

Research Article

**Zoology**

## The effect of electronic cigarette liquids on blood biochemistry during chemically induced liver carcinogenesis in rats

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### KEY WORDS

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### ABSTRACT

This study was conducted to evaluate the effects of E-liquids that contain or free nicotine on blood physiological and biochemical parameters during the stages of chemically induced rat liver carcinogenesis after intraperitoneal injection of Diethylnitrosamine (DEN). 10 weeks old, male Sprague Dawley (S.D.) rats weighing 120 - 125 grams, were split into 4 groups: G1 (-ve control), G2 (DEN only), G3 (DEN + Nicotine-free e-liquid, 0.5 mg/kg of body weight), and G4 (DEN + E-liquid with nicotine, 0.5 mg/kg of body weight). After 32 weeks of experimentation, rats were killed. Blood samples in G4 showed increased ALT, decreased AST, and platelet counts. Kidney function levels were significantly increased after both E-liquids containing nicotine with higher levels. Moreover, E-liquids dramatically increased the triglycerides and decreased the HDL levels. Additionally, the blood glucose and serum electrolyte levels were markedly elevated by E-liquid with nicotine other than that without nicotine. In conclusion, the E-liquid with nicotine exerted a deleterious effect on blood parameters during liver carcinogenesis.

## Introduction

The majority of young adults and teenagers use E-cigarettes, also referred to as electronic nicotine delivery systems (ENDS). E-cigarette liquid (E-liquid) is added with various nicotine concentrations, just like regular cigarettes. However, because of additional ingredients like vegetable glycerin, propylene glycol, and flavors (Pang et al., 2023). The major component of both regular and electronic cigarettes, nicotine, causes neurological effects that lead to addiction and may damage the lungs in the process, resulting in multifaceted, complex pathological conditions (Herman and Tarran, 2020).

The liver is a vital organ that is necessary for the synthesis of proteins, the elimination of toxins, and the preservation of metabolic homeostasis (Cheng et al., 2021). In addition to oxidizing lipids, the liver can package excess lipids for secretion and storage in other tissues, including fat. Finally, the liver is important for handling the metabolic processes of proteins plus amino acids because it can handle most of the proteins discharged into the bloodstream (by their weight or the number of unique proteins they contain), utilize amino acids to produce energy, as well as transport nitrogenous waste in

the form of urea metabolism from the breakdown of proteins (Trefts et al., 2017).

Hepatocellular carcinoma (HCC) is a primary liver cancer that frequently develops in conjunction with cirrhosis or chronic liver disease through a multistep, intricate process known as hepatocarcinogenesis (Fung et al., 2021; Gilles et al., 2022). Hepatitis B or C virus, chronic infection, and alcohol abuse are the primary risk variables for the evolution of HCC. However, HCC is also linked to being exposed to B1 aflatoxin, non-alcoholic fatty liver disease, and hazardous industrial and environmental chemicals (Galicia-Moreno et al., 2020).

Diethylnitrosamine (DEN) injection has been shown to cause liver pathologies in mice that frequently result in HCC resembles that seen in human patients, and to produce various stages of tumor formation stages (i.e. foci of cellular alterations, benign adenomas, and carcinomas) (Schulien and Hasselblatt, 2021).

The main objective of this study was to assess the e-liquid's inherent toxicity in comparison to nicotine after a brief exposure to a rat model, through the use of an intraperitoneal route. The 28-day course of treatment was chosen to assess

the brief impact of e-liquid, and a recommended dosage of nicotine was 0.5 milligrams per kilogram of body weight because it is similar to that of an average human smoker (El Golli et al., 2016).

## Material and methods

### Material

Diethylnitrosamine (DEN) was obtained from Sigma (St. Louis, Missouri, USA). The DON JUAN Company, Shiko store in Giza, Egypt, was the source of the E-liquids of two types, with or without nicotine. All of the E-cigarettes used in the present study were carefully selected without the addition of any flavors.

### Animals and experimental designates

Healthy 36 male Sprague Dawley (S.D.) rats, approximately 8 weeks of age, were acquired from The Holding Company for Biological Products & Vaccines (Vaccera), a Helwan, Egypt-based company. The rats were kept in plastic cages with bedding made of wood chips and metal grids on top before being split up into experimental groups. After that, they were housed for two weeks so they could get used to the surroundings of the animal facility. Under the number IACUC-SCI-TU-0254, the research protocol was approved by the Faculty of Science's Institutional Committee for Ethics of Animal Handling at Tanta University in Egypt.

