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Antihyperlipidemic, Hepatoprotective, and Nephroprotective Activity of Two Different *Matricaria pubescens* Methanolic Extracts in Rats

Kherraz Khaled [1], Mohammed Messaoudi[2*], Laouedj Hacene[3], Ghemam Amara Djilani[3], Chefrour Azedinne[4], Maria Atanassova [5], Barbara Sawicka[6], Ayomide Victor Atoki[7], Wafa Zahnit[8]

[1] Laboratoire d'Ethnobotanique et Substances Naturelles, Ecole Normale Supérieur- kouba, Algeria
[2] Nuclear Research Centre of Birine, P.O. Box 180, Ain Oussera, Djelfa 17200, Algeria.
[3] Laboratory of Biology, Environment and Health, faculty of S N V Department biology, University of ElOued 39000, Algérie
[4] Department of biology, Faculty of Nature and Life Sciences, University Mohamed-Chérif Messaadia Souk Ahras, Algeria
[5] Nutritional Scientific Consulting, Chemical Engineering, University of Chemical Technology and Metalurgy,1734 Sofia, Bulgaria.
[6] Department of Plant Production Technology and Commodities Science, University of Life Science in Lublin, Akademicka 15 Str., 20-950 Lublin, Poland.
[7] Department of Biochemistry, Kampala International University, Ishaka, Uganda
[8] Department of Chemistry, Faculty of Sciences, University of Ferhat ABBAS Setif 1, 19000 El Bez, Algeria

ABSTRACT

Matricaria pubescens, an aromatic plant, is traditionally utilized for treating rheumatism, gout, and asthma. This work assessed the therapeutic potential of two methanolic extracts from *M. pubescens* (EMMP1 and EMMP2) against obesity symptoms like overweight and hyperlipidemia in male rats. These rats, after receiving a dose of Triton X-100, showed notable gains in body weight, leptin levels, and serum levels of LDL-cholesterol, triglycerides, and overall cholesterol, coupled with a significant decrease in HDL-cholesterol. However, the administration of two extracts to hyperlipidemic rats ((Hyp + EMMP1) and (Hyp + EMMP2)) significantly reduced their body weights by 14% and 19%, and serum leptin levels were significantly reduced by 24% and 19%, respectively. These results indicate liver damage that happened after CCl4 exposure, resulting in a 64%, 29%, 65%, and 233% a rise in the serum concentrations of liver enzyme activity including ALAT, ASAT, LDH, and ALP. The study indicates that extracts from *M. pubescens* have notable effects in reducing obesity and managing fat levels, while also protecting the liver from damage and reducing oxidative stress. This suggests they could be valuable in treating conditions related to obesity.

Keywords: *Matricaria pubescens*, Antihyperlipidemic, Hepatoprotective, Nephroprotective, Triton X-100, CCl4, Cisp, EMMP.

1. INTRODUCTION

Obesity, a severe energy and metabolic disease, was becoming A serious problem for public health [1, 2]. The change in lifestyles and the increased consumption of dietary fat are indeed contributing to the epidemic explosion of this high-risk pathology [3].

[*]***Corresponding author: Mohammed Messaoudi***
messaoudi2006@yahoo.fr
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Excessive or abnormal fat accumulation in the body can result in numerous public health issues and serves as a major risk factor for the development of various severe chronic diseases, such as cardiovascular and type II diabetes [4]. On the other hand, a stringent diet that controls hyperlipidemia may slow the progression of several metabolic illnesses and lower morbidity and death rates [5].

Various synthetic medications, including fenofibrates and statins, are commonly prescribed for the treatment of hyperlipidemia and obesity. In contrast, synthetic obesity

drugs have unwanted side effects that bother the patient [6]. Because of their superior health advantages and capacity to preserve and enhance food quality and nutritional content, phenolic substances are valued by both individuals and companies. [7]. An organism's natural physiological state permits it to absorb substances that are liquid, solid, or gaseous. These substances can enter an organism by a variety of routes, including contact with the skin, inhalation, or ingestion. The kidneys and liver are just two of the many animal tissues that these xenobiotics target. Numerous environmental variables, such as chronic drug use or illnesses like diabetes, might have an impact on the kidneys [8]. In addition, the liver is crucial in the detoxification of various medications and harmful substances. Many of these compounds can be converted into ROS, which have been demonstrated in multiple animal and human hepatotoxic tests to have hepatotoxic effects [9The anticancer medication cisplatin and the CCl4 have been employed as models to assess their respective nephrotoxicity and hepatotoxicity [10]. Using alternative treatments in this situation may be a cost-effective and patient-friendly approach. In traditional Algerian medicine, *M. pubescens* named in Algeria with *Guertoufa.* is used as an active treatment against rheumatism, gout, and asthma. The plant is widely distributed in the southern Algeria deserts [11]. Therefore, the present work aims to invest the therapeutic effects of two methanolic extracts of *M. pubescens* from the Eloued region (EMMP1) and (EMMP2) against the manifestations of obesity such as overweight and hyperlipidemia observed in male rats rendered obese by the use of Triton X-100Additionally, to investigate the protective properties of these two extracts against CCl4- and Cisplatin-induced hepatotoxicity and nephrotoxicity, respectively.

2. MATERIAL AND METHODS

2.1. Extraction procedure

The research was based on *M. pubescens* samples; The plants were collected during the spring season in the El Oued region (located in the southeast of Algeria) in April 2022. The Plant was identified by Pr. Djilani Gh. (Eloud University) and a voucher specimen (SN-S22-012a). One of the plants was cultivated, while the other grew naturally. After collection of plant material, the aerial part was air-dried at room temperature, away from direct sunlight. The extractions were carried out using methanol. The resulting extracts were concentrated using a rotary evaporator. The extracted was stored in sealed glass vials at 4°C under suitable conditions until further analysis.

2.2. Animals

The investigation was conducted on Wistar strain male rats weighing 140 ± 23 g. The animal facility was kept at 22 ± 2°C with a 12-hour light/dark cycle, and the relative humidity was approximately 40%. The animals were cared for during the experimentation time in accordance with the moral guidelines that apply to animal experimentation.

