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Evaluation of the hepatoprotective role of ethanolic *Saussurea lappa* root extract in female rats experimentally exposed to propylthiouracil

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ABSTRACT

Propylthiouracil (PTU) is often used to produce experimental hypothyroidism. In general, PTU generates hepatotoxicity, albeit with dissimilar incidence rates of hepatotoxicity. This study examined the hepatoprotective effects of *Saussurea lappa* root ethanol extract on experimentally induced hepatotoxicity in female rats. For this study, 25 adult female albino rats were placed into five equal groups: control, PTU, post treated with *S. lappa* extract, co-administered PTU with *S. lappa* extract 300mg/kg, and post-treated with levothyroxine. Serum gamma-glutamyl transferase (GGT) activity, total protein, thyroid hormones (T3, T4, and TSH), and oxidative stress parameters (catalase, superoxide dismutase, reduced glutathione, and lipid peroxidation levels) were measured. The liver tissue underwent histological examination. Current findings revealed that *S.lappa* ethanol root extract significantly improved hepatotoxicity as evidenced by reversal of various biochemical and histopathological changes in female rats. Current study has shown that this promising impact may be due to the antioxidant and free radical scavenging characteristics of *S.lappa* constituents.

1. Introduction

Since the 1940s, PTU has been utilized, and throughout time, hepatic adverse effects have been recorded, until the food and drug administration published a black box warning on the prescription label in 2010. About one in a way associated with an elevated risk of hepatotoxicity, but not cholestasis or abrupt liver failure [1]. PTU is the third drug most significantly associated with liver transplantation, and approximately 25% of PTU-induced hepatotoxicity-related deaths have been documented [2]. Recent European guidelines and consensus by experts from Italian endocrine and gynecologic scientific societies recommend limiting the use of PTU to the first trimester of pregnancy [3,4] and as a second-line antithyroid drugs treatment, if methimazole caused toxic reactions, and as a short-term treatment, while awaiting radioiodine therapy or thyroid surgery [3]. Also, PTU should be avoided in children [3]. The largest and most economically important family of angiosperms is Asteraceae. This family has over 1,620 genera and 23,000 species [5]. Asteraceae family members have significant medicinal potential and are utilized by locals to cure a wide range of ailments [6]. The *Saussurea lappa* (Costus) an important medicinal plant belonging to the Asteraceae family [7,8]. It is a perennial herbaceous plant that has been used for centuries in various traditional medicinal practices all over the globe to cure conditions including diarrhea, tenesmus, dyspepsia, and vomiting [9,10]. Antioxidants found in abundance in *S.lappa* may fight against germs, fungus, worms, cancers, inflammation, ulcers, diabetes, and liver damage while boosting the immune system [11]. This study aims to evaluate whether the root of *S.lappa* protects the liver from PTU-induced hepatic damage.

2. Materials and Methods

2.1. Plant material and Preparation of Extract

The *S.lappa* roots were supplied from a herb store in Kirkuk, Iraq, and then identified and certified by a

botanist in the Biology department/College of sciences of Kirkuk University. According to [12], a weight of 100 grams of the root powder of the *S.lappa* plant soaked in 400 of 70% ethanol alcohol for 72 hours at laboratory temperature, with continuous shaking from time to time then filtered three times and evaporated to obtain a crude *S.lappa* extract.

2.2. Chemicals

PTU is manufactured by the Italian business RECORDATI ILAC. Euthyroxin (100µg) was manufactured by the German corporation Merck KGaA. The reagents and chemicals used in this study were of high purity and analytical grade. Also, kits from Sigma (Sigma kit- SE120135, SE120121, SE120132) were used to determine the concentration of thyroid stimulating hormone (TSH), triiodothyronine(T3), and thyroxine (T4).

2.3. Animal and Experimental Design

Twenty-five albinos female Wistar rats weighing between 200 and 250 grams were used. Before commencing the experiment, the animals were acclimatized in their separate cages for 2 weeks at hygienic and under stable environmental conditions (28 ± 2°C, 60-70 % humidity, and a 12-hour light/dark cycle), with free access to water and food. Rats got comprehensive treatment according to conventional management standards. After acclimating to the conditions of the laboratory, the rats were randomly divided into 5 groups (5 rats in each group):

