

## Some Biological Effects of Libyan Propolis extract on Male albino Rats Treated with Aluminum chloride

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### المخلص

يعد استخدام المنتجات الطبيعية وسيلة أساسية للتوصل إلى عقاقير جديدة لاكتشاف وتطوير أدوية جديدة لعلاج الأمراض، أجريت هذه الدراسة لمعرفة التأثيرات الوقائية للبروبوليس (الصمغ) على الإجهاد التأكسدي الناجم عن الألومنيوم والتغيرات البيوكيميائية في الفئران. لذلك، أجريت التجربة الحالية لتحديد مدى فعالية البروبوليس في تخفيف سمية كلوريد الألومنيوم ( $AlCl_3$ ) على المعايير الكيموحيوية لذكور فئران ويستار ألبينو. تم تقسيم أربعين من ذكور الفئران البيضاء البالغة إلى أربع مجموعات متساوية وتلقت العلاج لمدة 6 أسابيع، (GI): المجموعة الضابطة تلقت الماء المقطر، (GII): مجموعة البروبوليس 50 ملغم/كجم، (GIII): مجموعة كلوريد الألومنيوم 475 ملغم/كجم، (GIV): مجموعة البروبوليس وكلوريد الألومنيوم. أظهرت المجموعة المعالجة بـ  $AlCl_3$  زيادة ملحوظة في نشاط انزيمي اسباريتيت ترانامينيز (AST)، الألانين ترانس أمينيز (ALT) والبيلوروبين الكلي في البلازما، كما تم زيادة مستوى الكرياتينين واليوريا في البلازما بشكل ملحوظ بينما انخفض البروتين الكلي بشكل ملحوظ، كما أدت المعاملة بالبروبوليس مع  $AlCl_3$  إلى تحسين التغيرات البيوكيميائية والنسجية الناجمة عن  $AlCl_3$ .  
الكلمات المفتاحية: المنتجات الطبيعية، الصمغ، كلوريد الألومنيوم، الكبد.

### ABSTRACT

The use of natural products is an essential way to new pharmaceutical leads for the discovery and development of new drugs to treat diseases. The present study was carried out to investigate the protective effects of propolis on aluminum-induced oxidative stress and biochemical alterations in rats. Therefore, the present experiment was undertaken to determine the effectiveness of propolis in alleviating the toxicity of aluminum chloride ( $AlCl_3$ ) on biochemical parameters of male Wistar Albino rats. Forty adult male albino rats were divided into four equal groups received treatment for 6 weeks: (GI) Control group received distilled water. (GII) Propolis group 50 mg/kg. (GIII) Aluminum chloride group 475mg/kg. (GIV) Propolis and aluminum chloride group. The  $AlCl_3$ -treated group showed a significant increase in the activities of aspartate transaminase (AST), alanine transaminase (ALT) and total bilirubin in the plasma. Also, creatinine and urea, in the plasma were significantly increased while total protein was significantly decreased, propolis treatment with  $AlCl_3$  improved the biochemical and histological changes induced by  $AlCl_3$ .

