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Effect of Resveratrol on Some Biochemical Parameters in Lead-intoxicated Male Wistar Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Author SMH performed the experiments, designed the study, managed the analyses of the study, performed the statistical analysis, and wrote the protocol and wrote the first draft of the manuscript. Author DNM supervised the study and managed the literature searches. Author MA supervised the study and did all correction mentioned by the reviewers. All authors read and approved the final manuscript.

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ABSTRACT

Resveratrol is a potent antioxidant, demonstrated to ameliorate adverse effects of heat stress-induced toxicity. Information on the ameliorative effect of resveratrol on heavy metals induced organ toxicity is scanty. The aim of this experiment was to investigate the effect of resveratrol on some biochemical parameters in lead-intoxicated male Wistar rats. The study employed 36 male wistar rats (150 - 250 g) divided equally into six (6) groups. The first group (negative control) was administered carboxymethylcellulose (CMC) 10 g/l body weight (BW) daily for 19 days. The second group (positive control) was administered lead acetate solution (120 mg/kg BW) daily for 2 weeks. The third group was administered lead acetate solution (120 mg/kg BW) daily for 2 weeks then treated with succimer (10 mg/kg BW) daily for 5 days. The fourth group was administered lead

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acetate solution (120 mg/kg BW) daily for 2 weeks then treated with resveratrol (200 mg/kg BW) daily for 5 days. The fifth group was administered lead acetate solution (120 mg/kg BW) daily for 2 weeks then treated with resveratrol (400 mg/kg BW) daily for 5 days. The sixth group was pretreated with resveratrol (400 mg/kg BW) daily for 5 days then administered lead acetate solution (120 mg/kg BW) daily for 2 weeks and considered as prophylactic group. All treatments were administered orally by *gavage*. The acute toxicity of Resveratrol was evaluated using Organization of European Economic Community (OECD) up and down method via oral routes in rats and the LD_{50} was found to be above 5000 mg/kg. Relative organ weights (ROW) of the animals were evaluated after euthanization. No significant ($P > 0.05$) difference in ROW of resveratrol treated groups when compared with positive control group. Blood lead levels (BLLs) and biochemical parameters were evaluated. The results showed no significant ($P > 0.05$) difference in BW of resveratrol-treated group when compared to the positive control group. Resveratrol-pretreated group showed improved BW when compared to that of the positive control group rats, although the difference was not significant ($P > 0.05$). There was significant decrease in BLLs of Resveratrol-treated groups ($P < 0.001$) when compared to both negative and positive control groups. No significant ($P > 0.05$) change was recorded for the liver function parameters and electrolytes concentration, when the resveratrol-treated rats were compared to negative and positive control groups. Resveratrol has showed an improved body and relative organ weights in lead poisoned male wistar rats. Resveratrol has significantly decrease BLLs in lead poisoned male wistar rats. The result obtained from this study suggests that resveratrol possess ameliorative effects in lead poisoning.

Keywords: Male rats; resveratrol; succimer; lead acetate; CMC.

1. INTRODUCTION

Lead is a heavy metal with a bluish-grey colour. It has a low melting point, is easily moulded and shaped, and can be combined with other metals to form alloys. For these reasons, lead has been used by humans for millennia and is widespread today in products as diverse as: pipes; storage batteries; pigments and paints; glazes; vinyl products; weights, shot and ammunition; cable covers; and radiation shielding. Tetra-ethyl lead was used extensively from the 1930 s to the 1970 s as a petrol additive to improve engine performance [1,2]. Tetra-ethyl lead has been eliminated from the petrol supplies of the majority of countries, but is still used in about nine countries [3].

Lead poisoning (also known as *plumbism, colica Pictonum, saturnism*, Devon colic, or painter's colic) is a medical condition in humans and other vertebrates caused by increased levels of the heavy metal lead in the body [4]. Lead interferes with a variety of body processes and is toxic to many organs and tissues including the heart, bones, intestines, kidneys, reproductive and nervous systems. It interferes with the development of the nervous system and is therefore particularly toxic to children, causing potentially permanent learning and behavior disorders. Symptoms include abdominal pain, confusion, headache, anemia, irritability, and in severe cases seizures, coma, and death [4].

