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# Hepatoprotective Effect of *Rosmarinus Officinalis* Ethanolic Extract against Damage Induced by Cadmium in Wistar Rats

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**Abstract**

EXPOSURE to cadmium (Cd) causes damage to various human and animal organs, including liver. In Morocco, *Rosmarinus officinalis* (RO) is widely used for treating various liver disorders. The study aimed to assess the effects of RO on liver functions in Wistar female rats exposed to cadmium. 30 Wistar female rats were divided into 5 groups; the control group received orally distilled water, group receiving 1 mg/kg of Cd, group received the ethanolic extract of RO at doses of 200 mg/kg, and the last group received 200 mg/kg of RO and 1 mg/kg of Cd, administered for 8 weeks. At the end of the treatment, the rat blood samples were taken for biochemical analysis, including cholesterol, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), glucose, total cholesterol, and triglycerides (TG). Oxidative stress biomarkers, nitric oxide (NO), and the antioxidant enzyme catalase (CAT) were assessed in the liver. The results show Cd exposure induced a significant increase in blood glucose, cholesterol, and triglycerides in rats, reflecting a metabolic disorder of hepatic origin. RO attenuated these alterations and brought the values of the measured parameters closer to those of the control group, suggesting a hepatoprotective and metabolic regulatory effect. The RO ethanolic extract exerts antioxidant activity, manifested by an decrease of NO level and an increase of catalase level in the liver. *Rosmarinus officinalis* ethanolic extract showed appreciable protective effects on the liver against Cd by decreasing oxidative stress markers, suggesting using *Rosmarinus officinalis* as a dietary supplement for patients with liver disorders.

**Keywords:** *Rosmarinus officinalis*, liver, cadmium, oxidant activity, rats.

## Introduction

Cadmium (Cd) is a highly toxic heavy metal and a major environmental pollutant, present in soil, water, air, certain foods, and cigarette smoke [1]. Exposure to Cd causes damage to various human and animal tissues. This metal is also known to be carcinogenic and to have deleterious effects on reproduction, including growth retardation and infertility [2-4]. At the blood and tissue levels, Cd induces the production of reactive oxygen species (free radicals and peroxides), causing oxidative damage and altering the functionality of erythrocyte membranes and other cell types [5,6]. It is widely accepted that the majority of Cd toxic effects result from an imbalance in essential trace elements such as zinc (Zn), known for its antioxidant properties [3,7].

In Morocco, traditional medicine remains deeply rooted in healthcare practices. However, although liver disease constitutes a major public health problem, scientific work devoted to the identification of new molecules capable of preventing or delaying the emergence of complications associated with liver dysfunction remains very limited [8,9].

For several decades, extensive research has been conducted on the toxic effects of exogenous substances, particularly in the areas of nephrotoxicity and hepatotoxicity. The liver, a central organ of metabolism and detoxification, is particularly vulnerable to the deleterious effects of xenobiotics and heavy metals [10]. Among these, cadmium (Cd) is a major environmental pollutant, recognized for its carcinogenicity and hepatic tropism. After absorption, it preferentially accumulates in the liver and kidneys, where it induces excessive production of reactive oxygen species (ROS), leading to severe oxidative stress. This mechanism leads to lipid peroxidation, alteration of hepatic enzymes, and disruption of endogenous antioxidant systems, resulting in structural and functional liver damage.

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In this context, medicinal plants constitute a privileged source of bioactive compounds capable of exerting protective activity against oxidative damage [11,12]. These compounds, or phytochemicals, are used as precursors for therapeutic molecules and are widely used in the pharmaceutical, cosmetic, and nutraceutical fields [13].

Among them, *Rosmarinus officinalis* (rosemary), a plant of the Lamiaceae family, is traditionally used in Moroccan folk medicine for the treatment of various liver and kidney conditions, including lithiasis [14]. This species is listed on List A of the French Pharmacopoeia and is distinguished by the richness of its secondary metabolites, alkaloids, tannins, terpenes, and flavonoids, which confer antioxidant, antimicrobial, antifungal, and anti-inflammatory properties [15].

