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Haematological effects of ethanolic extract of *Blepharis linariifolia* alone or co-administered with aluminum chloride in rats

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Abstract
Background and objectives: The indigenous medicinal plants in Sudan form an important component of the natural wealth of the country. Most of these plants have been used indiscriminately by many local populations for managing various diseases without actually knowing how relief is brought about or its safety/toxicity risks. The effect of oral administration of *Blepharis linariifolia* ethanolic extract alone and/or co-administered with aluminium chloride at different doses on haematological profile in white albino rats was investigated in this study.
Materials and Methods: The animals were divided into five groups of five animals each. Group A: Control, Group B, C were administered orally by $AlCl_3$ alone (0.5 mg/Kg BW), plant extract (400 mg/ml), plant extract (200 mg/ml), respectively, throughout the experiment which continued for consecutive 14 days and 28 days Group E was administered with plant extract (400 mg/ml) concurrently with AlCl3 for consecutive 14 days and 28 days. The blood parameters measured were: White Blood Cells count (WBCs), Red Blood Cells count (RBCs), Haemoglobin concentration (Hb), Haemocrit value (HCT), Mean Cell Volume (MCV), Mean Cell Haemoglobin (MCH), Mean Cell Haemoglobin Concentration (MCHC), Platelets (PLT) and Lymphocytes (LYM).
Results: Treatment of rats (B group) with $AlCl_3$ after 14 days caused significant difference at $P<0.05$ and $P<0.01$ in total RBC count, Hb, HCT and MCV. Whereas after 28 days caused a significant difference in WBC and MCV. Treatment of rats (C group) with 400 mg/ml/Kg BW of plant extract after 14 and 28 days caused significant difference at $P<0.05$ in the WBC count and Hb values relative to their respective control. Administration of rats (D group) with 200 mg/ml of plant extract plus $AlCl_3$ did not produce any significant change ($P<0.05$) on the RBC and factors relating to it (Hb,HCT,MCV,MCH and MCHC) on 14 days. Interestingly, administration of the plant extract 200 mg/ml plus $AlCl_3$ produced significant alterations only in the platelets. Administration of 200 mg/ml plant extract plus AlCl3 for 28 days produce significant change ($P<0.05$) on the RBC, Hb and HCT.There was no significant difference ($P<0.05$ and $P<0.01$) after treatment with 400mg/ml extract plus $AlCl_3$ for 14 days between the two control group and the treated (E group) for RBC, Hb, HCT, MCV, MCH, MCHC and LYM, and at $P<0.01$ for WBC. The PLT values were significantly different at $P<0.05$ and $P<0.01$ between the control and treated group after 14 and 28 days.
Conclusion: uptake of ethanolic extract of *B. linariifolia* alone or co-administered with $AlCl_3$ had mitigated aluminum chloride – induce anemia and raised the values of blood indices of anemia, almost, to their normal levels.

Keywords: haematological profile; toxicity; *Blepharis linariifolia;* aluminum chloride; rats

1. Introduction
Many people are relying on herbal medicines for health care, because the other treatment options available are more expensive and are often associated with serious side effects. Therefore, there should be scientific documentation of information on the safety/toxic risk potentials of plants. One of such plants is *Blepharis linariifolia*. It has been widely used by many localities in Africa including Sudan in venereal diseases such as syphilis. Various workers had shown that haematological investigations among others could be used to evaluated the health status of an animal (de Gruchy, 1976) [1].
The aim of the present research work were to assess the effect of ethanolic extract of *Bleparis linariifolia* (200 mg/ml and 400 mg/ml) on the treatment of aluminum chloride – induced anemia in white albino rats when administered for 14 and 28 days.

2. Materials and Methods
2.1 Materials
2.1.1 Animals
White albino rats weighing between 100-120 g were used for the studied experiments. They were housed in standard rat cages under laboratory conditions with 12:12 h light /dark cycle at 30 + 2 C. The animals were allowed to acclimatize for 2 weeks. The experiment was conducted in accordance with the guidelines of the US National Institute of Health (NIH) on the care and use of laboratory animals.

2.1.2 Plants
The whole plant of *Blepharis linariifolia* were collected in September 2014 from Omdurman North, Khor Omer. Plant was

washed and dried in shades. The dried plant was blended into powder and was stored in clean container prior extraction.

