Macedonian Veterinary Review Mac Vet Rev 2016; 39 (1): 23-32

Available online at
www.macvetrev.mk

DE GRUYTER OPEN

Original Scientific Article

THE PARADOX OF HUMAN EQUIVALENT DOSE FORMULA: A CANONICAL CASE STUDY OF ABRUS PRECATORIUS AQUEOUS LEAF EXTRACT IN MONOGASTRIC ANIMALS

Saganuwan Alhaji Saganuwan, Patrick Azubuike Onyeyili

Department of Veterinary Physiology, Pharmacology and Biochemistry
College of Veterinary Medicine, University of Agriculture,
Makurdi, Benue State, Nigeria

Received 16 May 2015; Received in revised form 1 September 2015; Accepted 10 October 2015

ABSTRACT

There is abundant literature on the toxicity of *A. precatorius* seeds. However there is a need to define the toxicity limit of the *Abrus precatorius* leaf in monogastric animals. Human Equivalent Dose (HED) which is equal to animal dose multiplied by animal km (metabolism constant) divided by human km was used to project the LD_{50} of fifteen monogastric animals , where human km factor is body weight (kg) divided by body surface area (m^2). Human Equivalent No-observable Adverse Effect Doses were determined by multiplying the animal no-observable adverse effect dose by animal weight (Wa) divided by human weight (Wh). The LD_{50} of the aqueous leaf extract of *Abrus precatorius* in mice was estimated to be between 2559.5 and 3123.3 mg/kg body weight. The LD_{50} extrapolated from mouse to rat (1349.3-1646.6 mg/kg), hamster (1855.3-2264.1 mg/kg), guinea pig (1279.5-1561.4 mg/kg), rabbit (618.4-754.7 mg/kg), monkey (593.7-724.5 mg/kg), cat (392.7-479.2 mg/kg), dog and baboon (371.1-452.8 mg/kg), child (297-362 mg/kg) and adult human (197.8-241.5 mg/kg) body weight respectively could be a reality. The therapeutic safe dose range for the animals was 1-12.5 mg/kg body weight for a period of 7 days, but at a dose (≤ 200 mg/kg body weight) the leaf extract showed haematinic effect. However, at a higher dose (> 200 mg/kg), the extract showed haemolytic activity in rats, whereas at a dose (≥25.0 mg/kg), the leaf extract might be organotoxic in hamster, guinea pig, rabbit, monkey, cat, dog, baboon, child and adult human if administered orally for a period of 7 days.

Key words: monogastric, toxicity, *Abrus precatorius*, mice, human

INTRODUCTION

Abrus precatorius is highly regarded as a universal panacea in a herbal medicine (49). The aqueous leaf extract of *Abrus precatorius* showed 99.4% clearance of *Plasmodium berghei* in mice within 11 days (47), significant antimicrobial activity against *Staphylococcus aureus, Streptococcus pyogenes, Klebsiella pneumoniae, Escherichia coli* and *Salmonella typhimurium* (4, 42, 43). The plant showed significant inhibition of human metabolic breast cancer cell line (MDA-MB 231). The ethanolic extract of *Abrus precatorius* leaves may be used in the management of asthma (52). It also inhibited acetylcholine-induced contractions of both toad rectus abdominis and rat phrenic nerve-diaphragm muscle preparations and caused flaccid paralysis in the young chicks (56). Both natural and heat denatured forms of abrusagglutinin are potential immunomodulators (54).

The leaves are used to cure fever, stomatitis, bronchitis (29), epilepsy (6), neuronal damage (35) and diabetes (13). Two triterpernoid saponins isolated from aerial parts of *Abrus precatorius* exhibited activity against inflammation (5), gonorrhoea, diarrhea and dysentery (8). The ethanol acetate of the leaf extract showed anti-serotonergic activity in frog fundus strip (11). The leaves also have astringent, emetic, antihelmintic, alexeteric and diuretic properties in addition to being useful in cough (32), pharyngodynia, pectoralgia (28), strangury and vitiated condition of vata (25, 29). Isoflavanquinone, abruquinone B and abruquinone

Corresponding author: Dr. Saganuwan Alhaji Saganuwan, PhD
E-mail address: pharn_saga2006@yahoo.com
Present address: Department of Veterinary Physiology, Pharmacology and Biochemistry, College of Veterinary Medicine, University of Agriculture, P.M.B. 2373, Makurdi, Benue State, Nigeria
Phone: +2347039309400

Competing Interests: The authors have declared that no competing interests exist.
Available Online First: 4 November 2015
Published on: 15 March 2016
http://dx.doi.org/10.1515/macvetrev-2015-0061

G isolated from aerial parts of the plant exhibited antitubercular, antiplasmodial, antiviral and cytotoxic activities (30). The leaves are sweet tasting due to the presence of glycyrrhizin component. The leaves are also used for the treatment of scratches, sores and wounds caused by dogs, cats and mice. Fresh leaves may be pressed on the gum for the treatment of stomatitis, skin cancer and nervousness (8), suppuration, acne, boils, abscesses, tetanus, rabies (58), colic, convulsion (27), cough, sore throat and insomnia (33). Aqueous extract of the plant has haematinic and plasma expander effects in mice (38).

