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Toxicity of Aqueous Extract of *Senna alexandrina* Miller Pods on Newzealand Rabbits

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Authors' contributions

This work was carried out in collaboration between all authors. IBE performed the chemical analysis, managed the literature searches and wrote the first draft of the manuscript. AIY managed the analysis of the study. SMAEB and SMY wrote the protocol, designed the study, performed the statistical analysis and managed the discussion. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: The herbal extract of *Senna alexandrina* pods is used commonly to treat constipation. The study was designed to evaluate the effect of oral administration of aqueous extract of *S. alexandrina* pods at varying doses on Newzealand rabbits for 2 and 4 weeks.
Study Design: Biochemical and cross-sectional study.
Place and Duration of Study: Botany Department, Faculty of Science and Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine Science, University of Khartoum.
Methodology: Rabbits of either sex were divided into four groups of 8 animals each. Group I served as control and groups II, III and IV were orally treated with doses of 50, 100 and 300 mg/kg body weight for up to 4 weeks. Toxicity was evaluated using biochemical, hematological and histopathological assays.
Results: No significant pathological changes were observed in rabbits given a dose of 50 mg/kg/day. However, at higher doses alterations in the levels of blood haematological

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parameters, transaminases, creatinine, albumin and globulin were observed; such changes are likely to occur due to spleen, hepatic and renal injury, which was confirmed by histopathological analysis.
Conclusion: The data suggest that administration of the aqueous extract of *S. alexandrina* pods at 50 mg/kg/day is not toxic. The observed toxic effect might be due to higher doses and/or frequency of administration. Although in traditional medicine the extract is administrated at a low dose, the results suggest the necessity of standardization of the drug.

Keywords: Senna; rabbits; serum; haematology; histopathology; safety.

1. INTRODUCTION

Plants commonly used in traditional medicine are assumed to be safe. This safety is based on their long usage in the treatment of diseases according to knowledge accumulated over centuries. Although limited evidence suggests that adverse effects associated with the use of herbal drugs are less likely to occur than with conventional drugs, they do occur though usually mild and only affecting a small number of people. Recent evidence suggests that some of the herbs considered to be safe over the last many decades have proven to be associated with health hazards. Herbal remedies can act either as agonists or antagonists that potentiate some drug therapies (George, 2011). Adverse reactions may also result from irrational usage, such as excess dosage. Therefore, with the growing need for safer drugs more attention has been drawn to their quality, efficacy and standard formulations.

S. alexandrina Miller. (Syn. *Cassia senna*, Family Caesalpiniaceae), cultivated in the Sudan and was formerly exported through Alexandria is mentioned in all famous herbals of the 15th and 16th century and is described in the last editions of the pharmacopoeias of countries all over the world (WHO, 1999). The pods and leaves are considered as one of the most used laxatives (Lemli, 1988; Migahid, 1978). The laxative quality of senna is due to the presence of sennosides A and B in its leaves and pods, which were isolated in pure form by Stoll et al. (1950).

Senna, can have adverse effects on the heart because regular consumption is reported to deplete the body of potassium causing fatalities. Other adverse reactions include grand mal seizures, circulatory failure, hypertension and anaphylactic reaction (George, 2011). As the use of senna as laxative drug is wide worldwide, experimental screening of the toxicity of this plant is crucial to assure the safety and effectiveness of this natural source. The aim of this study was to evaluate the toxicity of the aqueous extract of *S. alexandrina* pods in order to establish a safe use of this plant as a medicine.

2. MATERIALS AND METHODS

2.1 Plant Material

Pods of *S. alexandrina*, wildly growing, were collected from Borry, Khartoum State, Sudan. The plant was identified and a voucher specimen was deposited in the Herbarium of Botany Department, Faculty of Science, University of Khartoum for future reference.

2.2 Preparation of Plant Extract

Water extract was prepared by simple maceration of 150g of powdered pods in 1500mL of distilled water maintained at ambient temperature for 4 h. Extract was first filtered on filter paper and then freeze-dried to yield 13g of water extract.