Routes of exposure to lead include contaminated air, water, soil, food, and consumer products. Occupational exposure is a common cause of lead poisoning in adults. According to estimates made by the National Institute of Occupational Safety and Health (NIOSH), more than 3 million workers in the United States are potentially exposed to lead in the workplace [5]. One of the largest threats to children is lead paint that exists in many homes, especially older ones; thus children in older housing with chipping paint or lead dust from moveable window frames with lead paint are at greater risk. Prevention of lead exposure can range from individual efforts (e.g. removing lead-containing items such as piping or blinds from the home) to nationwide policies (e.g. laws that ban lead in products, reduce allowable levels in water or soil, or provide for cleanup and mitigation of contaminated soil, etc.).

Elevated lead in the body can be detected by the presence of changes in blood cells visible with a microscope and dense lines in the bones of children seen on X-ray. However, the main tool for diagnosis is measurement of the blood lead level. When blood lead levels are recorded, the results indicate how much lead is circulating within the blood stream, not the amount being stored in the body [4]. There are two units for

reporting blood lead level, either micrograms per deciliter (µg/dl), or micrograms per 100 grams (µg/100 g) of whole blood, which are numerically equivalent. The US Centers for Disease Control (CDC) has set the standard elevated blood lead level for adults to be 10 µg/dl of the whole blood. For children however, the number is set much lower at 5 µg/dl of blood as of [6] down from a previous 10 µg/dl [7]. Children are especially prone to the health effects of lead and as a result, blood lead levels must be set lower and closely monitored if contamination is possible [4]. The major treatments approaches are; the removal of the source of lead and chelation therapy (administration of agents that bind lead so it can be excreted) [4].

Humans have been mining and using this heavy metal for thousands of years, poisoning themselves in the process. Although lead mining is one of the oldest known work and a contributor to environmental hazards, the modern understanding of the small amount of lead necessary to cause harm did not come about until the latter half of the 20th century. No safe threshold for lead exposure has been suggested that is, there is no known amount of lead that is too small to cause the body harm.

Resveratrol (3, 5', 4-trihydroxystilbene) is a polyphenol that occurs naturally in foods and drinks made from grapes and peanuts, and also in a number of herbal remedies, both alone and as part of plant extracts. Resveratrol attracted little interest until 1992, when it was postulated to explain some of its cardioprotective properties and was thought to account in part for the so-called 'French Paradox', that is, the finding that the rate of coronary heart disease mortality in France is lower than that observed in other industrialized countries with a similar risk factor profile [8]. Since then, reports have shown that resveratrol prevents or slows the progression of a wide variety of illnesses, including cancer, cardiovascular disease [9] and ischaemic injuries [10]. Resveratrol enhances stress resistance and extends the lifespan of various organisms from yeast to vertebrates [11]; it reduces the incidence of breast cancer [12-15], cardiovascular diseases [16,17], and possesses antioxidant properties [18]. Resveratrol is a potent antioxidant, demonstrated to ameliorate adverse effects of heat stress-induced toxicity [19-21]. Information on the ameliorative effect of resveratrol on heavy metals induced organ toxicities is scanty. The present study was undertaken to assess the ameliorative effect of resveratrol on lead induced organ toxicities in rats.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Chemicals

Trans-resveratrol (60 g) of analytical grade was purchased from Candlewood Stars Incorporated, Danbury, USA (Batch Number: MR 110218). Lead acetate (product No; 10142, BDH Laboratory chemicals limited Poole, England), Carboxymethylcellulose CMC (10 g) (Product No: 27929, BDH Laboratory chemicals limited Poole, England) were obtained from the Department of Pharmacology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria. *Trans*-Resveratrol, due to its low solubility in water, was suspended in 10 g/L CMC [22].

2.1.2 Equipment

Lead Care II User's Guide, Lead Care II blood analyser, Automated Haematology Analyzer (Sysmex model 2 X-12 N, USA). Automated Biochemistry Analyzer (Selectra XL, Vital Scientific, Netherlands) Dissecting sets, syringes, and needles, spatula, regent bottles, digital weighing balance, Sensors (2 containers of 24 each), Treatment Reagent tubes, Capillaries/plungers, Transfer droppers, Calibration button, Alcohol wipes, Gauze pads, Power free Gloves, High and low controls.