The leaf components are made of choline, trigonellin (III) (22), flavonoids, total glycosides, saponin glycosides, saponins and tannins in higher concentration, but alkaloids, steroids and cardiac glycosides are present in moderate concentration. Calcium (10.2mg), magnesium (5.2mg), Sodium (6.8mg), Potassium (10.8 mg), Phosphorous (2.4 mg), nitrogen (30.5 mg) (45), triterpenoid saponin, 3-0-β-D-glucopyranosyl-(1→2)-β, D-glucopyranosyl subprogenin D together with six triterpenoids, subprogenin D, abrusgenic acid, triptotriterpenic acid B, abruslactone A, abrusogenin and abrusoside are also present (57). Other triterpenoids isolated are 20S, 220S)-β, 22-dihydroxycucubitacin, 24-diene-26, 29-dioc acid δ lactone, 3-0- (6'-methyl-β-D-glucurunopyranosyl)-3β, 22β-dihydroxylean-12-en-29-oic acid methyl ester, 3-0β-D-glucuronopyranosylsophoradiol methyl ester and sophoradiol (29). Abrusagglutinin, a low-toxicity protein present in every part of the plant is less lethal (LD_{50}=500μg/kg) than abrin A (LD_{50}=20μg/kg) (31).

The clinical features of *Abrus precatorius* leaf poisoning were pulmonary oedema and hypertension (16). The aqueous extract of *A. precatorius* leaf caused decreased levels of packed cell volume, haemoglobin concentration, red blood cell count, white blood cell count, mean corpuscular volume and mean corpuscular haemoglobin concentration in rats. The extract also resulted in increased levels of total serum protein, albumin, alanine amino transferase, aspartate amino transferase, alkaline phosphatase and total bilirubin. It also caused testicular degeneration characterized by decreased numbers of epithelial lining and reduction in sperm cells at dose range between 400 and 1600 mg/kg body weight (3). The foliage of *Abrus precatorius* contains abrin, which is among the most potent toxins. Clinical toxicosis was characterized by gastroenteritis, weakness and death (2, 10, 20). Abrin is present in the leaf and is known to cause hyperactivity of physiological system (8). The parenteral LD_{50} of abrin in mice is less than 0.1μg/kg (8). All parts of *Abrus precatorius* are toxic (9). Acute toxicity study of aqueous extract of *Abrus precatorius* leaf in mice showed shallow respiration, sedation, weight loss, penile prolapsed and limbs paddling within 48 hours of extract administration. Haematological analysis revealed significant increased packed cell volume, red blood cell and white blood cell count (44). The biochemical analysis showed increased aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, creatinine, chloride ion, hypophospataemia, hyponatraemia, hypokalaemia and hypoglycaemia after 3 weeks of oral administration of the extract at dose range between 25.0 and 200 mg/kg body weight. At 12.5 mg/kg only the urea increased on the 7th day of the extract administration (46). *In vitro* cytotoxicity assay of *Abrus* leaf against rat myoblast (L_6) cell line showed that chloroform fraction was the most toxic with inhibitory concentration (IC_{50}) value of 43.7μg/ml followed by n-hexane fraction (44.3μg/ml). In vitro antiplasmodial assay against plasmodium chloroquiune-pyrimethanine resistant strain (K_1) showed that n-hexane fraction has the best activity with IC_{50} value of 12.1μg/ml followed by chloroform fraction (23.0μg/ml) (40). The LD_{50} of oral and intraperitoreal aqueous extract of *Abrus precatorius* leaf in mice were 2559.5 to 3123.2 mg/kg and 866 mg/kg body weight respectively (45). In view of the toxic potential of *Abrus precatorius* and also in line with the principle of replacement, reduction and refinement, the toxicity potential of the plant was extrapolated from mice to other fifteen species of monogastric animals.