The desired ranges were  $22\pm 1^{\circ}\text{C}$  and  $55\pm 5\%$ , respectively, for temperature and relative humidity, in addition to the light-dark cycle. The water supply to the rats was unrestricted and typical experimental pelleted animal food. Every day during the experiment, the animals were closely observed, and every week, their body weights were measured precisely for any indications of either abnormality or toxicity.

After two weeks of acclimation to the animal facility's conditions, the rats were split up randomly into 4 groups. Group 1 was a negative control that was not given any treatment; Group 2 served as the cancer-positive control group and received DEN treatment four times once a week at a 50 mg/kg body weight dosage (10 rats); The Injections of DEN dissolved in sterile saline solution (0.9%) were intraperitoneally (i.p.) administered to the animals (Solt and Farber, 1976); Group 3 received the identical DEN dosage as Group 2, 0.5 mg/kg of body weight e-liquid free nicotine was then administered intraperitoneally (10 rats); Group 4 received the identical DEN dosage as Group 2, 0.5 mg/kg of body weight e-liquid containing nicotine was then administered intraperitoneally (10 rats). The dose of the E-liquid with nicotine was calculated as 50 milligrams of nicotine per kilogram of body weight per

day, dissolved in 0.9% saline (the dose (0.5 mg) was estimated similar to that of the human regular daily consumption (**El Golli et al., 2016**). The i.p. administration of the E-liquids started two days after the final DEN injection, and lasted for almost 20 weeks, three times a week.

Every day, the rats were observed for medical signs and morbidity. All of the animals were sacrificed after the experiment's 32-week duration. At the time of sacrifice, all rats underwent macroscopic gross examinations. The testes, kidneys, spleen, and liver were quickly removed during necropsy, cleaned in cold saline, and either processed or examined. Following organ necropsy the weights of the organs (organ wt/b.wt x 100) were determined for each rat, obtaining percentage absolute and relative organ weights.

### **Methods**

For hematological and serum biochemical investigations, The Dirui BCC-3600 automated hematology analyzer was utilized to automatically calculate the complete blood count (CBC). To calculate alanine aminotransferase (ALT), methods suggested by **Thefeld et al., (1974)**; **Thomas, (1998)** were used. The methods of **Thefeld et al., (1974)** and **Rej, (1984)** were used to calculate aspartate aminotransferase (AST).

**Thomas, (1998)** method was used to measure urea in serum. Creatinine was measured using the **Newman and Price, (1999)** method. The **Allain et al., (1974)** method was used to measure the serum total cholesterol. Based on the method developed by **Fossari and Prencipe, (1982)**, the serum triglycerides were measured. Measuring the serum HDL-cholesterol levels was established by the **Burstein et al., (1970)** and **Lopez-Virella et al., (1977)** methods. Low-density lipoprotein cholesterol was calculated using **Friedwald et al., (1972)** method. Sodium was calculated using the method of **Berry et al., (1988)**, Potassium was calculated using the method of **Hillmann and Beyer, (1967)**, and chloride, calcium, and glucose levels were measured using the method of **Thomas, (1998)**.

### **Statistical analyses**

Using the Statistical Package for Social Science (SPSS) version 17.0, USA, the ANOVA test was employed in the analysis of group data expressed as means  $\pm$  S.D., and Chi-squared (X) data expressed as percentages. In this study, a statistical analysis was considered significant if P was less than 0.05.

### **Results**

#### **Average body, absolute and relative organs weights:**

Significant differences between administered and non-administered rats

in final body weights are shown in **Table (1)**, while **Fig. (1)** shows growth curves. The absolute liver, kidney, and testes weights were notably lowered in G3 and G4 than in the -ve control group and DEN-administered G2. The absolute spleen weights were significantly less in G4 compared with -ve control and the DEN-administered G2. The relative weights of the liver in G3 and G4 were considerably lowered in comparison with -ve control and DEN-administered G2. Relative weights of the kidney in G3 and G4 were considerably lowered when compared with DEN-administered G2. Also, the relative Spleen weights were significantly decreased in G4 versus -ve control and DEN-administered G2. In addition, when comparing G3 and G4 to -ve control and DEN-administered G2, the relative testes weights were significantly lowered.

#### **Hematological investigations (Complete blood count (CBC)):**

The changes in WBC numbers were considerably lower in G4 compared to -ve control and DEN-administered G2. No notable alterations in RBC numbers in various groups. The HGB and The levels of HCT were markedly elevated in G4 versus -ve control and DEN-administered G2. Also, the platelet numbers were notably lowered in G3 and G4 compared to the -ve control group and DEN-administered G2.

