TOXICITY OF AQUEOUS EXTRACT OF *EUCALYPTUS* IN SWICE ALBINO MICE

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ABSTRACT

Aqueous extract of *Eucalyptus* have been traditionally used as a medicinal agent for treatment of a variety of diseases, or as a pesticide original botanic in many researches. There have been only a few reports on the toxicity of the aqueous extracts of *Eucalyptus*. Oral toxicity studies of aqueous extract of *Eucalyptus* was carried out in males' mice to evaluate the morphological hematological, biochemical and histopathological changes, As well as to evaluate its effect on the general health if used as pesticide. Twenty adult healthy male mice were divided into two groups of 10 animals each were used. The first group received orally aqueous extract of *Eucalyptus* at a dose level of 2000mg/kg b.w (0.2ml of the extract/mouse/day). Mice in control group were given an equivalent volume of distilled water. Blood samples were collected at the end of experimental period for hematological and biochemical analysis. Selected organs from both control and treated animals were examined microscopically for histopathological changes. The aqueous extract of *Eucalyptus* induced undesired behavior and external features. However, treatment with aqueous extract of Eucalyptus induces significant decrease in body weight gain of mice. Hematological studies revealed a significant decrease in hemoglobin level, RBC, WBC and platelets count of treated mice. Also the treated mice showed dramatic alterations in hepatic and renal functions as indicated by the biochemical estimation of several parameters (ALT, AST, and creatinine and urea level). Histological examination revealed that, the treatment with aqueous extract of *Eucalyptus* induced different drastic lesions in many organs which were more pronounced in liver and lung. The obtained results collectively

indicated that subchronic administration of aqueous extract of *Eucalyptus* induced severe morphological, and biochemical perturbations. Also our examinations seem to prove that aqueous extract of *Eucalyptus* at a dose level used in the present work plays prominent role in the development of histopathological alterations in Swiss albino mice.

Key words: Toxicity, aqueous extract *Eucalyptus*, morphological, histopathological, hematological, hepatic and renal functions, mice.

INTRODUCTION:

Eucalyptus globulus (Family Myrtaceae) is a tall evergreen tree native to Australia and Tasmania. Today, most commercial herbal preparations originate in Mediterranean and subtropical regions, including Spain and Morocco. The leaves and oil of Eucalyptus plant are used for medicinal proposes. The plants have been considered as sources of medicinal agents for the treatment of many diseases. *Eucalyptus* is a traditional remedy for a variety of common ailments, particularly of respiratory tract, and burns in China. Also, it widely used as natural antioxidant food additives. **(Amakura et al., 2009).**

Experimentally, it has been demonstrated that this plant posses a broad therapeutic properties as antimicrobial and antidiabetic. **(Atta & Alkofahi, 1998; Gray & Flatt, 1998; and Sartorell et al., 2006).**

Eucalyptus leaves contain tannins (which are belived to reduce inflammation), flavonoids (such as quercetin, which has antioxidant properties), and volatile oils **(Atta & Alkofahi, 1998; Lee et al., 1998; cermelli et al., 2008 and Amakura et al., 2009).** It was reported that *Eucalyptus* contain high levels of phenolics and terpenoids which can be toxic **(Whitman & Ghazzadeh, 1994).** Based on rodent studies, the oral LD50 for *Eucalyptus* oil is very high 4.44g/kg for rat and 3.32g/kg for mice **(Whitman & Ghazzadeh, 1994).**

Several adverse reactions have been attributed to the use of or contact with *Eucalyptus* oils, extracts, and fresh and processed plant material. Some of the specific compounds that can be toxic or cause adverse reactions include: 1,8-cineole, cyanogenic glycosides, rutin, and tannins.**(Bianchetti et al., 1970 and Cheeke, 1998).**

Eucalyptus Contain high levels of phenolics and terpenoids which can be toxic, animals such as the koala which eat *Eucalyptus* have developed methods for detoxifying these compounds in the liver **(Whitman & Ghazzadeh, 1994).**

Eucalyptus oil possesses a wide spectrum of biological activity including antimicrobial, fungicidal, insecticidal, insect repellent, herbicidal, acaricidal and nematicidal **(Batish et al., 2008).** The use of *Eucalyptus* oils as a natural pesticide is of immense significance in view of the environmental and toxicological implications of the indiscriminate use of synthetic pesticides and overcoming/reducing the problem of increasing pest resistance **(Batish et al., 2008).**

Hence, the current study was aimed to evaluate the toxicity properties of repeated dose of aqueous extract of *Eucalyptus* in *Swiss albino* mice based on biochemical and haematological changes as well as pathological changes in liver, kidney, Lung, Spleen, brain and cardiac muscle.