MATERIAL AND METHODS

Literature on the medicinal uses, phytochemical components, toxicological effects, therapeutic and toxic doses of aqueous extract of *Abrus precatorius* leaf was searched. The toxicological doses and toxic effects of *Abrus precatorius* aqueous leaf extract in rats as reported by Adedapo et al. (2) were compared to toxicological doses and toxic effects of aqueous extract of *Abrus precatorius* leaf in mice as reported by Saganuwan (39), Saganuwan and Onyeyili (46) and Saganuwan et al. (44). Oral LD_{50}, (2559.5 – 3123.3 mg/kg) safe (12.5 mg/kg) and toxic (25 – 200 mg/kg) doses of aqueous extract of *Abrus precatorius* leaf were translated from mice to human, hamster, rat, guinea pig, rabbit, monkey, cat, dog, baboon, ferret, marmoset, squirrel monkey, micro-pig, mini-pig and child weighing 0.02, 60, 0.08, 0.15, 0.4, 1.8, 3, 7, 10, 12, 0.3, 0.35, 0.6, 20, 40, 20 kg body weight respectively (17, 37, 41, 48, 51, 55). The weights of the animals corresponded with the animal models used. The extract treatment doses

(400 – 1600 mg/kg) in rats were translated to human treatment doses. Saganuwan (39), Saganuwan and Onyeyili (46) and Saganuwan et al. (45) used 10% concentration of cold water extract of *A. precatorius* dry leaves. Adedapo *et al.* (2) used 50% cold water macerated extract of *Abrus precatorius* leaf for their study. Twenty (20) gramme and 150 g weighed mouse and rat between 5 – 7 weeks and 7 – 8 weeks respectively were used for the studies.

Animal-human and human-animal dose translations of LD_{50}, toxic and therapeutic doses of aqueous leaf extract of *Abrus precatorius* were determined using the human equivalent dose formula. Human Equivalent Dose (HED) is equal to animal dose multiplied by animal km factor divided by human K_m factor. The K_m factor is body weight (kg) divided by body surface area (m^2). Human equivalent no-observable adverse effects dose is equal to animal no-observable adverse effect level (NOAEL) multiplied by animal weight (Wa) divided by human weight (Wh) to the power of 0.33 was used to confirm 12.5 mg/kg body weight of mice (relatively safe dose) translated to human and other animals' safe doses (4, 8, 9, 17, 34, 41, 51, 55). A safety factor between 10^{th} and 1000^{th} was used to determine ideal safe therapeutic doses.

RESULTS

The range of LD_{50} estimated by Saganuwan (38, 39) was between 2559.5 and 3123.3 mg/kg body weight of mice. Adedapo et al. (3) did not conduct LD_{50} test on aqueous extract of *Abrus precatorius* leaf in rats. They investigated only haematological and biochemical effects of the extract on rats. The median lethal dose (2559.5-3123.3 mg/kg) of mice was translated to adult human LD_{50} (197.9-241.5 mg/kg), child (297-362.3 mg/kg), mini-pig (211.4-258 mg/kg), micro-pig (274.9-335.4 mg/kg), squirrel monkey (1107.6-1351.7 mg/kg), marmoset (1279.5-1561.4 mg/kg), ferret (1060.2-1293.8 mg/kg), baboon and dog (371.1-452.8 mg/kg), cat (392.7-479.2 mg/kg), monkey (593.7-724.5 mg/kg), rabbit (618.4-754.7 mg/kg), guinea pig (1279.5-1561.4 mg/kg), rat (1349.3-1646.6 mg/kg) and hamster (1855.3-2264.1 mg/kg) respectively (Table 1).

Table 1. Mouse-human and human-other animals' extrapolated median lethal dose (LD_{50}) of aqueous leaf extract of *Abrus precatorius*

S/No.	Species	Body weight (kg)	BSA (m2)	K_m factor	LD_{50} (mg/kg)	Toxicity rating
1.	Mouse	0.02	0.007	2.9	2559.5-3123.3	Slightly toxic
2.	Hamster	0.08	0.02	4.0	1855.3-2264.1	,,
3.	Rat	0.15	0.025	6.0	1349.3-1646.6	,,
4.	Guinea pig	0.4	0.069	5.8	1279.5-1561.4	,,
5.	Rabbit	1.8	0.15	12.0	618.4-754.7	,,
6.	Monkey	3.0	0.24	12.5	593.9-724.5	,,
7.	Cat	7.0	0.37	18.9	392.7-479.2	Moderately toxic
8.	Dog	10	0.5	20.0	371.1-452.8	,,
9.	Baboon	12	0.6	20.0	371.1-452.8	,,
10.	Ferret	0.3	0.043	7.0	1060.2-1293.8	,,
11.	Marmoset	0.35	0.06	5.8	1279.5-1561.4	,,
12.	Squirrel monkey	0.6	0.09	6.7	1107.6-1351.7	,,
13.	Micro-pig	20	0.74	27.0	274.9-335.4	,,
14.	Mini-pig	40	1.14	35.1	211.4-258.0	,,
15.	Child	20	0.8	25.0	297-362.3	,,
16.	Adult human	60	1.6	37.5	197.9-241.5	,,

Note: Body weight and body surface area of animals and humans were taken from Reagan-Shaw et al. (7) and USEPA (55)

The therapeutic doses (12.5, 25, 50, 100 and 200 mg/kg) in mice translated to 1, 1.9, 3.9, 7.7 and 15.5 mg/kg body weight in human. On the other hand the therapeutic doses (400, 800 and 1600 mg/kg) in rats translated to 58.7, 117.3 and 234.7 mg/kg body weight in human (Table 2).

marmoset, squirrel, monkey, micro-pig, mini-pig, dog, baboon and mice to child translated doses are presented in Table 3.

