Consequence of *Lepidium Sativum* Seeds on Flat of Biochemical Parameters in Albino Male Rats Treated with Acetaminophen

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Abstract

Experiment is to assess efficiency of alcoholic extract of *Lepidium sativum* seeds in improving erythropoietin levels and some other biological parameters against acetaminophen-induced hepatotoxicity and nephrotoxicity. The study was worked in Labs / Unive. Kufa for the period from 1/10/2021 to 1/12/2021, with a follow-up of (42) three-month-old male albino rats, their weights ranged between 215-242 g to assess the protective role of the alcoholic extract of *Lepidium sativum* seeds in inhibiting acetaminophen-induced hepatotoxicity and nephrotoxicity, the rats were divided into six groups with seven animals for each group. The first group, which is the control group, and they were dosed with tap water once a day, the second group, that were orally dosed with acetaminophen 1000mg\kg once, and the third group was treated with the alcoholic extract of *Lepidium sativum* seeds at a concentration of 250 mg/kg and an hour later was given acetaminophen 1000 mg/kg orally, while the fourth group was treated with alcoholic extract of *Lepidium sativum* seeds at a concentration of 500 mg/kg and an hour later they were given acetaminophen 1000 mg/kg orally, and the fifth group was treated with alcoholic extract of *Lepidium sativum* seeds at a concentration of 250 mg/kg orally only, and with regard to the sixth group, it was treated orally with the alcoholic extract of *Lepidium sativum* seeds at a concentration of 500 mg/kg only, and the treatment continued for a period of 60 days, once a day, in the morning (at half past eight). The study included evaluation of some biochemical parameters such as levels of erythropoietin hormone, iron ion, total iron binding capacity, total bilirubin, creatinine, urea, reduced and oxidized glutathione, malondialdehyde and lipid peroxide, decreasing of erythropoietin, iron ion, total iron binding capacity, reduced and oxidized glutathione, and important increase ($P<0.05$) in the levels of total bilirubin, creatinine, urea, malondialdehyde and lipid peroxidation in the group that was treated with the drug compared to the control group. As for the group that was given the alcoholic extract of *Lepidium sativum* seeds at a concentration of 250 mg/kg + acetaminophen, it did not show a protective role for this concentration against the toxic effects of the drug, as it showed important differences ($P<0.05$) in all parameters included in the current study compared with the control group. Contrary to above, the group that was given the alcoholic extract of *Lepidium sativum* seeds at a concentration of 500 mg/kg + acetaminophen did not reveal important alterations ($P\geq0.05$) in the study criteria compared with the control group. Concern to the group of rats treated with alcoholic extract of *Lepidium sativum* seeds concentration 250 mg/kg only, it did not give important differences in the study parameters compared with the control group, except for the level of reduced glutathione, which showed important increase ($P<0.05$).

Finally, the group that orally dosed the alcoholic extract of *Lepidium sativum* seeds at a concentration of 500 mg/kg only, recorded important elevation ($P<0.05$) in the levels of erythropoietin hormone, iron ion, total iron binding capacity, reduced and oxidized glutathione, and in contrast important reduction ($P<0.05$) in the levels of total bilirubin, creatinine, urea, malondialdehyde and lipid peroxide in comparison with the control group.

Key Words: Alcoholic Extract of *Lepidium Sativum* Seed, Acetaminophen, Biochemical Parameters, Erythropoietin Hormone.

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Introduction

Recently, a wide and rapid spread of the use of medicinal plants has been observed in the prevention and treatment of common diseases, due to their safety and effectiveness, as well as many of them have been used in the manufacture of various pharmaceutical compounds because they contain many active elements and compounds, among these plants is the *Lepidium sativum*, its properties pharmacologically similar to the properties of non-steroidal anti-inflammatory drugs, as it is an analgesic, antihypertensive, anti-inflammatory, anti-oxidant, anti-bacterial, and others[1], witnessed a steady increase in the number of recorded cases of liver poisoning caused by the use of high doses of the drug worldwide [2]. Nephrotoxicity also occurs because it is very common, as well as causes many pathological impacts in the kidney tissues [3, 4].