**Keywords:** Natural products, Propolis, Aluminum chloride, Liver.

## Introduction

Humans and animals interact daily with their environment and are exposed to a wide range of chemicals and heavy metals, which can bio-accumulate in the body and collect in tissues with low excretion [1]. The third most abundant metallic element in Earth's crust is aluminum (Al) [2]. Avoiding exposure to Al is almost impossible as it is used in various daily applications, such as water treatments, wood preservation, shampoos, vitamins, food additives, packaging materials, antiperspirants, toothpaste, medicines, or as fillers in plastics [3]. Commonly, Al reaches humans by breathing ambient air and intaking contaminated food and water [4]. Aluminum distributes in varying human tissues including liver, lung, brain, heart, blood, kidney, bone and other organs, Humans are exposed to Aluminum Chloride that is present in food, drinking water, and soil [5]. The elemental aluminum does not occur in its pure state, rather it is always combined with other elements, such as chloride, silicate, sulfate, phosphate, and hydroxide. The wide distribution of this element ensures the potential for causing human exposure and harm [6]. The liver is the main organ responsible for processing toxic elements inside the body; therefore, it is involved in aluminum absorption and excretion through biliary flux [7]. The liver is a primary metabolic organ and is responsible for many critical functions within the body. Indeed, if the liver becomes diseased or injured, the ensuing threat to the body's metabolic system can be life threatening. Many researchers have previously demonstrated that antioxidants prevent hepatotoxicity by inhibiting lipid peroxidation, reactive oxygen species (ROS) generation, and also by suppressing the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) [8,9,10]. A natural product, propolis is a resinous hive product collected by honeybees from various plant sources. The use of propolis goes back to ancient times, at least to 300 BC, and it has been used as a medicine in local and popular medicine in many parts of the world, both internally and externally. In recent years, propolis has attracted researchers' interest because of its many beneficial biological effects, such as hepatoprotective, antitumor, antioxidative, antimicrobial, anti-inflammatory activity [11,12]. Besides, propolis-containing products have been intensely marketed by the pharmaceutical industry and health-food stores. The chemical composition of propolis depends on the specificity of the local flora at the site of collection. More than 300 constituents have been identified from propolis, among which phenolic compounds such as flavonoids, phenolic acids and phenolic acid esters have been reported as major constituents of propolis from the temperate zone [12]. Therefore, the present study was designed to assess the potential protective effects of propolis in modulating the harmful impacts induced by aluminum in male rats.

## Materials and Methods

### Chemicals

- Propolis was obtained from herbal markets, Libya.
- Aluminum chloride powder was purchased from El Gomhoreya Company, Egypt. Both chemicals dissolved in distilled water (10 mg Propolis, and 95 mg Aluminum chloride). Continuous shaking was done for complete dissolving. The solution was prepared fresh every day.

### Animals

Forty male albino rats weighting 165-180 grams. The rats were purchased from Faculty of Pharmacy, Tripoli University, Libya. Rats were housed in plastic cages and received

water and diet at good conditions for six weeks (experimental period). Animals were categorized randomly into four groups, ten rats in each group (n=10 rats).

### Animal's groups

**Group I (control):** received 2ml distilled water by oral route and kept without any treatment for 6 weeks.

**Group II (Propolis supplemented):** rats received propolis at a dose of 50 mg/kg b.w/day[13]. Each rat received 1 ml distilled water containing 10 mg propolis by oral route for 6 weeks.

**Group III (aluminum chloride treated):** rats treated by aluminum chloride at dose of 475 mg/kg b.w[14], once daily, by oral gavage for 6 weeks. Each rat received 1 ml distilled water containing 95 mg aluminum chloride.

**Group IV (Propolis and aluminum chloride):** rats received both aluminum chloride and Propolis once daily, by oral gavage for 6 weeks. The doses were similar to that of the previous experimental groups.

### Biochemical analysis

After 6 weeks of treatments, the animals of each group were scarified, and the collected blood was putted in a tube containing anticoagulant. It was centrifuged at 3000 rpm for 20 min to obtain plasma. The obtained plasma was stored frozen at  $-20^{\circ}\text{C}$  until use. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined as described by [15]. The estimation of total protein and total bilirubin were carried out by the method of [16]. Plasma urea, and creatinine concentrations were measured by the methods of [17], and [18], respectively.

### Histological examination

After 6 weeks of treatments, the liver of different animal groups were prepared for histological examination through the routine technique according to the method of [19], and stained with couple stain haematoxylin (H) and eosin (E). The slides were examined and photographed as required.

### Statistical analysis

Results were presented as means  $\pm$  SD. The student's t-test was used for comparison of different experimental animal groups and control ones, and the results were considered significant at  $P \leq 0.05$ .