At dose range between 400 and 1600 mg/kg body weight reported by Adedapo et al. (3), there was decreased RBC, PCV and Hb which were

Table 2. Mouse-human and rat-human equivalent therapeutic doses of aqueous leaf extract of *Abrus precatoirus*

Publications	Animal doses (mg/kg)	Human equivalent doses (mg/kg)
Saganuwan and Onyeyili (38, 46), Saganuwan (37), Saganuwan et al. (47)	12.5*	1.0*
	25	1.9
	50	3.9
	100	7.7
	200	15.5
Adedapo et al. (3)	400	58.7
	800	117.3
	1600	234.7

* = Safe dose for a period of 7 days

Human-animal equivalent therapeutic dose translation showed that 1 mg/kg body weight of adult human translated to 1.1 mg/kg in mini-pig and 9.1 mg/kg body weight in hamster respectively. But, 1.9 mg/kg body weight in human translated to 2.02 mg/kg in mini-pig and 18.1 mg/kg in hamster respectively. However, 15.5 mg/kg in human translated to 16.6 mg/kg in micro-pig and 145.0 mg/kg in hamster (Table 3). Human to hamster, rat, guinea-pig, rabbit, monkey, cat, baboon, ferret,

increased in mice (40, 44). White blood cells and lymphocytes were decreased in rat (3) (Table 4).

Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, protein, albumin, globulin, albumin/globulin ratio were reported to have increased in rats and mice (3, 46). Total bilirubin, direct bilirubin and indirect bilirubin were reported to have increased in rat (3) but decreased in mice (46). Urea, creatinine, chloride ion, calcium ion and glucose increased as sodium ion

Table 4. Comparative haematological effects of aqueous extract of *Abrus precatorius* leaf

Parameters	Adedapo et al. (2)	Saganuwan (40)
Body weight	ND	↑
Red blood cells	↓	↑
Packed cell volume	↓	↑
Haemoglobin concentration	↓	NS
Mean Corpuscular Volume	↓	↑
Mean Corpuscular Haemoglobin	↑	↓
White Blood Cells Count	↓	↑
Neutrophils	↑	NS
Lymphocytes	↓	↑
Eosinophils	NS	↓
Monocytes	NS	↑
Basophils	ND	↓

Keys: ND=No data, NS=Not significant; ↑ =Increase; ↓ =Decrease

Table 3. Human-animal equivalent therapeutic doses of aqueous leaf extract of *Abrus precatorius*

Animal-human translated doses (mg/kg)														
Human	**Hamster**	**Rat**	**Guinea pig**	**Rabbit**	**Monkey**	**Cat**	**Dog**	**Baboon**	**Ferret**	**Marmoset**	**Squirrel Monkey**	**Micro-pig**	**Mini-pig**	**child**
1.0	9.1*(1.0)	6.6*(0.9)	6.5*(1.2)	3.0*(0.9)	2.9*(0.9)	1.9*(0.9)	1.8*(1.0)	1.8*(1.1)	5.4*(0.9)	6.5*(1.2)	5.6*(1.2)	1.4*(1.0)	1.1*(1.0)	1.5*(1.0)
1.9	18.1	13.2	12.3	6.0	5.8	3.8	3.6	3.6	10.2	12.3	10.6	2.6	2.0	2.9
3.9	36.3	26.4	25.2	12.1	11.6	7.7	7.3	7.3	20.9	25.2	21.8	5.4	4.1	5.8
7.7	72.5	52.7	49.8	24.2	23.2	15.3	14.5	14.5	41.3	50.0	43.1	10.9	11.6	11.6
15.5	145.0	105.5	100.2	48.3	46.4	30.7	29.0	29.0	23.0	100.2	86.8	16.6	23.3	23.2

Note: * = Human-animal safe equivalent dose for a period of 7 days
The values in the brackets are the confirmed human equivalent safe doses approximated to 1 decimal place

Table 5. Comparative biochemical effects of aqueous extract of *Abrus precatorius* leaf

Parameters	Adedapo et al. (3)	Saganuwan and Onyeyili (37, 45)
Alanine aminotransferase	↑	↑
Aspartate aminotransferase	↑	↑
Alkaline phosphate	↑	↑
Cholesterol concentration	ND	NS
Protein	↑	↓
Albumin	↑	↑
Globulin	↑	↑
Albumin/globulin ratio	↑	↑
Urea	ND	↑
Creatinine	ND	↑
Total bilirubin	↑	↑
Direct bilirubin	↑	↓
Indirect bilirubin	↑	↓
Glucose	ND	↑
Sodium ion	ND	↓
Potassium ion	ND	↑
Calcium ion	ND	↓
Chloride ion	ND	↑
Biocarbonate ion	ND	NS
Phosphate ion	ND	↓