2.3 Animals and Experimental Design

Healthy 6-months old Newzeland rabbits of 2-3 kg body weight and of both sex were purchased from Balsam Pharmaceutical Industries and were maintained under standard conditions (temperature 22 ± 1ºC, relative humidity 60 ± 5%, 12h light/dark cycle) with diet and water *ad* libitum. The rabbits were given 5 days adaptation period. This research was carried out according to the international rules governing the use of laboratory animals.

At the end of the adaptation period, rabbits were divided into 4 groups of eight rabbits each, group 1 served as control. The aqueous extract of *S. alexandrina* pods was administered to groups 2, 3 and 4 at 50, 100 and 300 mg/kg body weight respectively by daily oral intubation for 4 weeks. After 2 and 4 weeks, 4 animals from each group were weighed, euthanized and blood and tissues were obtained for biochemical, hematological and histopathological analysis.

2.4 Biochemical and Hematological Parameters

Blood samples were collected from the ear vein before the experiment started and then after 14 and 28 days for haematological investigation and serum analysis. An automated cell counter (Sysmex LX-21N) was used to analyse blood for haematological parameters, to determine the haemoglobin concentration (Hb), red blood cell count (RBC), packed cell volume (PCV), Mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC). For serum, clotted blood was centrifuged for 10 min at 3000 rpm and separated sera stored at −20ºC until analyzed. Serum samples were analyzed for the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and concentrations of creatinine, albumin and globulin applying colorimetric procedures using commercial kits (Randox Laboratories LTD., UK). Values were read using a spectrophotometer (Jenway 6100, Dunmow, Essex, UK).

2.5 Histopathological Analysis

Small pieces (5–8 mm) of tissue from the kidney, liver and spleen in all groups of treatment were excised and were immediately fixed in 10% neutral buffered formalin. Fixed samples were trimmed and processed for paraffin embedding. Sections (5–7 µm) were cut and picked up on clean silane-coated glass slides. After de-waxing and rehydration through descending concentrations of ethanol, the sections were stained with haematoxylin and eosin (H and E) and examined microscopically.

2.6 Statistical Analysis

Data were reported as mean ± S.E.M. and statistical analysis for significance was done by ANOVA test. Data from the test groups were compared with controls.

3. RESULTS AND DISCUSSION

3.1 Clinical Findings

Rabbits in group 2 which received *S. alexandrina* at 50 mg/kg/day showed diarrhoea, while in group 3 rabbits that were given the dose at 100 mg/kg/day showed no clinical signs. One rabbit in group 4 that were given the plant at 300 mg/kg/day died at day 10. Diarrhoea appeared in group 2 rabbits might have been due to enteritis and erosion on the intestinal mucosa. Death in rabbits given higher doses indicates toxicity of the active ingredient in the plant and mostly due to the severe damage of the vital organs seen in the histopathology.

3.2 Effect on Body Weight

Results are presented in Fig. 1. Rabbits which orally dosed with *S. alexandrina* aqueous extract at 50 mg/kg/day and those given the dose at 100 mg/Kg/day showed no significant differences in body weights during the whole period of the experiment, while body weights of rabbits that given the extract at 300 mg/kg/day significantly decreased ($p<0.01$) at weeks 2 and 4 of the experiment. This growth depression was probably due to reduced feed intake and/or inefficiency of feed utilization.