2.3. Obesity Protocol

Male rats are subdivided into 6 distinct groups of 8 animals for each: A group of control rats who were force-fed olive oil (Control); One group (EMMP1) was received a solution of the extract one dissolved in olive oil via gavage at a dosage of 50 mg/kg/Bw for a duration of 15 days. One group (EMMP2) received by gavage a solution of the extract two of dissolved in olive oil at a rate of 50 mg/kg/Bw, for a duration of 15 days. A group of rats named (Hyp) administering a single intraperitoneal dose of Triton X100 (100 mg/kg bw) in typical saline. A group of animals made hyperlipidemic and which received the methanolic extract of *M. pubescens* dissolved in olive oil at a rate of 50 mg / Kg of BW by gavage (Hyp + EMMP1). A group of animals made hyperlipidemic and which received the methanolic extract of *M. pubescens* dissolved in olive oil at a rate of 50 mg / Kg of BW by gavage (Hyp + EMMP2) [12].

2.4. Hepatotoxicity and nephrotoxicity protocols

The hepatotoxicity activity tests were carried out using adult male rats are subdivided into six groups according to the treatment of eight animals for each they receive. Two groups, EMMP1 and EMMP2 received by gavage a

solution of the extract *M. pubescens* dissolved in olive oil at a rate of 50 mg/kg/Bw for duration 30 days. A group of rats rendered hepatotoxic by CCL4 at a rate of 1 ml/kg/BW; A group of rats that received methanolic extract of *M. pubescens* dissolved in olive oil at a rate of 50 mg/kg/BW by gavage for 30 days, then CCL4 at a rate of 1 ml/kg/BW, CCL4+EMMP1; a group of rats that received methanolic extract of *M. pubescens* from the second region dissolved in olive oil at a rate of 50 mg/kg/BW by gavage for duration 30 days, Next, CCL4 at a 1 ml/kg PC CCL4+EMMP2 rate.

The nephrotoxicity activity tests were carried out using adult male rats are subdivided into six groups according to the treatment of eight animals for each they receive, A group of rats rendered nephrotoxic by Cisplatin at a rate of 13 mg/kg/BW (Cisp); A group of rats received an extract of *M. pubescens* dissolved in olive oil at a rate of 50 mg/kg/BW by gavage for 30 days, then cisplatin at a rate of 13 mg/kg of body weight. Cisp+EMMP1; a group of rats that received extract of *M. pubescens* dissolved in olive oil at 50 mg/kg/BW by gavage for duration 30 days and after that cisplatin at 13 mg/kg cisp+EMMP2; CCl4 and Cisplatin were given to the animals via gavage twice a week for a period of 4 weeks. EMMP1 and EMMP2 pre-treatment was carried out seven days before Cisplatin or CCl4 therapy, and it continued every day for the duration of the investigation. 24 hours following the final Cisplatin or CCl4 dosage, the animals were anesthetized and subsequently sacrificed.

2.5. Assay of serum lipid profile parameters

- Determination of cholesterol, triglycerides, HDL-Chl and LDL-Chl

A kit from Biolabo, France (Ref. 80106) was used to perform the cholesterol analysis utilizing the enzymatic cholesterol oxidase method. A kit from Biolabo, France (Ref. 80019) was used to perform the enzymatic glycerol kinase technique for determining triglycerides. Using a kit from Biolabo in France (Ref. 90206), the HDL-Cholesterol assay was carried out enzymatically. A straightforward computation using Frielwald's formula is used to obtain the serum LDL-Cholesterol level [13].

2.6. Exploration of liver function enzymes

- Assay of transaminases (ASAT and ALAT)

Serum aspartate aminotransferase (AST) activity is determined by the IFCC colorimetric kinetic method without pyridoxal phosphate using a kit from Biolabo, France (Ref. 80025). Serum alanine aminotransferase (ALAT) activity is determined by the IFCC colorimetric kinetic method without pyridoxal phosphate using a kit from Biolabo, France (Ref. 80027).

2.7. Histological study

Throughout this study, we followed the method that Gabe described[14].

2.8. Statistical analysis

The standard deviation of the mean (SEM) ± mean is how the data are shown. XLSTAT 2012 was used for statistical analysis, and Duncan's Multiple Interval Analysis of Variance was used to evaluate group differences. A significant p-value was one that was less than 0.05.

3. RESULTS

3.1. The effect of EMP extract on body weight change in hyperlipidemic rats

The weights of the animals were checked over the course of the 4-week study (Figure1). Rats given a single dosage of Triton X (Hyp group) had a noteworthy 27% raised their weight in comparison to the control group. Nevertheless, the getting of two extracts of *M. pubescens* (50 mg/kg/BW) to hyperlipidemic rats (Hyp + EMMP1 and Hyp + EMMP2) significantly reduced their body weights, respectively, by 14% and 19% ($P<0.05$), in contrast to the induced non-treating. Notably, there was no significant difference in these rates between the rats treated with the two *M. pubescens* extracts (EMMP1 and EMMP2) and the control group.

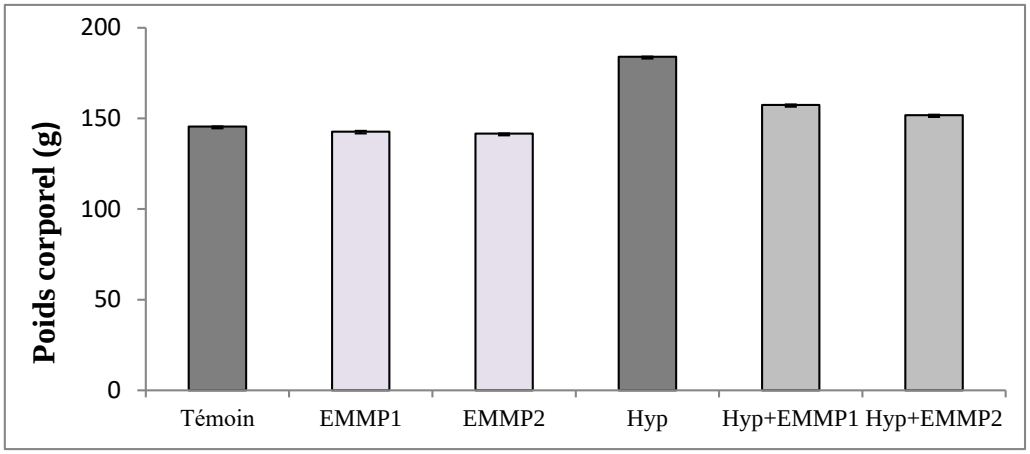

Figure1: Effect of EMMP on the body weight of hyperlipidemic Hyp rats.

