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EFFECT OF HONEYBEE VENOM (*APIS MELLIFERA*) ON RESPIRATORY FUNCTIONS OF HYPERCHOLESTEROLEMIC MALE ALBINO RATS

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ABSTRACT

Hypercholesterolemia can be defined as the presence of high plasma cholesterol levels, with normal plasma triglycerides, as a consequence of the rise of cholesterol and apolipoprotein B (apoB)-rich lipoproteins, called low-density lipoprotein (LDL) and characterized by very high levels on the blood cholesterol which is a risk factor of cardiovascular health. Medicines which formed from chemical compounds cause serious side effects that cause an imbalance in the body's functions. Therefore, using of natural substances may be an innovative method for the treatment of diseases, as they do not have any side effects on human health. Bee venom can be used as a drug due to its beneficial effects on many disorders, such as neurological, cardiovascular, hematological, musculoskeletal, and dermatological disorders. In the present work, we found that treatment of hypercholesterolemic rats with bee venom (BV) revealed significant increases in Hb, Hct, and RBCs count and showed a significant increase in PaO_2, % O_2 saturation, O_2 carrying capacity. These results suggest that BV can enhance respiratory functions of blood and can be used in respiratory diseases to enhance the respiration and hematological parameters. Also, BV could be used as a prophylactic agent (food protector) to protect us from the harmful effects of cholesterol.

Key words: Honeybee venom, *Apis mellifera*, Hypercholesterolemia, Respiratory functions.

INTRODUCTION

Hyperlipidemia suggests abnormally increased levels of lipids or lipoproteins in the blood due to abnormal fat metabolism or function, and it is induced by dietary disorders, obesity, genetic illnesses such as familial hypercholesterolemia (FH) or different ailments such as diabetes (Yao *et al.*, 2020) which caused a reduction in O_2 transport due to increasing the cholesterol content in RBCs membrane delay diffusion of O_2 in and out of RBCs (Buchwald *et al*., 2000) and caused respiratory alkalosis and decrease O2 saturation (Abd-El-Maksoud, 2009). Nowadays many types of research were directed to natural therapy to avoid the side effects of drugs used as anti-hypercholesterolemia. Honey bee venom (Apis mellifera) is a bitter, colorless liquid, and its active portion contains many peptides (adolapin, apamin, melittin, and mast cell degranulating peptide), enzymes (phosphatase, hyaluronidase, α-glucosidase, phospholipase B, and phospholipase A2) and low molecular weight components. It also had a non-peptide fraction (histamine, dopamine, and nor-epinephrine) (Raghuraman and Chattopadhyay, 2007).

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BV has various polypeptides, the primary one is that melittin and is also the major component of BV and it has many favorable biological effects and low toxicity. BV has been used as a drug because of its beneficial effects on many diseases (Abdela and Jilo, 2016; Sforcin *et al.*, 2017). Studies on the use of BV to treat patients with various nervous system degenerative disorders such as multiple sclerosis (MS) have been published, Alzheimer's disease, and Parkinson's disease (Kim *et al.*, 2011 and Lee *et al.*, 2012). In cell and animal studies BV has also been found to work against different types of cancers (Orslic, 2012). However, no differences between the cancer incidences in normal humans and beekeepers have been reported (Mcdonald *et al.*, 1979). reactive oxygen species (ROS), free radicals, and reactive nitrogen species are the most recognized cellular oxidants (Asmat *et al.*, 2016) and BV is believed to be counteracting oxidant activity (Roy *et al.*, 2015). BV also had decreased effects on elevated blood glucose and dyslipidemia (Gawad, Fikry, Amin, Elmahdi, and Elaziz, 2016). The present work aimed to evaluate the potential effects of honeybee venom (BV) on the hematology and respiratory functions of hypercholesterolemic male albino rats.