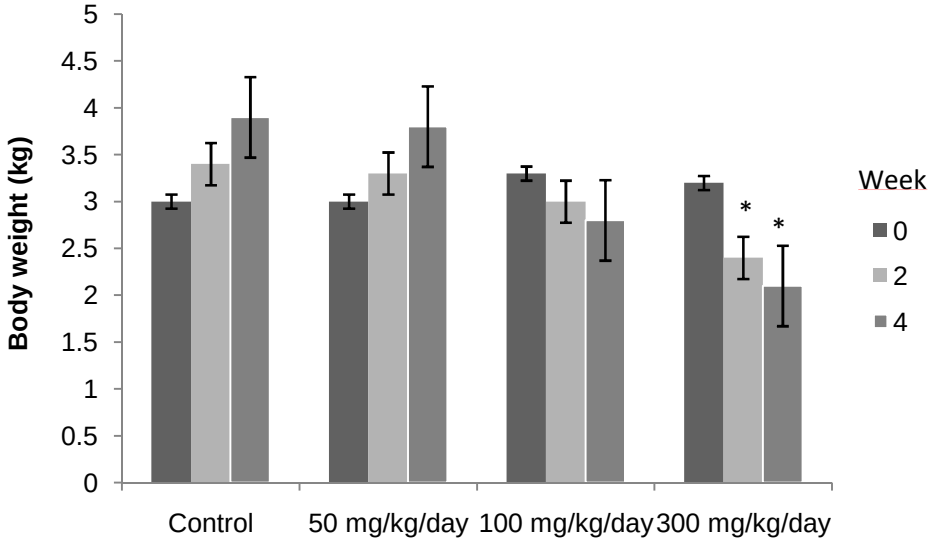

Fig. 1. Effect of aqueous extract of *Senna alexandrina* pods on rabbits' body weight
*The results are shown as mean (n = 4) ± standard deviation. No symbol: not significant compared to control. * P < 0.01.*

3.3 Haematological Findings

Haematological findings are presented in Table 1. Haemoglobin concentration decreased in all groups at week 2 through week 4, but this decrease was not significant in groups given the dose at 50 and 100 mg/kg/day at week 2 and 4; however, haemoglobin decrease was significant in the high dose group which was dosed at 300 mg/kg/day ($p<0.01 – 0.001$); this decrease might have been due to disorder in the activity of ferritin which is important in iron metabolism or due to iron deficiency.

Table 1. Hematological parameters of rabbits treated orally with *Senna alexandrina* pods aqueous extract

Group	Parameters				
	Mb (g dL^{-1})	RBC (10^6 mm^3)	PCV (%)	MCV (m^3)	MCHC (%)
G1 (Control)					
0	10.51 ± 0.37	07.25 ± 0.10	37.20 ± 0.96	51.33 ± 1.26	28.32 ± 0.58
2	09.02 ± O.02	05.97 ± 0.13	33.40 ± 0.87	56.04 ± 1.28	27.05 ± 0.75
4	09.07 ± 0.25	07.15 ± 0.03	34.00 ± 1.70	47.57 ± 2.40	27.02 ± 1.48
G2 (50 mg/Kg/day)					
0	09.66 ± 0.16	07.02 ± 0.05	34.60 ± 2.15	51.96 ± 2.37	28.40 ± 1.63
2	08.47 ± 0.24	05.53 ± 0.01**	30.20 ± 1.06	56.52 ± 2.09	27.93 ± 0.00
4	08.68 ± 0.29	05.42 ± 0.42*	27.30 ± 4.37	50.32 ± 1.59	32.49 ± 1.89
G3 (100 mg/Kg/day)					
0	09.28 ± 0.24	06.92 ± 0.10	34.30 ± 0.34	49.64 ± 1.39	27.06 ± 0.63
2	09.02 ± 0.14	05.11 ± 0.15**	32.80 ± 3.70	64.45 ± 1.16*	27.49 ± 0.31
4	08.79 ± 0.12	04.27 ± 0.28***	29.20 ± 2.05	67.46 ± 3.92*	28.45 ± 0.15
G4 (300 mg/Kg/day)					
0	09.17 ± 0.04	07.07 ± 0.08	35.00 ± 0.57	48.16 ± 0.80	26.21 ± 0.30
2	07.70 ± 0.21**	04.47 ± 0.06**	32.00 ± 1.58	69.40 ± 0.68**	24.38 ± 0.59
4	08.12 ± 0.00*	05.91 ± 0.13***	31.57 ± 1.11	49.73 ± 4.06	27.33 ± 0.32

The results are shown as mean (n = 4) ± standard deviation. No symbol: not significant compared to control.
** P < 0.05. ** P < 0.01, ***P < 0.001.*
0, 2 and 4 = weeks of experiment

Red blood cells values decreased significantly in all groups throughout the experiment, ($p<0.05$ – 0.001 for group 2; $p< 0.01$ - 0.001 for group 3 and 4). The decrease in RBCs might have been due either to haemolysis or disorder in the bone marrow function as well as bleeding leading to anaemia (Eichiner, 1973, 1984). PCV values were decreased in all groups. The values of MCV differed significantly in the group given a dose of 100 mg/kg/day ($P< 0.05$) and the group given 300 mg/kg/day ($P< 0.01$). There was no significant difference in MCH in all groups.