2.2 Methods

2.2.1 Plant Extraction

One hundred grams of dried whole plant of *B. linariifolia* were extracted by Soxhlet Apparatus for 6 hours with 70% ethanol. The extract was filtered and the solvent was evaporated with Rota-evaporator and then was dried at room temperature for two weeks.

2.2.2 Blood collection

Two ml of blood samples were collected by using haematocrit capillary tubes from retro-orbital plexus of each rat (Khanna *et al.,* 1992). Each blood sample was placed in ethylene diamine tetra-acetic acid (EDTA) container.

2.2.3 The Experimental Protocol

The animals were divided into five groups of five animals each. Group A: Control. Group B (denoted B-1 and B-2) was administered orally by $AlCl_3$ (0.5 mg/Kg BW) as stated by Weber (2002) throughout the experiment which continued for consecutive 14 days (B-1) and 28 days (B-2). Group C (denoted C-1 and C-2) was administered orally by Plant extract (400 mg/ml) for consecutive 14 days (C-1) and 28 days (C-2). Group D (denoted D-1 and D-2) was administered with plant extract (200 mg/ml) concurrently with $AlCl_3$ for consecutive 14 days and 28 days. Group E (denoted E-1 and E-2) was administered with plant extract (400 mg/ml) concurrently with $AlCl_3$ for consecutive 14 days and 28 days.

Collected blood were used for the measurement of blood parameters using automated Haematology Analyzer (Sysmex Apparatus of the type 8999). The blood parameters measured were: white blood cells count (WBCs), red blood cells count (RBCs), haemoglobin concentration (Hb), haemocrit value (HCT), mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), platelets (PLT) and lymphocytes (LYM).

2.2.4 Statistical Analysis

Student t test was used for comparison between (mean ± standard deviation) values of $AlCl_3$ – treated group and control group and each of them with the mean values of the group treated with $AlCl_3$ plus *B. linariifolia* (400 mg/ml), the group provided with $AlCl_3$ plus *B. linariifolia* (200 mg/ml) and the group provided with *B.linariifolia* (400 mg/ml). The significance is taken at $P<0.05$ and $P<0.01$. t-test parameter was performed using SPSS 20.0 Software for Windows.

3. Results and Discussion

The haematological effect of ethanolic extract of *B. linariifolia* was evaluated in male albino rats during 14 and 28 days administrations of aluminum chloride alone (0.5 mg/ml /Kg bw), plant extract at 400 mg/ml /Kg bw, 200 mg/ml plus aluminum chloride and 400 mg/ml plus aluminum chloride, orally. Parameters evaluated include WBC, RBC, Hb, HCT, MCV, MCH, MCHC, PLT and LYM.

3.1 The effect of $AlCl_3$ alone on haematological parameters in albino rats

The effect of $AlCl_3$ alone on haematological parameters of albino rats after treatment for 14 and 28 days are shown in the Table 1. Treatment of rats (B-1 group) with $AlCl_3$ alone after 14 days caused significant difference at $P<0.05$ and $P<0.01$ in total RBC count, Hb, HCT and MCV. The oral administration of $AlCl_3$ alone after 28 days (B-2 group) caused a significant difference ($P<0.0$ and $P<0.01$) in WBC and MCV. Also caused a significant difference ($P<0.05$) in Hb, MCH and MCHC.

Table 1: The effect of $AlCl_3$, plant extract and $AlCl_3$ plus plant extract on haematological parameters in male rats