### Results

Table (1), shows that there are highly significant differences in the activity of ALT between groups ( $P < 0.001$ ). Student t-test indicated that, a significant increase in activity ALT in  $\text{AlCl}_3$  group, in comparing with that of normal group, In addition, the AST activity was no significant difference between groups. However, t-test shows a significant increase activity of AST in  $\text{AlCl}_3$  group, compared with normal group. The activity of AST enzyme significantly decreased in  $\text{AlCl}_3$  & Propolis group compared with the activity of  $\text{AlCl}_3$  group, the level of total protein indicates an highly significant difference ( $P < 0.001$ ) between groups. Student t-test analysis showed a significant decrease in the level of total protein in propolis group,  $\text{AlCl}_3$  group and  $\text{AlCl}_3$  & Propolis group compared with the levels of normal group. From table (1), it can be observed that, there is a significant

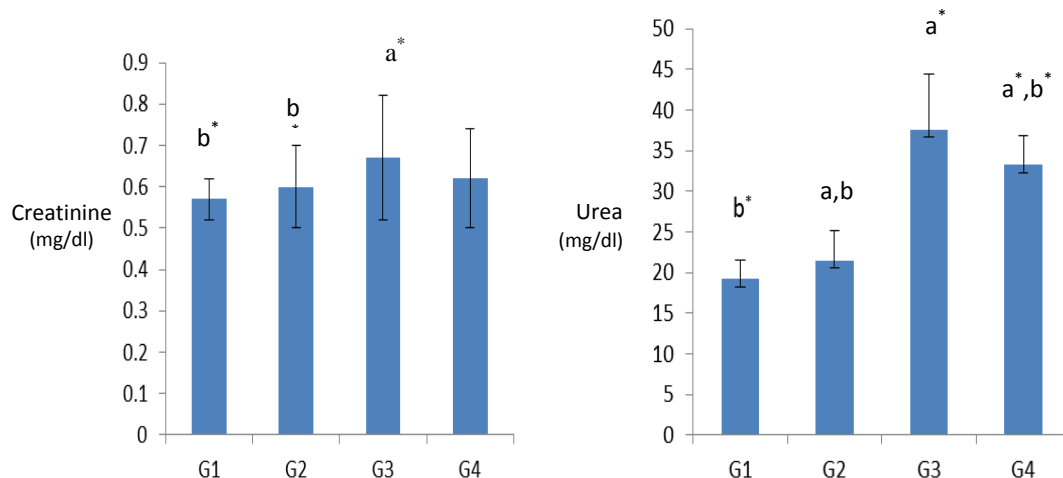
difference between all groups as indicated by one-way ANOVA analysis ( $P < 0.05$ ), the level of total bilirubin was highly significantly decreased ( $P < 0.001$ ) in propolis group and  $AlCl_3$  & Propolis group, compared with the level of normal group.

**Table (1).** Effects of treatments on some biochemical parameters in plasma of control and treated rats:

Parameters	G1	G2	G3	G4
ALT (U/ml)	39.90±0.64 <sup>b*</sup>	35.55±0.41 <sup>a*b*</sup>	61.30±0.25 <sup>a*</sup>	49.30±0.57 <sup>a*b*</sup>
AST (U/ml)	102.20±0.93 <sup>b*</sup>	110.20±1.76 <sup>a*b*</sup>	150.00±0.64 <sup>a*</sup>	132.00±1.11 <sup>a*b*</sup>
T-Protein (g/L)	6.35±0.43 <sup>b*</sup>	5.74±0.55 <sup>a</sup>	5.13±0.43 <sup>a</sup>	5.50±0.54 <sup>b</sup>
T-Bilirubin(mg/dl)	0.32±.04 <sup>b</sup>	0.21±0.01 <sup>ab</sup>	38±0.03 <sup>a*</sup>	0.27±0.08 <sup>ab*</sup>

