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Estimate the role of *Symphytum officinale* root extract against the hepatotoxicity effect of Orlistat in male rats

Zainab Hasan Majeed
Biology Department, College of Education for Pure Science, Kirkuk University, Iraq.
Zaiynab.hassan@uokirkuk.edu.iq

Abstract

The current study aimed to find the effective role of S. officinale root extract against the hepatotoxicity of Orlistat in male rats. The University of Kirkuk's College of Science is where the current study was carried out. 24 mature male rats were purchased from an Iraqi care facility and a pharmaceutical research facility in Baghdad. They ranged in age from 12 to 16 weeks, and their average body weight was 175 to 200 g. The animals were kept in sanitary conditions, were clinically healthy, and were housed in metal cages and glass bottles. Throughout the duration of the trial, food and water were freely available. 24 male albino rats were placed into four groups, each with six rats: Negative group: which received orally normal saline (0.5) ml/kg BW. Positive group: which received orally Orlistat 2 ml/kg BW. Extract group: which received orally S. officinale 150mg/kg BW. Treated group: which received orally Orlistat 2 ml/kg and treated by S. officinale 150mg/kg. About the results of Orlistat administration, the liver showed hypertrophy of certain areas of hepatocytes, congestion and hemorrhage noticed in certain places, hepatocyte degeneration was linked with auxes of nuclei, ambiguous nuclei, karyolysis of nuclei, and fibrosis. Aggregation of lymphocytes was evident in some areas and had a nodular appearance. After administration of Orlistat to induced various liesions in liver and treated with S. officinale root extract, The liver's cross sections revealed a semi-normal structure, a normal central vein, a semi-normal organization of hepatocytes around the vein, and sinusoids with the same width as those in the control group.

Keywords: Symphytum officinale, Orlistat , hepatotoxicity effect.

Introduction

Symphytum species are members of the Boraginaceae family and number approximately 35 species [1-2]. The most widely utilised species is S. officinale [3-4]. For over 2000 years, comfrey has been suggested for both external and internal utilization as a botanical preparation [5]. Comfrey root contains allantoin [6], abundant mucilage polysaccharides made up of fructose and glucose components [7], and phenolic acids including such rosmarinic, chlorogenic, caffeic acisd, and a-hydroxy caffeic acid [8-10]; Glycopeptides and amino acids [11], also monodesmosidic and bidesmosidic glycosides of the triterpene saponins hederagenin, oleanolic acid, and lithospermic acid [12, 13]. Synphytum's effectiveness is mostly attributed to its analgesic, anti-inflammatory, antiexudative, and granulation-promoting characteristics [14]. Antibiotics are widely used in agriculture, medicine, and veterinary care, which has significantly accelerated the emergence of microbial strains that are more resistant to them and, as a result, made it more difficult to eradicate harmful germs especially the multi-drug resistance bacteria [15-24]. There is growing understanding of how certain plants and the extracts they produce, including those that have antibacterial, antifungal, astringent, and other properties, promote wound healing. The anti-inflammatory, analgesic, and anti-exudative actions of S. officinale were primarily credited by Koll et al. with the plant's medicinal capabilities, along with its capacity to stimulate granulation and tissue regeneration [25]. The only OTC weight-loss medication currently on the market that has been approved by the FDA and EMA [26–27] is orlistat. It has been demonstrated to be a potent, selective inhibitor of gastric and pancreatic lipases, whose primary job is to break down dietary fat [28–29]. liver injury. Since 2001, sporadic occurrences about orlistat's possible liver damage have been documented in the literature [30]. According to a 2012 comprehensive analysis by the European Medicines Agency, orlistat use between 2007 and 2011 was linked to 21 cases of serious liver

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injury globally [31]. Therefore, the objective of the current investigation was to determine the efficacy of S. officinale root extract in protecting male rats' livers against the hepatotoxicity of orlistat.

Materials & methods

Preparation of extracts:

25 grams of the S. officinale root, which had been well cleaned and cut, were placed one at a time in an electric grinder with 100 mL of distilled water. These were centrifuged afterward, and the result was then considered to be 100%. Then, preparations for a study were made with the proper attentiveness.