3.2. The effect of EMMP on blood levels of leptin in hyperlipidemic rats.

The results showed a notable rise in leptin concentration of 128% in the Hyp group relative to the standard ($p<0.05$). Nevertheless, in reply to the two extracts of *M. pubescens* Hyp + EMMP1 and Hyp + EMMP2, serum leptin levels in the groups receiving a dose of Triton X-100 were significantly reduced by 24% and 19%, correspondingly, likened to the untreated Hyp group ($p<0.05$) (Figure2).

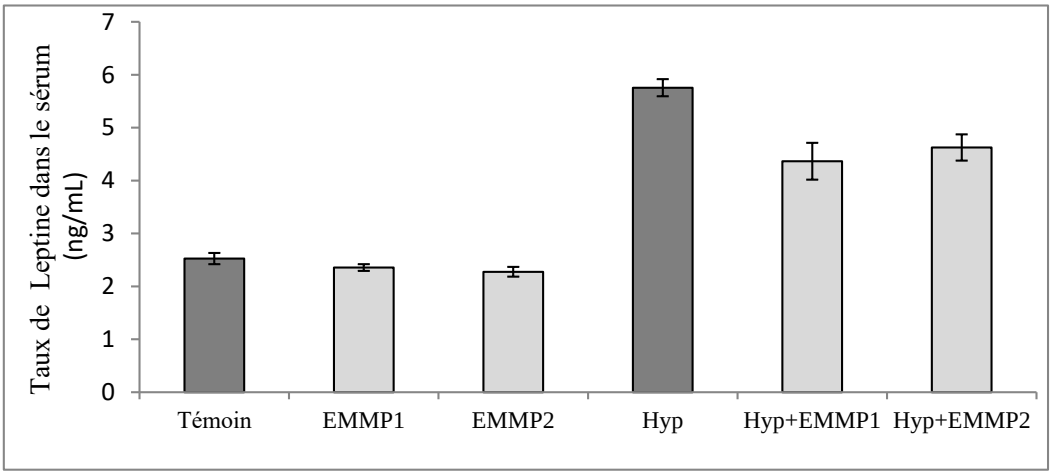

Figure2: the effect of EMMP1 and EMMP2 on serum leptin level in hyperlipidemic rats.

3.3. The antihyperlipidemic effect of EMMP in hyperlipidemic rats.

Serum pancreatic lipase activity in hyperlipidemic animals showed a remarkable 55% increase when contrasting with the control group (figure 3)($P <0.05$).

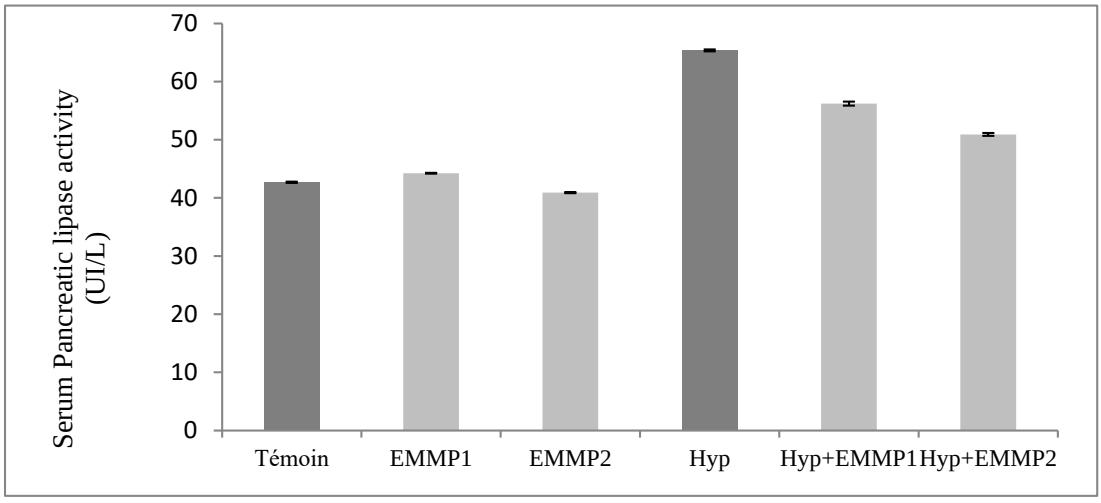

Figure3: Effect of EMMP1 and EMMP2 on serum pancreatic lipase activity in hyperlipidemic rats.

The increased lipase enzymatic activity actually improves lipid absorption, which leads to a disturbance of the lipid profile: blood levels of T-Ch, TG, and LDL-c rise by 133%, 112%, and 110%, respectively, while serum HDL-c decreases by 38% as compared to normal rats (table 01). Conversely, though the two extracts, Hyp + EMMP1 and Hyp + EMMP2, inhibited serum lipase activity by 14%, resulting in decreased levels of LDL-c, TG, and T-Ch, while increasing HDL-c concentration.

Table1: blood concentrations of TG (T-Ch, LDL-c, and HDL-c.

Groups	Control	MMP0	EMMP2	Hyp	Hyp+EMMP1	Hyp+EMMP2
TC (mmol/L)	78.23 ± 1.25	79.43 ± 1.45*	78.9 ± 1.81	182.7 ± 1.26	141.3 ± 2.1	139 ± 1.93$^{\#}$
TG (mmol/L)	55.52 ± 0.71	54.04 ± 0.71	54.69 ± 0.54	117.7 ± 0.75$^{*\#}$	71.31 ± 0.81	70.98± 1.5$^{*\#}$
LDL-c (mmol/L)	36.04 ± 1.11	37.85 ± 0.87	36.84 ± 0.6	75.9 ± 1.32*	59.58 ± 1.49$^{\#}$	59.52 ± 0.85$^{\#}$
HDL-c (mmol/L)	39.8 ± 0.54	40.16 ± 1.03	41.43 ± 1.21	24.14 ± 1.08$^{\#}$	31.68 ± 0.35$^{\#}$	33.26 ± 1.09$^{\#}$

The values are presented as mean ± standard deviation (SEM).

3.4. The hepatic and renal function effect

The different experimental group's animals showed no significant elevation in serum ASAT, ALAT, PAL, and Bilirubin Total. Same observation for the serum concentration of creatinine, urea and uric acid (Table2).

Table2: Hepatic toxicity parameters study (ASAT, ALAT, PAL and Bil-T) and renal toxicity indices (urea, uric acid, and creatinine) in the experimental animals.

