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Potential hepatoprotective effect of the crude extract of *Lepidium sativum* on an experimental model of hepatotoxicity

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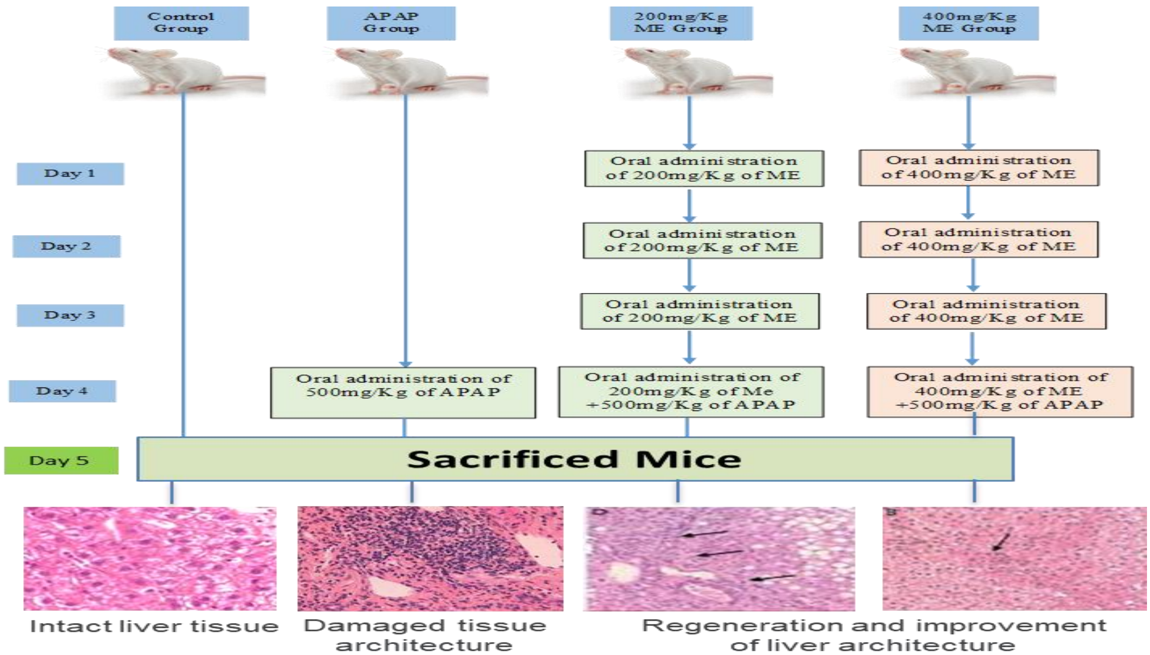
ABSTRACT

To investigate the effect of the high paracetamol doses on liver damage, we developed an experimental model of hepatotoxicity induced by paracetamol. In our study, we were interested in the evaluation of the potential hepatoprotective effect of the methanolic extract of Lepidium sativum (L.sativum ME). The latter, was prepared by maceration in methanol and then analyzed qualitatively, using staining and precipitation methods. Mice were randomly allocated into four groups: Ctrl, Paracetamol, ME (200mg/Kg) /Paracetamol and Paracetamol groups /ME (400 mg/Kg). Mice were euthanized and associated indications were investigated to evaluate the histological changes in the liver of the different groups as well as the degree of liver damage caused by paracetamol with and without treatment. With regard to our results, we have noted with interest a hepatoprotective effect of L.sativum ME. Indeed, our results indicate an improvement of the anatomopathological architecture of the hepatic sections following treatment with L. sativum ME. These observations could promote a potential target for the treatment of hepatic injury.

Keywords: Hepatoprotective; methanolic extract (ME); Hepatotoxicity; Paracetamol; *Lepidium sativum*

Graphical abstract



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1. Introduction

The liver is the main organ that plays a vital role in performing several fundamental functions such as metabolism, detoxification, secretion, storage and energy supply [1, 2]. It represents the main site of metabolism and biotransformation of most xenobiotics such as drugs. This biotransformation results in the formation of free radicals such as reactive oxygen species (ROS) and nitrogen species (RNS) in response to oxidative stress, which can be neutralized by the body's antioxidant system.