Moreover, In G4 the lymphocyte counts were significantly decreased, but the monocyte count was significantly increased versus DEN-administered G2. The granulocyte counts were notably lowered in DEN-administrated G2, G3, and G4 compared to -ve control as shown in **Table (2)**.

#### **Liver functions parameters:**

**Table (3)** shows that the ALT levels were markedly elevated in G3 and G4 versus -ve control and DEN-administered G2. The AST levels were considerably lower in G4 but significantly elevated in G3 versus -ve control and DEN-administered G2. The total bilirubin levels were increased slightly in DEN-administered rats versus -ve controls. The albumin, Globulin, and A/G Ratio levels were notably lowered in G3 versus -ve control and DEN-administered G2. No significant changes in the total protein levels in the different groups.

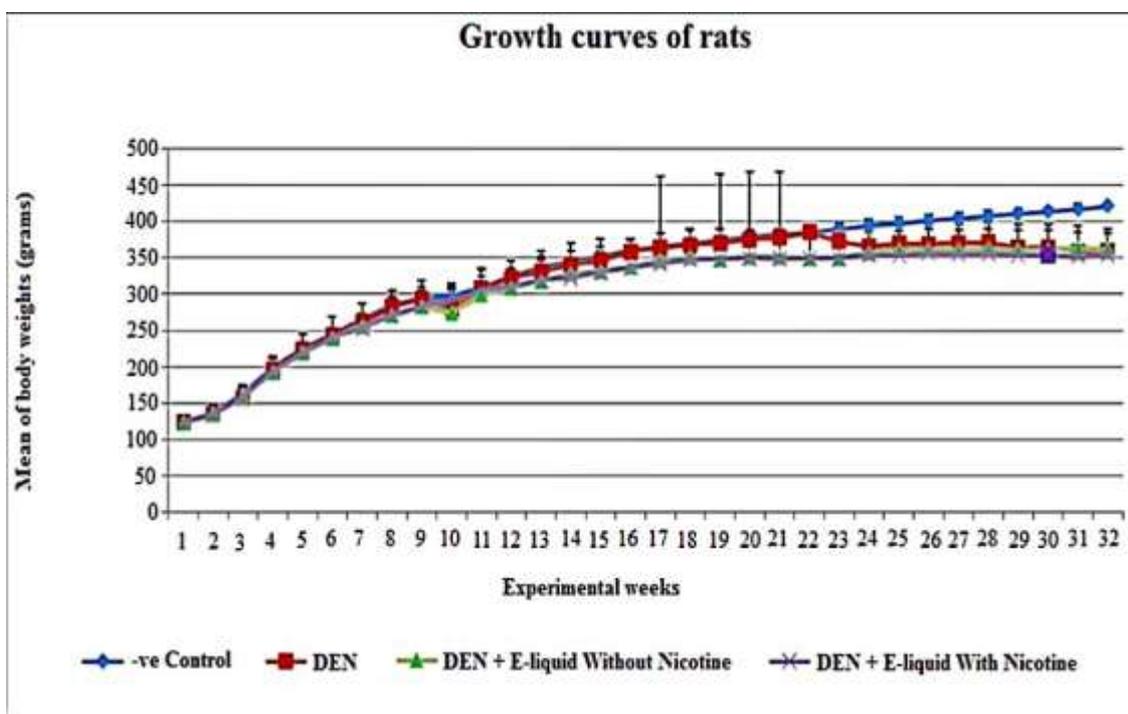
#### **Kidney functions parameters:**

**Table (4)** shows the urea and creatinine levels were markedly elevated in G3 and G4, especially E-liquid with nicotine compared to -ve control and DEN-administered G2.