MATERIALS AND METHODS

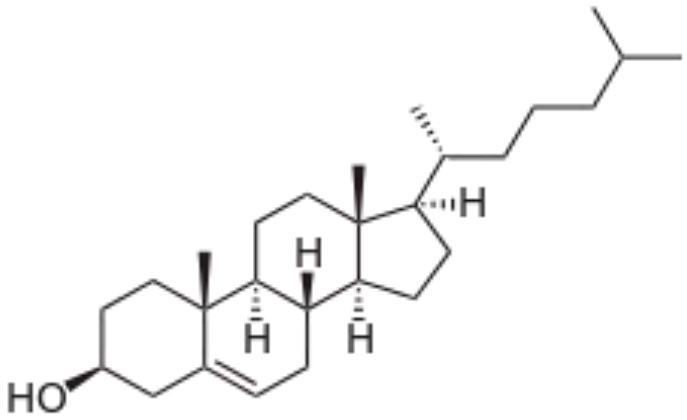
1. Experimental animals

Forty-two male albino rats (*Rattus norvegicus*) weighing 100-150g were collected from Helwan Farm of the Egyptian Organization for Vaccine and Biological Preparations. Rats were caged at 25±2 ° C, 12 hours light / dark cycle and given food and water ad libitum for 10 days before the start of the experiment in the laboratory.

2. Cholesterol

It was purchased from the Middle East Company for Medical and Scientific Apparatus Laboratory Equipment and Chemicals, Cairo, Egypt, it is white crystalline powder, dissolved in coconut oil

-**Chemical name**: (3β)-cholest-5-en-3-ol
-**Empirical formula**: $C_{27}H_{46}O$
-**Molecular weight**: 386.65 g/mol
-**Density**: 1.052 g /cm^3
-**Structure formula**:



3. Coconut oil

It was purchased from a pyramid company for new industry, used for dissolving of cholesterol.

4. Honeybee venom

Lamarck's honeybee or the Egyptian honeybee, *Apis mellifera lamarckii.*BV was purchased from the Faculty of Agricultural Environmental Sciences, Benha University. The venom was collected from healthy colonies of local *A. mellifera lamarckii*. The collection was made following the standard electroshock method (Pence, 1981), when the wires at the top of the hive were electrified and a very mild shock was applied to the bees, they covered the surface of the wired glass plate and stung the surface of the glass plate in response to the electrical stimulation. Secreted venom from bee sting dried rapidly when exposed to the air. Dried venom was scraped off with a sharp scalpel and transferred to the laboratory and was stored at a temperature of −20 ◦C until further analysis. Extraction was made for 15–20 min on each colony and was repeated twice every 2 weeks.

5. Induction of Hypercholesterolemia

Cholesterol was dissolved in coconut oil and was given to the rats by oral gavage at a daily oral dose of (450 mg/kg b.wt) dissolved in 0.5 ml coconut as described by Nwichi *et al.* (2012), the presence of hypercholesterolemia in the induced rat model was documented by evaluating the lipid profile at the end of induction period (6 weeks) in the cholesterol group as compared to negative control and coconut oil groups.

6. Experimental groups and design of the work:

Animals were divided randomly into six groups (7 animals each), fed on a standard diet, and supplied with water *ad libitum*.

6.1. First group: (control group). Normal untreated rats.

6.2. Second group: (coconut oil group). Rats administered a daily oral dose of coconut oil (0.5ml) for 6 weeks.

6.3. Third group: (cholesterol group). Rats administered a daily oral dose of cholesterol (450 mg/kg b.wt) dissolved in 0.5 ml coconut oil for 6 weeks.

6.4. Fourth group: (Bee venom group). Bee venom was freshly prepared by dissolving in distilled water just before treatment and was injected intraperitoneally (IP) at a concentration of 0.5 mg/kg for 6 weeks (Mousavi *et al.*, 2012).

6.5. Fifth group: (prophylactic group). Rats injected intraperitoneal (IP) with bee venom 0.5 mg/kg for 6 weeks then administered cholesterol for another 6 weeks (450 mg/kg b.w dissolved in 0.5 ml coconut oil).