Drug

20 mg of orlistat from an Actavis, Ireland, capsule was dissolved in 10 ml of isotonic saline (0.9% NaCl), yielding a final concentration of 2 mg/ml that was employed in this experiment.

Experimental animals

The University of tikrit's College of Science is where the current study was carried out. 24 mature male rats were purchased from an Iraqi care facility and a pharmaceutical research facility in Baghdad. They ranged in age from 12 to 16 weeks, and their average body weight was 175 to 200 g. The animals were kept in sanitary conditions, were clinically healthy, and were housed in metal cages and glass bottles. Throughout the duration of the trial, food and water were freely available. 24 male albino rats were placed into four groups, each with six rats:

- Negative group: which received orally normal saline (0.5) ml/kg BW.
- Positive group: which received orally Orlistat 2 ml/kg BW.
- Extract group: which received orally S. officinale 150mg/kg BW.
- Treated group: which received orally Orlistat 2 ml/kg and treated by S. officinale 150mg/kg.

Histological study

Fresh liver from each rat were rapidly dissected, fixed with 10% formalin, and dehydrated with ethanol in escalating quantities. Following dehydration, tissue samples were cleansed in two xylene variations, impregnated in two variables of liquid paraffin wax, then embedded, and blocked out. Haematoxylin-eosin was used to stain tissue slices that were 5 um thick [32].

Results

Control group

The liver's natural anatomy was shown under the microscope, along with its typical central vein, hepatocyte arrangement, and sinusoids (Fig.1).

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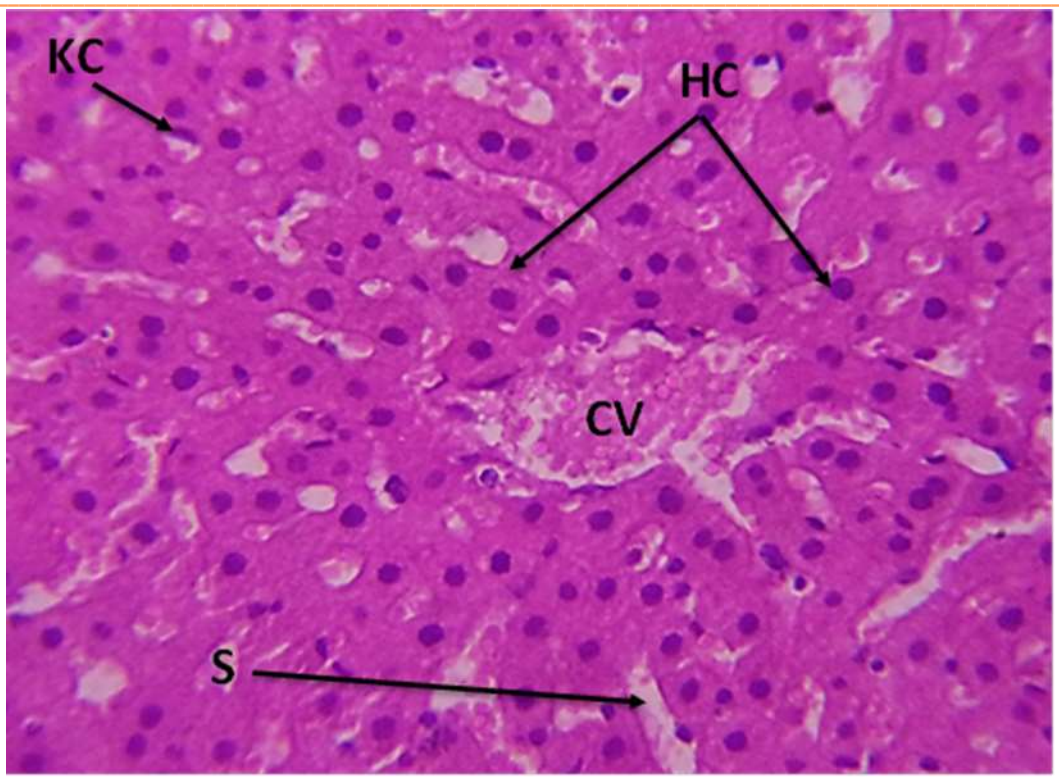