Erythropoietin (EPO) is made and released by the interstitial cells surrounding the renal tubules of the kidney through activation of hypoxia-inducible factor, alpha hypoxia-inducible factor (HIF), which controls the metabolic response of many genes to hypoxia, and the hormone stimulates erythroid-colony-forming unit (E-CFU) [5],mechanism that contributes to anemia, and the degree of oxidation is closely related to the state of inflammation, in addition, these mechanisms include distortion of the cellular membranes of red blood corpuscles, which leads to a shortened lifespan [6], and an increase in the production of the hormone hepcidin, which prevents the intestinal absorption of iron and the filling of iron stores by binding with ferropotine on the cell membrane, while stimulating resistance to erythropoietin [7].

Materials

Experiments was the period (1/10/2021 until 1/12/2021), and forty-two adult albino male rats were used, with average weights ranging between 215-242 g and three months old, exposed for the same duration of illumination at a rate of approximately 12 hours per day. The animals were provided with water and a diet rich in proteins.

Preparation of Acetaminophen

The drug was brought in a dose of 1000 mg/kg from the pharmacy, the dose assigned - each animal was given according to weight [8].

Preparation of Lepidium Sativum Seeds

The *Lepidium* in the present work purchased via markets, and then they were classified and diagnosed by specialized plant classification professors.

Preparation of Alcoholic

The alcoholic solution was prepared according to the method mentioned in [9].

Experimental Groups for Study

The first group, which is the control group, contained seven rats, and they were dosed with tap water for 60 consecutive days and once a day. The second group, the drug group, included seven rats that were orally submitted to acetaminophen drug once, and this continued for 60 consecutive days, at a rate of 1000 mg/kg. The third group, the drug and extract group, contained seven rats that were first administrated orally with an alcoholic extract of *Lepidium sativum* seeds at concentration 250 mg / kg, and an hour after the first dose was given, acetaminophen was dosed orally with 1000 mg / kg, and the dose was once a day for a period that lasted 60 consecutive days. The fourth group, the drug and extract group, contained seven rats that were first given orally an alcoholic extract of *Lepidium sativum* seeds at a rate of 500 mg / kg, and an hour after giving the first dose, acetaminophen was dosed orally with 1000 mg / kg, and the dose was once a day for a period of 60 consecutive days. The fifth group, the extract group, and this group included seven rats that were orally subjected to an alcoholic extract of *Lepidium sativum* seeds 250 mg/kg only and once a day for 60 days without interruption. Lastly, the sixth group, the extract group, this group included seven rats that were orally treated with an alcoholic extract of *Lepidium sativum* seeds 500 mg/kg only and once daily for 60 days without interruption.

Sacrifice of Laboratory Animals

Dosing period in the six animal groups, a substance (ketamine and xylazine) was used in a ratio of 3:1 for anesthetizing the animals. The blood sample for each animal and then (4 ml) was placed in a gel tube to evaluate the biochemical parameters.

Study of the Biochemical Parameters of the Blood

A. Assessment of Erythropoietin

The enzyme immunoassay method (Erythropoietin ELISA) was used to evaluate erythropoietin level in serum according to the method [10], which was supplied by IBL-International GMBH, Germany, and the absorbance was read at a wavelength of 450 nm.

B. Estimation of Iron Ion Level in the Serum

The colorimetric method test (CAB method) was used, supplied by Merck, Germany, according to the [11] method and the absorbance was read at a wavelength of 623 nm.

C. Estimation of the Fe- in the Serum

The colorimetric method test, supplied by Merck, Germany, was used according to the [12] method and the absorbance was read at a wavelength of 623 nm.

D. Estimation - Bilirubin Level

The level of total bilirubin was estimated by using the diagnostic kit supplied by France, Biolabo company according to the method [13], and it was measured at 550 nm wavelength.

E. Estimation of Creatinine

The creatinine was evaluated by using a ready-made diagnostic test kit as shown in [14], and the absorbance was recorded at the wavelength 490 nm.

F. Estimation of Urea

The serum urea level was estimated by using the ready-made diagnostic kit as stated in the creatinine assessment method [14].