6.6. Sixth group: (therapeutic group). Rats administered a daily oral dose of cholesterol (450 mg/kg b.wt dissolved in 0.5 ml coconut oil) for six weeks then injected intraperitoneal (IP) with bee venom 0.5 mg/kg for another six weeks.

7. Blood Sampling:

At the end of the experimental period, rats were fasted overnight then anesthetized by ether inhalation (Sinet *et al*., 1984). Rats were dissected to expose the dorsal aorta of each control and treated animals as previously described by (Eissa *et al.,* 1988; El-Shafey, 1990 and El-Shafey and Selim, 2002) and the arterial blood samples of the rats were collected into 1.0 ml syringes containing heparin (500 IU/ml). Heparin is used because of its limited effect on the biochemical composition of blood (Muller-Plathe and Schebusch, 1991).

8. Hematological analysis:

Determination of hemoglobin content, hematocrit value, and red blood cells "RBCs" count by Automated Hematology Analyzer (Diff3) Mek-6410/Mek-6420.

9. Determination of Respiratory Functions of Blood

9.1. Blood gases and acid-base balance

Determination of blood gases (oxygen and carbon dioxide partial pressures; PO_2 & PCO_2 in mmHg), % blood O_2 saturation, and blood acid-base status parameters (pH value, HCO_3) were carried out using MEDICA, REF7001, Analyzer, English. Oxygen carrying capacity was calculated as follows: -

One gm of Hb can hold about 1.34 ml of oxygen at 100% saturation, thus Oxygen-Carrying capacity = 1.34 X g/ L of Hb.

9.2. Blood oxygen equilibrium curve "OEC"

The best way to measure the oxygen affinity is to draw an OEC by plotting the percentage of O_2 saturation of hemoglobin at a different partial oxygen pressure using Sigma Plot (version 10) program produced by Systat Software, Chicago, USA and determination of the blood oxygen equilibrium curve "OEC" was performed as previously described by Eissa *et al.* (1988) and El-Shafey (1998)

10. Statistical analysis

The values of measured and calculated parameters were expressed as the mean of 7 individual values ± standard deviation "SD". Statistical analysis was carried out using a one-way analysis of variance (ANOVA) followed by Duncan´s test by using SPSS (version 20) program produced by IBM Software, Inc. Chicago, USA (George and William, 1980). In the same raw, similar letters mean a non-significant difference at $P< 0.05$ and different letters mean a significant difference at $P< 0.05$.

RESULTS

1. Hemoglobin content

By analysis of variance, hemoglobin content showed significant declines in Hb content in cholesterol treated groups as compared to the control group and other treated groups (Table 1). BV treatment caused a significant increase in Hb content. Treatment with BV before or after cholesterol help to return Hb content toward control value.

2. Hematocrit value

Hematocrit values (Table 1) showed a significant difference between control and treated groups by analysis of the variance. Rats treated with cholesterol showed significant decreases in Hct value as compared to all groups. BV and BV then cholesterol treatment (protective) induced

significant increases in Hct value as compared to control and other treated groups.

3. Red blood cells (RBCs) count

Data in table (1) showed a significant difference in RBCs count between control and all treated groups (ANOVA). After cholesterol treatment RBCs count showed significant decreases as compared to the control group and all other treated groups. Bee venom and BV then cholesterol treatments caused significant increases in RBCs count as compared to control and other treated groups.

4. Respiratory functions of blood

Data in table (2) showed a significant increase in partial pressure of oxygen (PO_2), oxygen saturation, oxygen carrying capacity in the bee venom group in comparison to all other groups. There was no significant difference between BV then cholesterol group, coconut, and control groups in partial pressure of oxygen, oxygen saturation, oxygen carrying capacity. There was a significant decrease in the cholesterol treated group in partial pressure of oxygen, oxygen-carrying capacity, oxygen saturation, and partial pressure of carbon dioxide (PCO_2). There was no significant difference between BV and BV than cholesterol, coconut, and control groups in partial pressure of carbon dioxide (PCO_2).

5. Blood acid-base status parameters

Table (3) illustrated the changes in blood pH, bicarbonate "HCO_3". Treatment with cholesterol and cholesterol then bee venom showed significant increases in blood pH and HCO_3 compared to the control group and other treated groups. There were non-significant differences between control, coconut oil, and BV in blood pH, bicarbonate "HCO_3". There were non-significant differences between BV and BV then cholesterol groups.

-Blood oxygen equilibrium curve "OEC" Fig (1) showed the oxygen equilibrium curves (OEC) of all groups. The OEC of cholesterol and cholesterol before BV treated groups showed a left shift in comparison with that of control and other treated groups. Blood oxygen half-saturation pressure (P_{50} value) found to be (28.52±1.3), (29.32±0.82), (24.10±1.76), (30.23±1.51), (29.32±0.95) and (25.51±2.31) for control, coconut oil, cholesterol, BV, BV then cholesterol and cholesterol BV treated groups respectively (Table 4). ANOVA showed significant decreases in cholesterol and cholesterol then RJ treated groups in comparison with those of control and other treated groups, while there were non-significant differences between all other treated

Table 1: Hb content, Hct value, RBCs count of hypercholesterolemic male albino rats before or after bee venom treatments

Groups / Parameter	Control	Coconut oil	Cholesterol	Bee venom	Bee venom then cholesterol	Cholesterol then Bee venom
Hemoglobin content (g/dl)	12.80±0.41^{b}	12.64±0.38^{b}	11.59±0.48^{c}	14.78±0.60^{a}	12.98±0.70^{b}	12.11±0.56^{bc}
Hematocrit value (%)	43.80±0.65^{b}	43.77±0.69^{b}	41.38±1.12^{c}	45.03±0.73^{a}	44.30±0.36^{a}	43.73±0.71^{b}
Red blood cells count (number of RBCsX10^{6}/mm3)	7.45±0.19^{b}	7.33±0.17^{b}	6.55±0.42^{c}	7.90±0.46^{a}	7.80±0.46^{a}	7.31±0.21^{b}

Table 2: Partial pressure of oxygen "PO_2", O_2 saturation "$\%O_2$ sat.", oxygen-carrying capacity and partial pressure of carbon dioxide "PCO_2" of hypercholesterolemic male albino rats before and after bee venom treatments.

Groups / Parameter	Control	Coconut oil	Cholesterol	Bee venom	Bee venom then cholesterol	Cholesterol then Bee venom
PO_2 (mmHg)	101.51±1.85^{b}	100.21±2.36^{b}	86.87±0.85^{d}	104.34±0.80^{a}	98.32±0.21^{b}	90.45±1.36^{c}
$\%O_2$ sat.	97.53±0.41^{b}	97.32±0.35^{b}	95.11±0.15^{d}	99.10±0.17^{a}	96.76±0.1^{b}	95.45±0.30^{c}
Oxygen carrying capacity	18.15±0.01^{b}	17.81±0.05^{b}	15.53±0.05^{d}	19.80±0.08^{a}	17.23±0.10^{b}	16.00±0.08^{c}
PCO_2 (mmHg)	22.07±0.09^{a}	22.01±0.64^{a}	17.13±0.15^{c}	22.00±0.62^{a}	22.50±0.58^{a}	21.37±0.58^{b}

Table 3: PH, bicarbonate concentration (HCO_3) of hypercholesterolemic male albino rats before or after bee venom treatments.

Groups / Parameter	Control	Coconut oil	Cholesterol	Bee venom	Bee venom then cholesterol	Cholesterol then Bee venom
pH (unit)	7.41±0.01^{bc}	7.40±0.02^{bc}	7.51±0.01^{a}	7.42±0.01^{bc}	7.38±0.08^{c}	7.46±0.07^{a}
HCO_3 (mmol/L)	22.30±0.88^{bc}	22.98±0.80^{bc}	23.55±0.85^{a}	22.13±0.85^{c}	22.50±0.58^{bc}	23.00±0.47^{a}

Table 4: Blood oxygen half-saturation pressure "P_{50}" of hypercholesterolemic male albino rats before or after bee venom treatments

Groups / Parameter	Control	Coconut oil	Cholesterol	Bee venom	Bee venom then cholesterol	Cholesterol then Bee venom
P_{50} (mmHg)	**28.52±1.3 [a]**	**29.32±٠.82 [a]**	**24.10±1.76 [b]**	**30.23±1.51 [a]**	**29.32±٠.95 [a]**	**25.51±2.31 [b]**

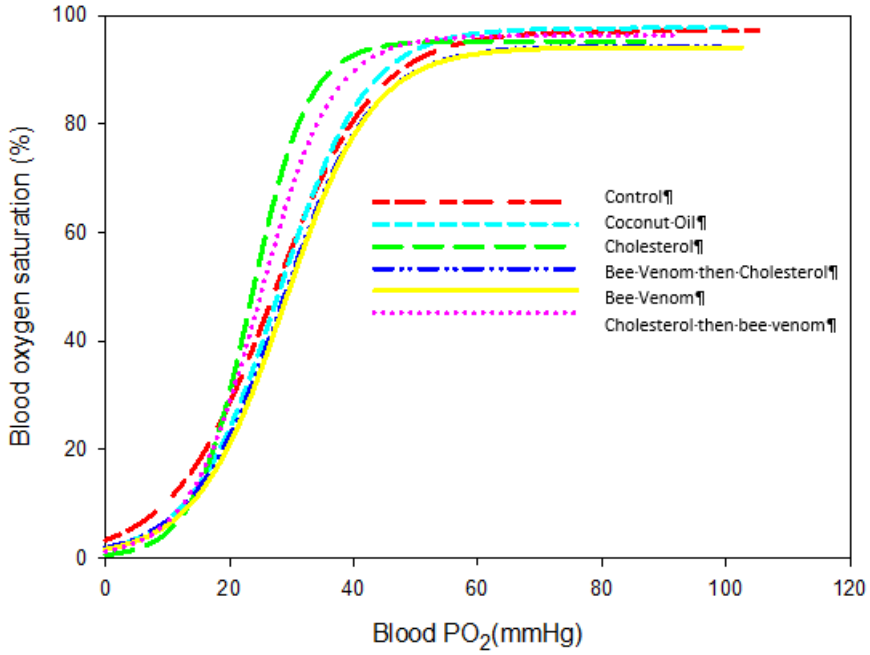


Fig.1. Blood oxygen equilibrium curves of hypercholesterolemic male albino rats before or after bee venom treatments.

DISCUSSION

Bee venom can have therapeutic, defensive, and hypolipidemic effects by increasing lipid consumption in adipose tissue and triglyceride hydrolysis (Hassan *et al*., 2019). Treatment with cholesterol, induced decreases in levels of Hb, Hct, and RBCs count. These results are in agreement with those of (Prasad, 2010) who reported that hypercholesterolemia caused reductions in the hematocrit and hemoglobin values. These reductions may be due to a decrease in RBC count which results from a decrease in the formation of RBCs, damage of erythrocyte membrane, generate micro-nucleated erythrocyte, and alteration in blood viscosity and increase in the fluid volume (Abd Elhalim and Alhadlaq, 2008).

Bee venom induced significant increases in Hb, Hct, RBCs count, PO_2, O_2 saturation, and O_2 carrying capacity this may be due to BV improves erythropoiesis and increases the Hb content, RBCs and Hct which improve O_2 transport by increasing coronary and peripheral circulation and improves circulation of blood in the micro blood vessels and these results are in line with (Mohammed and Hassan, 2019) and (Son *et al*., 2007). Using BV before cholesterol has a preventive role in the protection of the body from the high level

of cholesterol and improvement renewal of RBCs (Salman *et al*., 2015).

Cholesterol treated group showed a decrease in O_2 saturation, PO_2 and O_2 carrying capacity this may be due to increased RBC membrane cholesterol in hypercholesterolemia appears to decrease the transmembrane O_2 diffusion rate. (Buchwald *et al*., 2000 and Awwad, 2008) and also, this group showed respiratory alkalosis which indicated by a significant decrease in $PaCO_2$, increase in pH, and compensatory decreases in blood HCO_3 concentration (Johnson, 2015). The high RBC membrane cholesterol content seemed to impair O_2 diffusion into the RBCs, thereby maintaining higher PO_2 plasma levels in the cholesterol group (Buchwald *et al*., 2000). This data agreed with Menchaca *et al.* (1998) who compared arterial blood samples from cholesterol-supplemented rabbits and from non-supplemented control and reported that high cholesterol concentrations reduce blood O_2 transport and reported finally that increased RBC membrane cholesterol in hypercholesterolemic rabbits decreased the trans-membrane O_2 diffusion rate. The oxygen dissociation curve (ODC) describes the dependency of the oxygen saturation on the oxygen partial pressure (PO_2) and with its sigmoid shape, the curve is subjected to right or left shifts, thereby changing hemoglobin-O_2 affinity (Woyke *et al.*, 2020). A shift to the left implies an increased oxygen affinity and, hence, tighter binding due to the higher oxygen saturation to the PO_2. On the other hand, a shift to the right corresponds to a decreased oxygen affinity and easier release of oxygen to the tissues. It is well known that the ODC shifts in response to changes in pH, PCO_2 and 2,3 diphosphoglycerate (Hamilton *et al.*, 2004). The oxygen equilibrium curves (OEC) of all treated groups showed that there was a non-significant change in the curves of coconut, BV, BV then cholesterol (prophylactic) groups in comparison with the control group. The P_{50} (the oxygen tension at which hemoglobin is 50% saturated with O_2) and the blood oxygen affinity did not significantly affect. The OEC of cholesterol and cholesterol before BV treated groups showed a left shift (increase the affinity of O_2 to hemoglobin), this may be due to alkalosis, which was indicated in the cholesterol treated group, an increase in pH shifts the curve to the left so that P_{50} decreased so occur reducing in the unload of the O_2 to the tissues ,this finding is agreed with Buchwald (2000) who stated that high patient blood cholesterol concentrations were correlated with decreased blood transportation of O_2 and the curve of hemoglobin dissociation shifted to the left.

CONCLUSION

The present study indicates that BV has protective roles against the deleterious effects of cholesterol due to its high contents of antioxidant substances. In recommendation, The BV may be useful when taken as prophylactic to people who may suffer from high cholesterol levels in the blood.

Ethical statement: The study was conducted according to Approval No. 000051 from the Research Ethics Committee of the Faculty of Medicine, Benha University (REC-FOMBU) which operates according to international guidelines, including the declaration of Helsinki, Islamic Organization for Medical Sciences (IOMS), World Health Organization (WHO), and International Council on Harmonization and Good Clinical Practice (ICH-GCP).

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تأثير سم عسل النحل (ابيس ميليفرا) على الوظائف التنفسية لذكور الجرذان البيضاء عالية كوليستيرول الدم

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تعتبر زيادة نسبة الكولبستيرول فى الدم من الاسباب الأساسية لأمراض القلب والأوعية الدموية حيث يؤثر على كفاءة نقل الاكسجين بواسطة تراكمه على جدار كرات الدم الحمراء وإستخدام الأدوية الصناعية لها أعراض جانبية تؤثر على الوظائف الحيوية للجسم وإستخدام المركبات الطبيعية فى العلاج تعد الأستعمال الأمثل و هذه الدراسة تهدف إلى إيضاح التأثيرالحيوى لسم النحل (كعلاج أو كوقاية) وفي هذه الدراسة تم إستخدام ٤٢ من ذكور الجرذان وتم تقسيمها إلي ٦ مجموعات (٧ جرذان في كل مجموعة) واظهرت النتائج ان سم النحل يحسن الوظائف التنفسية والقياسات الدموية ويمكن استخدام سم النحل كواقى غذائى طبيعى لحماية الجسم من الاضرار الناتجة عن زيادة الكوليسترول.