MATERIALS AND METHODS:

Animals:

Male Swiss albino mice (Mus musculus, 2n= 40) weighing 20-27gm and 12 weeks old were used in this study. They were obtained from experimental animal house Arab Tebia University. The animals were quarantined and acclimated for 2 weeks and then randomly divided into 2 groups. The animals were housed in air condition room at 22±2 °C and maintained in mettle cages with regular light dark cycle(photoperiod of 12hr/days) and free access food (commercial pellet) and tap water ad libitum.

Preparation of plant extract:

Eucalyptus globulus (*E. globulus*) leaves were collected from few *Eucalyptus globulus* trees behind the faculty of Agriculture, University of Omar El Mukhtar El-Beida, Libya. The leaves were air dried and milled into powder. The dried powered plant leaves (5gm) was mixed with 200ml of distilled water and leaving the mixture overnight at 20-22°C. The mixture was then filtered though four folds of cheesecloth. Fresh preparation was used every day **(Somda et al., 2007).**

Experimental protocol:

The mice were randomly divided into 2groups of 10 mice each. Group I received distilled water (0.2ml/ mouse once daily orally for 10 successive days) and served as control, whereas mice in group II received aqueous extract of *Eucalyptus* at the dose of 2000mg/kg b.wt./day for 10 successive days (i.e. 0.2ml of extract/mouse/day).

Body weight: Initial and final body weight were measured and the changes in the mean body weight changes was estimated.

Haematological and biochemical studies:

Blood samples were collected from the neck blood vessels 24 hr.after the end of experimental period (10 days) into clean container containing EDTA (1mg/ml fresh blood) and were used for haemtological analysis. RBCs count , hemoglobin content haematocrit value, platelets count and total white blood cell count were counted and calculated according to **Dacia and Lewis (1995).** For biochemical parameters, the blood samples were collected into free anticoagulated containers and centrifuged at 3000 rpm for 10 minutes and the superanated serum was collected in eppendorf and utilized for estimation various biochemical parameters. Serum activities of alanine aminotransferas (ALT or SGPT) and asparatate aminotransferease (AST or SGOT) were determined according to the method recommended by **Reitman and Frankel (1957).** Serum creatinine and urea were determined according to procedures of **Henry (1974), Fawcett and Scott (1960)** respectively.

Histopathological analysis

Visceral organs were examined grossly in all the autopsied mice. The portions of selected organs (Brain, heart, liver, kidney, spleen and lung) were immediately fixed in 10% neutral formalin a period of at least 24 hours, dehydrated in several grad (70-100%) alcohol embedded in paraffin (58-60°C) and sectioned at 5 μm thickness . The sections were stained with hematoxyline and eosin **(Drury and Wallington, 1980).**

Statistical analysis

Was performed using t-test, the results were presented as means ± standard division (SD). P value < 0.05 considered statistically significant.

RESULTS AND DISCUSSION

Effect of Aqueous extract of eucalyptus on the clinical signs of mice: Administration of aqueous extract of eucalyptus at a dose of 2000mg/kg b.w. did not result in any mortality. However, administration of aqueous extract of eucalyptus induced undesired behavior and external features include general weakness, decrease in physical activities, and loss of body furs, ruffle fur and changing in white coat color which were more pronounced in most mice. The decrease in the physical activities may be due to reduce of the blood glucose level. **(Ahlem et al., 2009).** Aqueous extract of eucalyptus exhibited significant decline in the body weight gain as compared to control group. It was noticed that the final body weight of control animals increased by 1.65% (table I) and Fig :1, while the finale body weight of Eucalyptus treated mice decrease by -13.35% the their initial body weight.

Table (I) : Effect of oral administration of aqueous extract of Eucalyptus on Body weight gain of male mice

Treatment	Initial body weight (g)	Final body weight (g)	The mean of the changes in body weight (%)
Control	20.85± 2.27	21.20±3.00	1.65
Eucalyptus	24.10±3.92	21.26±3.621*	-13.35*

Each value represent the mean of body weight of survival in each group.
*significant as compared to Initial body

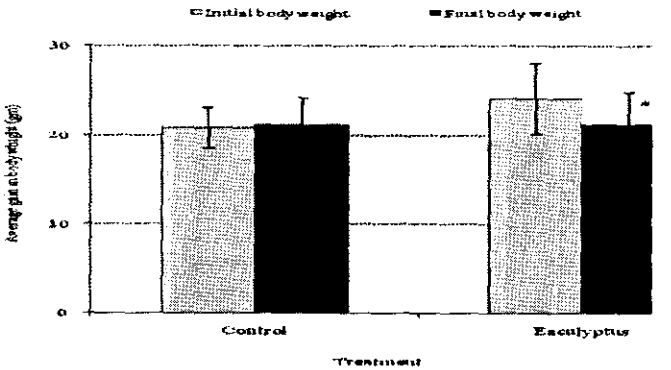


Fig (1) : Effect of oral administration of aqueous extract of Eucalypt on Body weight gain of male mice