**Table (1):** Initial, final body weights, absolute and relative organs weights

Groups	G1 (-ve control)	G2 (DEN)	G3 (DEN + E-liquid Without Nicotine)	G4 (DEN + E-liquid With Nicotine)
No. of rats	6	10	10	10
Initial body wt(g)	123.3 ± 6.06 <sup>a</sup>	123.5 ± 7.47	123.0 ± 6.75	123.5 ± 7.83
Final body wt(g)	420.83 ± 5.85	359.4 ± 44.19*	361.11 ± 28.91*	353.5 ± 30.65*
Liver wt(g)	10.40 ± 1.34 (2.47) <sup>b</sup>	8.32 ± 2.66* (2.32) *	6.45 ± 1.63*,** (1.79) *,**	6.37 ± 1.26*,** (1.8) *,**
Left kidney wt(g)	0.97 ± 0.14 (0.23)	1.01 ± 0.26* (0.28) *	0.79 ± 0.16*,** (0.22) *,**	0.78 ± 0.15*,** (0.22) *,**
Right kidney wt(g)	1.02 ± 0.15 (0.24)	0.93 ± 0.25* (0.26) *	0.82 ± 0.24*,** (0.23) *,**	0.80 ± 0.19*,** (0.23) *,**
Spleen wt(g)	1.10 ± 0.44 (0.62)	1.09 ± 0.24 (0.30) *	1.05 ± 0.22 (0.30) *	0.72 ± 0.11*,** (0.20) *,**
Testes wts(g)	2.79 ± 0.43 (0.66)	2.60 ± 0.76* (0.73) *	2.18 ± 0.47*,** (0.60) *,**	2.22 ± 0.44*,** (0.63) *,**

**a:** Each reading represents means ± S.D., absolute wts.; **b:** numbers between brackets are relative organs wt.: (weight ratio of the organ to body) X100; \*: Significant compared to G1 at  $P<0.05$ , \*\*: Significant compared to G2 at  $P<0.05$



**Fig. (1):** Rat growth curves for each group over the course of the experiment in weeks

**Table (2):** Changes in Complete Blood Count Levels (CBC) in All the Studied Groups

Groups	Unit	G1 (-control)	G2 (DEN)	G3 (DEN + E-liquid Without Nicotine)	G4 (DEN + E-liquid With Nicotine)
WBC	X10 <sup>3</sup> /μL	11.35 ± 3.81 <sup>a</sup>	13.83 ± 3.95*	13.23 ± 1.56*,**	10.08 ± 2.10*,**
RBC	X10 <sup>6</sup> /μL	7.51 ± 0.26	7.43 ± 0.79	7.42 ± 0.77	7.56 ± 0.79
HGB	g/dl	13.43 ± 1.02	13.28 ± 0.89	12.82 ± 0.93*	13.95 ± 0.54*,**
HCT	%	38.00 ± 3.83	36.05 ± 2.97*	36.1 ± 3.64*	39.58 ± 1.87*,**
MCV	fL	50.65 ± 5.75	48.63 ± 1.88*	48.7 ± 2.82*	52.6 ± 3.22**
MCH	Pg	17.85 ± 1.30	17.95 ± 1.17	17.3 ± 0.73	18.53 ± 1.23
MCHC	g/dl	35.43 ± 1.87	36.88 ± 1.38	35.63 ± 1.51	37.55 ± 4.12*
PLT	X10 <sup>3</sup> /μL	943.5 ± 122.1	1050.8 ± 144.1*	906.8 ± 60.1*,**	740.8 ± 57.1*,**
LYM.	X10 <sup>3</sup> /μL	78.45 ± 4.82	82.13 ± 5.48*	83.25 ± 2.31*	78.87 ± 2.43**
MON.	X10 <sup>3</sup> /μL	8.63 ± 0.90	7.55 ± 1.17*	6.93 ± 0.33*	8.88 ± 1.57**
GRA.	X10 <sup>3</sup> /μL	10.93 ± 3.97	8.33 ± 4.52*	7.83 ± 2.18*	9.5 ± 2.32*

**a:** Each reading represents means ± S.D. of 4 observations; \*: Significant compared to G1 at  $P < 0.05$ ; \*\*: Significant compared to G2 at  $P < 0.05$ . WBC: White blood cell count; RBC: Red blood cell count; HGB: Hemoglobin; HCT: Hematocrite; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; PLT: Platelets; LYM: Lymphocytes; MON: Monocytes; GRA: Granulocytes.