Thus, considering the strong involvement of oxidative stress in cadmium-induced hepatotoxicity and the documented antioxidant properties of rosemary, the objective of the present study is to evaluate the therapeutic and hepatoprotective effect of Rosmarinus officinalis against cadmium-induced liver injury in Wistar female rats.

## Materials and Methods

### *Plant preparation*

*Rosmarinus officinalis* was harvested in June 2023 in Ras El Ma (Taza region, Morocco). The leaves were dried at room temperature (25 ± 3°C) in the open air and protected from light to preserve their bioactive constituents, then finely pulverized and sieved (250–500 µm) to obtain a homogeneous powder with high yield. One hundred grams of this powder were subjected to continuous Soxhlet extraction with 500 mL of 95% ethanol. The solvent was then evaporated at 60 °C under rotation (2000 rpm) for 30 minutes, leading to a viscous solid residue [16].

Female rats were distributed into 4 groups (n = 6/group). The control group received orally distilled water; one group received 1mg/kg of cadmium, a group received 200mg/kg EERO, the fourth group received in addition of 200 mg/kg of EERO and 1mg/kg of cadmium, administered for 60 consecutive days. At the end of the treatment, the rats were anesthetized with chloral 7 g/100 ml of distilled water (0.5 ml/100 g of rat body weight) by intraperitoneal injection, and then blood samples were taken for hematological and biochemical study, for the dosage of biomarkers of oxidative stress such as nitric oxide (NO), and the antioxidant enzyme catalase (CAT) in the liver, as well as the study of histological sections of this target organ [17].

### *Rosmarinus officinalis toxicity assessment*

Biochemical analysis of the samples was performed using a spectrophotometer (J.P. Selecta S.A., Autovía, Abrera, Spain) for the quantification of the following parameters: alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), glucose, total cholesterol (CHO) and triglycerides (TG).

### *Oxidative stress markers determination*

#### *Nitric oxide determination*

Nitric oxide (NO) production in organ homogenates (liver, kidneys, etc.) was estimated indirectly by quantifying the end products of its synthesis, nitrates and nitrites, according to the method described by Bryan and Grisham (2007) [18]. The evaluation was carried out by the Griess reaction (solution A: 0.1% naphthylethylenediamine dihydrochloride; solution B: 1% sulfanilamide). One hundred microliters of the reagent and 100 µL of sample were mixed, incubated for 30 min at room temperature, and then the optical density was measured at 548 nm [19,20]. The results were expressed in µmol of NO per gram of tissue.

#### *catalase activity determination*

Catalase activity of organ homogenates was determined according to the method of Aebi (1984), based on spectrophotometric measurement (240 nm) of $H_2O_2$ disappearance. For each assay, 60 µL of tissue extract or phosphate buffer (0.05 mM, pH 7.4) was added to 2340 µL of phosphate buffer in a quartz cuvette, and then the reaction was triggered by 600 µL of $H_2O_2$ (1 M). Absorbance kinetics were monitored for 2 min (reading every 30 s) and the enzymatic activity was expressed in IU $min^{-1}$ $g^{-1}$ of tissue or in µmol of $H_2O_2$ degraded $min^{-1}$ $g^{-1}$ of tissue at 25 °C [21,22].

### *Statistical analysis*

Experimental data were processed using GraphPad software. Results are expressed as mean ± standard error of the mean (SEM). Intergroup comparisons were performed by one-way analysis of variance (ANOVA), followed by the Tukey-Kramer post-hoc test for the identification of specific differences. The statistical significance threshold was set at $p < 0.05$.

## Results

Glycemia

Figure 1 shows the evolution of blood glucose (mmol/L) in the different experimental groups. The group receiving cadmium (1 mg/kg) shows a significant increase in blood glucose compared to the control group ($p<0.05$). Administration of ethanolic extract of Rosmarinus officinalis (EERO, 200 mg/kg) alone maintains blood glucose at a level comparable to that of the control. In the co-treated group (EERO + Cd), blood glucose is reduced compared to the cadmium alone group and tends to approach the

control values, indicating a mitigating effect of the extract on Cd-induced hyperglycemia.