Parameters	control	EMMP1	EMMP2	Hyp	Hyp+ EMMP1	Hyp+ EMMP2
Hepatic Function						
ASAT (UI/L)	59.4 ± 0.08	56.74 ± 0.38*	57.86 ± 0.06	56.6 ± 0.04*	59.3 ± 0.28	57.58 ± 0.21
ALAT(UI/L)	49.05 ± 0.05	47.71 ± 0.07	49.2± 0.15	48.5± 0.11	48.36± 0.08	48.08± 0.03
PAL (UI/L)	211,28±22,8	210.34 ± 0.43	208.64 ± 4.15	214.2 ± 4.23	210.64 ± 6.47	213.4 ± 7.13
Bili-T (µmol/L)	2.45 ± 0.1	2.31 ± 0.14	2.07 ± 0.3	2.04 ± 0.33	2.64 ± 0.14	2.51 ± 1.46
renal Function						
urea (mmol/L)	32.6 ± 0.29	31.51 ± 0.13	32.62 ± 0.14	31.54 ± 0.20	30.7 ±0.25	31.08 ±0.21
uric A (µmol/L)	72.73 ± 2.34	72.15 ± 1.6	74.77 ± 2.64	71.34 ± 4.35	74.31 ±2.36	71.36 ±4.65
creatinine (µmol/L)	0.62 ± 0.01	0.64 ± 0.03	0.62 ± 0.01	0.63 ± 0.02	0.62 ± 0.001	0.62 ± 0.01

The values are expressed as mean ± standard deviation (SEM).

3.4.1. Effect of *Matricaria pubescens* extract on some renal biomarkers

Plasma concentrations of renal indicators such urea, uric acid, and creatinine are shown in Table 03. A significant increase of these renal markers in the plasma of the batch of rats treated with Cisplatin (Cisp) by 50%, 53%, and 600%, respectively, compared to the controls was observed. The significant increase in plasma urea, creatinine, and uric acid levels is indicative of kidney damage and renal dysfunction or failure in animals poisoned with cisplatin. Compared to the control group of rats, the group of rats treated just with the two methanolic extracts of *M. pubescens* (EMMP1 and EMMP2) (50 mg/kg/BW) did not exhibit any discernible change in these levels. Conversely, the pretreatment of the rats with the two methanolic extracts of *M.pubescens* with cisplatin (Cisp+EMMP1) and (Cisp+EMMP2) resulted in a significant decrease in renal marker levels compared to the group of rats treated solely with cisplatin.

Table 03: Impact of the two combinations, Cisp+EMMP1 and Cisp+EMMP2, on levels of uric acid, creatinine, and urea.

Parameters	Control	EMMP1	EMMP2	Cisp	Cisp+EMMP1	Cisp+EMMP2
Creatinine (mg/dL)	28.64±1.45	25.06±0.46	26.6±0.38	43.4±1.22*	31.22±0.92¥	37.4±2.14¥
urea (mg/dL)	6.2±0.1	5.7±0.11	6.08±0.14	8.78±0.11*	6.98±0.11¥¥	7.54±0.22¥
uric acid (mg/dL)	2.21±0.80	3.00±0.18	2.8±1.08	14.2±0.52*	9.05±1.06 ¥	11.05±1.26 ¥

Values are presented as mean ± standard deviation (SEM).

3.4.2. Effect of *M. pubescens* extract on some hepatic biomarkers

The results of plasma biochemical analyses of liver function are summarized in Table 04. The findings demonstrate liver damage caused by exposure to carbon tetrachloride (CCl_4), as evidenced by increased serum levels of liver enzyme activity, including ALP, LDH, AST, and ALT, which rose by 233%, 65%, 29%, and 64%, individually. This suggests a release of cellular enzymes into the bloodstream compared to the control group of rats. These biochemical disturbances are signs of hepatotoxicity. In contrast, the activity of these hepatic enzymes in the serum was reduced by 29%, 44%, 11%, and 30%, respectively, and by 26%, 37%, 10%, and 26% after administering the two extracts (50 mg/kg body weight) of CCL4 + EMMP1 and CCL4 + EMMP2.

Table 04: Effect of the CCL4+EMMP1 and CCL4+EMMP2 on the AST, ALT, ALP, and LDH in plasma.

Parameters	Control	EMMP1	EMMP2	CCL4	CCL4+EMMP1	CCL4+EMMP2
ALAT (U/L)	139.7±2.2	140.3±3.2	135.7±1.72*	228±2.7*	161.4±2.04¥	167.1±1.85¥
ASAT (U/L)	69.62±1.3	67.08±1.1	66.44±0.85	89.38±2.4*	49.06±1.39¥	56.56±1.41¥
LDH (U/L)	321.9±3.0	316.7±3.5	321.4±2.21	532±1.78*	473±2.9 ¥	477.8±2.02 ¥
ALP (U/L)	9.21±0.80	10.70±0.1	11.24±1.28	30.4±1.98*	21.05±1.06 ¥	21.64±1.33 ¥

Values are presented as mean ± standard deviation (SEM).

3.5. Effect of *M. pubescens* extract on hepatic and renal lipid peroxidation

Figure 04 illustrates the changes in tissue TBARS levels in the liver and kidneys across the various rat groups. Analysis of graph showed that the rate of hepatic TBARS in rats treated with carbon tetrachloride increased significantly by 30 to 40% compared to that of control rats.