Parameters	Control	AlCl3 alone After 14 days	AlCl3 alone After 28 days	400 mg/ml extract after 14 days	400 mg/ml extract after 28 days	AL Cl3 plus 200 mg/ml extract after 14 days	AlCl3 plus 200 mg/ml extract after 28 days	AL Cl3 plus 400 mg/ml extract after 14 days	AlCl3 plus 400 mg/ml extract after 28 days
WBC ($X10^3$/ul)	6.44±2.997	8.66±2.436	12.32±00*,**	10.52±3.01*	11.6±3.3176*	10.92±3.973*	5.2±5.069	9.2±1.56*	8.48±1.633
RBC ($X10^6$/ul)	7.87±0.304	5.52±0.187*,**	8.04	8.758±0.866*,**	8.44±0.63	7.624±0.30	5.83±1.786*	7.818±0.369	7.55±1.1466
Hb (g/dl)	13.46±0.21	12.74±0.187*,**	14.94*	14.18±0.432*,**	14.525±0.574*,**	13.2±0.18	11.234±0.106*	13.16±0.677	13.34±2.131
HCT (%)	44.14±1.60	41.34±1.72*,**	46.96*	47.44±1.98*,**	47.125±3.0598	43.05±1.771	32.97±10.152*	44.375±1.269	42.96±7.158
MCV (fl)	56.1±0.977	59.48±1.333*,**	58.4*,**	54.18±1.25*	55.9±0.868	56.24±1.632	56.5±1.916	55.9±1.15	56.76±1.443
MCH (pg)	17.14±0.69	18.34±0.372	18.58	16.22±0.63*	17.28±0.834	17.18±0.554	17.07±2.098	16.95±0.580	17.64±5.235
MCHC (g/dl)	30.52±1.13	30.84±0.680	31.82	29.92±0.687	30.85±1.60	30.58±0.759	31.57±0.777	30.28±0.576	31.1±0.418
PLT ($X10^3$/ul)	1083±192.283	950.4±59.584	1118	889.4±273.54	1067.75±99.28	829.4±98.865*	622.7±500.5	683.8±146.64*,**	739.4±72.3*
LYM (%)	48.92±7.09	41.66±7.618	44.66	52.52±7.84	44.575±11.092	46.86±9.755	45.75±19.163	41.22±8.963	46.1±4.729

Values are expressed as mean + SD, N=5, * for P=0.05 and ** for P= 0.01

3.2 The effect of *Blepharis linariifolia* extract (400 mg/ml) on haematological parameters in albino rats

The effect of plant extract at 400 mg/ml/Kg BW on the haematological parameters of albino rats after treatment for 14 and 28 days are shown in the Table 2. Treatment of rats (C-1 group) with 400 mg/ml/Kg BW of plant extract after 14 days caused significant difference at $P<0.05$ in the WBC, RBC, Hb, HCT, MCV and MCH values relative to their respective control, while treated rats were showed no significant ($P<0.05$) change in MCHC, PLT and LYM values relative to their respective control. Treatment of rats for 28 days caused significant ($P<0.05$) difference in the WBC and Hb values relative to their respective control, while no significant ($P<0.05$) change in RBC, HCT, MCV, MCH,MCHC,PLT and LYM values relative to their respective control.

Table 2: The effect of the $AlCl_3$ alone on haematological parameters in albino rats compared to representive control (A Group) when administered daily for 14 and 28 days

Blood Parameter	B-1 Group				B-2 Group			
	Change	Change %	P=0.05	P=0.01	Change	Change %	P=0.05	P=0.01
WBC	Increment	34.4	NS	NS	Increment	91.3	S	S
RBC	Decrement	29.9	S	S	Increment	2.2	NS	NS
Hb	Decrement	5.3	S	S	Increment	11.0	S	NS
HCT	Decrement	6.3	S	S	Increment	6.4	NS	NS
MCV	Increment	6.0	S	S	Increment	4.1	S	S
MCH	Increment	7.0	NS	NS	Increment	8.4	S	NS
MCHC	Increment	1.0	NS	NS	Increment	4.3	S	NS
PLT	Decrement	12.2	NS	NS	Increment	3.2	NS	NS
LYM	Decrement	14.8	NS	NS	Decrement	8.7	NS	NS

3.4 The effect of *Blepharis linariifolia* extract (200 mg/ml) plus $AlCl_3$ on haematological parameters after treatment of rats for 14 and 28 days

Administration of 200 mg/ml of plant extract plus $AlCl_3$ did not produce any significant change (P<0.05) on the RBC and factors relating to it (Hb, HCT, MCV, MCH and MCHC) on 14 days investigated rats Table 3. Interestingly, administration of the plant extract 200 mg/ml plus $AlCl_3$ produced significant alterations in the platelets. Administration of 200 mg/ml plant extract plus $AlCl_3$ produce significant change (P<0.05) on the RBC, Hb and HCT, and did not produce any significant change (P<0.01) on the all blood parameters and on WBC, MCV, MCH, MCHC, PLT and LYM at P<0.05 on 28 days of investigated rats.

