutic and preventive potential against a range of infections linked to oxidative stress (Li *et al*., 2019., Salman *et al*., 2021, Alshahrani *et al*., 2021). Oils extracted from cinnamon, such as *Cinnamomum zeylanicum* leaf oil and *C. zeylanicum* bark oil, are differentiated with eugenol (Gotmare and Tambe, 2019). Cinnamon oil, also derived from *C. cassia,* is used as anti-fungal agent, and cosmetics to minimize food loss (Kacaniova *et al*., 2021). Many doses help to reduce the risk of heart disease, cancers and type 2 diabetes problems. Toothaches and oral infections are two other positive (Hamidpour *et al*., 2015). Cinnamon has also been used to treat gastrointestinal colonic disorders. All of this made cinnamon so widespread that it is now utilized daily all around the planet due to various health advantages (Kumar *et al*., 2019). This oil is made up of a variety of minerals and nutrients (Kallel *et al*., 2019). These minerals and nutrients are essential for creating red blood cells and potassium, which is important for the circulatory system's health. The herb also provides magnesium and CO important to boost the activity of enzymes (Ose *et al*., 2020). This herb is regarded as an excellent antioxidant (Abeysekera *et al*., 2019). Cinnamon's active ingredients have been found to have insulin-mimetic effects, as they increase glucose absorption by stimulating insulin receptor (IR) kinase activity, IR autophosphorylation, and glycogen synthesis activity (Medagama, 2015). Thus, the present study aimed to reveal the protective effect of cinnamon oil on reducing the toxic effect of ciprofloxacin on the liver and kidneys of rats.

MATERIALS AND METHODS

Drug

Ciprofloxacin tablet 1000 mg was used in this experiment. The pills were ground, dissolved in drinking water and drenched to rats. Each pill, containing 1000 mg ciprofloxacin, was dissolved in 2ml of drinking water to get a stock solution of the dose of 500 mg/ml then 0.5 ml of stock solution was given to each male Wistar rat in the second group and the fourth group.

Herb oil

Bark oil *C. zeylanicum* was bought from NOW sports-Nutrition and wellness Company and used in this experiment. The oil was 100% pure and had no additives.

Designing of the experiment

Forty male Wistar rats weighing (250-300) g were employed in this study. The animals were kept in an animal house in the College of Pharmacy, University of Kerbala. Karbala city, Iraq. The rats were split into four groups, and each group comprised of ten male rats as the following:

Group 1. Healthy control group: Given no drug nor cinnamon oil.

Group 2. Ciprofloxacin group: Administrated 250 mg/kg/day of ciprofloxacin for 30 days

Group 3. Cinnamon oil group: Administrated 1ml/kg/day of cinnamon oil for 30 days.

Group 4. Ciprofloxacin+cinnamon oil group: administrated 250 mg/kg/day of ciprofloxacin and 1ml/kg/day of cinnamon oil for 30 days.

After 30 days, 2ml of blood was collected from each animal using a 5ml syringe from the heart after anaesthesia and put plain tube, then centrifuged at 5000 rpm for 10 minutes for serum separation. Finally, the ELISA method was used to estimate the parameters of the kidney (creatinine, urea and albumin) and liver enzymes like alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) in the serum.

Biochemical tests

Liver function parameters (AST, ALT and ALP) and kidney function parameters (creatinine, urea and albumin) were determined using ELISA kits from Elabscience company. The procedures that came with the Kits were followed.

Data analysis

All data were analyzed by one-way ANOVA with SPSS version (27) then results were represented as mean ± SE.

Ethics

The current study was conducted according to instructions of the Animal Ethics Committee in the Pharmacy Faculty, University of Kerbala, Karbala city, Iraq

RESULTS

Liver function

In the case of rats drenched with ciprofloxacin daily for one month (Group 2), the liver function enzymes in the serum (ALT, AST and ALP) showed a significant elevation, 82.66±9.95, 73.66±6.40 and 557.83±72.17 respectively relative to control (Group 1) healthy rats

40.16±3.87, 46±5.73 and 322±39.67. Also, the results showed the therapeutic effect of cinnamon oil for one month in reducing the toxic elevation in these parameters of the liver (Group 4), 49±5.74, 51.66±6.78 and 378.04±29.09 respectively. These changes were significant at (p≤0.05), as shown in Table 1. As well as, the results showed no significant change between the control group (Group 1) and the cinnamon-administrated group (Group 3). The samples of all groups were tested after thirty days of administration.

Kidney function

Table 2 shows the effect of the thirty-day administration of ciprofloxacin and cinnamon oil on kidney function. The ciprofloxacin group (Group 2) recorded significant elevation (p≤0.05) in creatinine and urea, 1.48±0.36 and 57.80±4.51 respectively, compared to the control group (Group 1), 0.31±0.05 and 38.16±4.7 respectively then creatinine and urea decreased to nearly normal values in ciprofloxacin+cinnamon group (Group 4), 0.65±0.14 and 40.83±5.19 respectively. Albumin did not record any significant change in all groups at (p≤0.05). As well as, there were no significant changes in the cinnamon-only group (Group 3) compared to the control group in all parameters at (p≤0.05).