*Cholesterol*

Figure 2 illustrates the variations in cholesterol levels (mg/dl) in the different experimental groups. Cadmium administration (1 mg/kg) induced a significant increase in serum cholesterol compared to the control group ($p<0.01$). The ethanolic extract of Rosmarinus officinalis (EERO, 200 mg/kg) administered alone maintained cholesterol values close to those of the control group. In the co-treated group (EERO + Cd), the cholesterol level was significantly reduced compared to the cadmium alone group ($p<0.05$) and tended to approach that of the control group.

*Triglyceride*

Figure 3 shows the effect of cadmium and ethanolic extract of Rosmarinus officinalis (EERO) on plasma triglyceride concentrations in rats. Cadmium administration (1 mg/kg) induced a significant increase in triglycerides compared to the control group ($p<0.05$). Administration of EERO alone (200 mg/kg) maintained values slightly lower than those of the control, without significant difference. In animals co-treated with EERO and cadmium, the triglyceride level was significantly lower than that of the cadmium alone group ($p<0.01$), and tended to approach the control level.

*ALAT and ASAT*

Figures 4 and 5 illustrate the effects of cadmium and ethanolic extract of Rosmarinus officinalis (EERO) on the liver enzyme levels of ALT (alanine aminotransferase) and AST (aspartate aminotransferase) in rats.

In Figure 4, administration of cadmium alone (1 mg/kg) resulted in a significant increase in ALT levels compared to the control group ($p < 0.05$). In contrast, the group treated with EERO alone (200 mg/kg) had ALT levels similar to those of the control group. The group receiving both cadmium and EERO (200 mg/kg EERO + 1 mg/kg Cd) showed a significant reduction in ALT levels compared to the cadmium group alone ($p < 0.01$), reaching values close to those of the control group.

In Figure 5, a similar trend is observed for AST. The cadmium group showed a significant increase in ASAT levels compared to the control group ($p < 0.01$). Treatment with EERO alone did not significantly modify this parameter. On the other hand, the combined administration of the extract with cadmium significantly reduced the cadmium-induced increase in ASAT levels, with levels approaching those of the control group ($p < 0.01$).

*Oxidative stress markers*

Figure 6 shows the effect of the different treatments on NO (nitric oxide) levels in liver tissue. The group treated with cadmium alone (1 mg/kg) showed a significant increase in NO levels compared to the control group ($p < 0.05$). This increase was even more pronounced compared to the EERO group alone ($p < 0.001$). In contrast, the group receiving EERO (200 mg/kg) and Cd (1 mg/kg) simultaneously showed a significant reduction in NO levels compared to the Cd group alone ($p < 0.05$), bringing them back to values close to the control.

Figure 7 illustrates the effects on the activity of CAT (catalase), an antioxidant enzyme. Administration of Cd alone resulted in a significant decrease in catalase activity compared to the control ($p < 0.05$). Conversely, the EERO alone group showed significantly higher catalase activity than the Cd group ($p < 0.001$). In animals treated with EERO + Cd, catalase activity was significantly increased compared to the Cd alone group ($p < 0.05$), reaching levels similar to those of the control group.

## Discussion

Medicinal plants are widely used by the Moroccan population for the prevention and the treatment of several diseases, including hepatic illness. The study aimed to evaluate the hepatoprotective effects of Rosmarinus officinalis in rats by biochemical and histological assessment.

Phytotherapy is the basis of traditional medicine, which is a treatment technique based on the use of plant extracts and their active ingredients to overcome the causes and symptoms of various diseases [23]. The effectiveness of any hepatoprotective substance (drug, plant extract, or food) depends primarily on its potential to correct negative effects that have been disrupted by known hepatotoxic agents.

These results suggest that cadmium exposure causes a disruption of carbohydrate metabolism resulting in hyperglycemia. Administration of EERO alone does not alter normal blood glucose levels, indicating its safety on this parameter. In contrast, co-treatment with EERO in rats exposed to cadmium significantly decreased blood glucose levels compared to the Cd alone group, which indicates a protective and potentially antidiabetic or regulatory effect of the extract. This action could be related to the antioxidant and hepatoprotective properties of Rosmarinus officinalis, which attenuate oxidative stress and liver damage induced by cadmium, restore liver metabolic functions, and contribute to normalizing blood glucose regulation [24]. Another study has also shown that administration of Rosmarinus aqueous extract at a dose of 200 mg/kg decreases glucose levels [25]. The decrease in glucose levels as the duration of food deprivation

increases clearly indicates how the body mobilizes its own tissues as an energy source, resulting in the destruction of visceral organs [26].