The decreased body weight gain observed in this study may be due to loss of appetite and concomitant decrease in food intake or an increase in the metabolic rate Ryu (1988). Who studied the acute and chronic toxicities of nivalenol in mice suggested that the decreased weight gain in treated animals may be caused by reduced feed conversion efficiency.

The haematological results of control and treated mice are given in table II and Fig. (2) administration of aqueous extract of *Eucalyptus* induced a marked depression in haemolglobin concentration (3.12%), PVC (3.11%), RBC (11.31 %) total WBC count (20.97%)indicated severe leucopaenia and platelet count (15.55%) compared with that found in control animals. It was found that administration of aqueous extract of *Eucalyptus* may be induce sever type of anemia.

Table (II): Effect of oral administration of aqueous extract of *Eucalyptus* on hematological parameters in male mice

Treatment	Hb (g/dl)	PCV (%)	RBC (10^6/mm^3)	WBC (10^3/mm^3)	PI (10^3/mm^3)
Control	12.49± 0.09	41.21±0.29	7.16±0.31	6.39±0.80	7.14±0.21
Eucalyptus	12.10±0.14*	39.93±0.47*	6.35±0.13*	5.05±0.13*	6.03±0.09*

Each value represent mean of five value ± SD , *significant as compared to control group
Hb: Hemoglobin concentration , PCV: packed cell volume (Ht : haematocrit) , MCV: Mean cell volume, RBCs: Red blood cells, WBCs: White blood cells , PI: platelets count

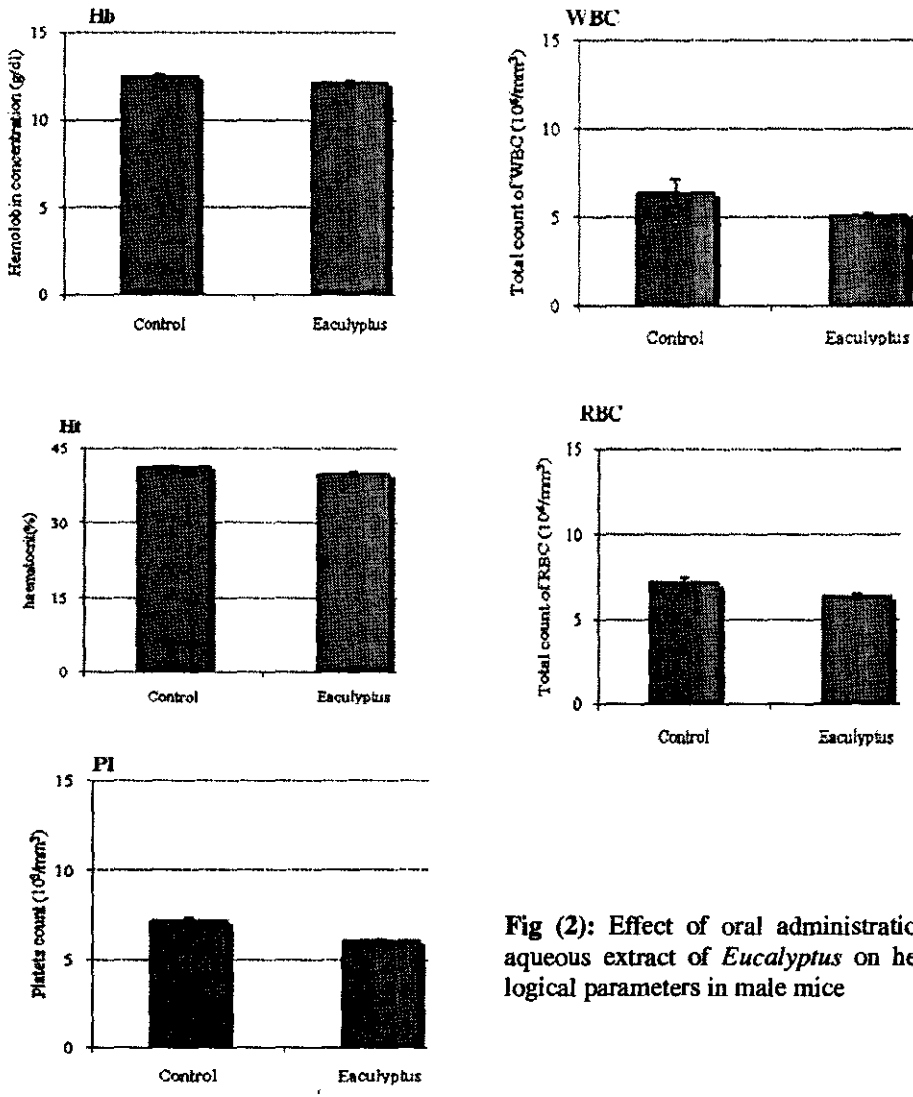


Fig (2): Effect of oral administration of aqueous extract of *Eucalyptus* on hematological parameters in male mice