- **GI:** For eight weeks, healthy animals in the control group had unfettered access to food and water.
- **GII:** Rats in the PTU group received 0.05 % orally [13] 6-n-propyl-2-thiouracil (PTU) per day for eight weeks.
- **GIII:** Post-treated by ethanol extract of *S.lappa* root (P-T-eSL), after being given 0.05% PTU orally every day for a period of four weeks to cause hepatotoxicity, rats were then given eSL 300 mg/kg orally [12] for a further four weeks (from 5th - 8th week) to cure the hypothyroid state.
- **GIV:** Co-administration PTU-eSL (CO-PTU-eSL); rats were given 0.05% PTU orally for eight weeks, coupled with eSL (300 mg/Kg).
- **GV:** Post treated by LT4 (P-T-LT4); to develop hepatotoxicity in rats, 0.05% PTU was orally delivered for 4 weeks, then animals were given levothyroxine (LT4) (0.4µg) [14] by gavage for an additional 4 weeks (from 5th - 8th week)

2.4. Biochemical blood serum assay

The activity of GGT and concentration of total proteins (TP) was done according to [15,16]. Additionally, TSH, T3, and T4 levels in serum were assessed using commercial kits by the manufacturer's recommendations. According to previously described procedures, the levels of the serum antioxidant enzymes super oxide dismutase (SOD), catalase (CAT), total reduced glutathione (GSH), and lipid peroxidation (MDA) were evaluated spectrophotometrically [17-20].

2.5. Statistical Analysis

One-way ANOVA and the Duncan multiple comparison test are used to analyse the values, which are shown as mean + standard error (SE) in SPSS Version 21.2. The threshold for significance was set at ($P \leq 0.05$) [21].

2.6. Histological techniques

The liver was taken, fixed in formalin solution at 10% concentration, dehydrated using increasing concentrations of ethanol alcohol, and xylene. Then, embedded in paraffin, sectioned at a thickness of 5µ, stained with haematoxylin and eosin (H&E), and examined under a light microscope [22].

3. Results

3.1. Liver function

In contrast to control rats, GII rats had higher levels ($P \leq 0.05$) of GGT and considerably lower levels of TP (table.1). Treatments with eSL substantially increased ($P \leq 0.05$) the levels of TP in GIV and a non-significant increase in GIII, and decreased levels of GGT in serum of GIII and GIV when compared to the GII. Additionally, there was a significant difference ($P \leq 0.05$) between the GII and the GV that received levothyroxine.

Table 1: Effect of eSL on serum TP and GGT.

Group	Total protein g/dl	GGT IU/L
I	7.619 ± 0.220 a	15.552 ± 0.576 c
II	6.573 ± 0.136 c	24.492 0.969 a
III	6.741 ± 0.215 bc	17.415 ± 1.284 bc
IV	7.546 ± 0.387 a	18.652 ± 0.451 b
V	7.059 ± 0.016 abc	16.082 ± 1.159 bc

* There is no statistically significant between letters that are similar to one another. ($P \leq 0.05$, n = 5). *Values are expressed as mean ± SE.***I**=control, **II**=PTU, **III**=P-T-eSL, **IV**=CO-PTU-eSL, **V**=P-T-LT4.

3.2. Oxidative – Antioxidants Parameters

GII rats exhibited significantly lower ($P \leq 0.05$) levels of GSH and lower SOD and CAT activities, and greater levels of MDA when compared to GI. In contrast, GIII and GIV, treatments with eSL significantly raised ($P \leq 0.05$) the activities of CAT, SOD, and GSH and lowered levels of MDA compered to GII. Additionally, the GV that got LT4 compared to the GII differed significantly from one another as well (table.2).

Table 2: Effect of eSL on serum liver antioxidants profile and MDA.

Group	MDA mmol/ml	SOD mmol/ml	GSH mmol/ml	CAT mmol/ml
I	1.596 ± 0.039 c	0.820 ± 0.032 a	0.422 ± 0.023 bc	1.580 ± 0.088 a
II	2.417 ± 0.257 a	0.433 ± 0.009 c	0.286 ± 0.011 f	1.014 ± 0.027 c
III	2.142 ± 0.186 b	0.629 ± 0.066 b	0.376 ± 0.015 cd	1.352 ± 0.090 b
IV	1.972 ± 0.069 b	0.563 ± 0.029 b	0.342 ± 0.009 d	1.206 ± 0.030 b
V	1.490 ± 0.047 c	0.830 ± 0.008 a	0.452 ± 0.0150 ab	1.612 ± 0.040 a

* There is no statistically significant between letters that are similar to one another. (P≤0.05, n = 5). *Values are expressed as mean ± SE.***I**=control, **II**=PTU, **III**=P-T-eSL, **IV**=CO-PTU-eSL, **V**=P-T-LT4.

3.3. Thyroid function test

By Comparing the GII to GI, T3, and T4 levels were considerably lower (P ≤ 0.05), and TSH levels were substantially higher (table.3). In contrast, GIII-IV had a substantial rise (P ≤ 0.05) in T3 and T4 levels and a reduction in TSH levels compared to GII. On the other hand, there was a statistically significant difference (P ≤ 0.05) between the levothyroxine-treated GV and the GII.