Figure (1): liver of control group showed the normal structure of central vein (CV), hepatocytes (HC), sinusoids (S), and kupffer cells (KC) H&E

Orlistat group

Under light microscopy, the liver displayed hepatocyte hypertrophy in specific regions, congestion and hemorrhage in specific locations, hepatocyte degeneration associated with auxes of nuclei, nuclei that appeared unclear, karyolysis of nuclei and fibrosis, and the lymphocyte aggregation that had a nodular appearance in particular areas (Fig.2).

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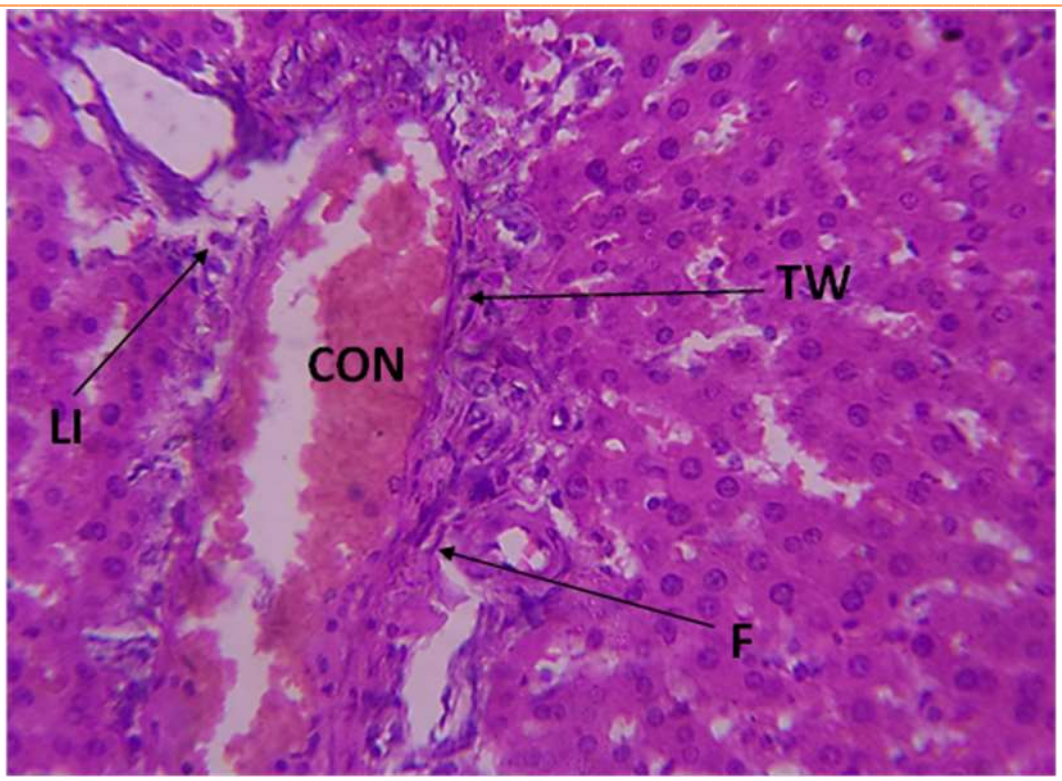

Figure (2): liver of Orlistat group showed thickening wall (TW) of central vein (CV), with congestion (CON), lymphocytes infiltration (LI), and fibrocytes (F)

S. officinale group

The histological analysis of the liver's sections revealed normal liver anatomy, including a normal central vein, hepatocyte organization, and normal sinusoids (Fig.3).