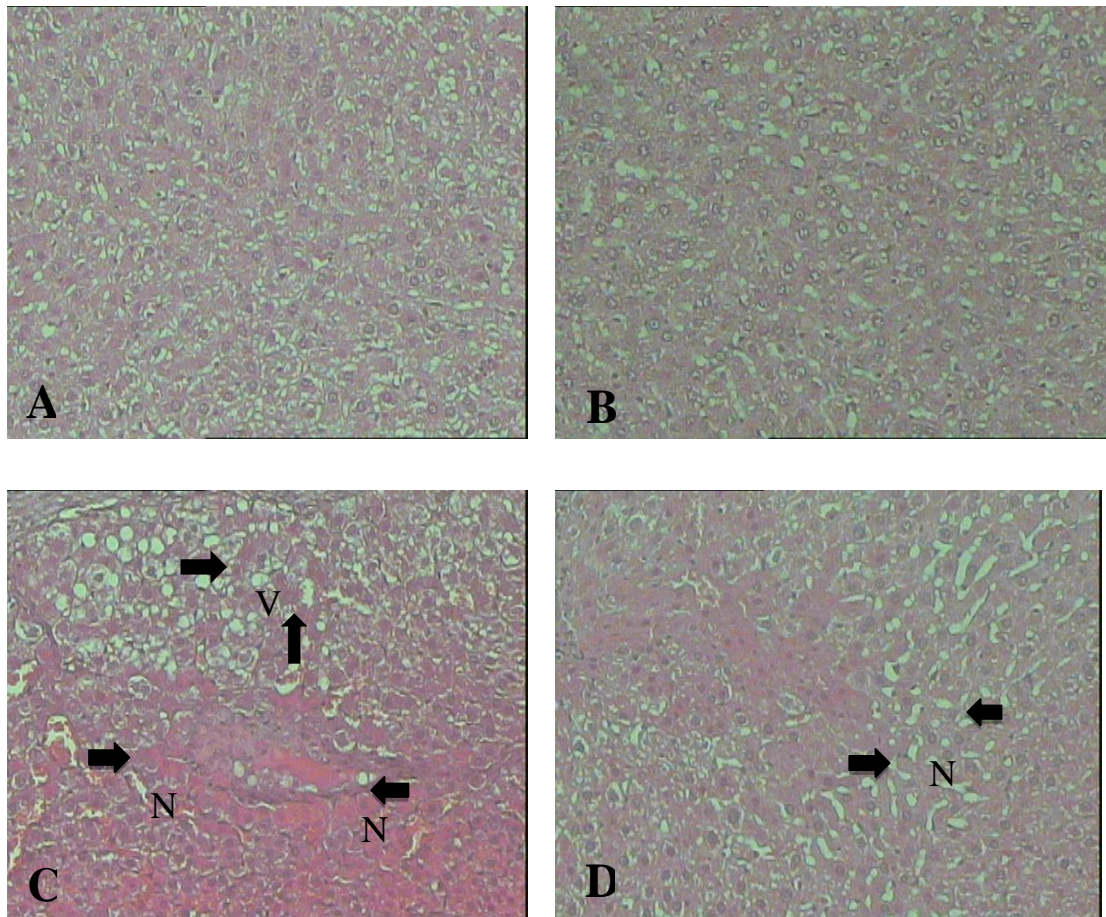
Significance (a): relative to the control group. Significance (b): relative to the  $AlCl_3$  chloride group Significance:  $P < 0.05$ , highly significance (\*):  $P < 0.001$ .

**Figure (1).** showed statistical analysis; one-way ANOVA, of level creatinine there is a significant difference ( $P < 0.05$ ) between groups. Student t-test, indicated that, there is a high significant increase ( $P < 0.001$ ) in  $AlCl_3$  group compared with the level of the normal group. In addition, that there is an high significant difference ( $P < 0.001$ ) between groups as indicates by one-way ANOVA, student t-test of level of urea shows that there is a significant increase in  $AlCl_3$  group, and  $AlCl_3$  & Propolis group, compared with normal group. At the same time the level is significantly decreased in  $AlCl_3$  & Propolis group compared with  $AlCl_3$  group.



**Figure (1).** Effect of propolis on the plasma level of creatinine, and urea of rats treated with  $AlCl_3$ . Significance (a): relative to the control group. Significance (b): relative to the  $AlCl_3$  group.