Table 3: Effect of eSL on serum TSH, T4, and T3.

Group	TSH (mlu/l)	T4 (ng/ml)	T3 (ng/ml)
I	0.083 ± 0.002 c	5.373 ± 0.253 a	3.37 ± 0.1520 a
II	3.412 ± 0.188 a	2.244 ± 0.344 c	1.497 ± 0.159 c
III	2.719 ± 0.154 b	3.000 ± 0.078 b	2.153 ± 0.112 b
IV	2.573 ± 0.213 b	2.993 ± 0.243 b	2.013 ± 0.078 bc
V	0.086 ± 0.001 c	5.757 ± 0.067 a	3.474 ± 0.2656 a

* There is no statistically significant between letters that are similar to one another. (P ≤ 0.05, n = 5). *Values are expressed as mean ± SE.***I**=control, **II**=PTU, **III**=P-T-eSL, **IV**=CO-PTU-eSL, **V**=P-T-LT4.

3.4. Histopathology

Light microscopy of GI tissue sections revealed normal appearance of liver tissue (Fig.1, section.1). Histological examination of GII liver tissue showed many histological changes, such as severe thickening of the central vein wall (TW) with moderate congestion (CON), as well as severe infiltration of lymphocytes (LI) with severe degeneration (D), as well as mild hemorrhaging (section 2, A and B). In contrast, tissue sections from both GIII-IV-V exhibited regenerative alterations in liver tissue architecture as compared to GII (Fig.1, sections.3A, B, 4A, B, and 5A, B).

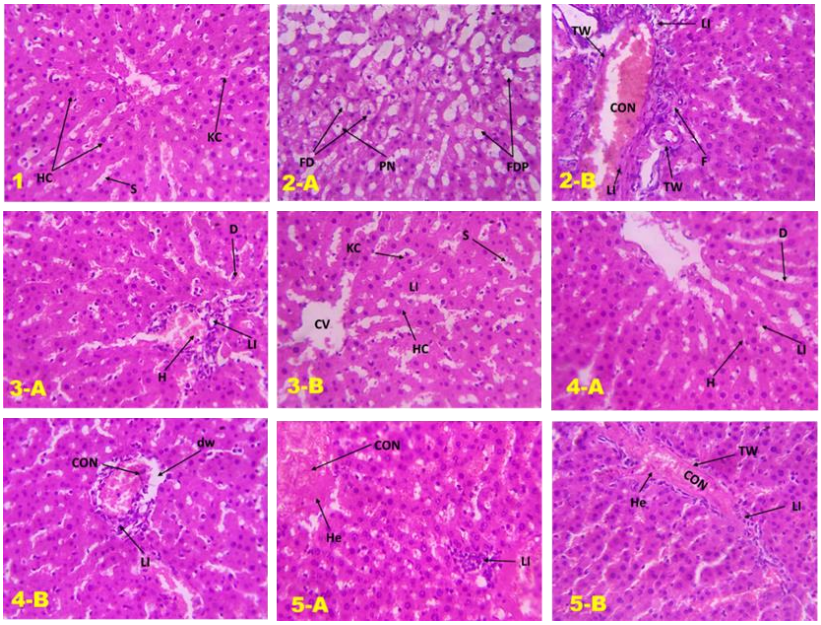

Figure 1: Effect of PTU 0.05% orally, eSL 300 mg/kg, CO-PTU-eSL, LT4 after PTU treatment on liver tissue of female rats. Section (1) of the GI shows the normal hepatic cells (HC), central vein (CV), Kupffer cells (KC), and normal diameter of sinusoids (S). Section (2 A, B) of the GII shows the presence of fatty droplets (FDP) with severe fatty degeneration (FD) observed in the hepatocytes with the presence of the pyknotic nucleus (PN), in addition to severe lymphatic infiltration (LI). Sections (3A, B, and 4A, B) of the GIII and IV showed the presence of trace hemorrhagic (H) in the central vein with mild thickening in its wall (TW) and discontinuous wall (dw) of the central vein in GIV liver tissue in addition to degeneration(D) of hepatocytes. Sections (5A, and B) of the GV indicate the presence of the trace of Hemolysis (He) and blood congestion (CON), and thickening in the wall (TW) of the central vein, as well as the presence of lymphatic infiltration (LI).