The cholesterol results indicate that cadmium exposure leads to dyslipidemia, characterized here by hypercholesterolemia, probably related to alterations in lipid metabolism and disruption of liver functions. Administration of EERO alone does not affect cholesterol, reflecting its safety. In contrast, EERO + Cd co-treatment significantly decreases cadmium-induced cholesterol, suggesting a hypocholesterolemic and hepatoprotective effect of the extract. This action could result from its antioxidant properties and its ability to preserve hepatic integrity and lipid regulation disrupted by Cd. [4,27]. In addition, another study showed that administration of EERO at 10 mg/kg by nasogastric gavage for 8 weeks reduces the cholesterol level [28]. These results are in line with other studies that have demonstrated that the administration of the hydroalcoholic extract of *Rosmarinus officinalis* for 28 days in the different groups of rats treated with 200, 500 and 1000 mg/kg does not cause any significant difference in cholesterol levels and no alteration of these parameters compared to the control rats [29].

Aminotransaminases enzymes are molecules of the cytoplasm and mitochondria [30]. The significant increases in ALT and AST levels in rats exposed to cadmium indicate liver damage. These two enzymes, located primarily in hepatocytes, are released into the blood in the event of cell injury, reflecting impaired liver membrane integrity. The toxic effect of cadmium on the liver is therefore clearly confirmed by these enzyme elevations.

The absence of an increase in liver enzymes in rats treated solely with *Rosmarinus officinalis* extract suggests that it is not hepatotoxic at the administered dose. Furthermore, the significant reduction in ALT and AST levels in animals receiving both the extract and cadmium demonstrates the protective effect of ROS against cadmium-induced liver toxicity [31].

This beneficial effect is likely due to the well-documented antioxidant properties of Rosmarinus officinalis. The extract is rich in phenolic compounds such as rosmarinic acid and carnosol, known for their ability to neutralize free radicals and strengthen antioxidant defense systems. Thus, EERO could attenuate cadmium-induced oxidative stress, protect hepatocytes from lipid peroxidation, stabilize their membranes, and limit the release of liver enzymes into the blood [18]. Similarly, another study showed that administration of a dose of 200 mg/kg EERO reduced the level of ALT, AST, and blood glucose [32]. The reduction in AST and ALT levels is an indication of hepatoprotection, and other studies even describe it as a process of liver cell regeneration [33]. This hepatoprotective effect is associated with the correction of daily weight variation in rats treated with our plant extracts.

According to oxidative stress, the increase in NO levels in the cadmium-treated group reflects an induction of hepatic oxidative stress. Indeed, although NO is a physiological molecule involved in cell signaling, its excessive production—particularly in response to toxic stresses such as cadmium—can promote the formation of free radicals such as peroxynitrite, thereby exacerbating cell damage. Rosmarinus officinalis extract, when co-administered with cadmium, significantly reduced this NO elevation, suggesting an antioxidant effect and a limitation of the oxidative inflammatory response [10].

Concurrently, the reduced catalase activity observed in the Cd-only group reflects an impairment of endogenous antioxidant defenses, typical of heavy metal-induced oxidative stress. Catalase is a key enzyme in the neutralization of hydrogen peroxide ($H_2O_2$), a toxic byproduct of metabolic reactions. Its decrease indicates that the liver is overwhelmed by excess free radicals. The increase in catalase activity in the EERO alone group, and especially in the EERO + Cd group, demonstrates that Rosmarinus officinalis strengthens antioxidant defense mechanisms. This confirms the protective role of the extract against the harmful effects of cadmium on the liver [3,34].