G. Estimation of Reduced-glutathione Level in the Serum

The level of reduced glutathione was measured by estimating its size using the optimal enzymatic cycling method and according to the [15] method, the absorbance was measured at a wavelength ranging from 405 - 414 nm.

H. Estimation of Oxidized Glutathione Level in the Serum

The level of oxidized glutathione enzyme in the serum was evaluated by using the assay kit equipped by BT-LAB company and the ELISA device according to the method [16], and its absorbance was estimated at a wavelength of 412 nm.

I. Estimation of Malondialdehyde Level in the Serum

The level of malondialdehyde was estimated according to the method of Armstrong and Brown [17], and the absorbance was read at wavelength 530 – 540 nm.

J. Estimation of Lipid Peroxide Level in the Serum

It was previously reported to evaluate the level of oxidized glutathione, and the absorbance was read at 450 nm wavelength.

Statistical Analysis of the Study

In addition to the study groups were compared by using the ANOVA test, and the value of the least important difference LSD below the probability ($P<0.05$) [18].

Results

From the statistical analysis of the results of the study, important ($P<0.05$) decrease of erythropoietin was observed in the group that was orally dosed with acetaminophen, and the group that was given an alcoholic extract of *Lepidium sativum* seeds 250 mg/kg + drug compared with the other study groups, in addition to recording this indicator when these two groups were compared with each other, on the other hand, the alcoholic extract of *Lepidium sativum* seeds 500 mg/kg caused a notable increase ($P<0.05$) in the level of erythropoietin hormone in compared to the control group and the group that was orally given the alcoholic extract of *Lepidium sativum* seeds 250 mg/ kg, as well as the group that administrated with alcoholic extract of *Lepidium sativum* 500 mg/kg + the drug.

Table 1. Treatment with *Lepidium sativum* and acetaminophen on the level of erythropoietin

Assemblies	Mean± standard error	
	Sum of trials	Erythropoietin, mlU/ml
G1	7	21.14 ±0.59 B
G2	7	10.57±0.84 D
G3	7	17.29±0.48 C
G4	7	20.57±0.81 B
G5	7	22.00±0.65 B
G6	7	24.43±0.72 A
L.S.D		1.802

Table 2. Impact - *Lepidium sativum* seeds and acetaminophen on iron ion level and total iron binding capacity

Groups of study	Means ± Standard Error		
	Number of samples	Iron ion µg/dl	General Fe-binding aptitude µg/dl
G1	7	97.40 ±0.94 B	229.20 ±0.79 B
G2	7	76.40±0.95 D	179.49 ±2.31 D
G3	7	88.71±0.77 C	192.25± 3.27 C
G4	7	96.09±1.13 B	227.25± 0.82B
G5	7	98.40± 0.55 B	230.60 ±0.64 B
G6	7	105.30±1.10 A	239.2±0.79 A
L.S.D		2.668	5.0178

Table (2),shown reduction (P<0.05) in the iron ion which treated with acetaminophen, as well as the group of alcoholic extract of *Lepidium sativum* seeds 250 mg/kg + the drug. Furthermore, there was a noticeable difference (P<0.05) in both criteria when comparing the above two groups with each other. With regard to the alcoholic extract of *Lepidium sativum* seeds 500 mg/kg, important increase (P<0.05) in the level of iron ion and the total iron binding capacity in the group dosed with it orally, that was given *Lepidium sativum* seeds extract 250 mg/kg only, as well as the one that was submitted to the extract 500 mg/kg + drug respectively.

The treatment with acetaminophen 1000 mg/kg caused an observable (P<0.05) increase in the levels of bilirubin, creatinine and urea, as well as important (P<0.05) rise in the levels of these biomarkers was obtained in the group that was given *Lepidium sativum* seeds extract 250 mg/kg + acetaminophen in comparison to the control group and the rest of the other study. Moreover, no remarkable differences (P>0.05) were indicated in the levels of the mentioned criteria when comparing the other groups included in the current study with each other.