DISCUSSION

The results of the present study revealed the toxic effect of thirty days-drenching of ciprofloxacin on the liver and kidney (Group 2) by elevated liver enzymes (AST, ALT and ALP) and kidney enzymes (creatinine and urea). The elevated levels of liver and kidney enzymes induced by ciprofloxacin are proven by many studies, including Hirsch and Lundquist (2009); Baloch *et al.* (2017) and Radovanovic *et al*. (2018). This elevation in the liver refers to a disorder in this vital organ and is good evidence of the toxicity of ciprofloxacin by attacking hepatocytes and injuring these cells, which in turn releases these enzymes into the bloodstream (Sellouti *et al.,* 2021). A histopathological study revealed that mixed inflammatory infiltrates with chronic inflammatory cells had invaded the portal tracts. In the center and pericentral zones, hepatocytes are visibly dilated and damaged in addition to elevated levels of AST and ALT (Sabeeh *et al.,* 2019). Hooper and Jacoby (2016) revealed that quinolone antibiotic impedes DNA and RNA replication, which in turn reduces cells growth and the synthesis of protein. Another study by Nadia (2006), found that pregnant rats and their babies' livers underwent several modifications after receiving ciprofloxacin at therapeutic and twice therapeutic dosages (58 and 115mg/kg) during the two stages of pregnancy (in preimplantation and postimplantation). In the kidney ciprofloxacin causes nephrotoxicity, which is allergic interstitial nephritis that leads to the ability of nephrons to filtrate creatinine (Alhassani *et al.,*2021).

The present results also showed the protective feature of cinnamon oil on the liver and kidney of male rats against the toxicity of ciprofloxacin (Group 4) by reducing the high levels of (ALT, AST, ALP, Creatinine, and Urea) as shown in Tables 1 and 2. The protective effect of cinnamon oil may belong to the presence of many natural antioxidants. This evidence is in line with

Table 1. Effect of cinnamon oil on liver parameters of rats drenched ciprofloxacin

Groups	ALT U/L Mean±SE After 30 days	AST mg/dl Mean±SE After 30 days	ALP mg/dl Mean±SE After 30 days
1. Control(n=10)	40.16±3.87[a]	46±5.73[a]	322±39.67[a]
2. Ciprofloxacin(n=10)	82.66±9.95[b]	73.66±6.40[b]	557.83±72.17[b]
3. Cinnamon oil(n=10)	47±4.98[a]	54.61±3.35[a]	342.50±41.89[a]
4. Ciprofloxacin +cinnamon(n=10)	49±5.74[a]	51.66±6.78[a]	378.04±29.09[a]

Different small letters in the same column mean significant differences (p≤0.05)

Table 2. Effect of cinnamon oil on kidney parameters of rats drenched ciprofloxacin

Groups	Creatinine mg/dl Mean±SE After 30 days	Urea mg/dl Mean±SE After 30 days	Albumin mg/dl Mean±SE After 30 days
1. Control(n=10)	0.31±0.05[a]	38.16±4.7[a]	4.12.0±3[a]
2. Ciprofloxacin(n=10)	1.48±0.36[b]	57.80±4.51[b]	3.0±98.25[a]
3. Cinnamon oil(n=10)	0.59±0.15[c]	43.16±6.[19a]	4.52.0±64[a]
4. Ciprofloxacin+ cinnamon(n=10)	0.65±0.14[c]	40.83±5.19[a]	4.640.2±9[a]

Different small letters in the same column mean significant differences (p≤0.05)

Mahdi *et al*. (2018), who mentioned that cinnamon oil contains many powerful antioxidant substances such as camphene, cinnamic acid, eugenol, salicylic acid, and epicatechin. Additionally, polyphenols, phenolic acid, and flavonoids provide medical benefits for cinnamon as an antioxidant, preventing oxidative stress in the body by responding to free radicals and reducing damage from metabolic illnesses in the body, as in the study of Abeysekera *et al*. (2019). Also, Ose *et al*. (2020) showed that allergen-specific T-cell proliferation and generation of Th1 and Th2 cytokines are greatly reduced by cinnamaldehyde, which inhibits dendritic cell maturation and this agreed with our results. Because of its anti-oxidative and anti-inflammatory characteristics, it has this medicinal efficacy. Cinnamic aldehyde and cinnamic acid reduce myocardial ischemic damage and lower lactate dehydrogenase levels, interleukin-6, and creatine kinase while boosting the activity of serum nitric oxide and the activity of superoxide dismutase as demonstrated by Kadhim *et al*. (2020). The present study disagreed with another study which found no significant effect of cinnamon on liver enzymes such as Shekarchizadeh-Esfahani *et al*. (2021) who found that there was no significant effect of cinnamon oil on liver enzymes, but there was a significant effect on ALT in high dosage of cinnamon, as well as Mousavi *et al*. (2021) found that there was no significance of cinnamon for reduction of elevated levels of ALT and AST in diabetic patients. This difference may be due to the non-reversible effects caused by some diseases, while the present study proved that oil could reverse the effects of the drug. These results are very important to reduce the harmful effects of this treatment.

Conclusion

The present study concluded that cinnamon oil has a powerful effect in reducing the toxicity of ciprofloxacin (after thirty days of drenching) by lowering the high levels of the liver (AST, ALT, and ALP) and kidney parameters (creatinine) of male Wistar rats induced by ciprofloxacin drug while there was no significant effect on albumin level.

Conflict of interest

The authors declare that they have no conflict of interest.

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