4. Discussion

The rats of GII had a significant increase ($P \leq 0.05$) in GGT and MDA concentration and a significant decrease ($P \leq 0.05$) in TP concentration and SOD, CAT, and GSH activities compared to GI. These results correspond to [23]. The exact mechanism of acute liver injury caused by PTU is unknown, it is most likely caused by an immune response to one of its metabolic by products. Lymphocyte activation by PTU has been reported to produce favourable results in a number of cases [24]. There is evidence that PTU and/or its metabolites inhibit glutathione transferase (GST) or glutathione peroxidase (GPx) enzymes in a dose-dependent manner [25].

So, the GSH reserves ran out, which came to an increase in free radicals' concentration compared to SOD, CAT, and GSH concentrations, which in turn damaged liver cells and released the GGT enzyme into the extracellular medium [26]. In addition, the current study's histopathological examination revealed several abnormalities in the liver tissue of GII animals. These results are in agreement with [23, 27]. The PTU is commonly used to induce hypothyroidism experimentally [28]. There is a connection between hypothyroidism and free radicals. Also, hypothyroid individuals have high levels of MDA [29] this is also what current results revealed caused the formation of free radicals and led to histological changes. In contrast, liver tissue of GIII and GIV rats improved greatly, as shown by current histological examination compared to GII. The results of our current study agree with [30]. In a recent study, it was found that the extract of the *S.lappa* root can protect the liver from the toxic effect of CCL_4 [31]. Yaeesh et al. have also noted that the aqueous-methanol extract of *S.lappa* has considerably slowed the progression of D-galactosamine and lipopolysaccharide induced hepatitis in mice [32]. These improvements could be attributable to phytoconstituents compounds such as flavonoids and phenols that act as anti-oxidant compounds to effectively prevent radical-induced oxidative damage [33, 34]. On the other hand, the administration of rats with eSL in GIII and GIV resulted in a considerable decrease ($P \leq 0.05$) in GGT, and MDA concentration and a significant increase ($P \leq 0.05$) in TP concentration, and SOD, CAT, and GSH activities. These results are in agreement with [35, 36]. This might be because phytochemical components including flavonoids, and chlorogenic acid function as antioxidants, reducing PTU toxicity by decreasing free radical-induced lipid peroxidation [30, 37]. Compared to the GI, the GII of rats had a significant increase ($P \leq 0.05$) in TSH, and a significant decrease ($P \leq 0.05$) in T4, T3 hormones, while the (III, IV) groups demonstrated the opposite result. The present study's findings are consistent with [35, 36], and this may be because the eSL includes a number of physiologically active compounds, such as phenols, in addition to dehydrocostus lactone, alkaloids, costunolide, and other medicinally significant chemicals [38-39]. Furthermore, may be due to the high content of flavonoids in eSL, which protect against inflammation and increase blood flow [40].

5. Conclusions

The current investigation revealed that administration of PTU to female rats was related to abnormalities levels of thyroid hormones, GGT activity and oxidative stress parameters and that therapy with *S.lappa* ethanol extract ameliorated these variations in blood, suggesting hepatoprotective properties of *S.lappa* root.

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الملخص

غالبًا ما يتم أستخدام عقار Propylthiouracil (PTU) لأستحثاث القصورالدرقية التجريبي. بالأضافة الى كونه يتسم بسمية كبدية. فقد أختبرت الدراسة الحالية التأثيرات الوقائية للكبد لمستخلص الأيثانولي لجذر نبات *Saussurea lappa* ضد السمية الكبدية المستحثة تجريبياً في إناث الجرذان بواسطة عقار PTU. في هذه الدراسة تم تقسيم 25 من أناث الجرذان البيضاء البالغة ذات أزوان تتراوح من 200−280 الى خمس مجموعات متساوية: المجموعة الضابطة ،ومجموعة PTU، ومجموعة PTU بعد المعالجة بمستخلص *S.lappa*، ومجموعة PTU المترافقة مع مستخلص *S.lappa*، ومجموعة PTU بعد المعالجة ببديل الدرقية اليفوثيروكسين. تم قياس فعالية GGT في المصل وقياس تركيز كل من البروتين الكلي وهرمونات الغدة الدرقية(TSH, T4, T3) ومتغيرات الإجهاد التأكسدي (CAT ، SOD ، GSH, و MDA). أيضاً خضع نسيج الكبد للفحص النسيجي. أظهرت النتائج أن المستخلص الإيثانولي لجذر *S.lappa* قام بتخفيض معنوي في فعالية GGT وتركيز MDA وكذلك أرتفاع معنوي في كل البروتين الكلي ومستويات مضادات الأكسدة بالأضافة الى تحسن كبيرفي نسيج الكبد. قد يرجع ذلك التأثير الواعد الى التركيز العالية من مضادات الأكسدة التي يحتويها مستخلص هذا النبات ، وذلك كما أتضح من درستنا الحالية.