Paracetamol (acetaminophen, N-acetyl-p-aminophenol) is a drug most used in the world for self-medication. It is widely known for its analgesic and antipyretic efficacy in relieving pain and fever [3, 4]. However, excessive consumption of paracetamol leads to several liver lesions, resulting in mild to severe acute liver failure and even death [5, 6]. These injuries caused by drug overdose, are at the origin of the formation of N acetyl-p-benzoquinone imine (NAPQI), a very reactive metabolite that binds to cellular macromolecules, leading to mitochondrial oxidative stress, impaired liver function and massive necrosis [6].

The exploitation of natural resources, especially medicinal plants, is of major importance for scientific research and traditional medicine because of their various bioactive compounds, having a wide range of therapeutic potentials effective against many diseases with little or no side effects [7]. Among these plants, *Lepidium sativum*, belonging to the Brassicaceae family and known as garden cress, or Hab Rched, has been the subject of numerous investigations by virtue of its valuable nutritional and medicinal properties [8-16].

It is in this perspective that we have targeted the use of this plant in order to highlighting the potential hepatoprotective effect of its methanolic extract on an experimental model of hepatotoxicity, induced by N-acetyl-p-aminophenol (APAP).

2. Materials and Methods

2.1. Preparation of L. sativum ME

L. sativum seeds were purchased from an herbalist in Algiers, Algeria. The extraction procedure was performed according Hadj Rabia et al. [15]. Briefly, crushed seeds were macerated in 80% methanol for 48h then the mixture was filtered through a nylon filter. Resulting filtrate was concentrated under vacuum at 37 °C using a rotary evaporator (Büchi Rotavapor), freeze-dried and finally stored at +4°C until use. The extraction yield, expressed as a percentage, was calculated according to the formula below.

$$\text{Yield (\%)} = (\text{mass of dry extract} / \text{mass of plant material}) \times 100$$

2.2. Phytochemical study of L. sativum ME

The main bioactive compounds contained in *L. sativum* ME were evaluated by qualitative analysis based on color and/or precipitation reactions [17, 18]. Tannins and phenolic compounds were searched using ferric chloride. The Cyanidin reaction and UV test were used to identified flavonoids and coumarins, respectively. The Wagner’s Reagent and Foam tests for alkaloids and saponins, respectively and that of quinones by the alkaline reagent test.

2.3. Acute toxicity study of L. sativum methanolic extract

The acute toxicity of methanolic extract of garden cress was evaluated via the limit test of the OECD Guidelines for Acute Oral Toxicity Tests 401[19]. In this study, mice were divided into two groups of 3 female mice where one group represented the negative control group and the other, the mice treated with ME.

For this, a dose of 2000 mg/Kg body weight of ME was administered to the mice by gavage in a single dose using a gastric tube. An intensive observation of the mice was carried out during the first four hours after administration, to detect any major behavioral changes such as twisting and convulsions. After 14 days, the mice were sacrificed in order to perform a histological study.

2.4. Experimental design of L. sativum ME-treatment of paracetamol-induced hepatotoxicity

Female Swiss Albino mice (4-6 weeks old) were purchased from the Pasteur Institute (Algiers, Algeria). These mice were acclimated for 1 week before the start of experiments and kept under normal conditions with a 12 h dark/light cycle with *ad libitum* access to food and water. Mice ranging in weight from 21 to 23 g were divided into three groups (n =6 mice per group) as presented in Fig. 1.

The control group (Ctrl) with no treatment. The Paracetamol group were treated by intragastric administration of 500mg/kg of Paracetamol during the fourth day. The ME (200mg/Kg) /Paracetamol and I (400mg/Kg) /Paracetamol groups were treated by daily intragastric administration of 500µl of ME at 200 mg/kg and 400mg/kg, respectively, for four days. All mice were euthanized 5 days post-treatment by using inhalation of anesthesia gas.

This study was approved by the National Thematic Agency Research in Health (N°43-ANDRS-2011).