Overall, these data show that EERO acts both by reducing NO production and by stimulating the activity of antioxidant enzymes such as catalase. This suggests a dual beneficial effect: limiting oxidative stress and restoring oxidative balance in the liver. These properties could be attributed to the extract's rich content of antioxidant phenolic compounds, flavonoids, and diterpenes (such as rosmarinic acid or carnosol), capable of scavenging reactive oxygen species and protecting tissues against lipid peroxidation. Indeed, the results of our phytochemical analysis suggest that the Rosmarinus officinalis extracts studied are rich in secondary metabolites such as total polyphenols, flavonoids, and moderate amounts of condensed tannins. These metabolites have the ability to neutralize radicals and thus prevent potential tissue damage [35]. Similarly, a comparative study carried out in intoxicated mice showed significant hepatoprotective activity of extracts of *Rosmarinus officinalis*, *Peumus boldus* and *Eupatorium cannabinum*, ranked in order of increasing effect with silymarin. Flavonoids are recognized for their hepatoprotective activities [22].

## Conclusion

Our study highlights the negative effects of cadmium on the liver, resulting in impaired liver function, disruption of metabolic parameters (hyperglycemia, hypercholesterolemia, hypertriglyceridemia), increased liver enzymes

(ALAT, ASAT), overproduction of NO, and inhibition of antioxidant activity (catalase). These alterations confirm significant oxidative stress and severe liver dysfunction induced by cadmium. In contrast, administration of the ethanolic extract of *Rosmarinus officinalis* not only restored liver function and antioxidant defenses but also corrected metabolic disorders.

These findings strongly support the hypothesis that EERO has a hepatoprotective, antioxidant and metabolic regulating effect, making it a promising natural therapeutic candidate to prevent or mitigate the toxic effects of heavy metals such as cadmium. It is recommended to consider the use of *Rosmarinus officinalis* in the context of complementary or preventive medicine, particularly for populations exposed to environmental contaminants. However, further studies are needed to further investigate the molecular mechanisms of action of EERO and test its efficacy at different doses or in combination with other natural extracts. Long-term clinical trials could also be considered to validate its use in humans.

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*Declaration of Conflict of Interest*

The authors declare that there is no conflict of interest.

*Ethical of approval*

This study follows the ethics guidelines of the Faculty of Sciences, Ibn Tofail University, Kenitra, Morocco (ethics approval number; 09/2024).