Table 3. Effect of treatment with alcoholic *Lepidium sativum* and acetaminophen on the of total bilirubin, and factors

Assemblies	Means ± Standard Error			
	Sum. samples	Total Bilirubin mg/dl	creatinine mg/dl	Urea mg/dl
G1	7	0.433 ±0.04 C	0.216 ± 0.02 C	21.57 ±0.68 C
G2	7	0.906 ±0.04 A	0.937 ±0.04 A	45.43 ±1.47 A
G3	7	0.610 ±01 B	0.503 ±0.009 B	30.29±0.94 B
G4	7	0.471± 0.03 C	0.251±0.01 C	21.87±0.86 C
G5	7	0.440 ± 0.02C	0.213 ±0.006 C	21.87 ±0.68 C
G6	7	0.423±0.02 C	0.204 ±0.006 C	21.00±0.87 C
L.S.D		0.0855	0.0506	0.3415

Otherwise, the alcoholic extract of *Lepidium sativum* seeds 500 mg/kg caused a important increase of reduced and oxidized glutathione in compared with the control group and the group that was given *Lepidium sativum* seeds extract 250 mg/kg, as well as the group that was dosed with the extract 500 mg/kg + the drug.

Concern to the levels of malondialdehyde and lipid peroxide in the serum, also the group that was given the extract 500 mg/kg + acetaminophen, while there were no notable changes (P>0.05) in the levels of those vital signs when comparing the group that was given *Lepidium sativum* seeds extract 250 mg/ kg with that dosed orally with the extract 500 mg/kg + drug, and also when comparing both groups with the control table (4).

Table 4. Effect of treatment with alcoholic and acetaminophen on the of antioxidants (GSHr and GPx1), oxidative stress markers (MDA) and lipid peroxide in serum

Groups of study	Means ± Standard Error				
	Number of samples	GSHr ng/ml	GPx1 nmol/ml	MDA nmol/L	Lipid peroxide nmol/ml
G1	7	168.00 ±0.72 C	37.96 ± 0.63B	0.914 ±0.12 C	3.947 ±0.07 C
G2	7	32.00 ±0.72 E	10.02 ± 0.05E	1.543 ±0.03 A	6.117 ± 0.06A
G3	7	101.85±1.9 D	26.03 ±0.51 D	1.301±0.05 B	4.953± 0.08 B
G4	7	165.85 ±1.3 C	36.04 ±1.03 C	0.934 ±0.01 C	4.076 ±0.06 C
G5	7	172.71 ±0.89 B	38.58 ±0.52 B	0.901 ± 0.006C	3.885 ±0.03 C
G6	7	191.29±1.27 A	41.09± 0.32 A	0.510 ±0.01 D	2.514 ±0.04 D
L.S.D		3.449	1.7021	0.0759	0.19

Discussion

Attribute to an obstruction in the response to hypoxia, which negatively affected the functional performance of the kidneys, and subsequent reduced levels of the hormone erythropoietin [17-20]. Also, the decreased levels of antioxidants (reduced and oxidized glutathione), which were documented in this study, may have had a negative effect in decreasing the biological production of the hormone by intercellular cells surrounding the renal tubules. In addition, the group treated with the alcoholic extract of *Lepidium sativum* seeds 250 mg/kg + the drug recorded a noticeable decline in the level of erythropoietin, may be explained to the dosing with this concentration for 60 days did not provide the preventive efficacy against hepatotoxicity and nephrotoxicity caused by acetaminophen. Otherwise, the group that was received the alcoholic extract of *Lepidium sativum* 500 mg/kg + acetaminophen organized not show important change in the level of erythropoietin hormone, may due to the antioxidant contained of *Lepidium sativum* seeds at this concentration revealed an anti-drug-induced nephrotoxic effect [21,22], especially vitamin C [23]. Besides, the group treated with a concentration of 250 mg/kg of alcoholic *Lepidium sativum* seeds extract did not appear a remarkable change in the level of the hormone, and this may explain to the physiological efficiency of the plant extract components in protecting the liver and kidney tissues from infections and various diseases.

Finally, the group submitted to alcoholic of *Lepidium sativum* 500 mg/kg showed important rise in the level the hormone erythropoietin, it is likely to be due to the chemically and biologically active contents of the extract such as amino acids, proteins, vitamins and minerals [24], which may have improved the functional performance of the renal interstitial cells and worked to activate and maintain them on its homeostasis, then consequent elevation the rate of bio-production of erythropoietin and importantly increase its levels in the lood.