2.1.3 Experimental animals

Thirty six wistar rats of male sex (weighing 150-250 g) were used for this study. The animals were housed in the Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria. They were given access to pelletized growers marsh and water *ad libitum*. The rats were acclimatized for two weeks in the home cages and environment before commencement of the experiment. All experimental protocols were in accordance with the Ahmadu Bello University research policy and of regulations governing the care and use of experimental animals (NIH publication number 85-23, revised 1996). The experiments were conducted in a quiet environment between the hours of 900 and 1600.

2.1.4 Experimental site

The experiment carried out during the hot-humid (rainy) season (August- September, 2014) at the

Department Pharmacology and Therapeutics, Ahmadu Bello University, Zaria (11º 10' N, 07º 38' E), at the elevation of 650 m above sea level, located in the Northern Guinea Savannah zone of Nigeria [23].

2.2 Experimental Procedures

2.2.1 Resveratrol preparation and administration

Trans-resveratrol (Batch Number: MR 110218), due to its low solubility in water, was suspended in 10 g/L Carboxymethylcellulose (CMC), and administered orally once daily for 14 days [24].

2.2.2 Lead acetate induction and resveratrol pretreatment

Male wistar rats were divided into six groups, of six animals each. The first group servered as negative control and animals were given carboxymethylcellulose (CMC) (10 g/L body weight) orally. The second, third, fourth and fifth groups were given lead acetate (120 mg/kg) body weight orally for 14 days and the sixth group was pretreated with resveratrol (400 mg/kg body weight) [25,26] orally for 5 days serving as prophylaxis.

2.2.3 Treatments with succimer and resveratrol

After the lead acetate induction for 14 days and resveratrol pretreatment for 5 days, the treatment commenced on the 15th day and lead acetate induction on the 5th day, where the second group was serving as the positive control (lead poisoned), the third group was treated with succimer (10 mg/kg body weight) [27,28] serving as standard drug group, the fourth group was treated with Resveratrol (200 mg/kg body weight) [27,28], the fifth group was treated with resveratrol (400 mg/kg body weight) orally for five (5) days and the sixth group was induced with lead acetate (120 mg/kg body weight) orally for 14 days serving as prophylactic group [29].

2.3 Methods

2.3.1 Acute toxicity test of resveratrol

The limit test dose of 5000 mg/kg was used as stipulated in Organization for Economic Cooperation Development (OECD) guidelines [30]. Three Male rats, each sequentially dosed at intervals of 48 h, were used for the test. The animals were observed individually for acute toxicity signs and behavioural changes 1 h post-dosing, 24 h and at 48 h for 14 days.

2.3.2 Induction of lead toxicity and measurement of Blood Lead Level (BLL)

In the six groups above (2.2.3), animals were assessed for clear signs of lead toxicity viz., weakness or aggressiveness, food refusal, loss of weight, diarrhea, discharge from eyes and ears, noisy breathing and mortality. Measurements of blood lead level were carried out according to procedure provided by the Lead Care II Blood Lead Test kit manufacturers (Michigan Regional Laboratory System). The CDC laboratory first analyzed samples with ICP-MS [31] using a modification of a method of [32] for analyses of metals in biological matrices. If sufficient blood remained, samples were then analyzed on LC II. Samples whose LC II results were > 65 µg/dL (reported as “HI” on the LC II) were prepared and analyzed using the blood dilution method. The goal of the dilution method was to dilute the sample to within the operating range of the LC II (3.3 – 65 µg/dL) without changing the matrix of the blood and reagent-mixture against which the analyzer is calibrated. The method presented here required the diluent to human blood or animal blood sample verified to have a BLL < 3.3 µg/dL (reported on the analyzer as “LOW”) using standard LC II analytic methods on a calibrated machine using the test kit materials [33].

