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Toxicological Profiles of Commercial Herbal Preparation, Jobelyn®

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Abstract

PURPOSE: Jobelyn® is a commercial herbal product recommended for the management of anemia related illnesses. Despite its wide use, there is limited report on its toxicological profile. This study examined the acute and short-term chronic toxicity profiles of the product with emphasis on the LD_{50}, gross morphological and histopathological effects.

METHODS: Albino mice (mean weight: 16.45±3.14g) were used in this study. For acute toxicity, graded concentrations of Jobelyn® were administered orally and intraperitoneally as single doses to the mice. Intraperitoneal administration of sub-lethal doses daily for 14 days was adopted for the short-term chronic toxicity studies.

RESULTS: The LD_{50} following oral and intraperitoneal administration were 215.06 mg/kg (r = 0.916) and 193.37 mg/kg (r = 0.995), respectively. The major behavioral/ morphological effects at high doses were reduction in motor activity, piloerection and sedation. The sub-lethal doses did not significantly modify the normal behavioral repertoire of licking, grooming and sniffing. Histopathological examination also did not indicate severe pathological changes. At the lethal doses, some degree of congestion was noticed in the lung, liver splenic and kidney tissues. Short-term chronic studies did not produce further toxic effects but transient mild sedation and piloerection and histopathological examination revealed only mild congestion in the organs. No death of the animals was recorded during the period of sub-chronic toxicity assessment.

CONCLUSION: Jobelyn® is likely to be safe for use in humans when administered at recommended doses.

Keywords: Jobelyn, safety profile, LD50, toxicity

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Introduction

The Alma Ata declaration of 1978 encouraged the use of all available resources for primary healthcare and recommended that government should give high priority to using traditional health practices and incorporate proven traditional remedies into National Drug Policy and Regulations [1]. As much as 80% of people in developing world are said to depend on traditional medicines for primary healthcare [2]. Over the years, there has been worldwide recognition of the vital role of herbal medicines in healthcare [3, 4]. Unfortunately, most of the herbal medicines are poorly regulated and controlled in many countries. Nevertheless, there is a dearth of scientific proofs of effectiveness and safety of herbal preparations, which is required for marketing authorization [5, 6].

Jobelyn®, manufactured by Health Forever Products Ltd., Lagos, Nigeria, is a commercial herbal preparation from Sorghum bicolor leaf-sheaths which contains carbohydrates, protein, tannins, saponins and iron. It is claimed to stimulate rapid production of red blood cells and maintains the integrity of white blood cells even with the presence of viral or bacterial infections. Jobelyn® is said to strengthen the immune system and thereby enhances body's defensive mechanisms. Unpublished studies revealed the anti-trypanosomal activities of the product and haematinic effects in laboratory animals. The manufacturers recommend it as remedy for anemia in sickle cell anemia, cancer, HIV/AIDS, malaria, typhoid fever, aplastic anemia and pregnancy. Preliminary pilot preclinical studies in mice showed that Jobelyn® does not create significant adverse effects but it significantly lowered serum creatinine and cholesterol levels. However, unpublished toxicological evaluation of the product in mice has shown its lethal effects at high doses. Although Jobelyn® is currently used by people in many countries, the clinical efficacy and safety have not been scientifically reported [7]. The main objective of this work was to evaluate its toxicity profiles after acute and short-term chronic administration.

Materials and Methods

Animals

Healthy albino mice (58 males and 50 females; average weight, 16.45 ±3.14 g; weight range 13.75 – 19.48 g) were obtained from the Animal House of the College of Medicine, University of Lagos, Nigeria. The animals were kept in clean cages (10 mice/cage) in well-ventilated room and allowed unrestricted access to livestock feeds (from Ladokun feeds, Ibadan) and fresh water. They were also allowed to acclimatize to the environment for one week before each experiment. During this period of acclimatization, the animals were periodically assessed for gross morphological/behavioral changes. The animal cages were cleaned out of waste alternate days.

Acute toxicity testing

This was carried out to determine dose-response effects, sub-lethal and lethal doses, and to calculate the LD_{50} using both the oral and intraperitoneal routes

Oral Route: 42 mice were divided into 7 equal groups (A – G). Mice in groups A to F were administered 6, 12, 18, 24, 30 and 42 ml/kg of 20% solution of JOBELYN® (8.2 mg/ml) orally. The animals in group G that served as control, were given 0.3 ml of deionized water orally.