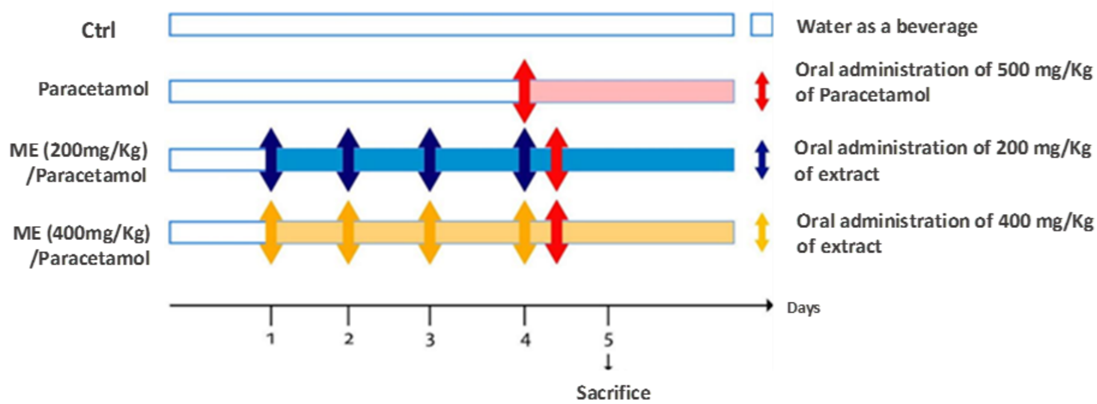

Fig. 1. Experimental plan.

2.5. Histopathological analysis

Liver samples were fixed in 10 % formalin, mounted in paraffin blocks and cut into 2-μm-thick sections. The sections were stained with Hematoxylin and Eosin stain to evaluate structural alterations of the hepatic parenchymal cells.

Histological criteria were based on the degree of architectural tissue changes and cellular infiltration. Images were captured from each slide with a digital camera (Casio) on a light microscope (Motic) with 10× and 40× objectives. Histopathological diagnoses were performed in double blinded fashion by pathologists.

We have established a score at the liver level corresponding to the histological activity index (HAI) as described by Labsi et al. [20, 21].

3. Results and Discussion

Liver diseases are a major health problem worldwide. Nowadays, their prevalence is linked to viruses due to ingestion or infection, various toxic chemicals as well as drugs such as paracetamol. Plants used in the traditional medicine for liver disorders are of great interest, as they may serve as potential sources for new therapeutic agents that could be applied in the management and prevention of hepatic injuries.

The valuable pharmacological effects of L. sativum, namely its antioxidant, anti-inflammatory and hepatoprotective properties, have prompted us to target this plant to explore its extract in a phyto-preventive approach, using mice poisoned with paracetamol as an experimental model.

In our study, we proceeded to the preparation of L sativum extract by maceration in methanol. The extraction was carried out at room temperature and with stirring in order to accelerate the extraction process. Moreover, we took care to concentrate our extract under vacuum at 37 ° C to obtain and preserve a maximum of bioactive compounds [22].

Based on previous works, reporting the importance of using suitable solvents for good solubility of bioactive compounds, we have chosen methanol since it allows the recovery of several polar and semi-polar compounds that belong to different chemical classes [23-26].

The methanolic extraction yield of our plant was obtained at 10.19%. By carrying out ethanolic and methanolic extractions of L. sativum seeds, from different regions of Morocco, Chatoui et al. [27] achieved the highest yields by methanolic extraction. However, the extraction rate, which varied from 19.03-31.9%, depending on the region, was found to be high compared to that obtained in our study. This was also observed by Chatoui et al. [24] and Omer et al. [28] who estimated rates of 34.2% and 18.7%, respectively.

This fluctuation in extraction yield could be due to the different chemical composition and which in fact depends on several factors, such as geographical origin, genetic properties of plants, the part of the plant used, age of the plant, the drying conditions, time of harvest and the extraction procedure and solvent [27] .