**Table (3):** Changes in Liver Functions in All the Studied Groups

Groups	Unit	G1 (-ve control)	G2 (DEN)	G3 (DEN + E-liquid Without Nicotine)	G4 (DEN + E-liquid With Nicotine)
ALT	IU/L	53.67 ± 5.51 <sup>a</sup>	55.00 ± 18.52	63.33 ± 1.53*,**	61.33 ± 11.06*,**
AST	IU/L	194.7 ± 23.3	228.3 ± 30.4*	262.0 ± 63.7*,**	129.7 ± 16.3*,**
Total bilirubin	Mg/dl	0.30 ± 0.07	0.36 ± 0.21	0.35 ± 0.04	0.42 ± 0.07
Direct bilirubin	Mg/dl	0.08 ± 0.01	0.09 ± 0.06	0.08 ± 0.01	0.13 ± 0.02
Indect bilirubin	Mg/dl	0.23 ± 0.09	0.27 ± 0.16	0.27 ± 0.04	0.30 ± 0.07
Total protein	g/dl	7.17 ± 0.31	7.13 ± 0.51	7.17 ± 0.31	7.17 ± 0.25
Albumin	g/dl	3.97 ± 0.23	3.83 ± 0.23	3.7 ± 0.1*,**	3.97 ± 0.23
Globulin		3.2 ± 0.2	3.3 ± 0.35	3.45 ± 0.38*,**	3.2 ± 0.10
A/G Ratio		1.27 ± 0.11	1.2 ± 0.1	1.1 ± 0.17*,**	1.23 ± 0.06

**a:** Each reading represents means ± S.D. of 4 observations; \*: Significant compared to G1 at  $P < 0.05$ , \*\*: Significant compared to G2 at  $P < 0.05$ . ALT: Alanine aminotransaminase; AST: Aspartate aminotransferase

**Table (4):** Changes in Kidney Functions in All the Studied Groups

Groups	Unit	G1 (-ve control)	G2 (DEN)	G3 (DEN + E-liquid Without Nicotine)	G4 (DEN + E-liquid With Nicotine)
Urea	Mg/dl	34.33 ± 2.51 <sup>a</sup>	30.0 ± 4.58*	40.0 ± 4.35*,**	41.67 ± 7.73*,**
Creatinine	Mg/dl	0.38 ± 0.07	0.40 ± 0.06	0.39 ± 0.05	0.47 ± 0.02*,**

**a:** Each reading represents means ± S.D. of 4 observations; \*: Significant compared to G1 at  $P < 0.05$ , \*\*: Significant compared to G2 at  $P < 0.05$

**Lipid profile levels:**

**Figure (3)** shows the cholesterol levels were slightly increased and the triglyceride levels were markedly elevated in DEN-administered rats versus -ve controls. The HDL levels in DEN-administered G2 were markedly elevated as compared with -ve controls but notably decreased in G3 and G4 as compared with DEN-administered G2. On the other hand, the LDL levels were significantly lower in DEN-administered rats versus -ve controls but slightly elevated in G3 and G4 as compared with DEN-administered G2.

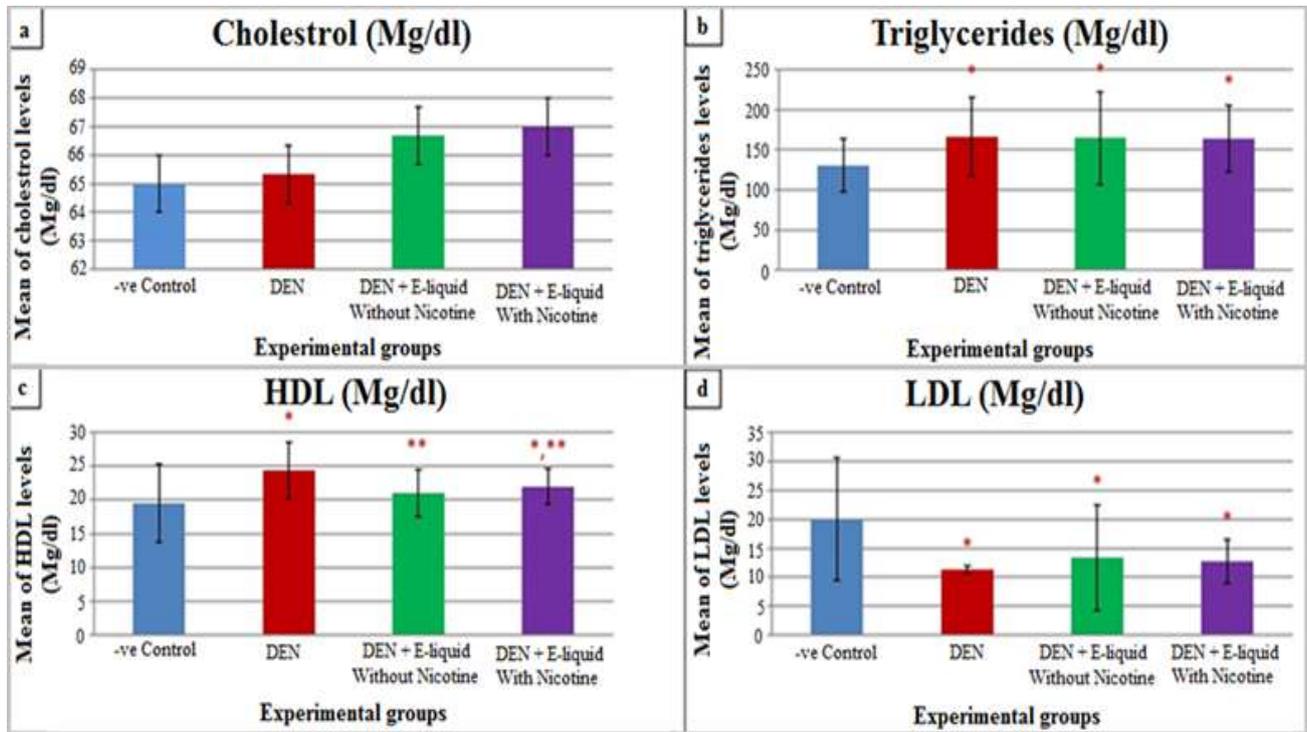
**Serum electrolytes (sodium, potassium, chlorides) and chlorides levels:**