3.4 Changes in Serum Constituent

Changes in the activities of serum AST, ALT and the concentration of creatinine, total protein, albumin and globulin on rabbits dosed with *S. alexandrina* aqueous extract are given in Table 2. There was no significance difference in the activity of AST in group 2 (50 mg/kg/day). In group 3 (100 mg/kg/day) there was no change in the activity of AST at week 2 but it differed significantly at week 4 ($P<0.01$). In group 4 (300 mg/kg/day) the change in the AST activity was significant at week 2 and 4 ($P<0.05$ -0.01) respectively. For ALT activity there was no significant change in group 2 (50 mg/kg/day), in group 3 (given the dose at 100 mg/kg/day) the change was significant at week 2 only ($P<0.01$) whereas in group 4 (given the dose at 300 mg/kg/day) the change was significant only at week 4 ($P<0.05$). It is well known that the release of AST and ALT enzymes into plasma is attributed to either liver damage (Ford et al., 1972; Adam et al., 1977; Adam et al., 1973), or altered membrane permeability (Cornelius and Kaneko, 1963).

There was no significance difference in the creatine in group given the dose at 50 mg/kg/day at week 2 through week 4. In the group given the dose at 100 mg/kg/day there was significant changes at week 4 ($P<0.01$). In group given the dose at 300 mg/kg/day the change in the creating activity was significant at week 2 and 4 ($P<0.01$). Creatinine plasma elevation is considered significant markers of renal dysfunction (Almdal and Vilstrup, 1988).
Total protein concentrations in serum of rabbits dosed orally with *S. alexandrina* aqueous extract decreased significantly in both groups given the dose at 50 and 100 mg/kg/day at week 2 through week 4 ($P<0.05$). Albumin concentration showed no change in all groups at week 2; however, at week 4 it increased significantly in groups given a dose of 100 and 300 mg/kg/day ($P<0.05$). The only significant decrease in globulin concentration was observed in group given a dose of 300 mg/kg/day at week 4 ($P<0.01$) suggesting hepatic and renal disorders.

3.5 Histopathological Changes

No pathological changes were seen in liver, kidney, spleen or the heart of the group given the dose at 50 mg/kg/day neither for the group given a dose of 100 mg/kg/day at week 2. However, at week 4, the group given 100 mg/kg/day showed congestion of the renal tubules (Fig. 2-A); in the group treated with 300 mg/kg/day there was lymphocytic infiltration in renal glomeruli and congestion in the cortex and medullary tubules (Fig. 2- A & B). The liver showed hepatocellular necrosis and hemorrhage (Fig. 2-C). The haemosiderin deposits in the spleen which is ill-defined molecule and appears from the partial degradation of ferritin, indicating excessive storage of iron (Fig. 2-D). The hepatic and renal lesions are constant features of the pathological picture in Senna poisoning (Bakhiet and Adam, 1998; Yagi, 1998).

Table 2. Serochemical parameters of rabbits treated orally with *Senna alexandrina* pods aqueous extract