2.3.3 Determination of relative organ weights in lead-induced toxicity in male wistar rats

Animals were weighed daily using a Mettler weighing balance (Mettler Toledo Type BD6000, Greifensee, Switzerland). At the end of treatment duration (5 days), animals were fasted and euthanized on day 6 with chloroform. The essential organs including the liver, kidneys, spleen, heart, lungs, brain and testes, were surgically harvested and weighed. Relative Organ Weight (ROW) was then calculated as follows:

ROW = (Absolute organ weight (g) / Body weight of rat on sacrifice day (g)) x 100

2.2.4 Determination of effect of resveratrol on biochemical parameters in lead-induced toxicity in wistar rats

Second portion (3 – 5 mls) of the blood sample from each animal after euthanasia was

dispensed into plain bottles, allowed to clot and then centrifuged. The sera was separated and used for evaluation of biochemical parameters, which include alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) levels, total and conjugated bilirubin, serum urea and creatinine using Automated Biochemistry Analyzer (Selectra XL, Vital Scientific, Netherlands) and kits obtained from ELITech reagent kits, Netherlands.

2.2.5 Statistical Analysis

Data obtained were expressed as mean ± SEM. Statistical analysis was carried out using SPSS version 20 and all the analysis were done using one way ANOVA followed by Turkey's post hoc test for multiple comparisons. Values of $P < 0.05$ were considered significant.

3. RESULTS

3.1 Effect of Resveratrol on Body Weights of Lead-induced Toxicity in Male Wistar Rats

There was no statistically significant ($P > 0.05$) difference in body weights in resveratrol-treated groups when compared to both negative and positive control groups. But there was decrease in body weights in positive control group when compared to resveratrol-treated groups (Table 3.1).

3.2 Effect of Resveratrol on Relative Organ Weights in Lead-induced Toxicity in Male Wistar Rats

There was no statistically significant ($P > 0.05$) difference in relative organ weights in Resveratrol-treated groups when compared to both negative and positive control groups. But there is decreased in relative organ weights in positive control group when compared to Resveratrol-treated groups (Figs. 3.1 and 3.2).

3.3 Effect of Resveratrol on Blood Lead Level (BLLs) in Lead-induced Toxicity in Male Wistar Rats

There was a statistically significant ($P < 0.001$) decrease in the BLLs in Resveratrol-treated groups when compared to negative (carboxymethylcellulose 10 g/l) and positive (lead acetate 120 mg/kg) control groups (Fig.3.3).

3.4 Effect of Resveratrol on Serum Kidney Function in Lead-induced Toxicity in Male Wistar Rats

There was no statistically significant ($P < 0.05$) difference in Urea and Creatinine levels in Resveratrol-treated groups when compared to negative (carboxymethylcellulose 10 g/l) and positive (lead acetate 120 mg/kg) control groups (Table 3.2).

3.5 Effect of Resveratrol on Serum Electrolyte Levels in Lead-induced Toxicity in Male Wistar Rats

There is no statistically significant ($P < 0.05$) difference in Sodium, Potassium, Chloride and Bicarbonate levels (mmol/l) concentration in Resveratrol-treated groups when compared to negative (carboxymethylcellulose 10 g/l) and positive (lead acetate 120 mg/kg) control groups (Table 3.3).

4. DISCUSSION

Lead is a ubiquitously found environmental and industrial pollutant that has been detected in nearly all phases of environment and biological system. Its persistence in human and animal tissues has quite often been associated with considerable health risks (Juberg et al. 1997). This study was designed primarily to assess the possible ameliorative effects of resveratrol on lead induced organ toxicity in male wistar rats.

Table 3.1. Effect of resveratrol on body weights in lead-induced toxicity in male wistar rats

Treatments (mg/kg)	Day 1	Day 7	Day 20
CMC (10 g/l)	191.00±10.28	201.50±11.37	209.50±10.80
LA (120)	234.67±07.41	227.83±07.50	219.00±07.72
LA (120)+S (10)	243.33±03.78	216.17±11.22	234.33±09.70
LA (120)+R (200)	216.00±12.96	207.00±13.10	230.50±08.26
LA (120)+R (400)	165.83±00.17	152.83±01.45	185.00±02.25
R (400)+LA (120)	152.50±00.89	159.17±01.42	158.83±01.45

Values are presented as means ± SEM (n=6). LA- Lead acetate, CMC-Carboxymethylcellulose, R-Resveratrol, S- Succimer