**Figure (4)** shows the sodium levels were markedly elevated G4 versus -ve control and DEN-administered G2. Also, the potassium levels were notably increased in DEN- DEN-administered

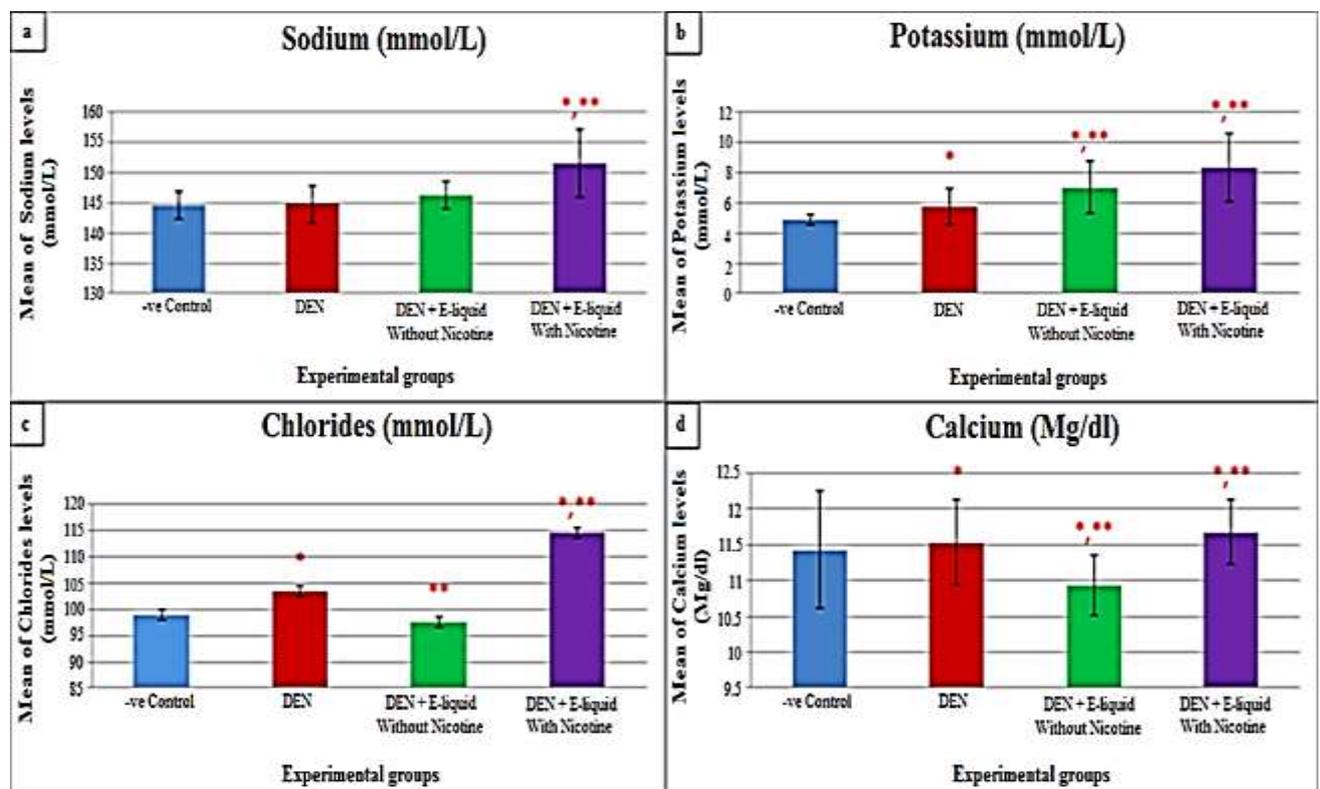
rats as compared with -ve controls. They were markedly elevated in G3 and G4 especially G4 as compared with -ve control and DEN-administered G2. The chloride levels were notably elevated in DEN-administered G2 as compared with -ve control, they were significantly decreased in G3 but significantly elevated in G4 as compared with DEN-administered G2. Moreover, the calcium levels were significantly lower in G3 but markedly elevated in G4 as compared with -ve control and DEN-administered G2.