The histopathology of the liver tissues in normal group, propolis group (fig 2.A and B) showed normal hepatic structure with no histopathological changes. The histopathology of the liver tissues in  $AlCl_3$  group (fig 2.C) showed wide spread inflammation, vascular congestion and dilated sinusoidal spaces.  $AlCl_3$  & propolis group (fig 2.D) showed less necrosis and vacuolization compared with  $AlCl_3$  group.



**Figure (2).** (A and B) showed normal liver with no pathological changes.( C) showed marked coagulative necrosis (N) with vacuolization (V). (D) showed less necrosis and vacuolization compared to (C) means more improvement.

### Discussion

The present study was carried out to evaluate the protective role of propolis against aluminum toxicity induced biochemical and histological alterations in the liver and kidney of rats. However, it is well known that the plasma enzymes are hepatic health markers, and the alteration in their levels is an indicator of the disturbances in the histological structure of hepatocytes. In the present study, the  $\text{AlCl}_3$ -treated group showed a highly significant increase in the plasma level of enzymes, ALT, and AST with marked detectable histopathological alternations in the liver tissues including severe vacillation with increased inflammatory infiltrated cells among the sinusoids and necrosis of cells. These results are in accordance with other findings showing that the increases in the levels of plasma enzymes are accompanied with histopathological changes in the liver tissue in  $\text{AlCl}_3$ -treated animals [20,21,22,23]. ALT is an enzyme present in hepatocytes. Upon cell damaged the enzyme leaks into the blood. ALT level rises dramatically in acute liver damage, such as viral hepatitis or paracetamol overdose [24]. Serum concentration of bilirubin is very specific for potentially serious liver damage, and is an important indicator of the loss of liver function [25]. However, the elevated liver enzymes in the plasma after administration of  $\text{AlCl}_3$  might be due to cellular degeneration and changes in permeability of hepatic cell membranes [26,27]. It had been reported that the accumulation of  $\text{AlCl}_3$  in the liver tissue is associated with necrosis and degeneration of hepatic tissue to escape of liver enzymes from the injured cells to the plasma [23,28]. In addition, histological changes in the liver and the increase of plasma enzyme activities may be due to free

radicals production and oxidative stress after  $AlCl_3$  administration in the liver tissue[22,26] . On the other hand, the administration of  $AlCl_3$  combined with propolis showed non- significant change on the plasma level of enzymes, ALT and AST, with normal liver histological structure, indicating that propolis tended to prevent damage and blocked the enzymes leakage through cellular membranes. These results are in agreements with findings of many studies [20, 27,29], who concluded that propolis mostly recovered the action of  $AlCl_3$  on the function and structure of the liver. Moreover, the hepatoprotective effect of propolis may be attributed directly to stabilization of redox state in the cells [30, 31].The total protein is made specifically by the liver. The TP levels will be depressed in hepatotoxic conditions due to defective protein biosynthesis in the liver. Restoring the normal levels of TP is an important parameter for liver recovery[32]. In the present study, there was a significant decrease in the level of total protein in  $AlCl_3$  compared with normal group. However, the level of total protein was increased in propolis group, compared with  $AlCl_3$  group. Urea and creatinine are waste products of protein metabolism that need to be excreted by the kidney, therefore marked increase in serum urea and creatinine, as noticed in this study, confirms an indication of functional damage to the kidney[33]. Urea level can be increased by many other factors such as dehydration, antidiuretic drugs and diet, whilst creatinine is, therefore, more specific to the kidney, since kidney damage is the only significant factor that increases serum creatinine level [34]. Therefore, significant increases in urea and creatinine levels noticed in this study are a classical sign that the kidney was adversely affected.

### Conclusion

The present results demonstrated that the exposure of animals to aluminum is able to induce significant detectable changes in histological and biochemical characteristics and enzymatic activities. Also, our study showed that the propolis reduced the toxic effects of  $AlCl_3$  by reducing degenerative changes in the liver and kidney tissues and alleviated biochemical parameters.

### Recommendations

Recommended to reduce exposure to aluminum in our daily lives and it is also recommended that eating foods rich in propolis may be a useful way to avoid aluminum toxicity.

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