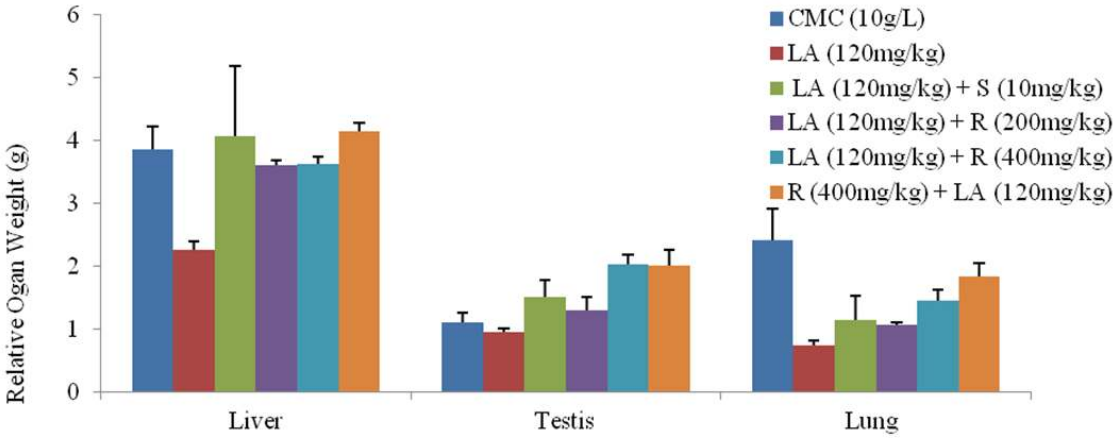

Fig. 3.1. Effect of resveratrol on relative organ weights in lead-induced toxicity in male wistar rats (n = 6)

Values are presented as means ± SEM. CMC- Carboxymethylcellulose, LA- Lead acetate, R-Resveratrol, S- Succimer

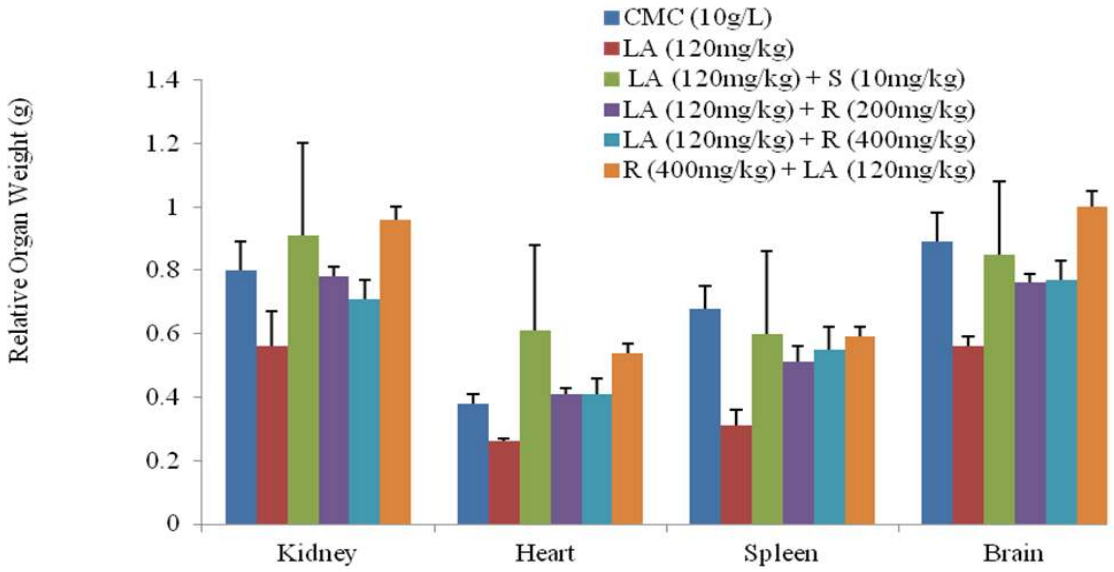

Fig. 3.2. Effect of resveratrol on relative organ weights in male rats (n = 6)

Values are presented as means ± SEM. CMC- Carboxymethylcellulose, LA- Lead acetate, R- Resveratrol, S- Succimer

Table 3.2. Effect of resveratrol on serum kidney function in lead-induced toxicity in male wistar rats