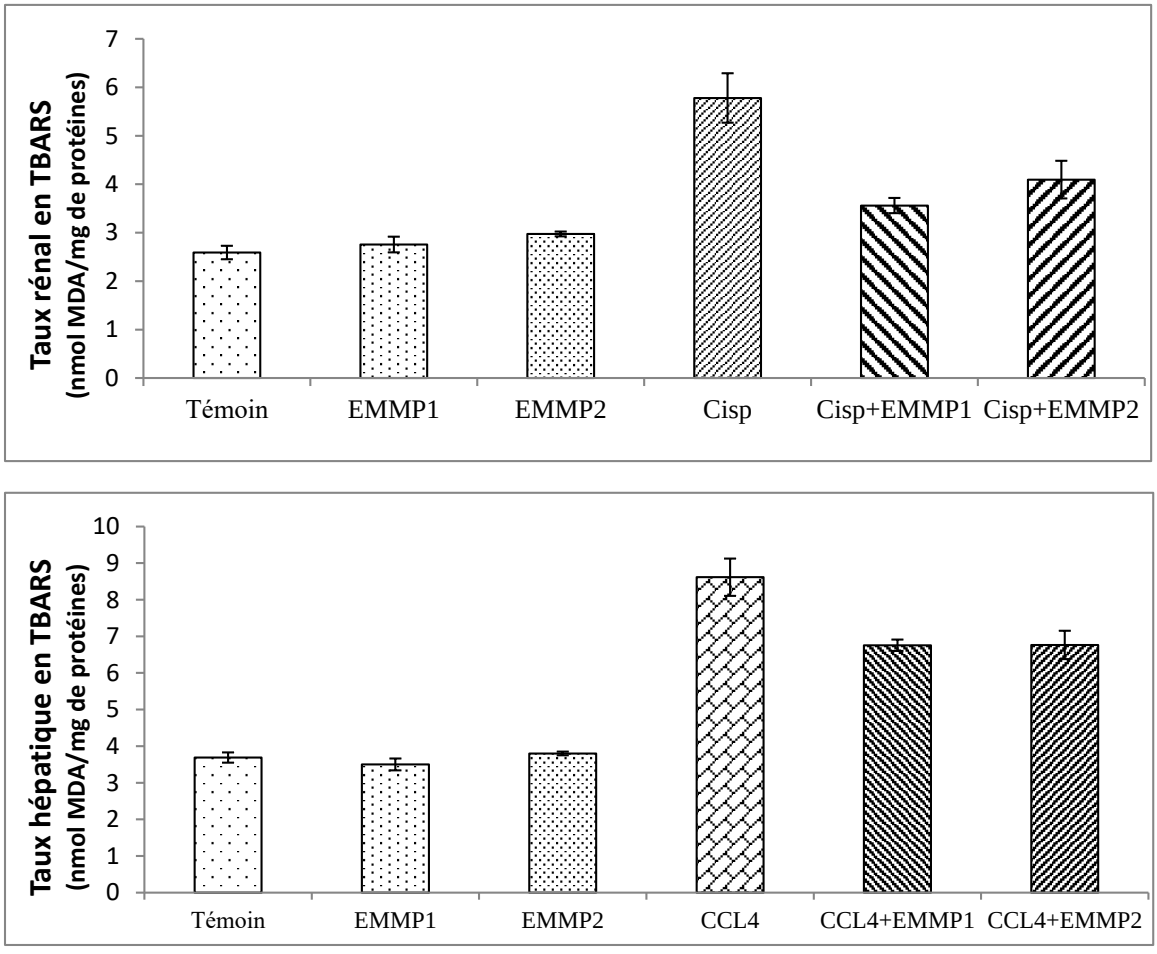

Figure 04: TBARS levels (nmol MDA/mg of protein) in the kidneys and liver of the different rat groups.

The administration of two extracts CCL4+EMMP1 and CCL4+EMMP2 (50 mg/kg bw/day) decreases the TBARS values by 12% compared to the group treated with carbon tetrachloride alone. The measurement of TBARS levels in the kidneys reveals a significant rise in this parameter in rats treated with Cisplatin compared to the control group. However, administering two extracts alongside Cisplatin (Cisp+EMMP1 and Cisp+EMMP2) resulted in a significant decrease in renal TBARS levels compared to the group of rats treated with Cisplatin.

3.6. Effect of *M. pubescens* extracts on hepatic and renal antioxidant enzyme activities

Table 05 presents the activity levels of several enzymes, including SOD, CAT, and GPx, in the liver and kidneys across different groups of rats. A notable reduction in antioxidant enzyme activities (SOD, CAT, and GPx) in the liver and kidneys of rats treated with carbon tetrachloride or Cisplatin was observed. The liver showed a reduction of 47% in CAT, 48% in SOD, and 43% in GPx activities compared to the control group. In the kidneys, the decreases were 51% for CAT, 62% for SOD, and 46% for GPx. Treatment with the two methanolic extracts of *M. pubescens* EMMP1 and EMMP2 (50 mg/Kg /BW) has no effect on the parameters analysed. However, the pre-treatment of rats with the two methanolic extracts of *M. pubescens* with CCL4+EMMP1 and CCL4+EMMP2 or with Cisp+EMMP1 and Cisp+EMMP2 significantly slowed down the decrease in enzyme activity induced by the two inducers. Indeed, we noticed in the liver an increase compared to the CCL4 group of 52%, 46%, and 38%, respectively, and of 58%, 32%, and 61% for CAT, SOD, and GPx, and in the kidneys, an increase compared to the Cisp group of 76%, 80%, and 43%, respectively, and 71%, 120%, and 62%.

Table 05: Changes in antioxidant enzyme levels in the kidneys and liver.

Parameters	**liver**					
	Control	**EMMP1**	**EMMP2**	**CCL4**	**CCL4+EMMP1**	**CCL4+EMMP2**
CAT (U/L)	34.86±1.86	36.33±1.16	31.82±0.47	17.95±0.97*	26.06±0.59¥	27.65±0.72¥
SOD (U/L)	54.41±2.92	56.28±1.2	52.96±0.28	28.46±2.84*	41.18±0.63¥	37.47±2.82¥
GPX (U/L)	55.4±1.29	53.66±0.7	51.18±1.18	31.41±1.04*	43.31±2.82 ¥	50.89±0.6 ¥
Parameters	**kidney**					
	Control	**EMMP1**	**EMMP2**	**Cisp**	**Cisp+EMMP1**	**Cisp+EMMP2**
CAT (U/L)	43.96±2.33	42.11±1.07	45.4±1.1.11	21.14±1.42*	37.29±1.18¥	36.17±1.4¥
SOD (U/L)	27.9±3.19	26.76±0.82	29.3±1.18	10.8±0.79*	18.94±0.41¥	22.16±2.83¥
GPX (U/L)	30.4±2.48	34.32±1.65	35.82±0.89	16.39±1.05*	23.66±0.72 ¥	26.2±0.78 ¥

The data is displayed for each group of eight rats as mean ± SEM.

3.6. Histological study

3.6.1. Histological exploration of lipid deposition

In the present work, we used frozen sections using a cryostat to preserve lipid deposits in the liver. For this, we used a special dye, Oil Red O stain (ORO). The microscopic observation of histological sections performed in the control rats' livers and rats pre-treated with the two extracts (EMMP1 and EMMP2) (Figure5) shows a normal structure of the hepatic tissue with low amounts of lipids distributed to hepatocytes with low red colouring. Nevertheless, the Hyp group showed a much higher level of lipid accumulation than the control group, which is manifested by the increase in the intensity of the red staining, indicating the installation of a hyperlipidaemic condition in the liver. Concerning the association with the two extracts Hyp + EMMP1 and Hyp

+ EMMP2. The study demonstrated that this extract offered protection against lipid imbalances caused by Triton X-100, as demonstrated by a reduction in the intensity of the red coloration.