Qualitative phytochemical screening is a very important step that serves to generate a large library of bioactive phytochemical constituents of plants with medicinal significance [28, 29]. The result of the phytochemical study of our extract revealed the presence of polyphenols, coumarins, flavonoids, catechic tannins, alkaloids, quinones as well as saponins. This reflects the richness of this plant in bioactive compounds [16], well known for their different biological properties [15]. Our results are in the same trend of those obtained by several researchers, who found the occurrence of these different classes of bioactive compounds in *L. sativum* extracts [24, 30].

The study of the acute toxicity of the prepared methanolic extract is considered an essential step in order to ensure its safety before use. This test, showed no signs of toxicity or death in mice at doses up to 2000 mg/kg body weight. However, the histological study revealed the presence of some slight lesions in the liver, which are represented by congestion of the hepatic veins, the presence of coagulation necrosis, binucleated nuclei as well as a slight infiltration by immune cells (Fig.2).

The evaluation of this toxicity was based on the limit test for chemical testing, carried out on a limited number of animals (6 mice were used in our study). According to the OECD, if at least three animals survive, the LD50 is greater than 2000 mg/kg [19] and therefore the toxicity is considered low. The plant will then be classified in category 5 (LD50 between 2000-5000 mg/kg), according to the classification of the Globally Harmonized System for the Classification of Chemicals Causing Acute Toxicity [31].

To study the hepatoprotective activity of our methanolic extract, this required an experimental model of hepatotoxicity that was induced in mice by administration of high doses of APAP. The latter turns out to be oxidized in the liver by cytochrome P450 enzymes to NAPQI (N-acetyl-p-benzoquinone imine), a harmful and highly reactive metabolite. In the normal case, this product is rapidly neutralized by cellular antioxidants, thus forming non-toxic complexes before their elimination. However, in case of overdose, the surplus of non-neutralized NAPQI leads to the excessive production and accumulation of free radicals such as reactive oxygen species (ROS) and nitrogen species (RNS). These species cause oxidative damage in liver cells (hepatocytes) including disruption of cellular functions, lipid peroxidation, inflammation and cell death by necrosis.

In the present study, the intoxicated groups (receiving high doses of paracetamol) pretreated with *L. sativum* methanolic extract (200 or 400mg/Kg ME), tested for 4 days, revealed a liver tissue architecture almost similar to that of the control group (Fig.3(a)). On the contrary, the paracetamol group (500mg/Kg Paracetamol) showed the presence of several quite flagrant lesions (Fig.3 (b)), which are represented by coagulation necrosis, several binucleated hepatocytes, quite severe congestion of the hepatic veins as well as an obvious infiltration by immune cells. While the liver tissues of both groups pretreated with 200 or 400 mg/kg ME exhibited a similar microscopic appearance with improved histological structure, showing the presence of some binucleated hepatocytes, slight cell infiltration, absence of congestion in the hepatic veins and decrease in necrosis (Fig.3(c)(d)).