Agar et al (2007) who studied the effect of Eucalyptus oil on the erythrocytes of koalas reported that koala erythrocytes are susceptible to eucalyptus oil-induced oxidative damage. The two types of Eucalyptus oils have different effects on the erythrocytes; monoterpenes appear to induce haemolysis through oxidative damage to the intracellular constituents, whereas sesquiterpenes may attack the red cell membrane. An erythrocyte membrane is rich in polyunsaturated fatty acid and thus is prone to oxidative insult by prooxidants. Haemoglobin may be reduced due to low erythrocyte counts and haematocrit and may be due to toxaemia. Dimri, et al., (2007).

The serum biochemical analysis presented in table III and Fig. (3) indicated that the treatment with aqueous extract of *Eucalyptus* resulted in dramatic changes in the liver and kidney functions. The serum ALT and AST increased significantly by 85.71% and 127.27% respectively compared to group control group indicating server damage in hepatocytes. In addition, significant increase ($p < 0.05$) in creatinine and urea levels was recorded in male mice treated with aqueous extract of Eucalyptus than their corresponding control .Hence, the possibility of renal injuries could be confirmed. Significant changes in enzymes like ALP AST and ALT represent liver impairment, since these are important indices of liver toxicity (Hayes, 2006).Arise et al. (2009) who studies the effects of Aqueous extract of *Eucalyptus globules* on lipid peroxidation and selected enzymes of rat liver reported that *E. globules* leaves may have deleterious effects on liver membrane structure and functional integrity. On the other hand, Mohamed et al (2005) who studied the hepatoprotective and antioxidant activities of the chloroformic extract of stems of Eucalyptus maculta in mice and rat reported that chloroformic extract 250mg /kg, significant reduced the increase in serum level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) produce by acetaminophen (640mg/kg).

Renal functions markers like urea and creatinine plasma level (Jesse 1982 and Abd wahab &Aly, 2003) were found to be increased significantly after administration of aqueous extract of Eucalyptus. Thus it can be stated that aqueous extract of Eucalyptus at a dose level used in the present work showed renal toxicity.

Table (III): Effect of oral administration of aqueous extract of Eucalyptus on hepatic and renal functions in male mice

Treatment	ALT orSGPT (Iu/L)	AST or SGOT (Iu/L)	Urea (mg/dl)	Creatinine (mg/dl)
Control	35.0±1.0	33.0±1.0	25.0±1.0	0.09±0.1
Eaculyptus	65.0±1.0*	75.0±1.0*	75.0±1.0*	1.90±0.1*

Each value represent mean of five value ±SD, ALT: alnine aminotransferase, AST: aspartate aminotransferase, *Significant as compared to control group