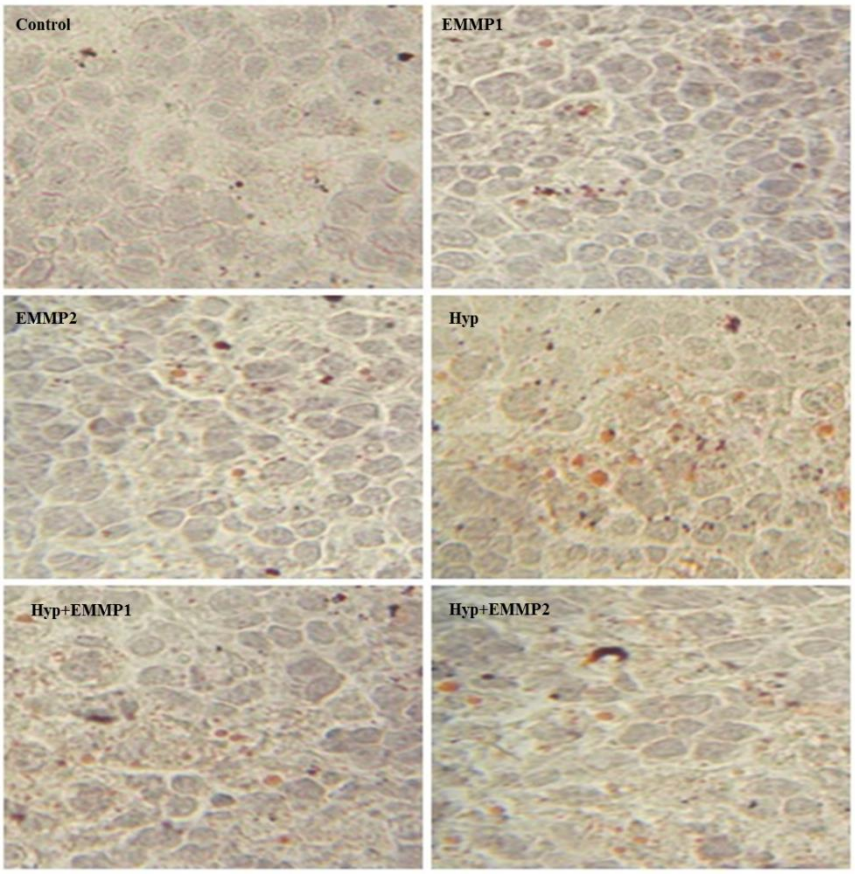

Figure05: liver Histology (oil red O staining) of (Control)normal rats, EMMP rats treated with EMMP, untreated Hyp and Hyp treated with EMMP (Hyp + EMMP).

3.6.2. Liver histology

according to the histological analysis of liver sections, the control animals had normal cellular structure, as seen in Figure 06. However, treatment with carbon tetrachloride (CCL4) induced histological changes causing severe liver damage, such as congestion, infiltration of inflammatory cells, necrosis, and the appearance of fatty cysts in sections of these tissues compared to the hepatic tissues of control rats. These changes were reduced in the liver of rats intoxicated and pre-treated with the two methanolic extracts of *M. pubescens* (CCL4+EMMP1) and (CCL4+EMMP2) (50 mg/kg of body weight). The histological appearance in the group of rats treated with only the two methanolic extracts of *M. pubescens* (EMMP1 and EMMP2) (50 mg/kg body weight) does not show any differences compared to the controls.

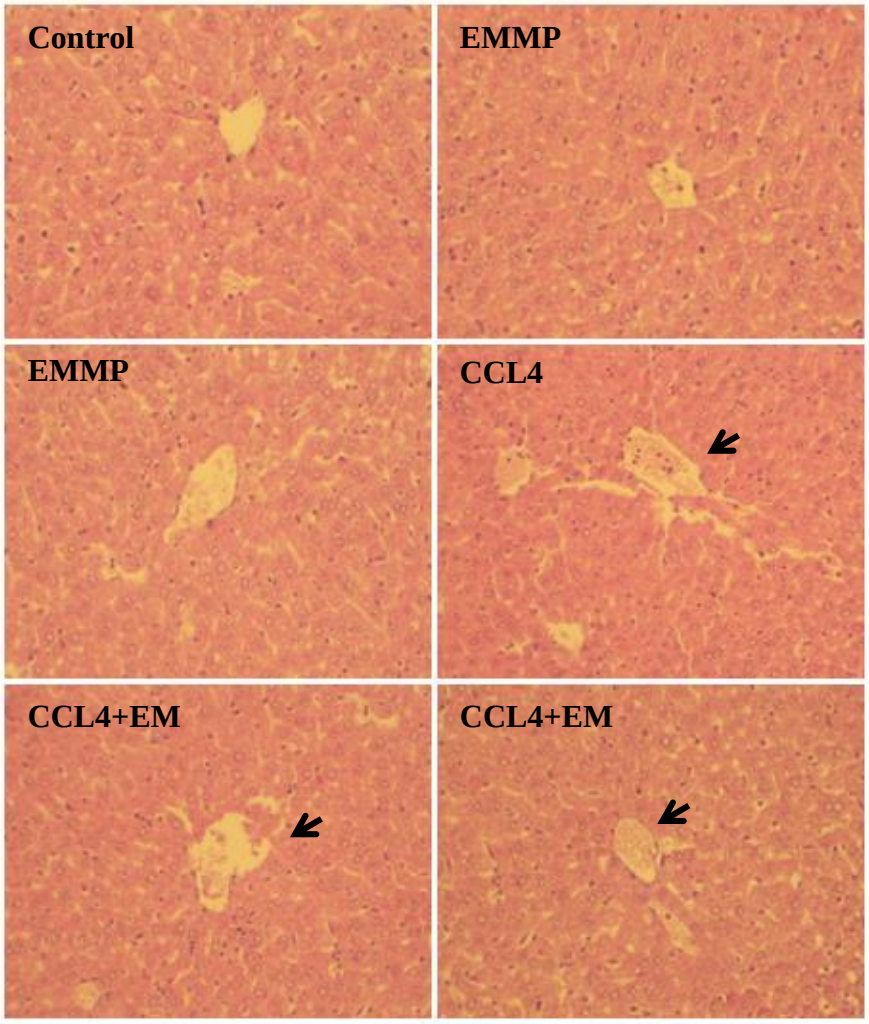

Figure 06: Histological structure of the liver in the different experimental groups of rats Staining: hematoxylin-eosin (Gr×100).