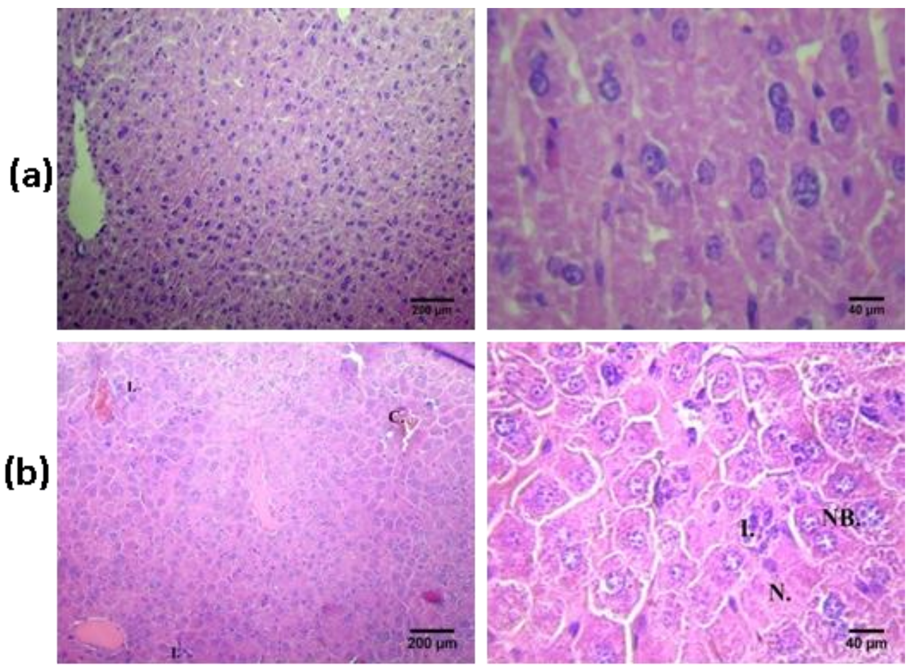

Fig. 2: Representative micrographs (x10 and x40) of liver sections from mice stained with Haematoxylin/eosin from the control group **(a),** treated with 2000 mg/kg ME (b). (N): Coagulation necrosis; (NB): Binucleated nucleus; (I): Infiltration of immune cells; (C): Congestion.

The histological activity index (HAI) which is a score based on histological examination of tissues, was used in our study to assess and quantify the extent of damage and inflammation in tissues. The result of this examination showed a significant decrease of HAI (Fig.4) in the treated group compared with that intoxicated, hence approving hepatoprotective effect of *L. sativum* ME. Our results are in agreement with previous studies whose histopathologic findings showed less inflammation, good hepatocyte restoration and reduced necrosis area unlike the intoxicated group [32, 33, 34]. Abuelgasim et al. [32] also stated the efficiency of *L. sativum* extract as hepatoprotective agent. They are also consistent with those of Raish et al. [12], reporting that the pretreatment with *L. sativum* ethanolic extract restored the antioxidant enzymatic status and total proteins to normal levels in addition to improving the degree of structural damage and reducing inflammatory cell infiltration. This indicates the effectiveness of *L. sativum* extract in alleviating liver failure and tissue damage through decrease in oxidative stress and inflammation. This improvement in the liver function as well as the reduction in the generation of free radicals could be attributed to the presence of flavonoids [35, 36] existing in our extract, knowing that they have the ability to trap radical species and reactive forms of oxygen [37]. This could be supported by the previous work that suggested the involvement of isoflavones in enhancing the antioxidant defense mechanism [38]. Lee et al. [39], also reported the essential role of phenolic compounds against oxidative stress related liver damage.

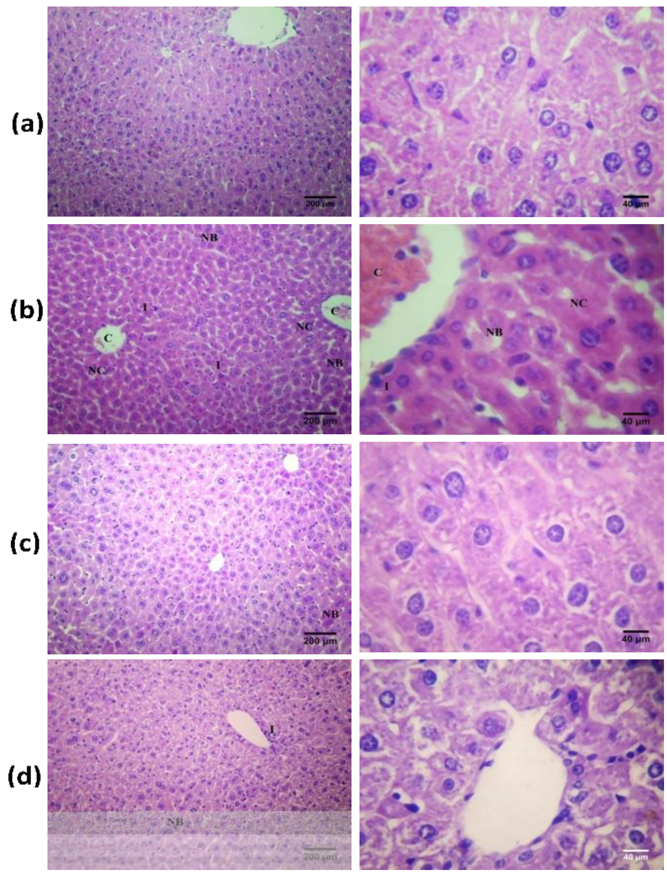

Fig. 3 Representative micrographs (x10 and x40) of liver sections from mice stained with haematoxylin/eosin from the control groups **(a)**, treated with 500 mg/kg paracetamol **(b)**, treated with 200 mg/kg ME **(c)**, treated with 400 mg/kg ME **(d)**. (NC): Coagulation necrosis; (NB): Binucleated nucleus; (I): Infiltration of immune cells; (C): Congestion.