The finding of the present study also indicated an observable decrease in the level of Fe- ion and total iron binding capacity in the group treated with acetaminophen be related to the decline in the levels of the hormone erythropoietin, the number of red blood corpuscles with the content of hemoglobin and the packed cell volume that are documented in the current study. In addition, the reduction in the total iron binding capacity may suggest to the decrease for transferrin in the blood, and therefore the values of the total iron binding capacity are low. Furthermore, the group administrated with the alcoholic extract of *Lepidium sativum* seeds 250 mg/kg + the drug experienced important decrease in the above vital parameters, may be due to this concentration of the extract did not prevent the patho- histological influences on the liver cells that caused by the drug, such as damage to some central hepatic veins with severe bleeding and the appearance of congestion in some of the others, which documented in the current study.

With regard to the group dosed with alcoholic extract of *Lepidium sativum* seeds 500 mg/kg + acetaminophen, it did not show important alterations in the level of iron ion and the total iron binding capacity in comparison to the control group.This may be explained to the active constituents of the *Lepidium sativum* seeds of enzymatic antioxidants such as glutathione and catalase as well as non-enzymatic antioxidants particularly vitamins and alkaloids that act to scavenge free radicals and rid cells of toxicity[25], and then preserving the renal and hepatic tissues,

as well as preventing the occurrence of bleeding in them, and this is supported by the histological examination of the livers of rats that were treated with the plant extract at a concentration of 500 mg/kg + the drug, which appeared to be healthy without any important damage.

The animals were given the alcoholic extract of *Lepidium sativum* seeds 250 mg/kg did not detect a noticeable difference in the level of iron and the total iron binding capacity, and the reason may be due to the effective contents of the extract preventively and curatively acted together to stimulate antioxidants and inhibit the increased production of free radicals, which resulted in the complete protection of hepatic tissues where excess iron is stored in the liver and released as needed [26], thus maintaining iron levels and binding capacity in the blood without important change.

Concern to the alcoholic extract of *Lepidium sativum* seeds 500 mg/kg, was caused a rise in the level of iron ion and the total iron binding capacity in the rats dosed with it compared with the rest of the experimental groups, and it is likely to be due to the extract contained of flavonoids, alkaloids and iron [27], which might have had a positive effect in activating bone marrow tissues to increase the production of red blood corpuscles, this was proven in the current study, which may have stimulated the rise in iron levels and the total iron-binding capacity. The levels of total bilirubin in the current study revealed important increase in the group treated with acetaminophen in compared to the control group, and these results in agreement with many studies [28,29], but did not agree with other studies [30], which confirmed that the level of total bilirubin was not affected by the drug. It is possible to explain this increase to the toxic effect of acetaminophen on the membranes of hepatocytes by stimulating the lipid peroxidation process and then structural disorder to the cellular membranes, as well as the inhibition of glycoproteins formation due to the increased generation of detrimental free radicals [31], which may cause the swelling of those cells and consequently cellular decomposition by phagocytic cells in the liver [32].

Besides, the same group also witnessed a remarkable rise in the level of creatinine and urea, this result comes along with some studies [28], but it differed with others [30], which did not show important difference in those vital criteria. The result was explained by the decrease in the functional performance of the renal glomeruli, which was negatively reflected in the filtration rates due to the oxidative stress resulting from the toxic effect of the drug, it has been documented that many patho-histological changes in the kidney tissues were induced by acetaminophen administration, such as the appearance of hemorrhage in some renal convoluted tubules, congestion, and edema. For the group treated with alcoholic extract of *Lepidium sativum* seeds 250 mg/kg + the drug, the results indicated important rise in the levels of total bilirubin compared with the control group, and this may due to the insufficiency of the physiological action of the alcoholic extract components of *Lepidium sativum* seeds at a concentration of 250 mg/kg in protecting liver tissue from various infections and diseases, as well as the toxic impacts of the drug on hepatocytes, and then subsequent an increase in bilirubin level. This group also recorded important elevation in the levels of creatinine and urea, which may be due to the antioxidants such as flavonoids, tannins and the rest of the phenolic components of *Lepidium sativum* seeds at a concentration of 250 mg/kg did not suppress the pathological effects of the drug, causing their levels to elevate in the blood.