Intra-peritoneal (IP) route: 36 mice were also divided into 6 equal groups (A – F). Mice in groups A to E were given 6, 12, 18, 24, 30 and 60 ml/kg of the stock solution of Jobelyn® (8.2 mg/ml) intra-peritoneally whilst animals in group F, serving as control, received 0.3 ml of de-ionized water IP.

For each of the above routes, all the animals were monitored for gross morphological and

behavioral changes (including changes in locomotor activity, pilo-erection, normal behavioral repertoire [grooming/licking/ biting], sedation, aggressiveness, catalepsy, appetite, urination, defecation, vomiting, sneezing/wheezing) over 72 hr and the LD_{50} was determined using probit analysis within 95% confidence limit. The animals were then sacrificed and essential organs (preserved in 10% formaldehyde solution for 4 weeks before processing) subjected to histological examination for pathological changes. The various organs were processed using the automatic tissue processor. This technique involved dehydrating the well-fixed 3 mm-sized tissues placed in tissue baskets with their respective labels by passing them through graded alcohol. They were then moved into xylene solution baths and then placed in molten wax for impregnation. The solidified blocks were trimmed and sectioned using the Rotary microtome at 5 µ thickness. Sections were then floated on water bath at 50 ^{o}C and picked up using albuminized microscopic slides. The cut sections were dried on hot plates at 60 ^{o}C and then stained by haematoxytocin and eosin to demonstrate tissue structures.

Sub-acute toxicity testing/short-term chronic toxicity

Thirty (30) mice were divided into three equal groups (A – C). Those in groups A and B were given 0.1 and 0.2 ml of 20% solution of JOBELYN® (8.2 mg/ml) IP daily for 2 weeks while those in group C (control) were given 0.3 ml de-ionized water intraperitoneally daily for the same period. The animals were monitored for morbidity and mortality (including changes in locomotor activity, piloerection, normal behavioral repertoire [grooming/licking/biting], sedation, aggres-siveness, catalepsy, appetite, urination, defecation, vomiting, sneezing/wheezing), sacrificed after 15 days and essential organs (preserved in 10% formaldehyde solution for 4 weeks before processing) were examined histologically for pathological changes as described earlier.

Results

Acute toxicity testing

Following oral treatment of the animals, the observed changes in behavior of the animals is presented in Table 1. The mortality rates and probit analysis report are recorded in Table 2. Reduced mobility accompanied the administration of Jobelyn® from the 0.3 ml dose level within 1 hr. However, the animals were alert, except at high doses where a slight degree of sedation was noted. There was also some degree of pilo-erection and the surviving animals recovered motility soon after 48 hr. The normal behavioral repertoire was maintained. There was no noticeable reduction in appetite or changes in urine output. The LD_{50} values for oral route was found to be 215.06 (147.30 – 313.99) mg/kg. The summary of observed behavioral changes following intraperitoneal administration of Jobelyn®, mortality rates and probit analysis are presented in Tables 3 and 4, respectively.

Short-Term Chronic Toxicity Testing

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The observed behavioral changes following the administration of 0.1ml and 0.2 ml of the stock solution of Jobelyn to 2 groups of ten mice each daily for 2 weeks are presented in Table 5.

Histopathological examination revealed no marked pathological changes in the heart and kidneys but moderate congestion in the lungs and liver and slight congestion in the spleen at lethal doses.

Discussion

Most of the toxicological studies report that toxic effects due to the use of herbal medicine are associated with hepatotoxicity. Other toxic effects on the kidneys, nervous system, blood, and cardiovascular system,

Table 1: Behavioral changes following acute oral doses of Jobelyn®

Dose (ml)	Dose (mg/kg)	Observations
Control	0.0	Normal behavioral repertoire; no sedation; no piloerection over the 72 hr of observation.
0.1	49.85	Mobile, alert, grooming and licking; slight piloerection. Very active over the 72 hr of observation
0.2	99.70	Slight reduction in motility; normal repertoire, slight piloerection. Active over the 72 hr of observation. No mouse died.
0.3	149.54	Reduced mobility, slight sedation and piloerection over 24 hr. Recovered motility, active and feed normally over the next 48 hr. 1 mouse died after 24 hr.
0.4	199.39	Reduced motility, sedation and piloerection over 24 hr. 2 mice died after 24 hr. Recovered motility after 36 hr although not very active. Fully recovered after 48 hr
0.5	249.24	Marked reduction in motility, sedation and piloerection over 48 hr. 3 mice died within 24 hr. Recovered motility after 72 hr
0.7	348.95	Marked reduction in motility. 5 mice died within 24 hr.