The presence in our extract of compounds having antioxidant and/or anti-inflammatory properties [13, 36, 40, 41, 42] could support the idea of some researchers who attributed the hepatoprotective effect to these two properties [34].

Our findings demonstrated that *L.sativum* ME exhibited a similar protective effect at both 200 and 400mg/Kg, as indicated by its ability to reduce tissue damage following the oxidative stress, caused by paracetamol toxicity. However, further investigations would be encouraging in order to better improving this hepatoprotective effect.

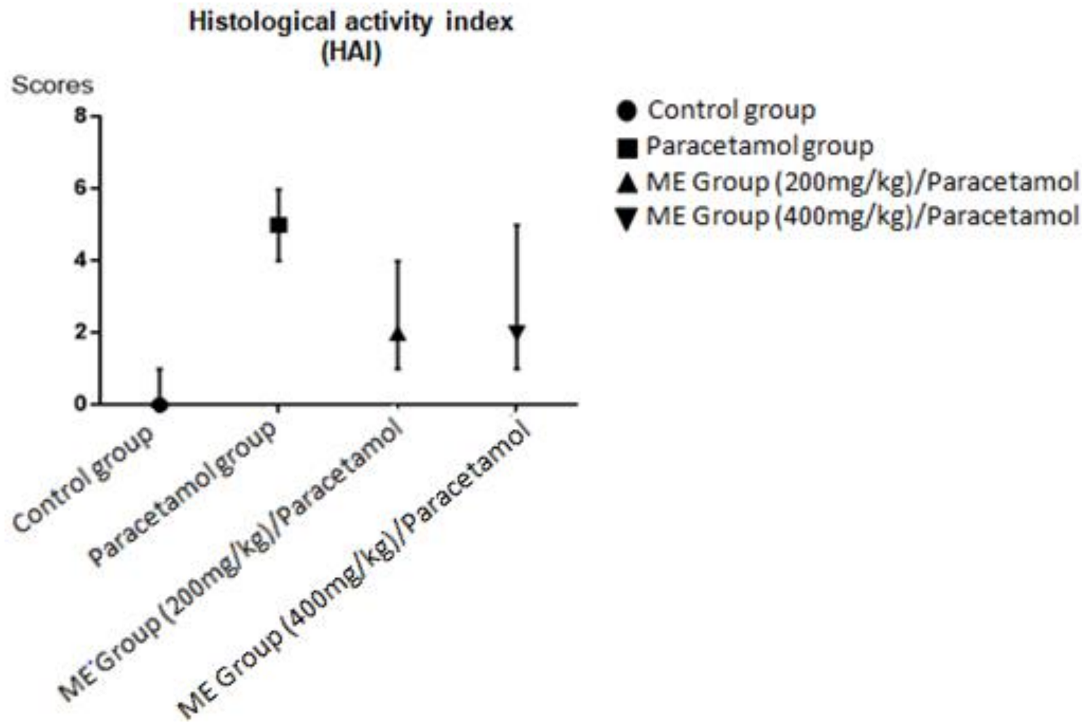

Fig. 4: Improvement of histological architecture by administration of ME in mice intoxicated with paracetamol

4. Conclusion

The results from this study provided insight into the potential biological activities of *L. sativum* ME. Our data support the hypothesis that ME treatment has both anti-oxydant and hepatoprotective effects through its ability to protect liver against tissue damage, enhancing antioxidant activity and reducing free radical production due to paracetamol-induced toxicity. This suggest that methanolic extract of *L. sativum* could be a good candidate in the treatment of hepatic injury.

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Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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