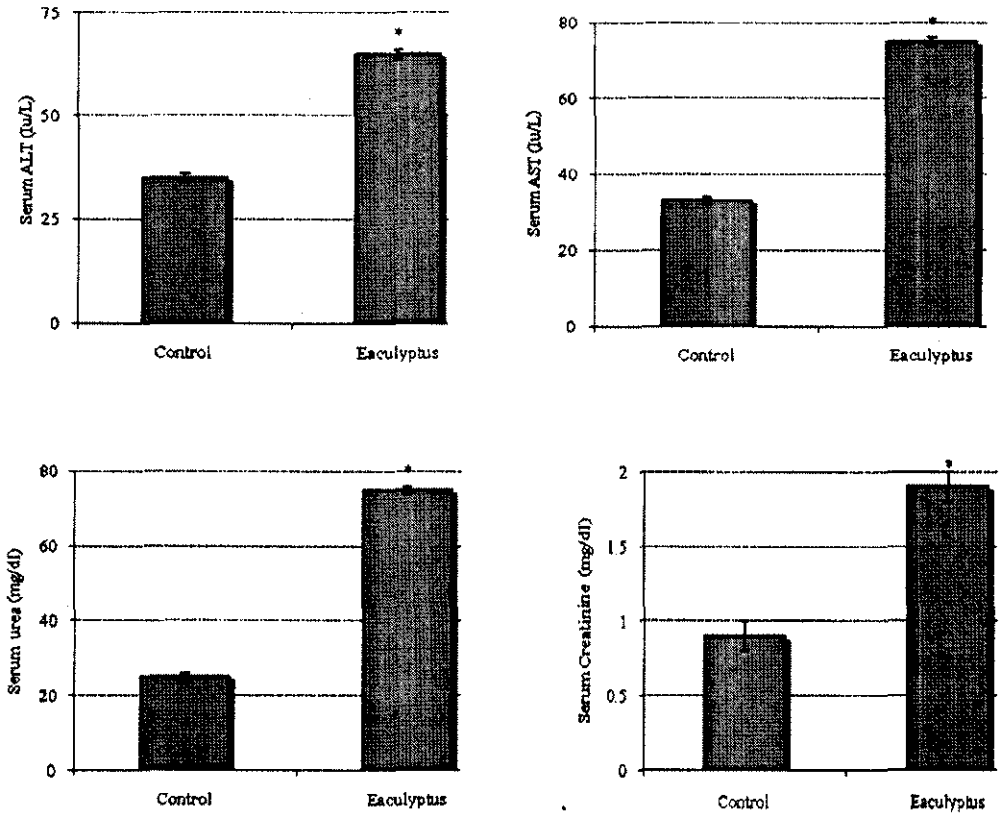


Fig. (3): Effect **of oral administration** of aqueous extract of Eucalyptus on hepatic and renal functions **in male mice**

Pathological findings:

Mild gross- pathological alterations were observed in the group of Eucalyptus treated mice. These mice showed pale liver, congestion and hemorrhages in the lung of some animals. In addition obvious enlargement of spleen and mild congestion in heart in some animals were evident .

Histopathological result:

There were no significant alterations in the **liver** of control group (Fig. 4), while remarkable histopathological change were observed in liver of mice treated with aqueous extract of Eucalyptus. The damage of hepatic cells were manifested by swollen hepatocytes with vacuolated cytoplasm which was so extensive in some cells. Necrotic cells with pyknotic or karyolysis nuclei were frequently observed. Some central veins were congested. Some hepatocytes appeared with enlarged nuclei (Fig. 5a and b).

There were no changes in **kidney** of control. Histological result revealed that renal tubules of Eucalyptus treated mice showed mild to severe degenerative changes. (Fig. 6 a and b) The degenerative changes seen in the tubular epithelium reflect failure of membrane ion pumps because of lack of celluler ATP, allowing the cell to accumulate fluid (Stevens et al., 2002). In addition similar histopathological changes in tissues of animals exposed to various chemical agents have been reported (Beniamin et al., 2006). The data in current study are in line with the data observed by Benjamin et al (2006) who studied the histopathological changes in liver and kidney of rats exposure to mixture of pesticides. Prominent fatty changes with necrosis in portal areas indicated that some toxic metabolites may be transported from intestine to liver, resulting in these changes (Beniamin et al., 2006 and Grant & Grasso 1978) reported that there is good correlation between in vivo carcinogenicity and the extent of nuclear enlargement in Hela cells in vitro.

The cerebrum of control mouse revealed no abnormal histological appearance (Fig.7). Administration of aqueous extract of Eucalyptus showed significant neurodegenerative changes included decrease in size and number of neurons in the cerebral cortex. In addition many glial cells with dense fragmented nuclei could be seen (Fig. 8). These histological changes suggest a toxic effect of the Eucalyptus administration Such alterations was noticed in the brain of young fluoride intoxicated (100ppm fluoride in drinking water) rats (Shivaraj ashankara et

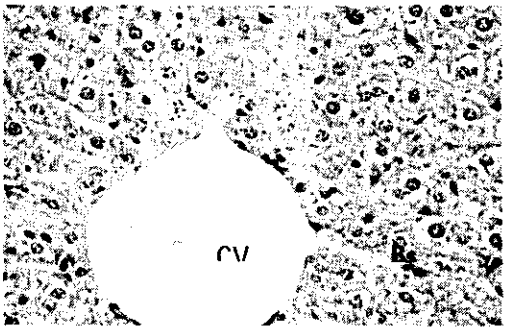
al., 2002).Brain tissue is highly susceptible to oxidative damage due to its high utilization of oxygen (20% of the total oxygen inhaled by the body) that accounts for the increased generation of oxygen free radicals and reactive oxygen substrates. Reactive oxygen species (ROS) are capable of oxidation of proteins, lipids and DNA leading to cellular damage (Sisodia et al.,2008). Oral administration of aqueous extract of eucalyptus may be leading to the formation of peroxides and oxidative reactive species.