**Blood glucose levels:**

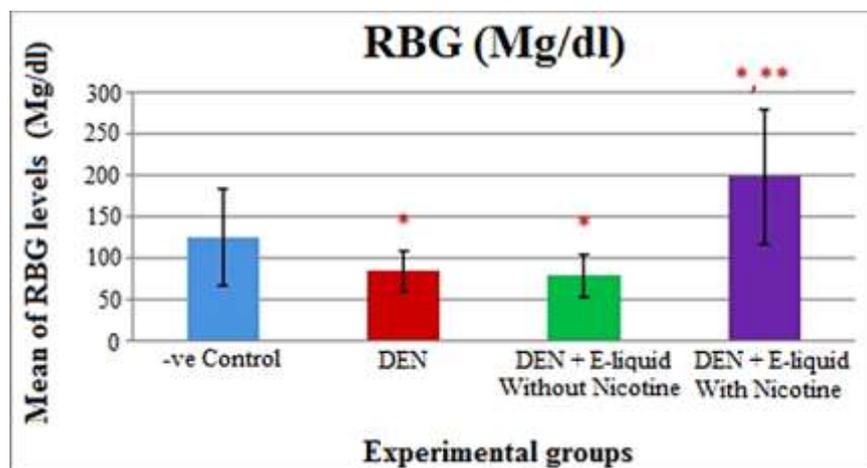
**Table (6)** shows the glucose levels were significantly lowered in DEN-administered G2 and G3 compared to -ve control, but notably increased in G4 compared to -ve control and DEN-administered G2 as shown in **Fig. (5)**.



**Fig. (3):** a) Changes in cholesterol levels. b) Changes in triglycerides levels. c) Changes in HDL levels. d) Changes in LDL levels. \*: Significant compared to G1 at  $P < 0.05$ ; \*\*: Significant compared to G2 at  $P < 0.05$



**Fig. (4):** a) Changes in sodium levels. b): Changes in potassium levels. c): Changes in chloride levels. d): Changes in calcium levels. \*: Significant compared to G1 at  $P < 0.05$ ; \*\*: Significant compared to G2 at  $P < 0.05$



**Fig. (5):** Changes in RBG in all studied groups. \*: Significant compared to G1 at  $P < 0.05$ ; \*\*: Significant compared to G2 at  $P < 0.05$ .

## Discussion

The hematological investigations in this study show when compared to the DEN- DEN-administered group, the E-liquid with nicotine group's WBC counts were significantly lower and showed a significant increase in HBG and HCT levels. Furthermore, both E-liquid administered groups showed a significant decrease in PLT numbers, with the E-liquid with nicotine showing a greater decrease than the DEN-administered group. **Ben Saad et al., (2018)** demonstrated that after two months of treatment, nicotine significantly reduced HBG, HCT, and RBC levels while increasing WBC levels. In this research, both E-liquid-administered groups especially the E-liquid with nicotine compared to the DEN-administered group had significantly higher ALT levels. The E-liquid with nicotine group

experienced a significant decrease in AST levels, whereas the E-liquid without nicotine group experienced a significant increase in AST levels. According to **Raeeszadeh et al., (2022)**, the intake of nicotine in the nicotine group resulted in a significant increase in the ALT, AST, ALP, GGT, and LDH serum activities versus the control group. According to **Ben Saad et al., (2018)**, the group receiving nicotine showed increased activities of LDH, ALT, AST, and ALP versus the control group.

In this study, both E-liquid-administered groups especially the E-liquid with nicotine compared to the DEN-administered group had significantly higher levels of urea and creatinine. These results align with the findings of **Chattopadhyay et al., (2018)**, who reported that urea and creatinine levels were considerably elevated in the rats exposed to nicotine than in the control

group. According to **Chakkarwar et al., (2021)**, rats that were given nicotine had higher levels of proteinuria, BUN, and serum creatinine than control rats.