Groups	Parameters	Weeks		
		0	2	4
		AST (I.U.)		
G1 (Control)		55.40 ± 0.92	54.10 ± 0.68	52.00 ± 0.56
G2 (50 mg/kg/day)		55.60 ± 1.12	54.40 ± 1.32	54.13 ± 1.16
G3 (100 mg/kg/day)		56.56 ± 1.46	54.20 ± 1.31	54.90 ± 0.66*
G4 (300 mg/kg/day)		55.80 ± 0.12	56.00 ± 0.06*	55.20 ± 0.06**
		ALT (I.U.)		
G1 (Control)		23.13 ± 0.20	22.98 ± 0.33	20.60 ± 0.67
G2 (50 mg/kg/day)		21.58 ± 0.42	22.05 ± 0.74	21.38 ± 0.61
G3 (100 mg/kg/day)		21.60 ± 0.60	19.84 ± 0.52**	20.91 ± 0.53
G4 (300 mg/kg/day)		22.56 ± 1.25	20.91 ± 0.53	23.20 ± 0.06*
		Creatine (mg/dl)		
G1 (Control)		0.50 ± 0.03	0.49 ± 0.01	0.52 ± 0.05
G2 (50 mg/kg/day)		0.52 ± 0.06	0.55 ± 0.02	0.50 ± 0.01
G3 (100 mg/kg/day)		0.35 ± 0.01	0.39 ± 0.07	0.49 ± 0.01**
G4 (300 mg/kg/day)		0.47 ± 0.10	0.52 ± 0.17**	0.78 ± 0.04**
		Total protein (g/dl)		
G1 (Control)		9.73 ± 0.51	9.82 ± 0.14	9.79 ± 0.64
G2 (50 mg/kg/day)		9.86 ± 0.43	8.86 ± 0.25*	8.39 ± 0.30
G3 (100 mg/kg/day)		9.12 ± 0.31	9.08 ± 0.13*	8.33 ± 0.01
G4 (300 mg/kg/day)		9.51 ± 0.32	9.09 ± 0.11*	8.33 ± 0.77*
		Albumin (g/dl)		
G1 (Control)		7.24 ± 0.20	6.46 ± 0.19	4.91 ± 0.72
G2 (50 mg/kg/day)		6.45 ± 0.10	5.85 ± 0.50	4.99 ± 0.71
G3 (100 mg/kg/day)		5.59 ± 0.62	5.88 ± 0.14	6.08 ± 0.25*
G4 (300 mg/kg/day)		6.59 ± 0.20	5.84 ± 0.20	6.75 ± 0.35*
		Globulin (g/dl)		
G1 (Control)		2.49 ± 0.46	3.23 ± 0.62	3.89 ± 0.25
G2 (50 mg/kg/day)		3.39 ± 0.47	2.90 ± 0.23	3.40 ± 0.44
G3 (100 mg/kg/day)		3.54 ± 0.63	3.41 ± 0.04	2.90 ± 0.49
G4 (300 mg/kg/day)		2.77 ± 0.52	3.23 ± 0.14	2.46 ± 0.00**

*The results are shown as mean (n=4) ± standard deviation. No symbol: not significant compared to control. * P < 0.05. **P < 0.01.*

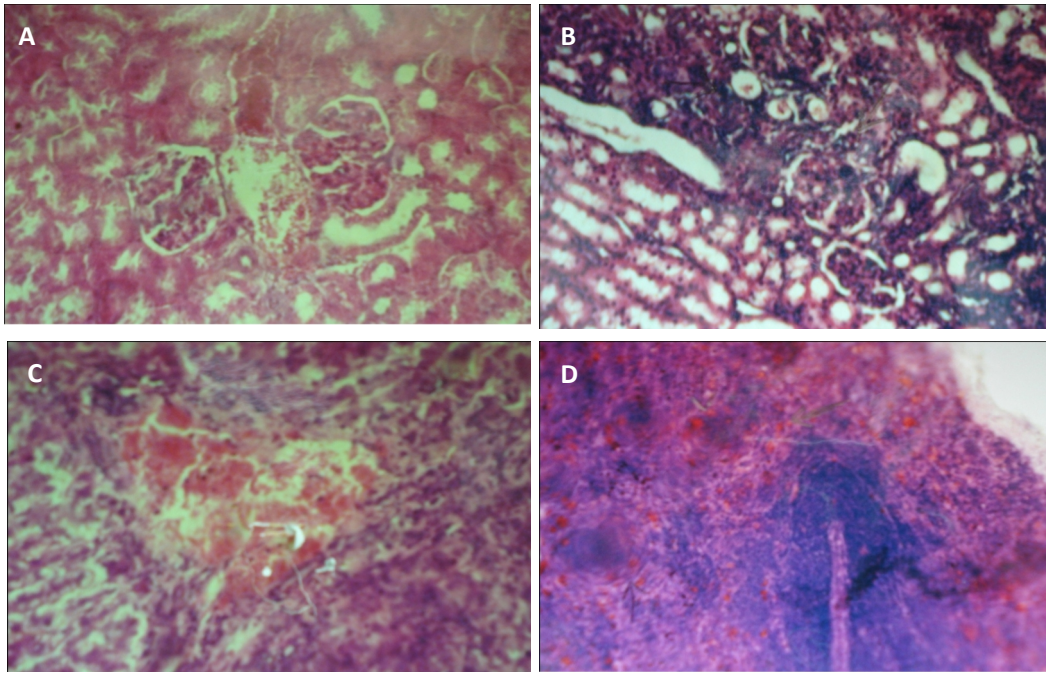

Fig. 2. A - D: Histopathological sections representative of different rabbit groups dosed orally with different doses of aqueous extract of *S. alexandrina* pods