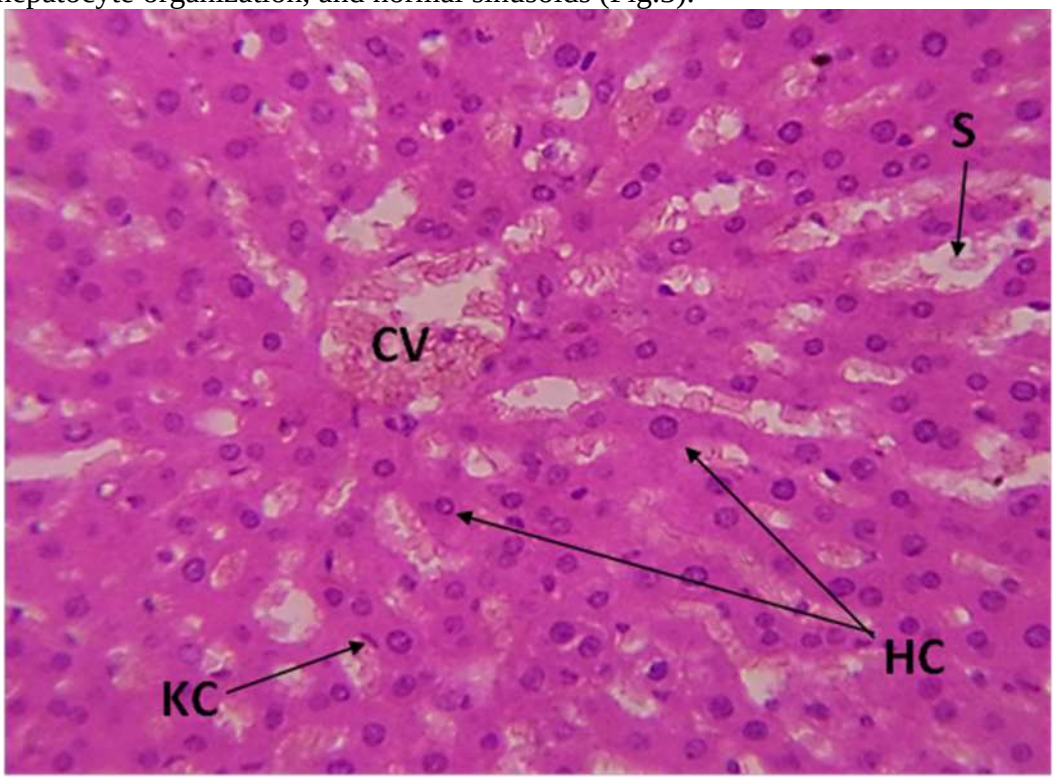

Figure (3): liver of extract group showed central vein (CV), hepatocytes (HC), sinusoids (S), and kupffer cells (KC) H&E X400.

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Treated group

The cross sections of the liver showed a semi-normal structure and demonstrated a normal central central vein, Hepatocytes are arranged somewhat normally around the vein, and the diameter of sinusoids appeared as in the healthy controls after the administration of orlistat to stimulate different liver lesions and treated with S. officinale root extract (Fig.4).