3.6.3. Kidney histology

Figure 07 presents histological sections of rat kidneys from various experimental groups. Control rats exhibited normal kidney structure, while cisplatin-treated rats showed glomerular atrophy and increased Bowman's space. However, rats pre-treated with two methanolic extracts of *M. pubescens* (Cisp+EMMP1 and Cisp+EMMP2) displayed improved histopathology compared to the cisplatin-only group, suggesting protective effects. Kidneys from rats treated solely with *M. pubescens* extracts (EMMP1 and EMMP2) had histological features similar to the control group.

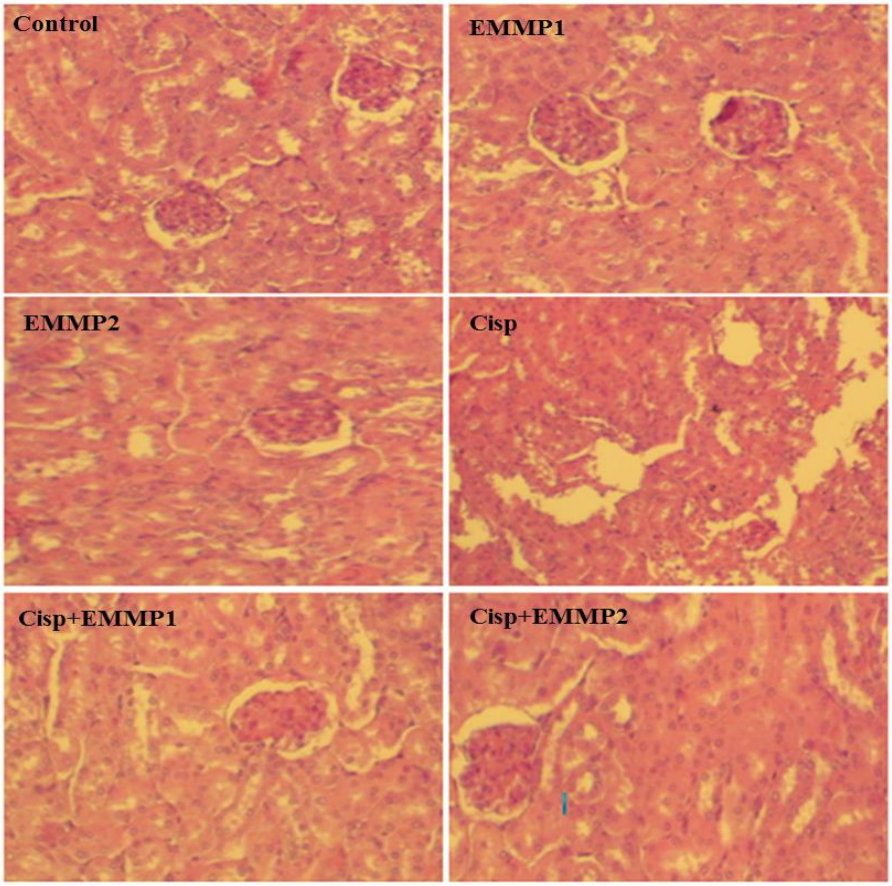

Figure 07: Histological structure of the kidneys in the different experimental groups of rats. Staining: hematoxylin-eosin (Gr×100)

4. DISCUSSION

Obesity is a multifactorial chronic disease; it is a major issue of public health [15] . The definition of this pathology is based on an increase in fat mass, it usually accounts for 10–15% of a man's body weight in youth and young adulthood and 20–25% of a woman's body weight. Obesity therefore results from an imbalance between energy intake and expenditure, leading to an inflation of adipose reserves and the installation of various metabolic disorders [16]. Indeed, the main complications of this epidemic concern cardiovascular pathologies (hypertension, coronary insufficiency, and heart failure), type 2 diabetes, insulin resistance, and dyslipidemia [17].

The use of complementary and alternative medicine, like herbal remedies, is now seen as an effective approach to treating obesity and its complications [18,19]. *M. pubescens*, a plant of the Asteraceae family, is widely distributed in southern Algeria. Bedouins use the plant in the treatment of diabetes mellitus, dermatitis, muscolotropic spasms, and diarrhea [20]. In this context, we were interested in evaluating the possible anti-obesity properties of the plant. The results of this investigation shown that the extract EMMP has a strong ability to suppress pancreatic lipase activity in vivo in the serum of rats with obesity. Inhibiting lipase activity is a medicinal strategy for treating obesity. Pancreatic lipase inhibitors

like Orlistat promote fat excretion, helping prevent obesity and hyperlipidemia[21]. In this study, *M. pubescens* inhibited serum lipase activity, leading to improved lipid profiles with reduced total cholesterol, triglycerides, and LDL cholesterol levels in both serum and liver of obese rats. This inhibition also reduced lipid accumulation in the liver and muscle, promoting weight loss [22]. Rats on a high-fat diet showed increased fat accumulation across various tissues, accompanied by a significant rise in serum leptin, consistent with findings by Prachi et al (2012) [23]., who showed that leptin concentration is directly correlated with the accumulation of adipocyte lipids. Therefore, the leptin level in the blood is a good indicator for the assessment of obesity in animals and humans [24].

Thus, we noticed that the administration of two extracts to obese rats caused a decrease in serum leptin concentration. Furthermore, the reduction in serum leptin levels observed in rats treated with EMMP could help avert the onset of various other conditions associated with hyperlipidemia, including hypertensionIndeed, numerous prior studies have established a significant relationship between leptin levels and body fat mass [25]. Conversely, research indicates that leptin affects the sympathetic, cardiovascular, and renal neural systems in a number of ways[26].

Obese rats in these studies showed a considerable increase in blood lipid values but no change in liver damage indicators., namely ASAT, ALAT, PAL, CPK, T-Bili, and GGT, or serum indices of renal dysfunction, namely urea, uric acid, and creatinine. These findings are supported by the histological analysis of the liver, which shows, in these animals, a predominance of lipid deposits. The supplementation of two extracts in obese rats ensured a partial restoration of the histological appearance of the liver.

We know that obesity is strongly linked to insulin resistance and is therefore one of the major complications of type2 diabetes. On the other hand, *M. pubescens* seems to be effective against the manifestations of obesity, and given its traditional use in the treatment of type2 diabetes, we have chosen to investigate the possible mechanisms by which our plant could exert its anti-diabetic powers in experimental diabetes.