Table 2: Mortality rates and probit analysis result after acute oral administration of Jobelyn®

Dose (ml)	Dose (mg)	Dose (mg/kg)	# mice	# mice that died	Mortality	% Mortality	Probit +5
Control	0.0	0.0	6	0	0/6	0	0.0
0.1	0.82	49.85	6	0	0/6	0	0.0
0.2	1.64	99.70	6	0	0/6	0	0.0
0.3	2.46	149.54	6	1	1/6	17	4.0458
0.4	3.28	199.39	6	2	2/6	33	4.5601
0.5	4.10	249.24	6	3	3/6	50	
0.7	5.74	348.95	6	5	5/6	83	5.9542

LD_{50} value = 215.06 mg/kg; r = 0.916; confidence limit = 147.30 – 313.99 mg/kg

Table 3: Observed behavioral changes after acute IP administration of Jobelyn®

Dose (ml)	Observations
Control 0.0	Normal behavioral repertoire. Alert.
0.2	Normal behavioral repertoire. Slight piloerection. 1 mouse died after 24 hrs. Full recovery after 48hrs
0.3	Slight reduction in motility, mild sedation over 24hrs. 2 mice died within 24hrs. Recovers fully after 48hrs
0.4	Reduced motility, sedation, piloerection over 48 hrs. 3 mice died after 24 hrs.
0.5	Reduced motility, marked sedation over 48hrs. 4 mice died after 24 hrs
1.0	Reduced motility, marked sedation over 12hrs. All died within 24hrs

Table 4: Mortality rates and probit analysis result after acute IP administration of Jobelyn®

Dose (ml)	Dose (mg)	Dose (mg/kg)	# mice	# mice that died	Mortality	% Mortality	Probit +5
Control	0.0	0.0	6	0	0/6	0	0.0
0.2	1.64	99.70	6	1	1/6	17	4.0458
0.3	2.46	149.54	6	2	2/6	33	4.5601
0.4	3.28	199.39	6	3	3/6	50	
0.5	4.10	249.24	6	4	4/6	67	5.4399
1.0	8.20	498.48	6	6	6/6	100	

LD_{50} value = 193.37 mg/kg; r = 0.995; confidence limit = 131.54 – 284.25 mg/kg

Table 5: Observed behavioral changes after subchronic IP administration

Dose (ml)	Observations
Control	Normal behavioral repertoire throughout the 14 days of observation. No mice died.
0.1	Normal behavioral repertoire. Slight piloerection. No mice died. Slight reduction in appetite
0.2	Reduced motility, piloerection. Slight sedation. No mice died. Slight reduction in appetite.

as well as medicinal herbs' mutagenicity and carcinogenicity have also been published in medical journals [5]. The true incidence of hepatic damage caused by herbal medications is unknown. In the case of Chinese herbal remedies, the incidence of hepatotoxicity has been estimated at between 0.2% and 1% [6]. No accurate estimate of the prevalence of herbal remedies in Africa has been reported.

The manufacturers of Jobelyn recommend as much as 500 mg per dose (2 capsules) and 1.5 g per day (6 capsules) for humans. For any average adult weighing 70 kg, the recommended doses translate to a dosage of about 7.14 mg/kg per dose and 21.42 mg/kg/day, which are much smaller than the LD_{50} in this study. Even though the extrapolation of data from animals to humans is anticipated and not definitive, the recommended dosage regimen in man can be said to be comparatively very safe. For the oral route, the product has a tolerance limit of 99.70mg/kg. This gives a large room for dosage manipulation, which may be applicable to man.In this study, Jobelyn® has been found to produce only toxic effects at high doses in the animals suggesting that Jobelyn is relatively safe when used at usual doses for a long time in the animals. Lethal consequences of the product may be expected in sufficiently high dosages.

Some behavioral changes in the animals (reduced motility and sedation) may not be mutually exclusive; i.e. one could be responsible for the other. These effects may also have been responsible for the seeming loss of appetite that was observed at high doses in this study. The eye irritation observed in the animals when the product was administred through the oral route is attributable to direct contact of the product with the eye during administration.

Conclusion

There are indications that Jobelyn could be safe in humans when used at at doses recommended by the manufacturers. However, further toxicological screening in

humans is required to ascertain the safety profile.

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