This study's findings show that when compared to over-controls, rats administered with DEN had considerably higher triglyceride levels and slightly higher cholesterol levels. Compared with rats treated with denaturation, both types of e-liquids revealed a notable decline in HDL levels and a tiny increase in LDL levels. **Khaled et al., (2022)** reported similar outcomes, observing that nicotine significantly raised cholesterol, triglycerides, LDL, and VLDL while decreasing HDL when compared to the control group. Additionally, **Raeeszadeh et al., (2022)** observed that the nicotine group's LDL and serum cholesterol levels had significantly increased compared to the control group.

Furthermore, the present research data indicated that the E-liquid group administered with nicotine had significantly higher levels of sodium, potassium, chlorides, and calcium than the DEN-administered group. These outcomes were consistent with those reported by **Nwaji et al., (2022)**, who discovered that the rats treated with the extract had significantly higher serum concentrations of potassium, sodium, and urea than the control group did.

Conversely, no discernible variations were found in the serum concentrations of chloride, bicarbonate, or creatinine between the groups that received treatment and the control group. Additionally, **Zahran et al., (2017)** discovered that renal dysfunction brought on by nicotine was distinguished by notably aberrant levels of kidney function indicators, including creatinine, urea, sodium, and potassium.

When comparing the RBG levels in the nicotine-infused E-liquid to the rats administered with DEN, the current study found a significant increase. **Dangana et al., (2019)** demonstrated that the use of nicotine treatment resulted in inadequate regulation of glucose as evidenced by elevated fasting glycemia, 1- and 2-hour post-load glyceamia, HOMA-IR, insulinemia, HOMA- $\beta$ , and reduced QUICKI (insulin sensitivity).

### **Conclusion and recommendations**

This study shows that E-liquids affected physiological parameters during the development of liver cancer in rats such as decreased platelet count; it increased ALT, decreased AST, and increased kidney functions. According to this study, using E-liquids to quit smoking should be avoided as it raises the risk of liver carcinogenesis.

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تأثير سوانل السجانر الإلكترونية على الكيمياء الحيوية للدم خلال مراحل تسرطن الكبد المستحث كيميائيا في الجرذان

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تهدف الدراسة الحالية إلى الكشف عن التأثيرات البيوكيميائية والفسلوجية لسوانل السجانر الإلكترونية مع أو بدون النيكوتين أثناء تسرطن الكبد الناجم من ثنائي إيثيل نيتروزامين عن طريق الحقن داخل الصفاق في الجرذان. تم تقسيم ذكور الجرذان في عمر ١٠ أسابيع وزن ١٢٠ - ١٢٥ جم إلى ٤ مجموعات: المجموعة الأولى وتعمل كمجموعة ضابطة سلبية ولا يتم معالجتها بأي دواء. المجموعة الثانية حددت كمجموعة ضابطة موجبة (ثنائي الإيثيل نيتروزامين) ، المجموعة الثالثة (ثنائي الإيثيل نيتروزامين + السائل الإلكتروني بدون النيكوتين 0.5 ملليجم /كجم من وزن الجسم)، المجموعة الرابعة (ثنائي الإيثيل نيتروزامين + السائل الإلكتروني 0.5 ملليجم /كجم من وزن الجسم والآخر يحتوي على النيكوتين). تم تشريح الجرذان بعد ٣٢ أسبوعا من بدء التجربة. تم تجميع عينات الدم بشكل فردي من كل جرد وأظهرت عينات الدم زيادة الألائين أمينوترانسفيريز وانخفاض الأسبارتات أمينوترانسفيريز في المجموعة الرابعة كما أدت سوانل السجانر الإلكترونية الى زيادة مستويات وظائف الكلى بشكل ملحوظ وخاصة في المجموعة الرابعة علاوة على ذلك زادت سوانل السجانر الإلكترونية من الدهون الثلاثية وانخفضت البروتين الدهني العالي الكثافة خاصة في المجموعة الرابعة. كما أدى سائل السجانر الإلكترونية الذي يحتوي على النيكوتين إلى زيادة كبيرة في مستويات الشوارد في الدم وارتفاع مستويات الجلوكوز في الدم. في الختام، كان لسائل السجانر الإلكترونية خاصة الذي يحتوي على النيكوتين تأثير ضار على مؤشرات الدم أثناء تسرطن الكبد.