In the present study **Lung** of control mice appeared with normal architecture (Fig. 9). On the other hand, histopathological result clearly indicates that oral daily administration of aqueous extract of Eucalyptus caused extensive damage to the lungs. Lungs of these animals exhibited distractive emphysema which demonstrated by dilated and distorted air space with destructed alveolar septa. Few respiratory epithelium with pyknotic nuclei were also noticed (Fig. 10).Thickened of alveolar walls due to mild fibrosis and inflammatory cell infiltration.

No histopathological changes was detected in the **spleen** of control mice, white and red plup appeared with normal architecture and megakaryocytes with normal lobuolated nuclei and red read plup with normal splenic cord, splenic sunisoid and trabeculae were seen (Fig .11).Many signs of pathological alterations were detected in the Spleen of mice treated with aqueous extract of eucalyptus. Administration of Eucalyptus. Induced remarkable depletion in the cellular accumulation in the white pulp follicles. In addition increase megakaryocytes with less stainability in red plup were evident (Fig. 12). Similar pathological findings were noticed by Singh et al., (1990). In CCL4 (0.5ml/kgb.w) intoxicated rats. Moreover, decrease cellularity of the white pulp can occure after exposure to irradiation, viruses or drugs that can cause necrosis or apptosis of the T cells (Elmore, 2006).

The heart of control mouse showed normal pattern of myocytes with elongated nuclei containing patches of condensed chromatin (Fig.13). Mice treated with aqueous extract of Eucalyptus showed tinker's necrosis and fibrillolysis. In addition, there was clear evidence of interstitial oedema and inflammatory cell infiltrations (Fig.14). Same changes were observed in cardiac muscle of fluoride- intoxicated rabbits (Shashi et al., 2001). The same author suggests that fluoride interferes with myocardial metabolism. Some studies have indicated that citronellal and phellandrene, which can be found in some Eucalyptus

spp. are weak mutagenics and carcinogenics, respectively. (Whitman & Ghazzadeh, 1994;Woolf, 1991 and Sartorlli etal., 2006). That may be explaining the adverse histopathological alterations which observed in the present work.



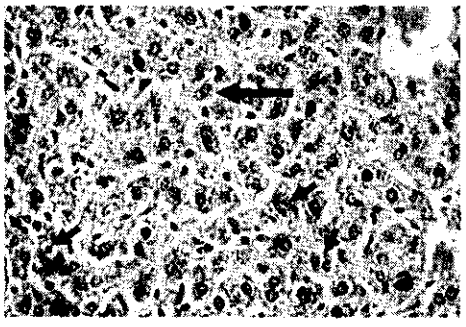


Fig. (4) Liver section of control mouse showing normal architecture organization. CV: central vein, Bs Blood sinusoids[10% neutral formalin fixed, haematoxylin and eosin stained preparation, 400X]

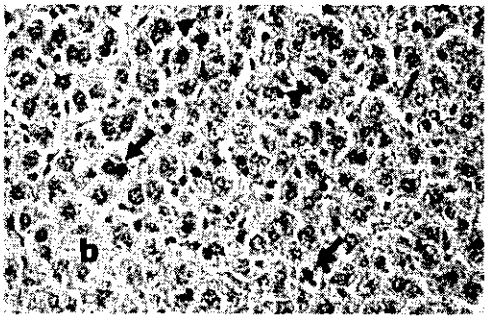
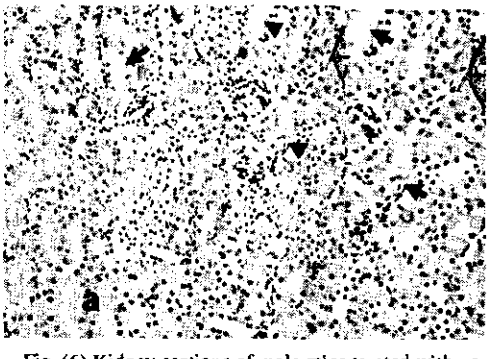


Fig (5) liver sections of male mice treated with aqueous extract of eucalyptus[10% neutral formalin fixed, haematoxylin and eosin stained preparation, 400X]
a) Showing swelling hepatocytes with vacuolated cytoplasm (Arrows). CV: congestion central veins. Arrows indicate abnormal nuclei.
b) Showing necrotic cells with abnormal nuclei (Arrowhead). Arrows indicating hepatocytes nuclei with dense abnormal chromatin feature.