(A) Kidney section from the group given a dose of 100 mg/kg showing congestion of the renal tubules; (B) Kidney section from the group given a dose of 100 mg/kg showing lymphocytic infiltration of the cortical and medullary regions; (C) Liver section from the group given a dose of 300 mg/kg showing hemorrhage and necrotic hepatocytes; (D) Spleen section from the group given a dose of 300 mg/kg showing haemosidrin deposits. H & E × 120.

Thus, at a dose of 50 mg/kg/day *S. alexandrina* aqueous extract did not cause changes in the renal and liver function of animals since there was no significant alteration in the creatinine, AST or ALT levels and no morphological alterations in the renal and liver tissue. The 50 mg/kg dose would correspond to 3.250 g of extract to a 65 kg human (Almdal and Vilstrup, 1988; Yousef et al., 2003; Baliga et al., 2004). However, *S. alexandrina* aqueous extract was toxic at high dose (300 mg/Kg/day) and at administration of 100 mg/Kg/day for long duration (4weeks).

Herbs in their natural state vary in potency and may contain multiple pharmacological substances, which can cause undesirable side effects. Senna contains various anthranoids, where the most important are sennosides A and B; followed by aloe-emodin, emodin and chrysophanol (Mengs et al., 2004). The toxicological and mutagenic status of the senna crude extract, however, is less characterized. In a study by Hietala et al. (1987), the laxative effect and the acute toxicity of certain fractions of senna extracts in rats were investigated. The same tests were carried out with various pure anthraquinone derivatives in senna pods. Results showed that the laxative and toxic components could be separated from pods and senna extracts. The most powerful laxative components, sennosides A + B have the lowest toxicity while the fractions with very low laxative activity have the highest acute toxicity. This suggests that there are other active molecules in the senna extract that could be responsible for its toxicity. Anthranoids such as chrysantine, hydroxyanthraquinones, presenting in trace

concentrations in the extract, show a different and highly controversial toxicological status to the sennosides. The hydroxyanthraquinones emodin and aloe-emodin gave positive results in genotoxic assays in *Salmonella typhimurium*, V79-HGPRT, rat hepatocytes, and mouse fibroblasts (Westendorf et al., 1990); however, in another study, such genotoxicity was not observed (Heidemann et al., 1993). In a study by Mori et al. (1990), the induction of neoplasms in the intestine, stomach and rat liver, subjected to a diet containing 1% hydroxyanthraquinones for 480 days, was induced. Therefore, standardization of herbal formulations of senna is essential in order to assess their efficacy and safety.

4. CONCLUSION

The prescription and use of traditional medicine in Africa is currently not regulated, with the result that there is always the danger of misadministration. Scientific validation of herbal medicine use lends support to the continued practice of traditional medicine in Africa. Eventually, this may lead to more widespread use of traditional medicine in health care systems, as in India and China. The herbal aqueous extract of *S. alexandrina* (50 mg/kg animal) was non toxic when administered orally, not causing biochemical and hematological changes, or provoking histopathological alterations. The detection of the toxic effects observed in rabbits might be due to the dose and/or frequency of administration, constituting chronic exposure. The safety of this plant in the traditional medicine should be verified by much further testing, including *in vivo* experiments and clinical studies.

ETHICAL APPROVAL

Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

Adam, S.E.I., Tartour, G., Obeid, H.M., Idris, O.F. (1973). Effects of Ipomea carnea on the liver and serum enzymes in young ruminants. J Comp Pathol, 83(3), 351-356.

Adam, S.E.I., Wasfi, I.A., Magzoub, M. (1977). Chronic copper toxicity in Nubian goats. J Comp Pathol, 87, 623–627.