Treatments	Urea levels (mmol/l)	Creatinine levels (mmol/l)
CMC (10 g/L)	6.88±0.57	86.50±8.39
LA (120 mg/kg)	9.10±0.00	94.67±3.67
LA (120 mg/kg) + S (10 mg/kg)	5.28±1.00	80.00±4.17
LA (120 mg/kg) + R (200 mg/kg)	4.48±0.82	63.60±5.96
LA (120 mg/kg) + R (400 mg/kg)	7.83±1.85	86.67±3.88
R (400 mg/kg) + LA (120 mg/kg)	6.83±1.07	85.25±5.53

Values are presented as Mean ± SEM, CMC-Carboxymethylcellulose, LA- Lead acetate, R-Resveratrol, S- Succimer

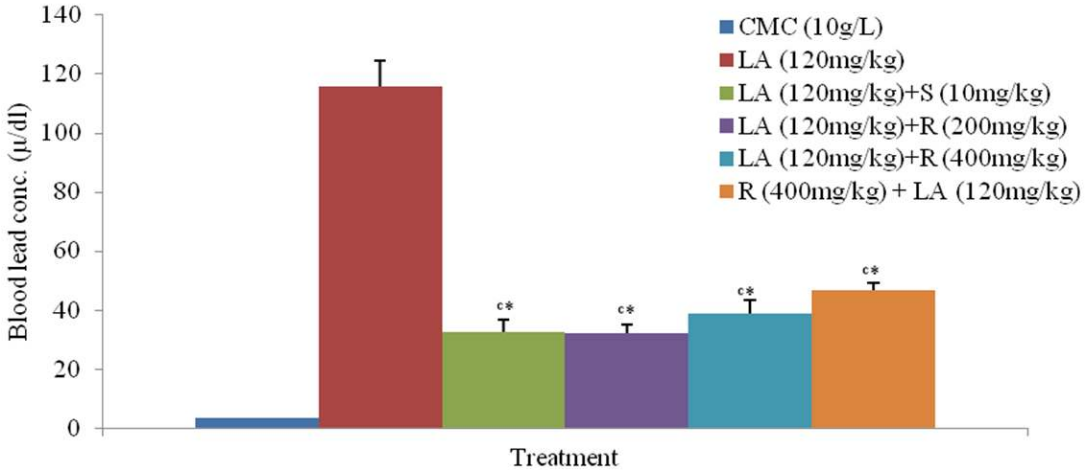

Fig. 3.3. Effect of resveratrol on blood lead levels in lead-induced toxicity in male wistar rats

Values are presented as means ± SEM. ^{c} = P < 0.001 compared to CMC (10 g/L) and Lead acetate (120 mg/kg). One way ANOVA followed turkey test. CMC-Carboxymethylcellulose, LA-Lead acetate, S-Succimer, R-Resxeratrol*

Table 3.3. Effect of resveratrol on serum electrolytes levels lead-induced toxicity in male wistar rats

Treatments	Sodium levels (mmol/l)	Potassium levels (mmol/l)	Chloride levels (mmol/l)	Bicarbonate levels (mmol/l)
CMC (10 g/L)	140.67±2.79	4.52±0.13	105.83±3.51	23.17±0.79
LA (120 mg/kg)	135.67±7.84	17.67±0.67	99.33±9.68	21.67±0.88
LA (120 mg/kg) + S (10 mg/kg)	135.40±4.23	4.40±0.43	96.40±3.82	23.60±0.51
LA (120 mg/kg) + R (200 mg/kg)	134.40±6.21	4.26±0.45	98.20±7.25	23.00±0.89
LA (120 mg/kg) + R (400 mg/kg)	130.50±2.93	3.95±0.28	93.50±3.14	22.33±0.84
R (400 mg/kg)+ LA (120 mg/kg)	142.00±5.43	16.88±12.04	102.75±3.82	24.75±1.49

Values are presented as Mean ± SEM, CMC-Carboxymethylcellulose, LA- Lead acetate, R-Resveratrol, S- Succimer

The results of the acute toxicity study indicate that the median lethal dose (LD_{50}) of the Resveratrol was more than 5000 mg/kg. The limit test is primarily used in situations where the investigator has information indicating that the test material is likely to be non-toxic or of low toxicity [30]. This finding, therefore, suggests that the Resveratrol at the limit dose tested is essentially non-toxic and safe in oral formulation. This result is in line with previous data [34-36].