In relation to the group submitted to the alcoholic extract of *Lepidium sativum* seeds 500 mg/kg + acetaminophen, it organized is not show any important change in the levels of total bilirubin comparison to the control group, and this possibly due to the efficiency of this concentration of the plant extract in preserving red blood corpuscles and protecting them from the influences of the drug, and then maintain bilirubin at its normal levels in the blood. As for the levels of creatinine and urea, they also did not show an observable difference in the same group, and this may explain that the extract possesses active natural antioxidants such as glycosides, steroids, alkaloids and vitamins [27], which may have worked synergistically to protect the renal tissues from the adverse effects of acetaminophen. In relation with concentrations of 250 mg/kg and 500 mg/kg of the alcoholic extract of *Lepidium sativum* seeds respectively, the levels of total bilirubin did not change in the blood when probably due to the protective and curative influences of the extract chemical components with antioxidant activity such as tocopherol and vitamins [33]. Furthermore, the levels of creatinine and urea did not importantly affected in the same group, and this

may be explained by the efficiency of the extract in scavenging free radicals and reducing oxidative stress.

The statistical analysis of the result compatible with some studies [21, 34, 35], which indicated lower levels of antioxidants and higher markers of oxidative stress when treated with the drug. This likely attribute to the dose of 1000 mg/kg of acetaminophen may stimulate the oxidative stress in the hepatic and renal tissues by activating the process of lipid peroxidation and thus the production of various types of free radicals and reactive oxygen species that cause histological damages in the liver and kidneys, as well as this was documented in the current trial were represented by the expansion of some central hepatic veins, hemorrhage, edema, infiltration of inflammatory cells and congestion.

The group that received the alcoholic extract of *Lepidium sativum* seeds 250 mg/kg + acetaminophen exhibited important reduction of antioxidants, while an increase in the bio-markers of oxidative stress, this may be due to the concentration of 250 mg/kg did not remove the free radicals that generated by the drug, which resulted in a defect in the efficiency and effectiveness of the antioxidant enzymes, and consequently a decrease in their levels in the blood.

On the other hand, the group treated with concentration of 500 mg/kg of alcoholic extract of *Lepidium sativum* seeds + acetaminophen did not record any noticeable change, malondialdehyde and lipid peroxide, but it witnessed important decrease in the levels of the oxidized glutathione compared to the control group, and this may be explained to the presence of large amounts of the most biologically active antioxidants in the *Lepidium sativum* seeds,in particular the catechins, which has the ability to endow hydrogen ions for the stability of free radicals [36, 37].

Regarding the group that treated with the alcoholic extract of *Lepidium sativum* seeds 250 mg/kg, it did not reveal important changes in the levels of antioxidants and of oxidative stress parameters, except for reduced glutathione, which recorded an observable increase in its levels compared to the control group. This possibly due to the *Lepidium sativum* extract contain numerous active compounds particularly phenolic compounds, such as tocopherol, which is one of the most powerful antioxidants, as vitamin A and essential fatty acids protect against oxidation, and work to prevent damage to various body tissues from the negative effect of free radicals [37], and then maintain a balance between the mechanisms that cause the production of free radicals and that help to get rid of those toxic radicals.

Finally, lipid peroxide compared to the control group, may be explained by the richness of *Lepidium sativum* seeds with many vitamins, including vitamin E, which is one of the important antioxidants that acts to protect unsaturated fatty acids from oxidative stress damage, which confirms that *Lepidium sativum* seeds can equip the body with vital antioxidants that reduce the adverse effect of free radicals, and thus increase the levels of antioxidants, and conversely decrease the oxidative stress parameters[38].

Conclusion

The alcoholic extract of *this plant* at a concentration of 500 mg/kg has a shielding efficiency contrary to the injurious belongings of acetaminophen, and this may be attributed to its active antioxidant components.

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