Almdal, T.P., Vilstrup, H. (1988). Strict insulin treatment normalizes the organic nitrogen contents and the capacity of ureanitrogen synthesis in experimental diabetes in rats. Diabetologia, 31, 114-118.

Bakhiet, A.O., Adam, S.E.I. (1998). Toxicity to Bovans Chicks of *Cassia italica* Seeds. Phytother Resh, 10(2), 156–160.

Baliga, M.S., Jagetia, G.C., Ullor, J.N., Baliga, M.P., Venkatesh, P., Reddy, R., Rao, K.V.N.M., Baliga, B.S., Devi, S., Raju, S.K., Veeresh, V., Reddy, T.K., Bairy, L.K. (2004). The evaluation of the acute toxicity and long term safety of hydroalcoholic extract of Saptharma (*Alstonia scholaris*) in mice and rats. Toxicol Lett, 151, 317–326.

Cornelius, C.E., Kaneko, J.J. (1963). Clinical biochemistry of domestic animals. Academic Press, New York.

Eichner, E.R. (1973). The hematologic disorders of alcoholism. Am J Med, 54, 621–630.

Eichner, E.R. (1984). The fundamentals of clinical hematology, 3rd Ed., J.L. Spivak and E.R. Eichner (Eds.), Philadelphia.

Ford, E.J., Adam, S.E., Gopinath, C. (1972). Hepatic amidopyrine N-demethylase activity in the calf. J Comp Pathol, 82(3), 355-64.

George, P. (2011). Concerns regarding the safety and toxicity of medicinal plants - An overview. J. App. Pharm Sci, 01(06), 40-44.

Heidemann, A., Miltenburger, H.G., Mengs, U. (1993). The genotoxicity status of senna. Pharmacol, 47, Supplement 1, 178–186.

Hietala, P., Marvola, M., Parviainen, T., Lainonen, H. (1987). Laxative potency and acute toxicity of some anthraquinone derivatives, senna extracts and fractions of senna extracts. Pharmacol. Toxicol, 61(2), 153–156.

Lemli, J. (1988). Senna an old drug in modern research. Pharmacol, 36 (Suppl.1), 3-6.

Mengs, U., Mitchell, J., McPherson, S., Gregson, R., Tigner, J. (2004). A 13-week oral toxicity study of senna in the rat with an 8-week recovery period. Arch. Toxicol, 78, 269–275.

Migahid, A.M. (1978). Flora of Saudi Arabia. 2nd Ed., Vol. 1, Riyadh University, Riyadh, Saudi Arabia.

Mori, H., Yoshimi, N., Iwata, H., Mori, Y., Hara, A., Tanaka, T., Kawai, K. (1990). Carcinogenicity of naturally occurring 1-hydroxyanthraquinone in rats: induction of large bowel, liver and stomach neoplasms, Carcinogenesis, 11(5), 799–802.

Omer, S.A., Ibrahim, F.H., Khalid, S.A., Adam, S.E.I. (1992). Toxicological interactions of *Abrus precatorius* and *Cassia senna* in the diet of Lohmann. Vet. Hum. Toxicol, 34, 310-313.

Stoll, A., Becker, B., Helfenstein, A. (1950). Die konstitution der sennoside. Helv Chim Acta. 33, 313-336.

Westendorf, J., Marquardt, H., Poginsky, B., Dominiak, M., Schmidt, J., Marquardt, H. (1990). Genotoxicity of naturally occurring hydroxyanthraquinones. Mutat Res, 240(1), 1–12.

WHO. (1999). Monograph on selected medicinal plants, Vol. 1, World Health Organization, Geneva, 250.

Yagi, S.M., El Tigani, S., Adam, S.E.I. (1998). Toxicity of *Senna obtusifolia* fresh and fermented leaves (Kawal), *Senna alata* leaves and some products from *Senna alata* on rats. Phytother Res, 12, 324-330.

Yousef, M.I., El-Demerdash, F.M., Kamel, K., Al-Salhen, K.S. (2003). Changes in some hematological and biochemical indices of rabbits induced by isoflavones and cypermethrin. Toxicol, 189, 223–234.