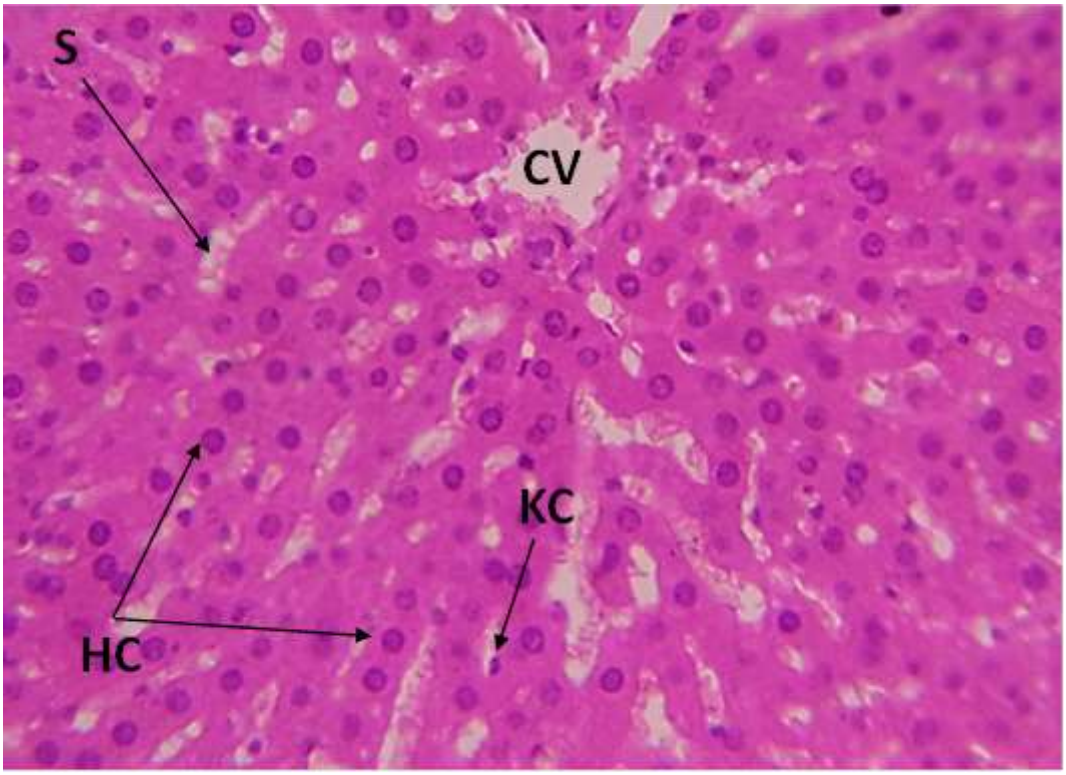

Figure (4): liver of treated group showed central vein (CV), hepatocytes (HC), sinusoids (S), and kupffer cells (KC) H&E X400.

Discussion

Orlistat is well-known for assisting weight loss by enhancing metabolism and, consequently, renal and liver function [33]. Large clinical trials found no difference in the frequency of serum liver test aberrations between orlistat and a placebo. However, the FDA expressed safety concerns about hepatotoxicity in 2010 due to a number of clinical studies of orlistat-associated clinically evident acute liver damage. In cases that were published, the damage began 2 to 12 weeks after beginning orlistat. Hepatocellular was the typical pattern of blood enzyme increases, and some instances were severe with symptoms of hepatic failure that eventually led to death or the requirement for liver transplantation. Both autoimmune markers and hypersensitivity characteristics were lacking. None of the published cases contained the outcomes of rechallenge [31–32], which would have helped to clarify orlistat's hepatotoxicity in the current study. The liver tissues exhibited a good improvement and returned to a semi- normal structure after utilizing S. officinale root extract in the treatment. The therapeutic effectiveness of the homoeopathic medication Symphytum officinale, which operated as an anti-inflammatory, analgesic medicament with specific hepatoprotective qualities, is responsible for the improvement in the liver tissue following treatment [34]. In the other trial, 42 albino rats (180-240 g) were examined in vivo with an alcoholic extract of the plant's roots that was given orally at 0.4 g/kg/day for two weeks [35]. Tetrachloromethane (20 mL/kg) was injected twice per week for two months in order to cause the chronic toxic hepatitis. The outcomes were contrasted for two weeks with those of the reference medication Silibor (30 mg/kg/day). The major results showed that S. officinale extract had effects that were comparable to or greater than Silibor, working by reducing lipodystrophy, restricting conjunctive proliferation in the liver interlobular grooves, and enhancing hepatocyte function. The majority of research has focused on S. officinale root and its constituents, which

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include allantoin, a polyphenol antioxidant, tannins, which are anti-inflammatory and autoimmune enhancers, and the root of S. officinale itself [36–38]. Indeed, a number of studies have shown that comfrey extracts have notable antioxidant properties when compared to other antioxidants [39], which helps to explain the beneficial benefits of S. officinale root extract in the present study.

Conclusions

According to the results of the current investigation, orlistat is harmful to hepatocytes because it causes deterioration and mononuclear cell infiltration. On the other hand, it was discovered in the present research that S. officinale root extract has anti-inflammatory and antioxidant characteristics in addition to being very helpful in protecting liver tissues.

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