Oxidative stress, hepatotoxicity and nephrotoxicity of aluminium sulfate in rats: The possible protective role of bee-propolis

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Abstract

Aluminum increased free radicals and caused alterations in antioxidant enzymes in both *in vivo* and *in vitro*. Propolis scavenges free radical and inhibits the membrane lipid peroxidation. Therefore, the present study aimed to investigate the protective effect of propolis against the toxicity of aluminum sulfate in male rats. Rats were divided into four equal groups. Group 1 received no treatment, Groups 2, 3 and 4 were treated orally with propolis (50 mg/kg BW), aluminum sulfate (106 mg/kg BW) and aluminum sulfate (106 mg/kg BW) plus propolis (50 mg/kg BW), respectively. Rats were administered their respective doses every day for 60 days. Aluminum sulfate caused changes in body and organs weights. The activities of transaminases and alkaline phosphatase were increased in plasma, while decreased in the liver of rats treated with aluminum sulfate. Acetylcholinesterase activity, total protein, albumin and high density lipoprotein were decreased, while urea, creatinine, bilirubin, total lipids, cholesterol, triglycerides, low density lipoprotein and very low density lipoprotein were increased in rats treated with aluminum sulfate. Treatment with aluminum sulfate increased thiobarbituric acid-reactive substances (TBARS), while decreased the activities of antioxidant enzymes (glutathione peroxidase, glutathione S-transferase, catalase and superoxide dismutase) and glutathione (GSH) in plasma, liver and kidney. On the other hand treatment with bee-propolis alone caused reduction in the levels of TBARS and increased the activities of antioxidant enzymes and GSH. The presence of bee-propolis with aluminum sulfate alleviated its toxic effects. These results concluded that bee-propolis minimized hepatotoxicity, nephrotoxicity and oxidative stress induced by aluminum sulfate in rats.

Key words: Aluminum sulfate; Bee-propolis; Antioxidant enzymes; Free radicals; Rats

1. Introduction

Aluminium is the most abundant metal on Earth and constitutes 8.13% of the crust (IPCS, 1997). It is released into the environment largely by natural processes, but also due to anthropogenic activities (Lantzy and Fred, 1979). While aluminium is inherently contained in most food stuff, its salts are artificially added to various food products (acidity regulator, raising agent, anti-caking agent, etc.). Use of aluminium in the processing, packaging and storage of food products is also a significant factor in the increased aluminium levels in foods (IPCS, 2007). On the other hand, aluminium salts are widely used as flocculants in the treatment of drinking water to reduce organic matter, color, turbidity and microorganism levels (WHO, 2008), which may lead to increased aluminium intake by the general public. Total dietary exposure to aluminium, including exposure via drinking water, has been assessed using a duplicate diet, total diet or market basket approach in a number of countries (IPCS, 2007). Yousef (2004) reported that aluminium-induced changes in hemato-biochemical parameters, increased lipid peroxidation and decreased the activities of the antioxidant enzymes in plasma and tissues of male rabbits. Also, Yousef et al. (2005 and 2007) demonstrated that $AlCl_3$ caused deterioration in sperm quality, enhancement of free radicals and alterations in antioxidant enzymes in both *in vivo* and *in vitro*. The mechanism of aluminium-induced toxicity is that it potentiates the activity of Fe^{2+} and Fe^{3+} ions to cause oxidative damage (Xie et al., 1996). Aluminum levels vary according to the levels found in the source of water and whether Al coagulants are used during water treatment.

Propolis, a complex mixture of compounds also called bee glue, is a natural resinous product that honey bees collect from several plants and mix it with beeswax and salivary enzymes (B-glucosidase) (Marcucci,1995; Bankova ,2005; Cardoso, 2011).

Propolis which is rich in polyphenols, flavonoid aglycones, phenolic acid and their esters, as well as phenolic aldehydes and ketones, terpenes, sterols, vitamins and amino acids (Khalil, 2006, Boufadi et al., 2014). Propolis possesses several biological properties such as anti-inflammatory, anticancer, antioxidant, antibiotic and antifungal activities (Burdock, 1998). It scavenges free radical and inhibits the membrane lipid peroxidation and free radical formation (Liu et al., 2004). It acts on antioxidant enzymes such as superoxide

dismutase (Jasprica et al., 2007). Therefore, the present study was carried out to investigate: (1) the alterations in biochemical parameters, free radicals and antioxidant enzymes induced by aluminium sulfate in liver, kidney of male rats, (2) the role of propolis in alleviating the negative effects of aluminium chloride, and (3) the effect of propolis alone on the tested parameters.