Keys: ND=No data, NS=Not significant; ↑ =Increase ↓ =Decrease

and phosphate ion decreased in mice (46). Adedapo et al. (3) didn't report the effect of aqueous extract of *Abrus precatorius* leaf on body weight, glucose, sodium ion, potassium ion, calcium ion, chloride ion, bicarbonate ion and phosphate ion (Table 5).

DISCUSSION

The mouse-human translated LD_{50} of 197.9-241.5 mg/kg body weight agrees with the report of Yamba et al. (58) indicating that the human translated LD_{50} should be between 10^{th} and 100^{th} of LD_{50} in mice. This shows that adult human is the most sensitive to acute poisoning of *Abrus precatorius* leaf followed by child, mini-pig, micro-pig, baboon, dog, cat, monkey, rabbit guinea pig, rat, hamster and mouse in that order (Table 1) invariably rating the extract as slightly to moderately toxic in monogastric animals (26, 40, 41). But the calculated higher LD_{50} of child (297 – 362.3 mg/kg) in comparison with the LD_{50} of adult human (197.9 – 241.5 mg/kg) may be caused by high body surface area of the child in comparison with that of the adult. Hence the child may require more amount of the extract than the adult. Generally the child weighing 20 kg should have developed fully metabolic enzymes. High body surface area is given low km. Connotatively, fatty individuals may be less susceptible to *Abrus precatorius* poisoning than lean individuals. However 12.5 mg/kg body weight that translated to 1.0 mg/kg showed no observable adverse effect when administered for a period of 3 days to *Plasmodium berghei* infected mice, although the dose cleared 98.7% of the parasites in the blood within 9 days after the extract treatment (47). These findings agree with the report of Saganuwan (40) indicating that the Nupe ethnic group from Bida emirate has been using *Abrus precatorius* leaf for the treatment of both acute and chronic malarial symptoms. The use of Abrus leaf in the treatment of malaria among Nupes is sometimes either the last option after the conventional antimalarial drugs might have failed or due to poverty. The administration of 12.5 mg /kg body weight of the extract for 7 days did not cause any observable adverse effect on the treated mice but caused slight increase in the plasma urea level (37, 45). Therefore 1 mg/kg body weight translated dose for a period of 3 days may be safe in human, but when administered for a period of 7 days may likely cause slight increased plasma urea in human. Hence, one–tenth safety factor of mouse therapeutic

dose can be adopted in human, whereas the 100th to 1000th safety factor of *Abrus precatorius* leaf extract may be adopted for doses between 10 and 100 mg/kg body weight of the extract. The least sensitive animal to *Abrus precatorius* aqueous leaf extract in this study may be mice, followed by hamster, rat and guinea pig respectively. However, doses higher than 1.5 mg/kg may be toxic to a child. Also doses higher than 9.1, 6.6, 6.5, 3.0, 2.9, 1.9, 1.8, 1.8, 5.4, 6.5, 5.6, 1.4 and 1.1 mg/kg body weight may be toxic to hamster, rat, guinea pig, rabbit, monkey, cat, dog, baboon, ferret, squirrel monkey, micro-pig and mini-pig respectively (Table 3). Animal human equivalent dose projections can be done in three ways; doses expressed in mg/kg body weight for the species where "the critical effect" leading to "the reference dose" are adjusted to mg/kg body weight$^{0.75}$ to reflect the dependence of pharmacokinetic elimination on metabolic rate-which may tend to scale with (body weight)$^{0.75}$ (1, 34, 53). Although when we scaled the body weight to 0.75 the estimated LD_{50s} were seriously higher in comparison with 0.67. A further adjustment factor may be applied to reflect the median human maximum tolerated dose (MTD) expected based on the identity and number of species that provided data that potentially could have been used as the basis for the reference dose (24). The expected geometric means of the ratios of human toxic potency ($\frac{1}{MTD}$) to the toxic potency estimated from the animal experiments ($\frac{1}{LD_{10}}$) or ($\frac{1}{TDL_0}$) are based on the ratios available for each species or combination of species shown (15). Looking from the single-species analyses to the cases for which data for increasing numbers of species are available for choice of "the most sensitive", it can be seen that the geometric mean ratios of the observed human potency to the human potency projected from the animal potency per (body weight)$^{0.75}$ tend to decline. This is the natural result of the fact that the lowest toxic dose inferred for data for more species will tend to make a more "conservative" prediction of human potency than when data are only available for a single animal species. Finally, the uncertainty in each type of animal-to-human toxic potency projection is inferred from variability of the ratios of the observed human potencies to the animal-projected potencies for different compounds. These variabilities are modelled as lognormal distributions with the standard deviations of the logarithms of the observed human to animal-projected potency ratios (24).