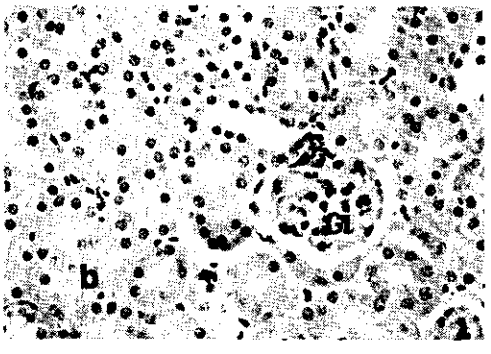


Fig. (6) Kidney sections of male mice treated with aqueous extract of eucalyptus[10% neutral formalin fixed, haematoxylin and eosin stained preparation]
a) Showing degenerated renal tubes with (arrow), inflammatory infiltration cells (Arrowhead). Gl: glomeruli [200X]
b) Showing renal tubules with cloudy swelling epithelium and pale staining vacuolated cytoplasm (arrows). Gl: glomerulus. Arrowheads indicate inflammatory infiltration cells[400X]

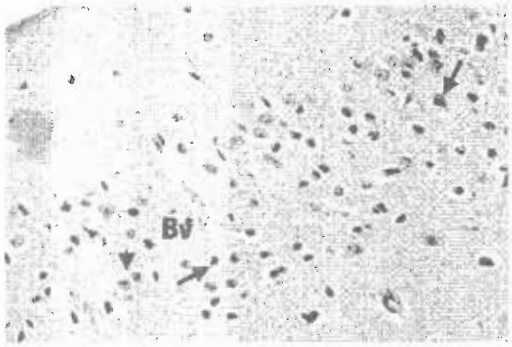


Fig. (7) Brain section of male control mouse showing normal cerebral cortex. Arrow indicate neuron. Arrowhead indicate glial cell. BV : Blood vessel [10% neutral formalin fixed, haematoxylin and eosin stained preparation, X400]

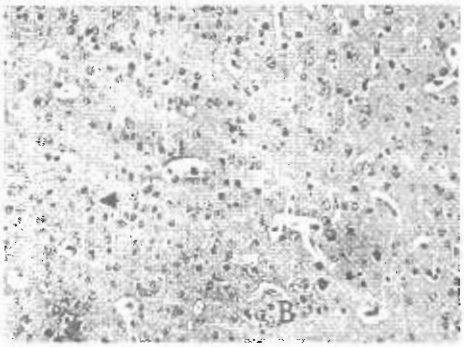


Fig. (8) Brain section of male treated with aqueous extract of eucalyptus showing necrotic decrease nerons and glial cell with dense fragmented nuclei (arrowhead). BV : Blood vessel[10% neutral formalin fixed, haematoxylin and eosin stained preparation, X200]

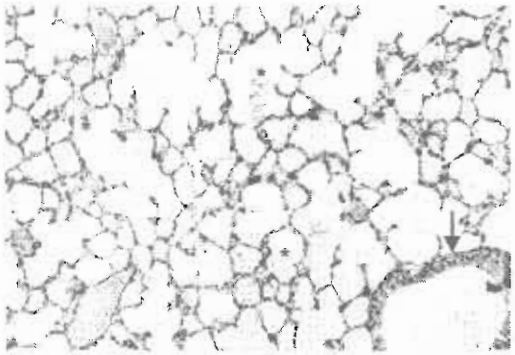


Fig. (9) Lung of control male mouse showing normal lung architecture. Arrow indicate respiratory epithelium. Alveoli (stars) [10% neutral formalin fixed, haematoxylin and eosin stained preparation, 200X]

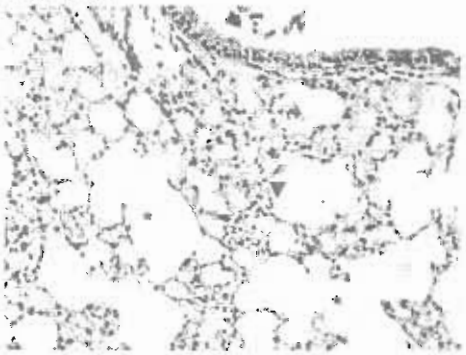


Fig. (10) Lung section of male mouse treated with aqueous extract of eucalyptus showing thickened alveolar walls due to mild fibrosis and inflammatory cell infiltration (arrowheads). Many air spaces are distorted (stars) [10% neutral formalin fixed, haematoxylin and eosin stained preparation, 200X]