The antioxidant, nephroprotective, and hepatoprotective effects of *M. pubescens* methanolic extracts are largely due to their phenolic compounds, key bioactive molecules found in plants. Cisplatin-induced renal damage is characterized by increased creatinine, urea, uric acid levels, and tubular necrosis, potentially causing renal failure[27]. These alterations are regarded as trustworthy endpoints for evaluating the nephrotoxicity of drugs in both people and animals [28]. Furthermore, the hepatotoxicity generated by (CCl4) has long been used by scientists as an experimental model to investigate liver damage [29]. The active metabolites of CCl4 are known to interact with the liver, resulting in the destruction of liver cells and causing an increase in serum enzymes such as AST and ALT [30].

Pre-treatment with two methanolic extracts of *M. pubescens* significantly reduced creatinine, urea, and uric acid levels elevated by Cisplatin. This protective effect is likely due to its phenolic compounds' free radical scavenging properties, which have been shown to protect against kidney damage [31]. The study found that EMMP reduced elevated serum levels of AST, ALT, and LDH caused by CCl4, indicating its hepatoprotective effects, likely due to its antioxidant properties, aligning with previous research [32].

Lipid peroxidation involves oxidative damage to polyunsaturated fatty acids, reducing membrane fluidity and impairing enzyme activity. In this study, EMMP administration reduced Cisplatin-induced lipid peroxidation, suggesting the presence of antioxidants in *M. pubescens* extract. Excessive ROS lowers CAT, SOD, and GPx activity, leading to membrane damage and functional loss. However, pre-treatment with EMMP significantly increased these enzyme activities, likely due to its antioxidant properties, which reduce lipid peroxidation by enhancing endogenous antioxidant enzymes [33].

M. pubescens may play a key role in nephroprotective and hepatoprotective mechanisms by boosting enzymatic and non-enzymatic antioxidants. Renal histological analysis supports this, aligning with biochemical findings when compared to cisplatin and CCl4-treated groups. Similarly, Pan et al. (2014) reported that Rutin offers hepatoprotection by inhibiting NF-kB, a crucial factor in immune response, hepatocyte survival, and liver damage [34,35].

Furthermore, Rutin's inhibitory impact on NF-kB and TNF-α is responsible for its protective effect against Cisplatin-induced nephrotoxicity, according to Arjumand et al. (2011) [36]. In actuality, cisplatin's nephrotoxicity may be avoided by inhibiting TNF-α's activity[37]. Gallic acid has been shown by Yousuf and Vellaichamy (2015) to have hepatoprotective and nephroprotective properties [38].

5. Conclusion

This study shows that two methanolic extracts of *M. pubescens* have hepatoprotective, nephroprotective, and antioxidant effects. The extracts reduced liver and kidney damage by preventing lipid peroxidation, normalizing biochemical markers, and boosting antioxidant enzyme activity. The protective effects may be due to the high phenolic content, supporting the plant's traditional use for treating liver and kidney disorders.

Conflicts of Interest: No conflicts of interest are disclosed by the authors.

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النشاط الخافض للدهون، والحامي للكبد، والواقي للكلى لمستخلصين ميثانوليين لنبات *Matricaria pubescens* على الجرذان

خراز خالد[1]، محمد مسعودي[2*]، لعوج حسن[3]، غمام عمارة الجيلاني[3]، شفرور عز الدين[4]، ماريا أتاناسوفا[5]، باربرا ساويكا[6]، أيوميد فيكتور أتوكي[7]، وفاء زهنيت[8]

[1]مخبر النباتات المستعملة شعبيا والمواد الطبيعية، المدرسة العليا للأساتذة بالقبة – الجزائر

[2]مركز البحث النووي بالبيرين ، الجزائر

[3]مخبر البحث البيولوجيا، المحيط والصحة لكلية علوم الطبيعة والحياة– جامعة الوادي

[4]مخبر البحث البيولوجيا، المحيط والصحة لكلية علوم الطبيعة والحياة– جامعة الوادي

[5]قسم البيولوجيا، لكلية علوم الطبيعة والحياة– جامعة الشريف مساعدية – سوق اهراس

[6]استشارات علمية في مجال التغذية، الهندسة الكيميائية، جامعة التكنولوجيا الكيميائية والمعادن، 1734 صوفيا، بلغاريا

[7]قسم تكنولوجيا إنتاج النباتات وعلوم السلع، جامعة علوم الحياة في لوبلين، شارع أكاديميكا 15، 20–950 لوبلين، بولندا.

[8]قسم الكيمياء الحيوية، جامعة كامبالا الدولية، إيشاكا، أوغندا

ملخص

يعتر نبات *Matricaria pubescens* من النباتات العطرية والطبية المستعملة في الطب الشعبي لعلاج العديد من الامراض. يهدف هذا البحث إلى دراسة الفعالية العلاجية لمستخلصين ميثانوليين لنبات *M. pubescens* EMMP1 وEMMP2 في الوقاية من أعراض السمنة، مثل زيادة الوزن ومستوى الدهون، أظهرت النتائج ان الجرذان التي حُقنت بمادة Triton X-100تعاني من زيادة واضحة في الوزن ومستويات اللبتين في الدم، بالإضافة إلى ارتفاع كبير في مستويات الكوليسترول (LDL)، والدهون الثلاثية، والكوليسترول الكلي، مع انخفاض في مستويات الكوليسترول (HDL). عند معالجة الجرذان المصابة بفرط الدهون بالمستخلصين (Hyp + EMMP1))و((Hyp + EMMP2)، انخفض وزنها بنسبة 14% و19%، كما تناقصت مستويات اللبتين في الدم بنسبة 24%و19 %على التوالي. كما أظهرت النتائج أن التعرض لمادة CCl_4أدى إلى تلف وتسمم في الكبد، مما نتج عنه زيادة بنسبة 64%، 29%، 65%، و233 %في تركيزات أنزيمات الكبد في الدم، بما في ذلك ALAT، ASAT، LDH، وALP.تشير هذه الدراسة إلى أن مستخلصات *M. pubescens* تلعب دورًا مهمًا في تقليل السمنة وتنظيم مستويات الدهون، فضلًا عن دورها الوقائي في حماية الكبد من التلف وتقليل الإجهاد التأكسدي، مما يجعلها من النباتات الواعدة لعلاج الاضطرابات المرتبطة بالسمنة ووقاية الكبد والكلى من التسمم.

الكلمات الدالة: *Matricaria pubescens*، خفض للدهون، تسمم للكبد، تسمم للكلى، Triton X-100، CCl_4، Cisp، المستخلص الميثانولي.

المؤلف المراسل: محمد مسعودي

messaoudi2006@yahoo.fr

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