2. Materials and Methods

2.1 Tested compounds

In this study, the effects of aluminium sulfate with or without propolis on biochemical indices, free radicals and enzyme activities of male rats were investigated. Aluminium sulfate ((Al2(SO4)3 Aqu.) was purchased from Aldrich chemical Company, Milwaukee Wis, USA, while propolis was obtained from Superior Nutrition and Formulation by Jarrow Formulas, Los Angeles, USA. All other chemicals used in the experiment were of analytical grade. The dose of aluminium sulfate was 106 mg/kg BW and given orally to rats. The dose was chosen according the previous study by Abd El-Rahman (2003). The dose of propolis was **50** mg/kg/BW. This dose was chosen based on previous studies of **Newairy et al. (2009) and Yousef and Salama (2009).**

2.2 Animals and treatments

Forty male rats weighing 160-170 g were used. Animals were obtained from Faculty of medicine, Alexandria University, Alexandria, Egypt. Animals were housed 5 per cage and kept on commercial diet and tap water which provided *ad libitum*. After two weeks of acclimation, animals were divided into four groups. The first group was used as control. Groups 2, 3 and 4 were treated orally with propolis (50 mg/kg BW), aluminum sulfate (106 mg/kg BW) and aluminium sulfate (106 mg/kg BW) plus propolis (50 mg/kg BW), respectively. Rats were administered their respective doses every day for 60 days.

2.3 Meassured parameters

2.3.1 Body and organs weights

At the end of the experimental period body weight of rats were recorded. Animals were sacrificed by decapitation and liver, brain, heart, lung, spleen, kidney and testes were immediately removed and weighed.

2.3.2 Blood biochemical parameters and enzyme activities

The blood samples were collected in tubes containing Heparin (anti-coagulant) and blood samples were placed immediately on ice. Plasma was obtained by centrifugation of samples at 860 xg for 20 min, and was stored at -60°C until used for analyses.

Stored plasma samples were analyzed for total protein (TP) by the Biuret method according to Armstrong and Carr (1964). Albumin (A) concentration was determined by the method of Doumas et al. (1977). Globulin was calculated as the difference between total protein and albumin. Plasma glucose, urea and creatinine concentrations were measured by the method of Trinder (1969), Patton and Crouch (1977) and Henry et al. (1974), respectively. Plasma total bilirubin was measured using the method of Pearlman and Lee (1974). Plasma concentrations of total lipids, cholesterol and triglycerides (TG) were determined according to the methods of Knigth et al. (1972), Watson (1960) and Fossati and Principe (1982), respectively. High-density lipoprotein-cholesterol (HDL-c) was determined according to the methods of Warnick et al. (1983). Low-density lipoprotein-cholesterol (LDL-c) was determined by the calculation (cholesterol-(TG/5+HDL). Very low-density lipoprotein-cholesterol (VLDL-c) was calculated by dividing the values of TG by factor of 5.

The activities of plasma aspartate transaminase (AST; EC 2.6.1.1) and alanine transaminase (ALT; EC 2.6.1.2) were assayed by the method of Reitman and Frankel (1957). Alkaline phosphatase (AlP; EC 3.1.3.1) activity was determined in plasma according to the method of (Principato et al., 1985). Plasma acetylcholinesterase (AChE; EC 3.1.1.7) activity was estimated using acetylthiocholine iodide as a substrate according to the method of Ellman et al. (1961). Glutathione S-transferase (GST; EC 2.5.1.18) activity was determined according to Habig *et al*. (1974). Catalase (CAT; EC 1.11.1.6) activity was determined using the Luck method involving the decomposition of hydrogen peroxide (Luck, 1974). Superoxide dismutase (SOD; EC 1.15.1.1) activity was measured according to Mishra and Fridovich (1972). Glutathione reduced (GSH) was determined according to the method of Beutler et al. (1963). The activity of Glutathione peroxidase (GPx, EC. 1.1.1.9) was assayed by the method of Chiu et al. (1976). Plasma thiobarbituric acid-reactive substances (TBARS) were measured by the method of Tappel and Zalkin (1959).

2.3.3 Organs Biochemical Parameters and Enzyme Activities

All animals of each group were sacrificed by decapitation after the end of the treatment period and liver and kidney was immediately removed, weighed and washed using chilled saline solution. Tissue were minced and homogenized (10% w/v) in ice-cold sodium potassium phosphate buffer (0.01 M, pH 7.4) containing 1.15% KCl in

aPotter–Elvehjem type homogenizer. The homogenate were centrifuged at 10,000 ×g for 20 min at 4°C. The resultant supernatant of the organs was used for different enzyme activities, glutathione reduced and free radicals according to the previous methods. In liver AST, ALT and AlP were determined. In liver and kidney GST, SOD, GPX, CAT, GSH and TBARS were determined. Tissue protein concentration was assayed by the method of Lowrey et al. (1951).

