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Origanum Majorana (O. M.) Ameliorate Ciprofloxacin-Induced Hepatotoxicity In Rats Via Antioxidant Defense Mechanism

Zainab Hussein[1] , Shaymaa Malik Yasir[2]

[1]Department of pharmacy, Al-Zahrawi university college, Karbala, Iraq, Email: zainab@g.alzahu.edu.iq, Orcid: 0000-0001-9350-8417
[2]Department of biology, college of education for pure science, university of Karbala, Iraq. Email: Shaimaa.malik@uokerbala.edu.iq, Orcid: 0000-0001-6023-8545.
Corresponding author: Zainab Hussein, Email: zainab@g.alzahu.edu.iq

Abstract

Background. The etiology of ciprofloxacin-induced hepatopathy is complicated by oxidative stress. The study intends and seeing if Origanum majorana (O.M.) could protect animals with antioxidant properties. Methods. G1 (control), G2 (ciprofloxacin group), G3 and G4 (two O.M. groups rats treated with O.M. 30 mg and 45 mg), and G5 and G6 (two O. M. groups rats treated with O. M. 30 mg and 45 mg) (two combinations at 30 mg and 45 mg; with ciprofloxacin 100 mg/kg). Liver function and anti-oxidant enzymes were among the tests performed. When ciprofloxacin produced hepatotoxicity, blood levels of anti-oxidant enzymes were lower in the ciprofloxacin group, whereas O.M. boosted these enzymes in rats. Conclusions. In vivo, O.M. reduces experimental hepatotoxicity. The antioxidant defense mechanism is hypothesized to be activated as a result of this impact.

Keywords: Origanum majorana, ciprofloxacin, hepatotoxicity, SOD, and anti-oxidants.

1. Introduction

Ciprofloxacin is a fluoroquinolone of the second generation that is used to treat infections of the gastrointestinal system, respiratory tract, and genitourinary tract. It works by interfering with the replication process of DNA gyrase to inhibit the growth of disease-causing bacteria through an enzymatic-inhibition catalytic mechanism (1). Oxidative stress not only causes liver damage by causing permanent damage to lipids, proteins, and DNA, but it also affects biological functioning through modifying pathways. Since these pathways control gene transcription, protein expression, cell death, and hepatic stellate cell activation, oxidative stress is one of the most important pathophysiological mechanisms behind the onset and progression of many liver illnesses (2). Ciprofloxacin's hepatotoxicity results could be due to oxidative stress in the liver induced by the drug's production of reactive radicals, which causes protein depletion in hepatocytes due to nucleic acid loss and DNA damage. This may lead to a significant decrease in mitochondrial number and degeneration, which is responsible for energy production (3). The liver damage markers ALT, AST, and ALP were elevated in ciprofloxacin-induced hepatotoxicity. The most specific and widely used markers of hepatocellular necrosis are amino-transferases. The presence of high levels of these enzymes may suggest the presence of liver injury. Hepatocytes, biliary epithelial cells, liver tubules, pancreas, and gut produce anti-oxidant enzymes such as SOD and GSH (4). Many naturally occurring antioxidants such as Origanum majorana L. which is an aromatic and medicinal plant found throughout the Mediterranean region. Traditional medicine has long utilized this species to treat a variety of ailments, including allergies, hypertension, respiratory infections, diabetes, stomach pain, and intestinal antispasmodic (5). Elevated levels of serum enzymes activity has been considered as a sensible marker of hepatic disorders (3). Pharmacological experiments related ethnopharmacological usage to biological activity and secondary metabolite content, but without exploring the real mechanisms of action, which were scientifically established for O. majorana.

The presence of antioxidant bioactive components, primarily phenolic chemicals, is responsible for the anti-oxidant action of O. majorana extracts and EOs. In addition, O. majorana has shown promising pharmacological effects in the treatment of oxidative stress-related disorders as cancer, inflammation, and diabetes. As a result, more in vitro testing is required for the development of O. majorana-based medicines for diabetes, inflammation, and cancer (6, 7). As a result, using the O. majorana to stimulate the production of cytoprotective anti-oxidants could be employed to treat liver diseases. The aim of study was to investigate if O. majorana could protect the liver in a chemical model of acute cipro-induced hepatotoxicity. Because O. majorana has been shown to activate anti-oxidant system, the hepatoprotective benefits of O. majorana against cipro were investigated. Rats were used to study hepatotoxicity.

2. Animals and Study Design

A total of 48 Rattus norvegicus male rats will be formed into six groups. Each group has eight rats for a duration of 30 days. Preparation of drugs: O.M dissolves in water and is administered orally in doses of 30 and 45 mg/kg. The animals were kept in the animal house at Faculty of Science's Karbala university. The experiment was approved by the University of Karbala's Animal Care and Research Committee, and the study followed the Laboratory Animals Guide Care. The animals will have unrestricted access to clean water and be divided into four groups: G1: water is given for 30 days; G2: medicine (ciprofloxacin) is given once day via oral administration at a dose of 100 mg/kg for 30 days. (8), **G3:** orally administration of O.M. at a dosage of 30 mg/kg once daily for a period of 30 days (9), **G4:** orally administration of O.M. at a dosage of 45 mg/kg once daily for a period of 30 days (10), **G5**: For 30 days, ciprofloxacin 100 mg/kg was administered orally once daily plus O.M. Orally at a dosage of 30 mg/kg (12 ,11), and **G6** : For 30 days, ciprofloxacin 100 mg/kg was administered orally once daily, plus O. M. orally at a dosage of 45 mg/kg starting (12 ,11). At the end of the investigation, animals will be slaughtered by heart puncture under ketamine (25 mg/kg) and xylazine (5 to 10 mg/kg) anesthesia. (13). The animals will be euthanized so that blood and liver tissues can be collected for further analysis (14).

3. Measurement of Oxidant Parameters

According to the manufacturer's technique and a previous study, two commercial detection kits were utilized to quantify the levels of CAT, SOD, and GSH enzymes, as well as Nrf2 (Nanjing Jiancheng Bioengineering Institute). (15).

4. Statistical Analysis

The information is presented in the form of means and standard deviations (SD). Using the SPSS program 26.0 and one-way analysis of variance, the significance of differences in different group comparisons was determined (ANOVA).

5. Results

O.M. reduced oxidative stress and increased anti-oxidant enzyme activities in hepatocytes

To see whether the O. M's hepatoprotective effect in ciprofloxacin-induced hepatotoxicity is associated to anti-oxidative activation, such as elevated CAT, SOD, and GSH enzyme elevated serum. According to our findings, O.M. significantly reduced ciprofloxacin-induced liver damage by increasing these enzymes. The treated group had significantly higher levels of CAT, SOD, and GSH enzymes in serum than the untreated group, CAT; 4.82 ± 0.29, 2.99 ± 0.35, 4.83 ± 0.34, 4.88 ± 0.25, 3.91 ± 0.25, and 4.43 ± 0.09, respectively. SOD: 4.82 ± 0.29, 2.99 ± 0.35, 4.83 ± 0.34, 4.88 ± 0.25, 3.91 ± 0.25, and 4.43 ± 0.091, respectively, as well as GSH: 12.37 ± 0.94, 6.97 ± 0.51, 12.50 ± 0.47, 12.92 ± 0.69, 9.23 ± 0.40, and 10.23 ± 0.56, respectively. See Table 1 and Figure 1 for more details. The G2 group had significantly lower enzymes levels in serum as compared the G1 group ($P<0.05$). O.M. significantly increased these decreases in anti-oxidant levels in the combination groups, whereas anti-oxidant levels were not significantly different between the control and combination groups. Furthermore, no statistically significant difference ($p>0.05$) exists between the O. M. groups and both the G5 and G6 groups. When comparing treated groups to the G2, there is, however, a significant increase ($p<0.05$).

Table 1: Antioxidant enzymes concentration among study groups

Groups / Markers	Catalase (U/l)	SOD (U/l)	GSH (U/l)	*p-value
G1 Control group	4.82 ± 0.29	9.69 ± 0.29	12.37 ± 0.94	0.00
G2 Ciprofloxacin	2.99 ± 0.35	5.84 ± 0.35	6.97 ± 0.51	
G3 OM 30mg (30day)	4.83 ± 0.34	9.87 ± 0.34	12.50 ± 0.47	

G4 OM 45mg (30day)	4.88 ± 0.25	9.81 ± 0.25	12.92 ± 0.69	
G5 (Ciproflox acin 750 mg + OM 30 mg) 30day	3.91 ± 0.25	7.24 ± 0.25	9.23 ± 0.40	
G6 (Ciproflox acin 750 mg + OM 45 mg) 30day	4.43 ± 0.09	9.38 ± 0.09	10.23 ± 0.56	

Each value is a mean of eight animals ± SD, *=one-way Anova

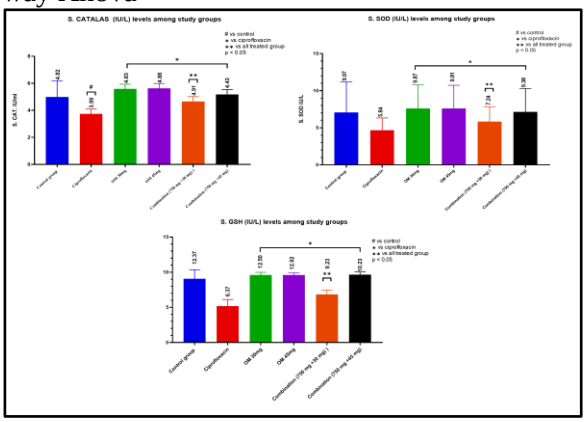

Figure 1: represent the anti-oxidant enzymes serum levels (U/L) among groups

O. M. Reduced the Hepatic Tissue Impairment

Figure 2 illustrates the degeneration and necrosis in hepatic sections from all groups. There were no significant histopathological alterations in the tissue sections of the control and O. M. groups of rats. The ciprofloxacin group's liver sections revealed significant damage, including lesions, epithelial necrosis, and hemorrhagic foci. In the combination group, the occurrence of these lesions and tissue damage is significantly reduced. O. M. may protect rats from ciprofloxacin-induced liver damage, according to this liver pathological finding.

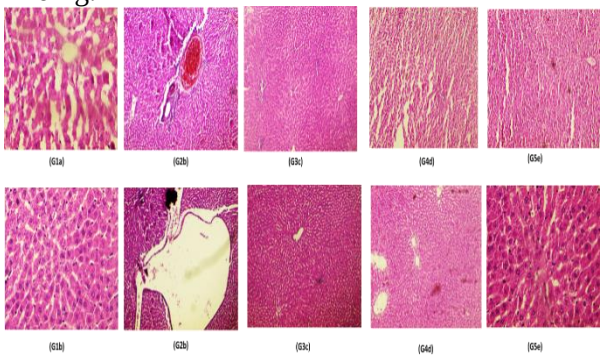

Figure 2: Representative histologic samples from several groups. G1 (a1, 1b), G2 (b1, b2), G3, G4 (b1, b2) (c1, c2), and G5, G6 (d1, d2) (e1, e2). Magnification: X40.

5. Discussion

The liver appears to be the most important organ in the maintenance of healthy. The majority of idiosyncratic medication reactions end in unfavorable effects, including revascularization, and are regarded to be a primary cause of cirrhosis of the liver. Oxidative stress has been identified as the primary cause of ciprofloxacin-induced ALF. Indeed, an oxidant/antioxidant imbalance is a key indication in the progression of various liver diseases (16-17). O. majorana is a significant fragrant plant that contains significant antioxidants such as flavonoids and triterpenoids (5, 18). It has been suggested that phenolic acids and flavonoids play a function in the prevention of human diseases. O. majorana is considered to be generally safe by the Food and Drug Administration. (19). Dosing of ciprofloxacin resulted in rapid liver damage, according to our findings. The rats' liver function had worsened, and there had been histological damage. In addition, the ciprofloxacin group showed considerably greater levels of reactive oxygen species (ROS) in liver tissue. Providing O. M. without an inducible agent, on the other hand, increased anti-oxidative enzyme activity by boosting antioxidant enzymes, suggesting that O. M. protects the liver. In the combination group, this protection showed after induction significantly reduced liver damage and reduced ROS levels. Reduced levels of CAT, SOD, and GSH enzymes in the liver tissues of the ciprofloxacin group in this study further suggested that oxidative damage had a role in the ciprofloxacin-induced liver injury in animals. Treatment with O. M. increased antioxidant enzyme activity to protect against oxidative damage in rats without harm, as shown in Figure 2. Furthermore, O. M. therapy quickly scavenged ROS and elevated anti-oxidant enzymes in animals with damage. The cytoprotective properties of O. M. are closely linked to the elimination of excess ROS. Previous research by Wessal Ouedrhiri. 2021 were reported O. M. could have therapeutic potential in the treatment of hepatotoxicity by inhibiting oxidative stress-induced hepatocyte cell membrane disruption during ciprofloxacin-induced changes (20) also, Gheitasi et al. 2021 They concluded that oral treatment with OM (300 mg/kg) produced a moderate hepatoprotective and inflammatory activity, as well as a significant increase in CAT activity. However, rats treated with OM did not show significant improvement in

histopathological changes, so they concluded that oral treatment with OM (300 mg/kg) produced a moderate hepatoprotective and inflammatory activity (21, 22). Finally, we have reported O. M.'s antioxidant properties, which are consistent with our findings. In addition, O. M. improved the viability of ciprofloxacin-induced injuries.

6. Conclusions

According to our findings, O. M. improves ciprofloxacin induce liver damage as assessed by liver function and liver pathology. The anti-oxidant protein was dramatically enhanced by O. M. These favorable effects are mostly due to improved antioxidant defense in the liver and O. M. may thus be an effective treatment for hepatotoxicity prevention, while more research and randomized clinical trials are needed to prove this.

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