Increased RBC, PCV and haematocrit at dose range between 25-200 mg/kg body weight showed that the plant aqueous leaf extract, have haematinic effect at lower dose levels (44). But at higher dose levels (400-1600 mg/kg), it caused haemolysis with resultant hyperbilirubinaemia (3). However, at both lower doses (25-200 mg/kg) and higher doses (400-1600 mg/kg) the plant leaf extract caused increase in biochemical parameters with resultant deleterious effect on kidney, heart, intestine, lung, spleen and liver. But Adedapo et al. (3) should have conducted acute toxicity study on rats to serve as a guide for their selection of therapeutic doses instead of using predetermined doses. More so, their histopathological studies were restricted to testes, kidney and liver bearing in mind the fact that the plant is organotoxic. When Saganuwan and Onyeyili (40) treated mice with 25-200 mg/kg body weight of Abrus leaf extract for 21 days, the extract caused death of some mice, most especially at higher doses (25 – 200 mg/kg). But, it looked strange that Adedapo et al. (3) didn't report death in their experimental animals with serious kidney and liver damage. The plant has been reported to contain toxalbumin (phytoprotein), abrin, which may be responsible for the observed toxicity effects (21). Abrin consists of abrus agglutinin, and toxic lectins [a] to [d], the five toxic glycoproteins found in the plant. Abrus agglutinin is non-toxic to animal cells but a potent haemaglutinator (7). The toxic portion of abrin is heat-stable to incubation at 60 ^{0}C for 30 minutes, but at 80 ^{o}C most of the toxicity is lost in 30 minutes (36). Although the plant, particularly the seed is known to be highly poisonous due to presence of abrin (7, 12, 14, 21, 36), the leaf in the present study was observed to be slightly toxic. The incubation of the abrus leaf extract at 60 ^{o}C for several hours must have reduced the toxicity of the leaf (46). Although the extract was administered orally, abrin is very stable in the gastrointestinal tract, from where it is slowly absorbed and thereby making it less toxic (19). Abrins's toxic effect is due to its direct action on the membrane of parenchymal cells (e.g. liver, kidney cells and erythrocytes) (23) via the B chain (haptomere) that binds to galactosyl-terminated receptors on the cell membrane, which is a prerequisite for the entry of the other subunit, the A chain (effectomere). This inactivates the ribosomes, arrests protein synthesis, and causes cell death (50). The A-chain attacks the 60s subunits of the ribosomes and by cutting out elongation EF_2 stops synthesis of protein (18). So the extraction and concentration of aqueous extract of *Abrus precatorius* leaf at 60 ^{o}C (46) and unknown temperature (3) must have reduced toxic effects of the leaf extract in mice and rats respectively.

CONCLUSION

The translated mouse-human LD_{50} is 197.9-241.5 mg/kg body weight, showing high level of sensitivity of humans to *Abrus precatorius* leaf poisoning. The safe human therapeutic dose for a period of 3 days may be 1.0 mg/kg body weight. But the safe therapeutic doses for other animals are; hamster (9.1 mg/kg), rat (6.6 mg/kg), guinea pig (6.5 mg/kg), rabbit (3.0 mg/kg), monkey (2.9 mg/kg), cat (1.9 mg/kg), dog and baboon (1.8 mg/kg) and child (1.5 mg/kg) respectively. However, the administration of the safe doses for a period of 7 days may cause slight increase in the plasma urea.