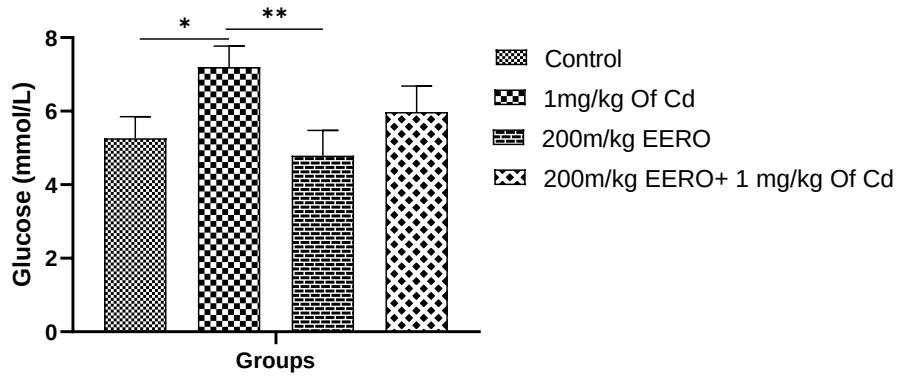


**Fig. 1. Effect of Rosmarinus officinalis on glycemia in rats. Results are expressed as mean ± SEM. (n=6). *p<0.05.**

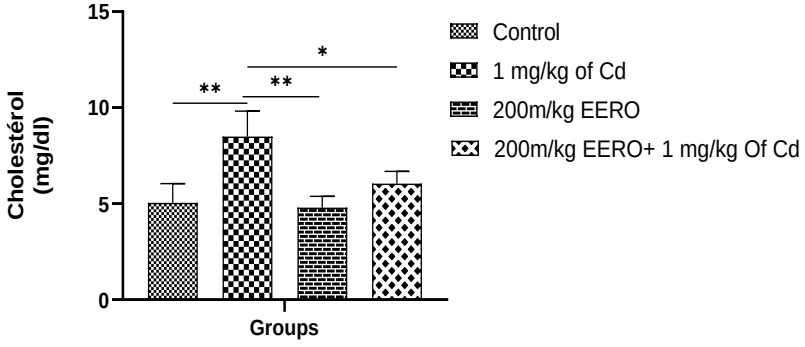


**Fig. 2. Effect of Rosmarinus officinalis on cholesterol levels.**

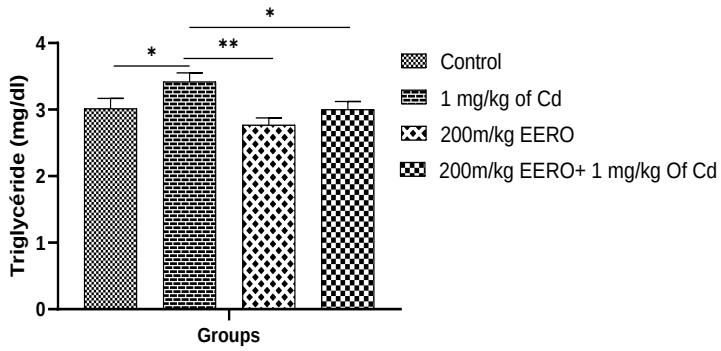


**Fig. 3. Effect of the ethanolic extract of Rosmarinus officinalis on triglyceride levels. (n=6).**

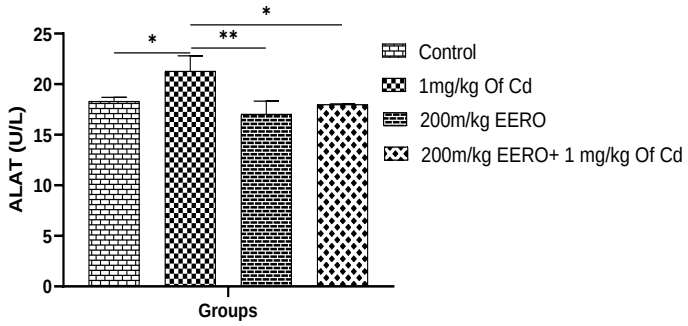


**Fig. 4. Effect of ethanolic extract of Rosmarinus officinalis on the levels of ALAT (n=6).**

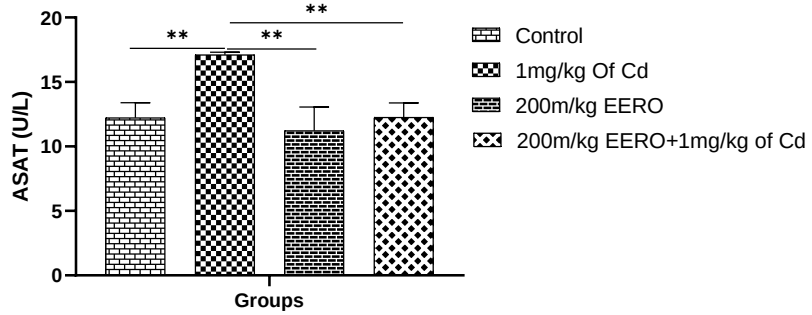


**Fig. 5. Effect of the ethanolic extract of Rosmarinus officinalis on the levels of ASAT (n=6).**

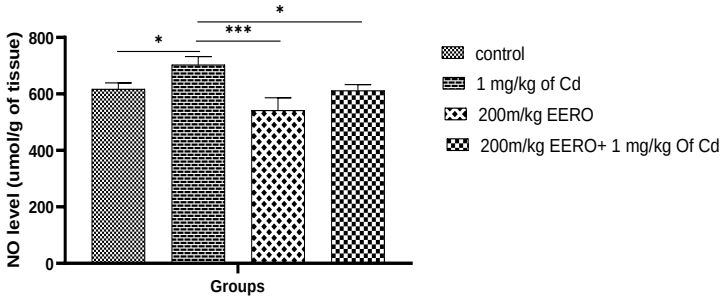


**Fig. 6. Effect of the ethanolic extract of Rosmarinus officinalis on the levels of nitric oxide (n=6).**

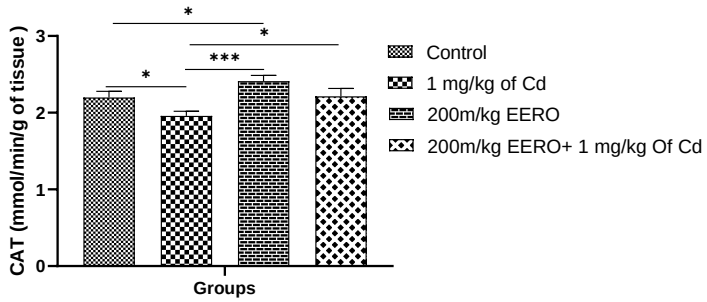


**Fig. 7. Effect of the ethanolic extract of Rosmarinus officinalis on the levels of CAT (n=6).**

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# التأثير الوقائي للكبد للمستخلص الإيثانولي لنبات إكليل الجبل ضد الضرر الناجم عن الكادميوم عند جرذان ويستار

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**الملخص**

الطب التقليدي منتشر على نطاق واسع، ولا يزال عدد الدراسات في البحث عن جزيئات جديدة قادرة على منع أو حتى تأخير ظهور المضاعفات المتعلقة بضعف وظائف الكبد محدودًا للغاية. في المغرب، يستخدم (Rosmarinus officinalis (RO على نطاق واسع لعلاج اضطرابات الكبد المختلفة. هدفت الدراسة إلى تقييم آثار RO على وظائف الكبد لدى إناث فئران ويستار المعرضة للكادميوم. تم