Table 3: The effect of the *Blepharis linariifolia* extract (400 mg/ml) on haematological parameters in albino rats compared to representive control (A Group) when administered daily for 14 and 28 days

Blood Parameter	C-1 Group				C-2 Group			
	Change	Change %	P=0.05	P=0.01	Change	Change %	P=0.05	P=0.01
WBC	Increment	63.4	S	NS	Increment	80.1	S	NS
RBC	Increment	11.3	S	S	Increment	7.2	NS	NS
Hb	Increment	5.3	S	S	Increment	7.9	S	S
HCT	Increment	7.5	S	S	increment	6.8	NS	NS
MCV	Decrement	3.4	S	NS	decrement	0.4	NS	NS
MCH	Decrement	5.4	S	NS	Increment	0.8	NS	NS
MCHC	Decrement	2.0	NS	NS	Increment	1.1	NS	NS
PLT	Decrement	17.9	NS	NS	decrement	1.4	NS	NS
LYM	Increment	7.4	NS	NS	Decrement	8.9	NS	NS

Table 4: The effect of the *Blepharis linarifolia* extract (200 mg/ml) plus $AlCl_3$ on haematological parameters in albino rats compared to representive control (A Group) when administered daily for 14 and 28 days

Blood Parameter	D-1 Group				D-2 Group			
	Change	Change %	P=0.05	P=0.01	Change	Change %	P=0.05	P=0.01
WBC	Increment	69.6	S	NS	decrement	19.3	NS	NS
RBC	Decrement	3.2	NS	NS	decrement	25.9	S	NS
Hb	Decrement	1.9	NS	NS	decrement	16.6	S	NS
HCT	Decrement	2.5	NS	NS	decrement	25.3	S	NS
MCV	increment	0.2	NS	NS	increment	0.7	NS	NS
MCH	Increment	0.2	NS	NS	decrement	0.4	NS	NS
MCHC	Increment	0.2	NS	NS	increment	3.4	NS	NS
PLT	Decrement	23.4	S	NS	decrement	42.5	NS	NS
LYM	Decrement	4.2	NS	NS	decrement	6.5	NS	NS

Table 5: The effect of the Blepharis linariifolia extract (400mg/ml) plus $AlCl_3$ on haematological parameters in albino rats compared to representive control (A Group) when administered daily for 14 and 28 days

Blood Parameter	E-1 Group				E-2 Group			
	Change	Change %	P=0.05	P=0.01	Change	Change %	P=0.05	P=0.01
WBC	Increment	42.9	S	NS	increment	31.7	NS	NS
RBC	Decrement	0.6	NS	NS	decrement	4.1	NS	NS
Hb	Decrement	2.2	NS	NS	decrement	0.9	NS	NS
HCT	Increment	0.5	NS	NS	decrement	2.7	NS	NS
MCV	decrement	0.4	NS	NS	increment	1.2	NS	NS
MCH	Decrement	1.1	NS	NS	Increment	2.9	NS	NS
MCHC	Decrement	0.8	NS	NS	Increment	1.9	NS	NS
PLT	Decrement	36.9	S	S	decrement	31.7	S	NS

LYM	Decrement	15.7	NS	NS	decrement	5.8	NS	NS

3.5 The effect of *Blepharis linariifolia* extract (400 mg/ml) plus $AlCl_3$ on haematological parameters in albino rats

There was no significant difference ($P<0.05$ and $P<0.01$) between the two control groups and the treated group for RBC, Hb, HCT, MCV, MCH, MCHC and LYM, and at $P<0.01$ for WBC on 14 day. The PLT values were significantly different at $P<0.05$ and $P<0.01$ between the control and treated group. Administration of 400 mg/ml plant extract plus $AlCl_3$ did not produce any significant change ($P=0.5$ and $P=0.01$) in all investigated blood parameters (except PLT at P0.05) on 28 day.

In the present study, the decrease MCV, MCH and MCHC, in rats administered $AlCl_3$ alone refer to the type of anemia (microcytic - hypochronic anemia).

Jung-Hoon Jea *et al*., (2005) [2] studied the decline in RBC count, hemoglobin concentration and HCT presumably reflects erythrocyte hemolysis and due to either an increase in the rate at which hemoglobin concentration may be destroyed or a decrease in the hemoglobin synthesis. Decrease in hematocrit is attributable to the reduction in RBC count caused either destruction or reduction in size.