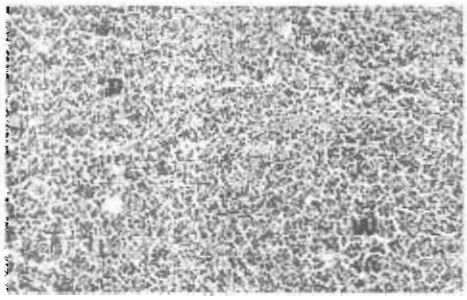


Fig. (11) Spleen section of control mouse with normal architecture. WP: white pulp follicle, RP: Red pulp. Arrow indicate megakaryocyte. [10% neutral formalin fixed, haematoxylin and eosin stained preparation, 200X]

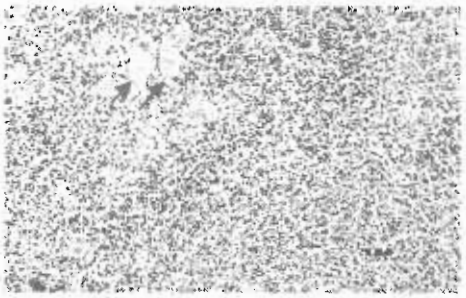


Fig. (12) Spleen section of male mice treated with aqueous extract of eucalyptus showing white pulp with hypocellularity (WP). Note many megakaryocytes in red pulp with less stainability (arrows). [10% neutral formalin fixed, haematoxylin and eosin stained preparation, 200X]

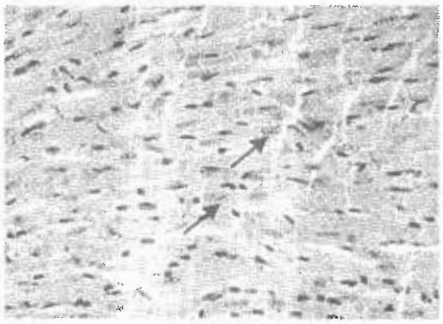


Fig. (13) Cardiac muscle section of control mouse showing normal pattern of myocytes, with elongated nuclei containing patches of condensed chromatin (arrows). BV: Blood vessel, ID: intercalated disk. [10% neutral formalin fixed, haematoxylin and eosin stained preparation, 200X]

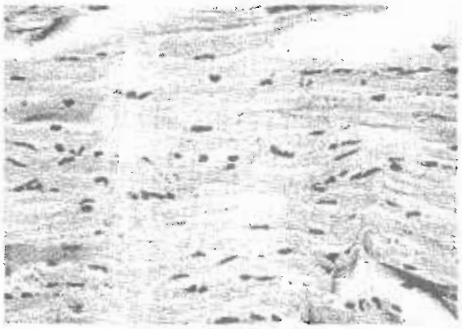


Fig. (14) Cardiac muscle section of mouse treated with aqueous extract of eucalyptus showing necrosis and fibrillolysis [10% neutral formalin fixed, haematoxylin and eosin stained preparation, 200X]Bv: Blood vessel, E: Endothelial cell

Conclusion

It was found that examinations seem to prove that aqueous extract of eucalyptus at a dose level used in the present work plays prominent role in the development of pathological alterations in Swiss albino mice.. So further more studies may still be needed to establish pathological alterations and side effects resulted in acute and chronic administration of aqueous extract of eucalyptus by different route and doses.

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الملخص العربي

سمية المستخلص المائى لنبات اليوكاليبتوس فى الفئران السويسرية البيضاء

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يستخدم نبات اليوكاليبتوس(نوع من أنواع الكافور) شعبيا في علاج كثير من الأمراض وله كثير من الخواص العلاجية كمضاد للميكروبات ومرض السكر أو كمبيد حشري ولكن كثير من الأعشاب الطبية التي تستخدم في العلاجات الشعبية تعتبر غير آمنه ولذلك أجريت الدراسة على ذكور الفئران السويسرية البيضاء لتقييم التغييرات المورفولوجية والهيماتولوجية والكيميائية والهستوباثولوجية الناتجة عن تجريع المستخلص المائي لنبات اليوكاليبتوس (2000مجم/كجم من وزن الجسم) أظهرت النتائج أن المستخلص المائي لنبات اليوكاليبتوس قد أدى إلى تغيير في نشاط و شكل فراء الفئران المعالجة كما أحدث نقص معنوي في وزن الجسم وتسبب المستخلص المائي فى نقص معنوي في معايير صورة الدم بالإضافة الى المقاييس الكيميائية لوظائف الكبد والكلية وأفقت النتائج الهستوباثولوجية التي أظهرت العديد من التغيرات الباثولوجية فى مختلف الأعضاء والتي كانت أكثر وضوحا في الكبد و الرئة مما يشير إلى سمية النبات.أن هذه النتائج مجتمعه تشير أن تجريع المستخلص المائي من النبات يؤدى إلى اضطرابات خطيرة.