REFERENCES

1. Ad Hoc Working Group (AHWG) (1992). Federal Coordinating Council for science, engineering and technology (FCCSET) Draft Report: A cross-section scaling factor for carcinogen risk assessment based on equivalence of mg/kg3 /day. Federal Register 57: 24152 – 24173.
2. Adedapo, A.A. (2002). Toxicological effects of some plants in the family euphorbiaceae in rats. PhD Thesis, University of Ibadan, Nigeria.
3. Adedapo, A.A., Omoloye, O.A., Ohore, O.G. (2007). Studies on the toxicity of an aqueous extract of the leaves of Abrus precatorius in rats. Onderstepport J Vet Res. 74, 31 36. http://dx.doi.org/10.4102/ojvr.v74i1.137
4. Adelowotan, O., Aibinu, I., Adenipekun, E., Odugbemi, T. (2008). The in vitro antimicrobial activity of Abrus precatorius (L) Fabaceae extract on some clinical pathogens. Niger Postgrad Med. J. 15 (1): 32-37. PMid:18408781
5. Anam, E.M. (2011). Anti-inflammatory activity of compounds isolated from the aerial parts of Abrus precatorius (Fabaceae). Phytomedicine 8(1): 24-27. http://dx.doi.org/10.1078/0944-7113-00001 PMid:11292235
6. Anand, R.S., Kishire, V.O., Rajkumar, V. (2010). Abrus prectorius. A phytopharmacological review. J. Pharm. Res. 3(11): 2585-2587.
7. Budavari, S. (1989). The Merak Index: An Encyclopedia of Chemicals, Drugs and Biologicals, 10th ed., Rahway, New Jersey, Merck and Co. Inc PMid:2666071
8. Burkill, H.M. (1997). The useful plant of West Tropical Africa, Vol 11, Royal Botanical Gardens, Kew.
9. Cheecke, P.R. (1998). Natural toxicants in feed, forage and poisonous plants. Interstate Publishers, Denville.
10. Cheecke, P.R., Shull, L.R. (1985). Natural toxicants in feeds and poisonous plants. The Connecticut: AVI Publishing Company.
11. Choudhari, A.B., Sayyed, N., Khairnar, A.S. (2011). Evaluation of antiserotonergic activity of ethyl acetate extract of Abrus precatorius leaves. J. Plant Res. 4(3): 570-572.
12. Davis, J.H. (1978). Abrus precatorius (Rosary pea). The most common lethal plant poison. J. Florida Med Assoc. 65, 189-191.
13. Dhawan, B.N., Patnaik, G.K., Singh, K.K., Tandon, J.S., Rastogi RP. (1977). Screening of Indian plants for biological activity. Indian J Exp Biol. 15, 208-219. PMid:914326
14. Dreisbach, R.H., Robinson, W.O. (1987). Handbook of poisoning: prevention, diagnosis and treatment. Los Altos, Appleton and Lange, California 497.
15. Faustman, E.M., Allen, B.C., Karlock, R.J., Kimmel, C.A. (1994). Dose-response assessment for developmental toxicity. 1. Characterization of database and determination of no observed adverse effect levels. Fundamental Appl. Toxicol. 23, 478-486. http://dx.doi.org/10.1006/faat.1994.1132
16. Fernando, C. (2011). Poisoning due to Abrus precatorius (Jequirity bean). Anaesthesia 56 (12): 1178-1180.
17. Freireich, E.J., Gehan, E.A., Rall, D. (1966). Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey and man. Cancer Chemother. Rep. 50, 219-244. PMid:4957125
18. Frohne, D., Pfander, H.J. (1983). A colour atlas of poisonous plants. Germany Wolfe Publishing Ltd., 291. PMid:6683299
19. Galey, F.D. (1996). Plants and other natural toxicants. In: (Smith BP. Ed), Large Animals Internal Medicine, 2nd ed., Boston: Mushby Publishers.
20. Garg, S.K. (2005). Veterinary toxicology. New Delhi CBS publishers and Distributors, p321.
21. Ghosal, S., Dutta, S.K. (1971). Alkaloids of Abrus precatorius. Phytochemistry 10(1): 195-198. http://dx.doi.org/10.1016/S0031-9422(00)90270-X
22. Hart, M. (1963). Jecquirity bean poisoning. N. Engl. J. Med. 268, 885-886. http://dx.doi.org/10.1056/NEJM196304182681608
23. Hatts, D.S., S. Goble, R. (2002). A straw-man proposal for a quantitative definition of the reference dose. DOD conference on Toxicology risk assessment, Dayton, Ohio, 25, 2001, p 1-48.

24. Hemadari, K., Rao, S.S. (1983). Leucorrhoea and menorrhalgia, tribal medicine, Ancient Sci. Life 3, 40-41.

25. Hodge, H.C., Sterner, J.H. (1949). Toxicity rating. Am. Ind. Hyg. Assoc. Q. 10(4): 93. PMid:24536943

26. Iwu, M.M. (1993). Handbook of African medicinal plants. London: CRC Press Boca Raton Ann Arbot.

27. Kim, N.C., Kim, D.S., Kinghorn, A.D. (2002). New triterpenoids from the leaves of Abrus precatorius. Nat. Prod.Let.16 (4): 261-266. http://dx.doi.org/10.1080/10575630290020596 PMid:12168762

28. Kirtikar, K.R., Basu, B.D. (1980). Indian medicinal plants. Vol. 1, Dehra Dun: International Book Distributors.

29. Klassen, C.D. (2011). Casarett and Doall's. Toxicology: The basic science of poisoning. 6th ed., New York: Mc Graw-Hill.