تقسيم 30 أنثى من فئران ويستار إلى 5 مجموعات؛ تلقت المجموعة الضابطة ماءً مقطرًا عن طريق الفم، والمجموعة التي تلقت 1 ملغم/كغم من الكادميوم، وتلقت المجموعة المستخلص الإيثانولي لـ RO بجرعات 200 ملغم/كغم، وتلقت المجموعة الأخيرة 200 ملغم/كغم من RO و 1 ملغم/كغم من الكادميوم، لمدة 8 أسابيع. في نهاية العلاج، تم أخذ عينات دم الفئران للتحليل الكيميائي الحيوي، بما في ذلك الكوليسترول، وألانين أمينوترانسفيراز (ALT)، وأسبارتات أمينوترانسفيراز (ASAT)، والجلوكوز، والكوليسترول الكلي، والدهون الثلاثية (TG). تم تقييم المؤشرات الحيوية للإجهاد التأكسدي، وأكسيد النيتريك (NO)، وإنزيم الكاتالاز المضاد للأكسدة (CAT) في الكبد. وُفحصت عينات من الكبد من كل مجموعة علاجية نسيجيًا. أظهرت النتائج أن التعرض للكادميوم أدى إلى زيادة ملحوظة في نسبة الجلوكوز في الدم، والكوليسترول، والدهون الثلاثية لدى الفئران، مما يعكس اضطرابًا أيضيًا ناجمًا عن الكبد. أدى الإعطاء المتزامن للمستخلص الإيثانولي لنبات إكليل الجبل (Rosmarinus officinalis) إلى تخفيف هذه التغيرات، وجعل قيم المعلمات المقاسة أقرب إلى قيم المجموعة الضابطة، مما يشير إلى تأثير وقائي للكبد وتنظيمي للأيض. يُظهر المستخلص الإيثانولي لنبات إكليل الجبل نشاطًا مضادًا للأكسدة، يتجلى في انخفاض مستوى أكسيد النيتريك وزيادة مستوى إنزيم الكاتالاز المضاد للأكسدة في الكبد والكلى. وخلصت هذه الدراسة إلى أن المستخلص الإيثانولي لـ Rosmarinus officinalis أظهر تأثيرات وقائية ملحوظة على الكبد ضد الكادميوم من خلال تقليل علامات الإجهاد التأكسدي، مما يشير إلى استخدام Rosmarinus officinalis كمكمل غذائي للمرضى الذين يعانون من اضطرابات الكبد.

**الكلمات الدالة:** إكليل الجبل *Rosmarinus officinalis* ، الكبد، كادميوم، النشاط التأكسدي ، جردان.