2.4 Statistical analysis

Data were analyzed according to Steel and Torrie (1981). Statistical significance of the difference in values of control and treated animals was calculated by F test with 5% significance level. Data of the present study were statistically analyzed by using Duncan s Multiple Range Test (SAS,1986).

3. Results and Discussion:

Data in **Table1** indicated that treatment with Bee-propolis alone significantly ($p<0.05$) increased SOD, GPx, GST, CAT and GSH activities and decreased TBARS levels in plasma, liver and kidney. On the other hand, aluminium sulfate (AS) has shown a significant ($p<0.05$) decrease in antioxidant enzymes activities but increased the levels of TBARs. The Co administration of Bee-propolis with (AS) has alleviated (As) toxicity compared to (AS) treated group. The present results are in agreement with data reported by Yousef (2004), Yousef et al. (2005, 2007), Nehru and Anand (2005) and Newairy et al. (2009) who indicated that aluminium intake produces oxidative stress.

Although aluminium is not a transition metal and therefore cannot initiate peroxidation, many investigations have searched for a correlation between aluminium accumulation and oxidative damage in the body tissues (Nehru and Anand, 2005). An *in vitro* study has indicated that aluminium greatly accelerates iron-mediated lipid peroxidation (Xie et al., 1996). In fact, aluminium, a non-redox-active metal, is a pro-oxidant both in *vivo and in vitro* (Exley, 2004). The primary effects of aluminium on the brain, liver and kidney functions are thought to be mediated via damage to cell membranes. Lipid peroxidation of biological membranes results in the loss of membrane fluidity, changes in membrane potential, an increase in membrane permeability and alterations in receptor functions (Nehru and Anand, 2005).

Orihuela et al. (2005) reported that at high doses, aluminium was able to induce oxidative stress in the intestinal mucosa, as indicated by

the significant increase in the concentration of both, Oxidized glutathione/reduced glutathione (GSSG/GSH) ratio and TBARS levels. These effects may have been produced owing to concomitant causes. Aluminium might affect the glutathione (GSH) synthesis by decreasing the activity of glutathione-synthase (GS), a non-limiting step of whole reaction, thus leading to a reduced GSH content. Likewise, a slowing down in the conversion of oxidized-to-reduced form of GSH due to the inhibition of glutathione-reductase (GR) by aluminium could explain the increment in GSSG/GSH ratio. On the other hand, it has been demonstrated that aluminium is able to inhibit NADPH-generating enzymes such as glucose 6-phosphate dehydrogenase and NADP-isocitrate dehydrogenase. Since, NADPH is shown to be a main factor for the GSH regeneration, the decreased GSH level could be also ascribed to insufficient supply of NADPH. Besides, aluminium is able to diminish the activity of enzymes related to cell antioxidant defense, such as super oxide dismutase, catalase and GSH-peroxidase, in brain and liver. Therefore, aluminium could indirectly contribute to unbalance redox equilibrium in the enterocyte (Orihuela et al., 2005).

Fuliang et al. (2004), Jasprica et al. (2007), Kanbura et al. (2009), Newairy et al. (2009) and Yousef and Salama (2009) reported that propolis caused reduction in TBARS levels and increase in SOD, GSH-Px, GST and CAT activities. Also, propolis is able to induce hepatoprotective effects on aluminium chloride induced liver damage in rats (Newairy et al., 2009). In addition, propolis is able to induce hepatoprotective effects on paracetamol induced liver damage in mice (Nirala et al., 2008). Taken together, these findings constitute evidence that the antioxidative properties of the propolis contribute to the prevention of damage induced by AS in rats.

Table 1. TBARS (nmol/ml), glutathione (GSH; U/ml), glutathione peroxidase (GPx; (U/ml), glutathione S-transferase (GST; ***µmol /hr/ml)***, catalase (CAT; µmol H_2O_2 consumed/min/ml) and superoxide dismutase (SOD; U/ml) activities in plasma, liver and kidney of male rats treated with Bee-propolis, aluminium sulfate (AS) and their combination.

Parameter	Experimental groups			
	Control	Porpolis	AS	Porpolis+ AS
Plasma				
TBARS	0.4 ± 0.065^{b}	0.2 ± 0.01^{c}	0.8 ± 0.06^{a}	0.6 ± 0.02^{b}
GSH	0.5 ± 0.023^{b}	0.8 ± 0.04^{a}	0.3 ± 0.01^{d}	0.4 ± 0.01^{c}
GPx	14.9 ± 0.69^{b}	24.2 ± 0.67^{a}	7.5 ± 0.27^{d}	12.2 ± 0.54^{c}
GST	1.2 ± 0.06^{b}	1.8 ± 0.05^{a}	0.6 ± 0.02^{d}	1.0 ± 0.09^{c}
Catalase	55 ± 1.69^{b}	84 ± 1.47^{a}	15 ± 1.05^{d}	45 ± 1.75^{c}
SOD	2.2 ± 0.10^{b}	4.1 ± 0.02^{a}	1.0 ± 0.08^{d}	2.1 ± 0.16^{c}
Liver				
TBARS	49 ± 2.9^{c}	26 ± 0.9^{d}	74 ± 2.4^{a}	57 ± 1.2^{b}
GSH	11.3 ± 0.47^{b}	16.9 ± 0.69^{a}	4.5 ± 0.17^{d}	9.6 ± 0.24^{c}
GPx	306 ± 13.5^{b}	417 ± 24.8^{a}	153 ± 5.3^{c}	267 ± 7.4^{b}
GST	2.1 ± 0.82^{b}	3.1 ± 0.10^{a}	1.1 ± 0.02^{d}	1.8 ± 0.05^{c}
Catalase	51 ± 3.1^{b}	75 ± 3.1^{a}	22 ± 0.99^{d}	44 ± 0.79^{c}
SOD	7.7 ± 0.39^{b}	11.2 ± 0.32^{a}	4.13 ± 0.27^{d}	6.2 ± 0.15^{c}
Protein content	139 ± 4.7^{b}	179 ± 4.8^{a}	57 ± 1.5^{d}	116 ± 6.1^{c}
Kidney				
TBARS	22 ± 0.98^{c}	15 ± 0.59^{d}	35 ± 1.11^{a}	25 ± 0.54^{b}
GSH	6.5 ± 0.34^{b}	9.7 ± 0.26^{a}	3.9 ± 0.19^{d}	5.5 ± 0.13^{c}
GPx	29.6 ± 1.35^{b}	39.9 ± 1.92^{a}	7.9 ± 0.49^{c}	26.3 ± 0.70^{b}
GST	0.8 ± 0.01^{b}	1.2 ± 0.05^{a}	0.4 ± 0.01^{c}	0.7 ± 0.02^{b}
Catalase	58 ± 1.15^{b}	98 ± 5.42^{a}	28 ± 1.00^{d}	48 ± 2.42^{c}
SOD	8.8 ± 0.51^{b}	13.0 ± 0.71^{a}	4.2 ± 0.23^{c}	7.2 ± 0.33^{b}
Protein content	120 ± 2.27^{b}	130 ± 2.58^{a}	90 ± 3.23^{d}	105 ± 2.52^{c}

Values are expressed as means ± SE; n = 10 for each treatment group. Mean values within a row not sharing a common superscript letters (a, b, c, d) were significantly different, $p<0.05$.

Table 2 showed that treatment with Bee-propolis alone caused a significant ($p<0.05$) decrease of aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (AlP) activities in plasma and increased in liver. while did not affect plasma and brain acetylcholinesterase (AChE). On the other hand, treatment with (AS) significantly ($p<0.05$) increased liver enzymes in plasma and decreased in liver compared to control. Also, (AS) caused inhibition in the activities of AChE as compared to control in both plasma and brain. The presence of Bee-propolis with (AS) in the combination group has minimized (AS) toxic effect on plasma and liver enzymes.

Gaskill et al. (2005) reported that releasing of transaminases (AST and ALT) and alkaline phosphatase (AlP) from the cell cytosol can occur secondary to cellular necrosis. The activity of AST is significantly increases in such cases and escapes to the plasma from the injured hepatic cells. In addition, ALT level is of value also indicating the existence of liver diseases, as this enzyme is present in large quantities in the liver. It increases in serum when cellular degeneration or destruction occurs in this organ (Hassoun and Stohs, 1995). Wilhelm et al. (1996) reported that aluminium exposure can result in Al accumulation in the liver and this metal can be toxic to the hepatic tissue at high concentrations. The inhibition of AlP activities in liver and increase in plasma caused by aluminium (Table 2), are in accordance with the findings of Ochmanski and Barabasz (2000),Yousef (2004) and Newairy et al. (2009).

Aluminium may bind to DNA, RNA and inhibit the activities of alkaline phosphatases (Ochmanski and Barabasz, 2000). Also, Rahman et al. (2000) suggested that the decrease in the activities of AlP in different tissues might be due to the increased permeability of plasma membrane or cellular necrosis, and this showing the stress condition of the treated animals. In addition, they reported that the increase in the activity of AlP in blood might be due to the necrosis of liver, kidney and lung. The increase in plasma AST and ALT may be due to the leakage of these enzymes from the liver cytosol into the blood stream and/or liver dysfunction and disturbance in the biosynthesis of these enzymes with alteration in the permeability of liver membrane takes place.

The inhibition in the activity of AChE in both plasma and brain (Table 2) could be referred to the effect of aluminium on the synaptic

transmission (Chinoy and Memon, 2001). Also, aluminium-induced accumulation of glutamate or other alterations in enzymes of the glutamate-GABA system may be one of the causes of aluminium-induced neurotoxicity (Nayak and Chatterjee, 2001). Moreover, Dua and Gill (2001) reported that aluminium phosphide exposure significantly enhanced neuronal lipoperoxidative damage with concomitant alterations in the antioxidant defence status thus having serious bearing on the functional and structural status of the central nervous system. On the other hand, Propolis exerted an antidepressant like activity in mice submitted to stress, suggesting that it could be an alternative treatment for patients with neuropsychiatric disorders and a novel therapy for depression (Lee *et al*., 2013).

Propolis tended to prevent damage and suppressed the leakage of enzymes through cellular membranes. This result is in accordance with the findings that propolis induced reduction of the increased activity of AST and ALT concentrations in plasma of rats treated with galactoseamine (Nirala et al., 2008). Propolis reduced *Leishmania amazonensis* induced inflammation in the liver of BALB/c mice, decreasing the levels of hepatic enzymes, collagen fibre deposition and pro-inflammatory cytokine production and reversing hepatosplenomegaly (Silva *et al*., 2015). Taiwanese green propolis protected the liver from the pathogenesis of fibrosis (Su *et al*., 2014).

Table2: The activities of an aspartate aminotransaminase, alanin aminotransaminase, alkline phosphatase in plasma and liver and acetylcholinesterase in plasma and brain of male rats treated with Bee-propolis, aluminum sulfate (AS) and their combination.

Enzyme	Experimental groups			
	Control	Propolis	AS	Propolis + AS
Plasma				
AST	40 ± 1.97b	26 ± 0.81c	61 ± 4.69a	47 ± 0.93b
ALT	49 ± 0.78c	33 ± 0.57d	74 ± 1.81a	59 ± 1.59b
ALP	122 ± 1.73c	86 ± 1.24d	220 ± 2.92a	146 ± 4.22b
Liver				
AST	308 ± 6.05b	443 ± 9.77a	210± 6.34d	270 ± 6.10c
ALT	104 ± 1.62b	137 ± 3.32a	69± 0.93d	93 ± 1.23c
ALP	264 ± 17.9b	353 ±21.2a	160 ±6.6c	223 ± 6.2b
Plasma AChE*	3.2 ± 0.20a	3.2 ± 0.30a	1.8 ± 0.12b	2.8 ± 0.17a
Brain AChE**	16.7 ± 1.33a	17.2 ± 0.54a	8.8 ± 0.30c	13.7 ± 0.40b

Values are expressed as means ± SE; n =10 for each treatment group. Mean values within a row not sharing a common superscript letters (a, b, c, d) were significantly different, $p<0.05$.
* Plasma AChE = µmole substrate hydrolyzed/µl serum/min
** Brain AChE = µmole substrate hydrolyzed/mg protein/min
AST (U/L) = Aspartate aminotransaminase, ALT (U/L) = Alanin aminotransaminase, ALP (U/L) = Alkline phosphatase, ACHE = Acetylcholinesterase.

Table 3 has shown that treatment with Bee-propolis alone increased plasma levels of TP, A and G. While, decreased bilirubin, urea and creatinine but did not affect glucose levels. On other hand, treatment with AS resulted in a significant ($P <0.05$) decrease in TP, A and G. While, increased plasma glucose, bilirubin, urea and creatinine compared to control group. The presence of Bee-propolis with AS in the combination group minimized the its toxic effects. The inhibitory effect of AS on protein profile is in agreement with the finding of Newairy et al. (2009) and Yousef (2004). Although the intestine regulates the uptake of amino acids, the liver is of major importance because it regulates protein metabolism. So, the significant decrease in the concentrations of total proteins in rats treated with AS particularly the albumin could be attributed the one hand to an under nutrition and on the other hand to a reduction of the protein synthesis in the liver (Cherroret et al., 1995). Also, their data indicated a very high accumulation of aluminium in the hepatic tissues of adult rats treated with aluminium. As early as 1972, Berlyne et al. (1972) observed high levels of aluminium in the hepatic tissues of rats exposed to high aluminium concentrations, leading to the proposal of a direct toxic action of aluminium ions in the liver, particularly a reduction of the protein synthesis.

The elevation in plasma urea and creatinine levels (Table 3) in AS-treated rats is considered as a significant marker of renal dysfunction, and this is supported by the finding of Rudenko et al. (1998) who reported that aluminium chloride intensifies acid–secrete function of kidney and change the transport of sodium. In addition, Katyal et al. (1997) reported that aluminium has been implicated in the pathogenesis of several clinical disorders, such as renal dysfunction. The increase in plasma total bilirubin (Table 3) is may be resulted from decreased liver uptake, conjugation or increased bilirubin production from hemolysis (Rana et al., 1996).

Yousef (2004) and Newairy et al. (2009). Also, Mahieu et al. (2005) reported that alterations in serum urea may be related to metabolic disturbances (e.g. renal function, cation–anion balance). In addition, Katyal et al. (1997) reported that aluminium has been implicated in the pathogenesis of several clinical disorders, such as renal dysfunction. The increase in plasma total bilirubin (Table 3) may result from decreased liver uptake, conjugation or increased bilirubin production from haemolysis (Yousef, 2004; El-Sharaky et al., 2007; Newairy et al., 2009). The increase in plasma total bilirubin

concentrations in rats treated with AS (Table 3) is in accordance with the previous studies of Yousef (2004); Newairy et al. (2009). Yousef (2004), Thomas et al. (2004) and Newairy et al. (2009) found that the induction rate in serum bilirubin was associated with free radical production and this is in accordance with the present results (Table 3).

Treatment with aluminium sulfate (AS) plus propolis decreased the plasma glucose levels, compared to the rats treated with AS (Table 3). Treatment with propolis alone caused significant decrease in urea, creatinine and bilirubin levels (Table 3). This suggests that propolis can control blood glucose and modulate the metabolism of glucose (Fuliang et al., 2004).Also, Sforcin et al. (2002) reported that treatment of rats with propolis does not induce kidney damage came from urea and creatinine determinations. Propolis dramatically reversed the alterations induced by beryllium (Nirala et al., 2008). Propolis exerted protective effects in different experimental models. It protected the renal tissue against toxicity, free radicals and other adverse effects induced by diatrizoate (Baykara et al., 2015). This effect may be related to the antioxidant properties of propolis.

Table 3. Plasma biochemistry of male rats treated with Bee-propolis, aluminium sulfate (AS) and their combination**.**

Parameter	Experimental groups			
	Control	Propolis	AS	Propolis + AS
Total protein (g/dl)	7.9 ± 0.09b	9.2 ± 0.30a	5.4 ± 0.39d	7.0 ± 0.25c
Albumin (g/dl)	5.3 ± 0.03b	6.0 ± 0.29a	3.4 ± 0.25d	4.6 ± 0.18c
Globulin (g/dl)	2.6 ± 0.09ab	3.2 ± 0.28a	2.0 ± 0.38 b	2.4 ± 0.20 b
Glucose (mg/dl)	96± 3.34c	91 ± 6.61c	134 ± 5.64a	112 ± 4.41b
Bilirubin (mg/dl)	0.9± 0.02c	0.7 ± 0.01d	1.2 ± 0.01a	1.0 ± 0.01b
Urea (mg/dl)	2.2 ± 0.90b	1.5 ± 0.62c	4.4 ± 1.82a	2.4 ± 0.84b
Creatinine (g/dl)	1.0 ± 0.04b	0.7 ± 0.03c	1.4 ± 0.04a	1.1 ± 0.02b

Values are expressed as means ± SE; n = 10for each treatment group. Mean values within a row not sharing a common superscript letters (a, b, c, d) were significantly different, $p<0.05$.

Data listed in **Table 4** showed the changes in plasma concentrations of lipid profile due to treatment with Bee-propolis, aluminium sulfate (AS) and their combination. Results indicated that treatment with Bee-propolis alone caused significant decrease ($p<0.05$)

in the concentration of all plasma lipid profile, while HDL-c increased. On the other hand, treatment with (AS) caused a significant increase ($p<0.05$) in plasma lipid profile compared to control group. The presence of Bee-propolis with (AS) showed a protective effect in all tested parameters. The present data indicated that plasma total lipids, cholesterol, triglycerides and LDL-c were significantly increased by aluminium sulfate (AS) treatment, while HDL-c levels were decreased (Table 4) and this is in accordance with the results reported by Yousef (2004) and Newairy et al. (2009). The increase in plasma lipids due to aluminium administration indicates a loss of membrane integrity. This was further confirmed when AS treatment resulted in a significant effect on the various membrane-bound enzymes in terms of increased plasma and decreased liver AST, ALT and AlP activities of (Table 2). Also, Wilhelm et al. (1996) reported that AlCl3 exposure resulted in aluminium accumulation in the liver and this may lead to disturbance of lipid metabolism and an elevation of serum cholesterol.

The present study showed that treatment of rats with AS plus propolis decreased total lipids, cholesterol, triglycerides and low density lipoprotein-cholesterol (LDL-c), and increased high density lipoprotein-cholesterol (HDL-c) levels compared to AS-intoxicated group (Table 4). These results are in agreement with Fuliang et al. (2004) and Newairy et al. (2009), who found that oral administration of propolis significantly lowered total cholesterol, triglycerides, LDL-c, very low density lipoprotein-cholesterol (VLDL-c) in serum of rats; and to increased serum levels of HDL-c. Also, Kolankaya et al. (2002) found that propolis significantly decreased cholesterol and triglycerides. Some studies suggested that propolis can act in several ways to lower plasma LDL-bound cholesterol. First, uptake of cholesterol in the gastrointestinal tract could be inhibited; second, LDL-c could be eliminated from the blood via LDL receptor; and finally, the activity of cholesterol-degrading enzymes, namely cholesterol-7-hydroxylase could be increased. It has been suggested that propolis decreased total cholesterol and LDL-c, while increased HDL-c due to absorption, degradation or elimination of cholesterol. Moreover, other studies showed that propolis reduced cholesterol and increased HDL-c, indicating that it may be mobilizing cholesterol from extra hepatic tissues to the liver where it is catabolised **(**Kolankaya et al., 2002; Fuliang et al., 2004). Alves et al. (2008**)** reported that the hypocholesterolemic effect of propolis is the result of a direct effect on liver or an indirect effect through thyroid hormones, since thyroid hormones affect reactions in almost all the pathways of lipid metabolism.

Table 4. Plasma lipid and lipoprotein profiles of male rats treated with Bee-propolis, aluminium sulfate (AS) and their combination.

Lipids Profile (mg/dl)	Experimental groups			
	Control	Propolis	AS	Propolis + AS
TL	529 ± 36.6b	420 ± 15.3c	706 ± 21.6a	587 ± 22.9b
Cholesterol	159 ± 5.0c	110 ± 7.8d	222 ± 5.9a	183 ± 3. 6b
TG	113 ± 2.51c	95 ± 1.13d	155 ± 2.39a	131 ± 1.06b
HDL-C	54.6± 2.30b	69.3 ± 1.79a	33.2 ± 1.98d	48.4 ± 1.91c
LDL-C	83.4± 4.26c	30.2 ± 1.15d	157.2 ± 2.40a	108.4 ± 2.29b
VLDL-C	21.2 ± 0.96c	15.9 ± 0.55d	30.4 ± 1.41a	25.2± 1.17b

Values are expressed as means ± SE; n=10 for each treatment group.
Mean values within a row not sharing a common superscript letters (a, b, c, d) were significantly different, $p<0.05$.
TL= Total lipids, TG= Triglycerides, HDL-C= High density lipoprotein, LDL-C= Low density lipoprotein, VLDL-C= Very low density lipoprotein.

Table 5 represents body weight and relative weight of kidney, liver, lung, brain, testes, heart and spleen of male rats treated with Bee-propolis, aluminium sulfate (AS) and their combination. Results indicated that treatment with Bee-propolis alone did not cause significant changes in body weight or relative weight of different organs, but increased relative weight of testes. On the other hand, significant ($P<0.05$) decrease in body weight, brain and testes weight, and increase in liver, Kidney, lung and spleen relative weights were observed in rats treated with AS compared with control. While, treatment with AS did not show significant effect on the relative weight of heart. The presence of Bee-propolis with AS alleviated its effects on the tested parameters.

The decrease in body weight of animals treated with aluminium sulfate (AS) are in agreement with the finding of Yousef et al. (2005 a and b) who found that body weight, feed intake and relative weights of testes and epididymis of rabbits were significantly decreased after treatment with aluminium chloride. Results obtained by Yousef and Salama (2009) indicated significant decrease in the relative weights of testes, seminal vesicle and epididymis in animals treated with $AlCl_3$ compared to control .In addition, Albina et al. (2000) found that rabbits treated with doses of aluminium 25, 100 and 400 mmol/kg showed decrease in body weight gain, especially with 400 mmol. Also, Gomez et al. (1997) found that treatment with aluminium in drinking water at

doses (50, 100 mg/kg/day) for 6.5 month, caused decreased in body weight of rats. Cherroret et al. (1995) suggested that the reduction in body weight of treated young rats with aluminium chloride (100 mg Al/kg/day) for 5 to 14 days by gastric intubation could be attributed to the decrease in food consumption. Also, Pandey and Jain (2017) found that the rats administered with aluminium chloride showed a significant decline in body weight at 60 mg/kg b.wt./day ($P < 0.05$, -3.73%) and 90 mg/kg b.wt/day ($P < 0.001$,-7.14%).

Treatment with propolis alone did not cause significant effects on the weight of the tested organs and this is in agreement with the obtained results of Yousef and Salama (2009). Also, the present study showed that the presence of propolis with aluminium sulfate (AS) alleviated its toxic effects and the weight of the tested organs reached that of the control values and this is in agreement with the obtained results of Yousef and Salama (2009).

Table 5. Body weight (BW; g) and relative weight (g/100 g body weight) of kidney, liver, lung, brain, heart, testes and spleen of male rats treated with Bee-propolis, aluminium sulfate (AS) and their combination.

Parameter	Experimental groups			
	Control	Propolis	AS	Propolis + AS
BW	185 ± 3.4ab	191 ± 3.0a	147 ± 3.7c	177 ± 4.0b
Kidney	1.4± 0.07b	1.3± 0.08b	1.7± 0.04a	1.5± 0.09ab
Liver	4.1 ± 0.23b	4.0 ± 0.24b	5.3 ± 0.18a	4.5 ± 0.13b
Lung	1.3 ± 0.13b	1.4 ± 0.08b	1.6 ± 0.05a	1.4 ± 0.07ab
Brain	1.5 ± 0.01a	1.5 ± 0.04a	1.3 ± 0.03b	1.5 ± 0.02a
Heart	0.5 ± 0.02a	0.5 ± 0.04a	0.5 ± 0.04a	0.5 ± 0.04a
Testes	2.9 ± 0.17b	3.4 ± 0.10a	2.1 ± 0.16c	2.8 ± 0.12b
Spleen	0.5 ± 0.03b	0.5 ± 0.05b	0.7 ± 0.03a	0.6 ± 0.05b

Values are expressed as means ± SE; n = 10 for each treatment group. Mean values within a row not sharing a common superscript letters (a, b, c) were significantly different, $p<0.05$

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الاكسدة الهادمة والسمية الكبدية والكلوية لكبريتات الألومنيوم في الجرذان: الدور الوقائي المحتمل لصمغ النحل (البروبوليس)

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الملخص العربي:

التعرض الى كبريتات الالمنيوم يؤدى الى زيادة مستوى الجذور الحرة وتثبيط الانزيمات المضادة للأكسدة وبالتالى يحدث اكسدة هادمة والتى تؤدى بالتالى الى اضرار فى وظائف الاعضاء واثبتت الدراسات ان صمغ النحل (البروبوليس) يرتبط بالجذور الحرة ويثبط الاكسدة الهادمة للدهون. لذلك ، هدفت الدراسة الحالية إلى التحقق من التأثير الوقائي لصمغ النحل (البروبوليس) ضد السمية الناتجة من التعرض لكبريتات الألومنيوم فى الجرذان. تم تقسيم الجرذان الى اربع مجاميع في كل منها عشر جرذان ومقسمة كالتالي: المجموعة الأولى استخدمت كمجموعة ضابطة، المجموعة الثانية عوملت بصمغ النحل (البروبوليس) (٥٠ مجم/ كجم من وزن الجسم). المجموعة الثالثة عوملت بكبريتات الالومنيوم (١٠٦ مجم/ كجم من وزن الجسم). بينما تم معاملة المجموعة الرابعة بصمغ النحل (البروبوليس) وكبريتات الالومنيوم معا، حيث كانت تعامل الحيوانات بصمغ النحل و كبريتات الالومنيوم يوميا وذلك لمدة ٦٠ يوم . تسببت كبريتات الألومنيوم في تغيرات في وزن الجسم والأعضاء. وزادت أنشطة الأنزيمات الناقلة للأمين و إنزيم الفوسفاتيز القاعدي في البلازما ، بينما انخفضت في الكبد . انخفض نشاط الأستيل كولين استيريز والبروتين الكلي والألبيومين والليبوبروتين عالي الكثافة ، في حين زادت اليوريا والكرياتينين والبيليروبين والدهون الكلية والكولستيرول والدهون الثلاثية والليبوبروتين منخفض الكثافة و والليبوبروتين منخفض الكثافة جدا لمجموعة الفئران المعاملة بكبريتات الألومنيوم. كما أحدثت المعاملة باستخدام كبريتات الألمنيوم ارتفاعا في تركيز الاصول الحرة، في حين انخفض نشاط الأنزيمات المضادة للأكسدة (الجلوتاثيون بيروكسيداز ، الجلوتاثيون س – ترانسفيراز ، الكاتاليز والسوبر أكسيد ديسميوتيز) ومستوي الجلوتاثيون في البلازما والكبد والكلى. من ناحية أخرى ، أدى وجود صمغ النحل (البروبوليس) مع كبريتات الألومنيوم إلى تخفيف آثاره الضارة. وخلصت هذه النتائج إلى أن االمعاملة بصمغ النحل (البروبوليس) يقلل من التسمم الكبدي والكلوى والإجهاد التأكسدي الناجم عن كبريتات الألومنيوم في الجرذان.

الكلمات المفتاحية: كبريتات الألومنيوم، صمغ النحل (البروبوليس) ؛ الانزيمات المضادة للأكسدة ، الشوارد الحرة؛ الجرذان.