Organ weight can be the most sensitive indicator of an effect of an experimental compound, as significant differences in organ weight between treated and untreated (control) animals may occur in the absence of any morphological changes (Bailey et al., 2004). The toxic signs observed in positive control group in the present experiment were similar to that of findings of other researchers such as [37-39]. The lost in the body and relative organ weights recorded in the positive control group might have been as a result of loss of appetite and gastrointestinal disruption caused by the lead acetate. This harmful effect of lead on the body weight gain was reduced relative to the increase of resveratrol dose as observed in this experiment. This showed that resveratrol has affected their appetite and there was a significant effect on catabolism of the male wistar rats.

The positive control group blood lead Samples whose Lead Care II analyzer machine results were greater than 65 µg/dL was reported as

"High level "on the Lead Care II and were prepared and analyzed using the blood dilution method for the actual values. Lowering of BLLs in resveratrol-treated groups is due to antagonistic effect of resveratrol on lead. However, the exact nature of this antagonism which might include chelation would require further evaluation. Group 6 also showed low BLLs compared to group 2 which may be as a result of the pretreatment with resveratrol (400 mg/kg) before the lead acetate administration. Therefore, resveratrol may likely have protective effect against lead poisoning and this protection appears to be dose related.

In the current study, the serum urea concentration was high in positive control group of the male wistar rats even though it wasn't significant. This suggested that the sub-acute administration of lead acetate to male wistar rats evoked renal impairment since the kidney primarily eliminates urea in the urine [40] and it was associated with glomerular and renal tubular degeneration, partially evoked by oxidative stress. Similarly, some researchers [41,42] reported increased urea concentration in rats exposed to sub-acute lead acetate intoxication. It is postulated in this research that the increased urea concentration recorded in positive control group may be attributed to induction of renal damage by the sub-acute treatment of male wistar rats with lead acetate. On the contrary, groups 4 and 6 male wistar rats evoked decreased urea concentration than positive control group and this may be a demonstration of its nephroprotective role of resveratrol. This finding was in line with the findings of [43,44].

Moreover, the elevated serum creatinine concentration in positive control group may be an indication of renal damage. This finding was in line with earlier findings [45-47]. About 50% of kidney function must be lost before a rise in the serum concentration of creatinine can be detected [48]. Therefore, urea, uric acid and creatinine could be considered as suitable prognostic indicators of renal dysfunction in case of lead exposure [49,50]. However, glomerular function was still intact since the level of creatinine did not differ from the negative control group in resveratrol-treated groups.

Electrolytes are molecules that are electrically charged, which help move nutrients into and waste products out of the body's cells. They maintain healthy water balance and help stabilize the body's acid level. The data presented in this research suggests that alteration in sodium levels are caused by kidney disease and adrenal disease, diuretics, and at times conditions that cause fluid to build up in the body. The most common cause of high sodium is dehydration [51,52]. The balance of sodium, chloride, potassium and bicarbonate ions in the body is a good indicator of how well the kidneys and heart are functioning. Chloride levels fluctuate with sodium levels. Low chloride levels can occur as a result of chronic lung disease, prolonged vomiting, and metabolic alkalosis. High chloride levels can be due to kidney disease as well as dehydration. Change in serum chloride indicates an alteration in status and/or acid-base balance [53]. Acid-base balance is partly regulated by renal production and excretion of bicarbonate ions. Carbon dioxide in the form of bicarbonate is excreted and reabsorbed by the kidneys. High or low bicarbonate levels may signify acid/base or electrolyte imbalance often due to dehydration or drinking too much water. The primary regulators of bicarbonate are the proximal tubules [53]. From the data revealed, the reduction in serum sodium, bicarbonate and chloride may be as result of tubular damage and necrosis as evidenced in the histopathological findings.

5. CONCLUSION

In conclusion, the induction of lead acetate in male wistar rats caused serious toxicopathological change in the internal organs of the animals. Resveratrol has showed an improved body and relative organ weights in lead poisoned male wistar rats. Resveratrol has significantly decrease BLLs in lead poisoned male wistar rats. These suggest that, resveratrol contain pharmacological activities that is useful in treatment of lead poisoning.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No.85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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