As inferred from other reports, two mechanisms were suggested for the prevention of aluminum toxicity by *B. linariifolia* : First the plant extract inhibited or reduced Al absorption from intestine, and the second: aluminum overload might modulate gastrointestinal iron absorption and hinder the cellular uptake and use of iron for hemoglobin synthesis (Cannata *et a*., 1991; Ganchev *et al*., 1998) [3, 4], and *B. linariifolia* corrected this toxic effect of Al by enhancing iron absorption, cellular uptake and use of iron for hemoglobin synthsis. The proposed mechanisms appear to involve inhibition of heme synthesis, either by inhibition of enzyme activity or interference with iron incorporation or utilization (Kaiser and Schwartz, 1985; Ganchev *et al*., 1998; Han *et al*., 2000) [5, 4, 6].

In a different studies, it were confirmed Al overload accumulation in all tissue to be the cause of anemia and it had led to AL-Zheimer s disease when accumulated in the tissue of the brain. Furthermore, disturbances in the distribution pattern of trace elements: zinc, copper and iron together with lipid peroxidation in plasma and erythrocytes were also suggested as a mechanism of aluminum-induced anemia in rats (Guo *et al.*, 2004) [7].

The calculated blood indices MCV, MCH and MCHC have a particular importance in anaemia diagnosis in most animals (Coles, 1986) [8]. The non- significant effects on these indices relating to RBC suggest that there was no effect on the average size of RBC (microcytes) and also in the haemoglobin weight per RBC. This implies that the plant extract 200 mg/ml plus $AlCl_3$ does not possess any potential of including anemia throughout the 28 days period of administration.

Other indices that relate to WBCs were significantly altered; an indication of pathological condition which may imply challenge on the immune system by the plant extract 200 mg/ml plus $AlCl_3$. The significant increase in WBC following the administration of the plant extract /$AlCl_3$ indicates a boost in the immune system. Such effects may also be due to increase in vascular permeability. The non-significant effect of the plant extract 200 mg/ml plus $AlCl_3$ on the RBC and indices relating to it (Hb, PCV, MCV, MCH and MCHC) throughout the experimental period is an indication that there was no destruction of matured RBC s and no change in the rate of production of RBC s (erythropoiesis). It further shows that the extract /$AlCl_3$ does not have the potential to stimulate erythropoietin release in the kidney, which is the humoral regulator of RBC production (Polenakovic and Sikole, 1996; Sanchez-EL-Sner *et al*., 2004) [9, 10].

The non-significant effect on the RBC and Hb also implies that there was no change in the oxygen-carrying capacity of the blood and amount of oxygen delivered to the tissues following the extract /$AlCl_3$ administration since RBC and Hb are very important in transferring respiratory gases (de Gruchy, 1976) [1].

The results obtained from the present study, referred to the type of anemia caused by $AlCl_3$ exposure in male rats, which is microcytic - hypochromic anemia. Anemia that is partially due to a shortened life span of circulating erythrocytes and reduced RBCS production in bone marrow. This Shortened RBCS survival and expected premature elimination of circulating erythrocytes, however, could be explained by much mechanism, one of these is the oxidative stress caused by $AlCl_3$ in increase production of free radicals, decrease catalase activity, and decrease the erythrocyte ATP concentration (AL-Hashem, 2009; Newairy *et al*., 2009) [11, 12].

All or some of these deleterious effects of $AlCl_3$ on RBCs membrane caused increased membrane fragility, increased RBCs destructions. The reduced level of hemoglobin content in rats administered $AlCl_3$ can be associated with RBCs hemolysis which confirmed by reduced RBCs count in the present study, or disturbances in heme biosynthesis.

Aluminum-induced haematolotgical alterations leading to microcytic hypochromic anemia in albino rats of this study are similar to previous reports on the same blood parameters in rats (Zaman *et al*., 1993; Chmielnicka *et al*., 1994; Osman *et al*., 2012) [13, 14, 15].

4. Concluson

The effect of the ethanolic extracts of B.linarifolia on haematological parameters was compared to that of control group. Uptake of ethanolic extract of *B. linariifolia* alone or co-administered with $AlCl_3$ had mitigated aluminum chloride – induce anemia and raised the values of blood indices of anemia, almost, to their normal levels. The findings of this study could provide satisfactory pre-clinical evidence of safety to launch clinical trial on standardized formulation of plant extracts. Bioassay-guided fractionation and purification lead to isolation of active ingredient which can help in production of compounds with improved characteristics.

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