30. Limmatvapirat, C., Sirisopanapom, Kittakoop, P. (2004). Antitubercular and antiplasmodial constituents of Abrus precatorius. Planta Med. 70 (3): 276-278. http://dx.doi.org/10.1055/s-2004-818924 PMid:15114511

31. Liu, C.L., Tsai, C.C., Lin, S.C. Wang, L.I., Hsu, C.I., Hwang, M.J., Lin, J.Y. (2000). Primary structure and function analysis of Abrus precatorius agglutinin A by site-directed mutagenesis, Pro (199) and amphiphilic alpha-helix H impairs protein synthesis inhibitory activity. J. Biol. Chem. 275 (3): 1897-1901. http://dx.doi.org/10.1074/jbc.275.3.1897 PMid:10636890

32. Mann, A., Gbate, M., Nda, Umar, A. (2003). Medicinal and economic plants of Nupeland. Bida: Jube Evans Books and Publications, p.191.

33. Mordent, J. (1986). Man versus beast: pharmacokinetic scaling in mammals. J. pharmaceut. Sci. 75, 1028–1040. http://dx.doi.org/10.1002/jps.2600751104

34. Premanand, R., Ganesh, T. (2010). Neuroprotective effects of Abrus precatorius Linn. Aerial extract on hypoxic neurotoxicity induced rats. Intern. J. Chem. Pharmaceut. Sci. 1(1).

35. Rajaram, N., Janardhanan, K. (1992). The chemical composition and nutritional potential of the tribal pulse, Abrus precatorius L. plant. Foods Human Nutr. 42(94): 285-290. http://dx.doi.org/10.1007/BF02194088

36. Reagan-Shaw, S., Nihal, M., Amhad, N. (2007). Dose translation from animal to human studies revisited. The FASEBJ 22, 659-661. http://dx.doi.org/10.1096/fj.07-9574LSF PMid:17942826

37. Saganuwan, S.A., Onyeyili, P.A. (2012). Haematonic and plasma expander effects of aqueous leaf extract of Abrus precatorius in Mus musculus. Campar Clinical Pathol. 21(6): 1249-1255. http://dx.doi.org/10.1007/s00580-011-1274-8

38. Saganuwan, S.A. (2011). A modified arithmetical method of Reed and Muench for determination of a relatively ideal median lethal dose (LD50). Afr. J. Pharm. Pharmacol. 5(12): 1543-1546. http://dx.doi.org/10.5897/AJPP11.393

39. Saganuwan, S.A. (2012). Toxicological and antimalarial effect of aqueous leaf extract of Abrus precatorius (Jacqurity bean) in Swiss albino mice. PhD Thesis, Usmanu Danfodiyo University, Sokoto Nigeria.

40. Saganuwan, S.A. (2012b). Principles of pharmacological calculations. 1st ed., Zaira: Ahmadu Bello University Press Ltd.

41. Saganuwan, S.A., Gulumbe, M.L. (2005a). In vitro antimicrobial activities testing of Abrus precatorius cold water leaf extract on Salmonella typhimurium, Escherichia coli and Klebesiella pneumoniae. J. Sci. Technol. Res. 4(3): 70-73.

42. Saganuwan, S.A., Gulumbe, M.L. (2005b). In vitro antimicrobial activities testing of Abrus precatorius cold water leaf extract on Streptococcus pyogenes and Streptococcuspneumoniae. Proc 2nd Annu Conf Nigerian Soc. Indigen Knowl Dev., 9th-12th Nov., Cross River State Univ. Technol Obubra, 93-97.

43. Saganuwan, S.A., Onyeyili, P.A., Etuk, U.E. (2009). Acute toxicity and haematological studies of aqueous extract of Abrus precatorius leaf in Mus Musculus, African Education Initiative Conf. p65.

44. Saganuwan, S.A., Onyeyili, P.A., Suleiman, A.O. (2011). Comparative toxicological effects of orally and intraperitoneally administered aqueous extracts of Abrus precatoriusleaf in Mus musculis. Herba Polonica 57(3): 32-44.

45. Saganuwan, S.A., Onyeyili, P.A. (2010). Biochemical effects of aqueous leaf extract of Abrus precatorius (Jecurity bean) in Swiss albino mice. Herba Polonica 56(3): 63-80.

46. Saganuwan, S.A., Onyeyili, P.A., Ameh, I.G., Etuk, E.U. (2011). In vivo antiplasmodial activity by aqueous extract of Abrus precatorius in mice. Rev. Latinoamer. Quin. 39(1-2): 32-34.

47. Sawyer, N., Ratain, M.J. (2001). Body surface area as a determinant of pharmacokinetics and drug dosing. Invest New Drugs 19, 171-177. http://dx.doi.org/10.1023/A:1010639201787 PMid:11392451

48. Sofi, M.S., Sateesh, M.K., Bashir, M.,Harish, G., Lakshmeesha, T.R., Vedashree, S., Vedamurthy, A.B. (2012). Cytotoxic and pro-apoptotic effects of Abrus precatorius L. on human metastatic breast cancer cell line, NDA-NB-231. