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Effect of Garlic Oil on Cyclosporine Induced Liver toxicity in Rats

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ABSTRACT

Cyclosporine (CsA) is currently one of the most important immunosuppressive agents for a wide range of organ transplantations; however, it has also side effects including renal, hepatic, neural and cardiac toxicity. Garlic is a commonly worldwide used food which acts as an antioxidant and has been shown to inhibit lipid peroxidation and toxicity.This study aims to investigate the possible protective effect of garlic oil in preventing hepatic injury which is caused by administration of CsA through the histopathological study of changes in the liver tissue. In this study, we used twenty-four male rats weighing 230-250g which were randomly divided into four groups having 6 rats in each: group 1 was the control group, group 2 was given cyclosporine 12.5 mg/kg/day orally via gavage, group 3 was given garlic oil 5ml/kg/day orally via gavage and group 4 was given cyclosporine 12.5 mg/kg/day and (after 3 hours) garlic oil 5ml/kg/day orally via gavage. The administration period continued for 28 days. Histopathological examination of the liver tissue of cyclosporine-treated group showed hepatocyte necrosis and steatosis with sinusoidal dilatation when compared with the liver tissue of control group. These histopathological changes of hepatic tissue were improved by giving garlic oil with Cs A for group 4.

INTRODUCTION

CsA was discovered in the lab of Sandoz in Switzerland in 1972. It is a cyclic endecapeptide with a molecular weight of 1202 Daltons (Fig 1) [1]. CsA was found to have many immunologic properties that made it an attractive agent for immunosuppression following renal and other solid organ transplant [2]. In fact, after introducing CsA to transplant medicine, survival of transplanted organs increased considerably to more than 80% at 2 years post-transplantation. A large number of transplanted patients receive CsA as an essential immunosuppressant drug [3]. A European multicenter trial confirmed one-year graft survival of 72% and 52% in recipients of cadaveric renal transplants allocated to receive CsA and 52% in recipients of renal transplants who receive azathioprine and steroids, for immunosuppression. Clinical approval of CsA for use in the early 1980s came from such promising results [4]. CsA has become the main drug for improving rates of acute rejection in transplanted patient [5].

Several side effects like hepatic and renal toxicity associated with CsA an administration despite the marked improvement in the rates of acute rejection and one-year graft survival. Clinically, CsA hepatotoxicity is a serious side effect that can restrict its medical application. Reports demonstrated that a rate of 20-50% of CsA-treated patients suffers from hepatic dysfunction [3].

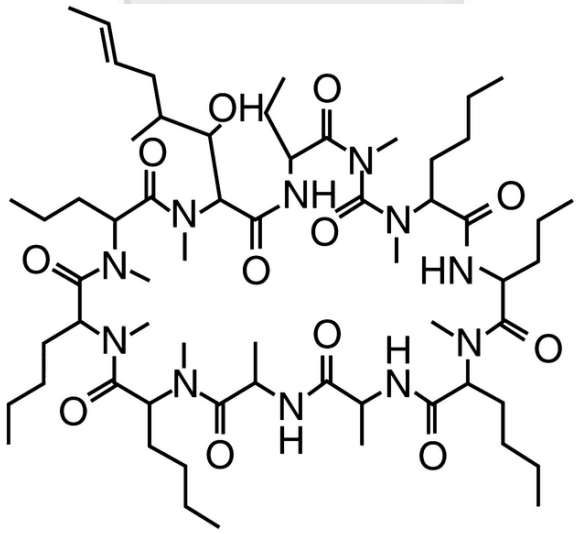

Fig (1) Chemical structure of CsA

Hepatotoxicity induced by CsA has been reported in both transplant and non-transplant pathological conditions (autoimmune diseases). Although the exact mechanisms by which CsA

an administration results in hepatotoxicity are not completely understood, several researchers have suggested that CsA induced hepatotoxicity may be caused by reactive oxygen species (ROS) production, depletion of hepatic antioxidant system and oxidative stress [6-8].

Plant foods are beneficial diet and are advised by the folklore of many cultures over centuries. Garlic belongs to the Lily family, along with onions, chives, and shallots [9,10]. Garlic has many uses in different traditions as a therapeutic and prophylactic medicinal herb in addition to its dietary roles throughout the world. In Avesta, some of the earliest references to this medicinal plant were found [11]. Sumerian and the ancient Egyptians used garlic as an important medicine. There is some evidence that garlic was fed to the athletes for increasing stamina during the earliest Olympics in Greece [12].

In the medieval period, garlic was also played an important role in the treatment of different diseases. Avicenna recommended garlic as a useful compound in the treatment of arthritis, toothache, chronic cough, constipation, parasitic infestation, snake and insect bites, gynecologic diseases, as well as in infectious diseases (as antibiotic) [13].With the onset of Renaissance, special attention was paid in Europe to the health benefits of garlic. Garlic has attracted particular attention of modern medicine because of widespread belief about its effects in maintaining good health. The biological effects of garlic have been largely attributed to the reduction of risk factors for cardiovascular diseases and cancer, stimulation of immune function, antimicrobial effect, antioxidant effect, enhancement of detoxification of foreign compounds, hepatic protective effect and restoration of physical strength [14-16].

Several studies have shown that garlic can protect the liver cells from some toxic agents including drugs like acetaminophen and gentamicin. Dietary inclusion of garlic powder improves antioxidant status and modulates oxidative stress caused by gentamicin [17]. In addition, garlic attenuated hepatotoxicity effect of nitrate in rats. Garlic extract may enhance an antioxidant defense system and reduce lipid peroxidation [18].

The aim of this study is to investigate the possible protective effect of garlic oil in preventing hepatic injury caused by administration of CsA through the study of histopathological changes in the liver tissue.

MATERIALS AND METHODS

Chemicals

CsA was obtained from Novartis Pharma AG, Basle, Switzerland and was given to the experimental rats orally via gavage at a daily dose of 12.5 mg/kg body weight [19]. Garlic oil was purchased from a local market (Kerbala, Iraq). Garlic oil was given orally by gavages at a dose of 5ml/Kg/day [20].

Animals

In this study, we used twenty-four male rats weighing 230-250 gm purchased from the international center of drug researches (Baghdad, Iraq). Rats were left in our laboratory for one week before beginning the experiment for acclimatization. The animals were kept under good ventilation and received a balanced diet and water throughout the experimental period. They were kept with a 12 h light/dark cycle and received human care. The experimental protocol and procedures used in this study was approved by the Ethics Committee of the Kerbala University, Kerbala, Iraq for the care and use of laboratory animals. The animals were randomly divided into four groups each having 6 rats.

Group 1. Animals of this group were considered as a control group. They were fed with only standard rat diet and tap water for 28 weeks.

Group 2. Animals of this group were treated with CsA orally via gavage at a dose level of 12.5 mg/kg body weight, every day for 28 days.

Group 3. Animals of this group were treated with garlic oil orally via gavage at a dose level of 5ml/kg body weight, every day for 28 days.

Group 4. Animals of this group were given orally similar dose of CsA as group 2 after 3 hours of garlic oil administration orally (5 ml/kg body weight) for 28 days.

At the end of the experiment, rats were sacrificed 24h after the last garlic oil and CsA received.

Histopathological Examination

The animal was killed under anesthesia and its extremities were fixed to the dissection board with drawing pins. Vertical midline incision was given from the xiphoid process to pubic symphysis and skin and abdominal muscles were retracted laterally before fixing them. Kidneys and livers were freed from connective tissue coverings and gently removed and examined macroscopically. 3-5 mm^2 thick tissue pieces were excised from the organ and were fixed in 10% formalin solution, dehydrated in ascending grades of alcohol, cleared in xylene and embedded in paraffin. 5µm thick sections were obtained and subsequently stained with eosin and hematoxylin and examined under light microscope (Leica DM 5000B) [21].

RESULTS

Histopathological examination showed no changes of hepatocytes structure of the liver tissue of garlic oil group when we compared it with the liver tissue of the control group as in figures (2) and (4). On the other hand, we noticed that administration of CsA alone resulted in necrosis and fatty infiltrate as seen in figure (3); but these defects were ameliorated by giving garlic oil with CsA as in figure (5).

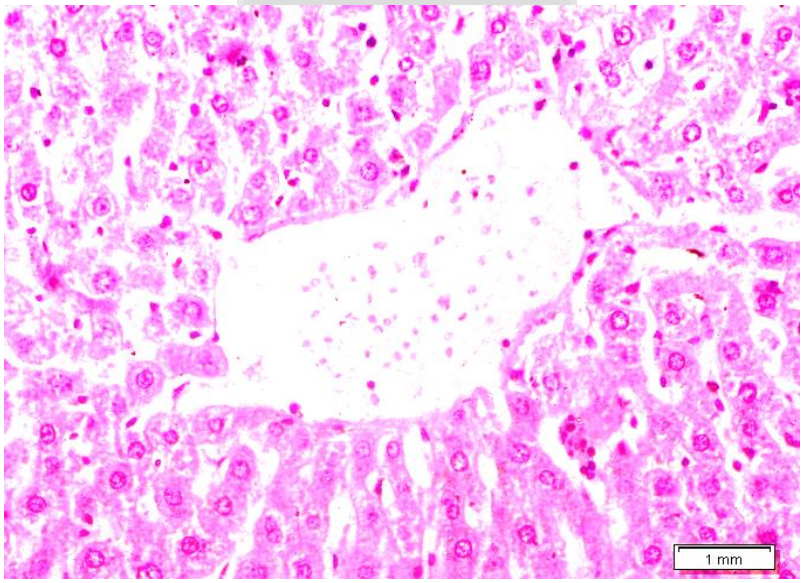

Figure (2): Liver section from a control rat showing normal histological appearance of hepatocytes, central vein and sinusoids (400).

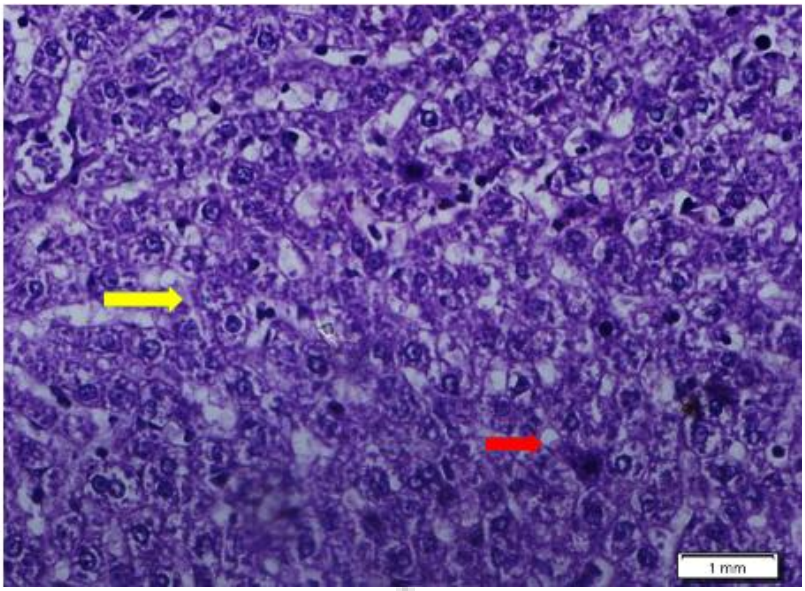

Figure (3): Liver section from CsA-treated rat showing diffused scattered moderate hepatocyte necrosis (yellow arrow) and macrovesicular steatosis with sinusoidal dilation (red arrow). (400).

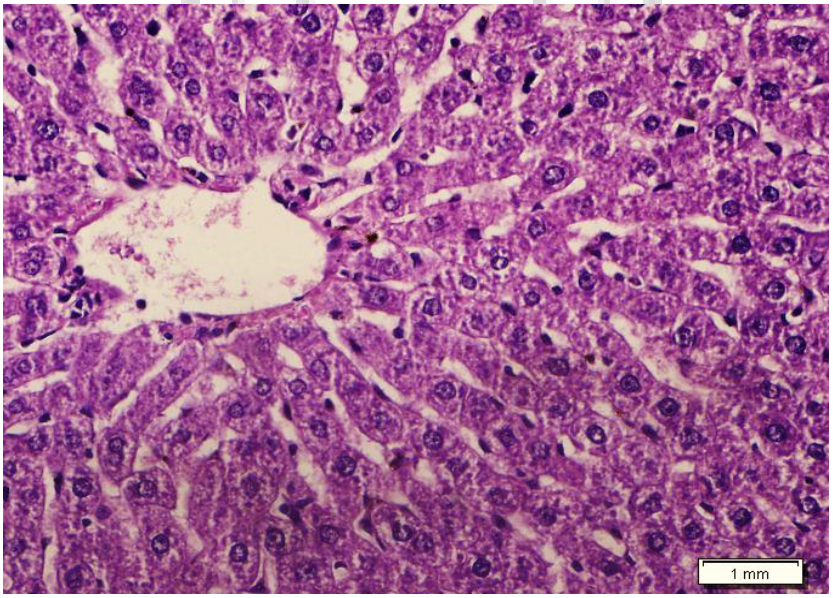

Figure (4): Liver section from garlic oil-treated rat showing normal histology as compared to control rat (400).

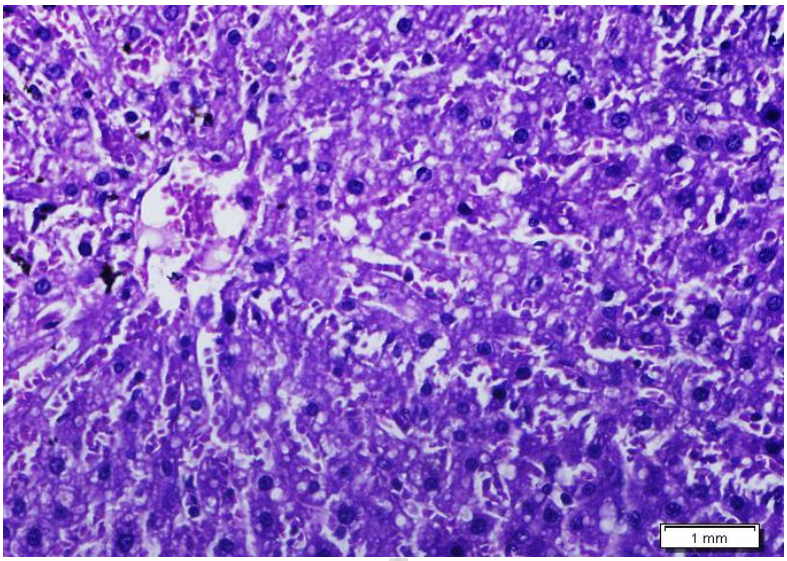

Figure (5): Liver section from (CsA + garlic oil)-treated rat showing reduction of necrosis which manifested as pericentral hepatocyte necrosis and reduction of fatty degeneration (microvesicular steatosis) as compared with CsA-treated rat (×400).

DISSCUSION

This study aims to evaluate the protective effect of garlic oil on CsA induced hepatic toxicity. In this study, we investigated hepatic toxicity through the study of histopathological changes in the liver tissue of rats after administration of Cs A.

Liver is the most important organ**.** It is a key organ regulating homeostasis within the body by various functions, such as metabolism, secretion and storage. Liver injury caused by toxic chemicals and certain drugs has been recognized as a toxicological problem. Hepatotoxicity is one of very common ailments resulting into serious debilities ranging from severe metabolic disorders to even mortality. Most of the hepatotoxic chemicals damage liver cells mainly by inducing lipid peroxidation and other oxidative damages [22-25].

The mechanism underlying CsA hepatotoxicity is not completely cleared but cumulative data showed that oxidative stress plays an important role in its toxicity [26].

In our study the histopathological changes, which occurred in the liver, comprised diffused scattered moderate hepatocyte necrosis and macrovesicular steatosis with sinusoidal dilatation and this is nearly similar to other research [27].

Several studies indicated that garlic has the ability to protect cells of the liver from some toxic agents [28]. We noticed that administration of garlic oil ameliorated the histopathological changes of its effect in reduction of hepatocyte necrosis and fatty degeneration that caused by CsA.

CONCLUSION

To conclude, the study has shown that garlic oil administration provides a protection against cyclosporine-induced injury in the liver of rat and may have hepatic protective effect in the patient experiencing cyclosporine treatment.

RECOMMENDATION

A serious evaluation of the risk-benefit ratio should be taken for each CsA-treated patient with rigorous laboratory and clinical evaluation of each patient.

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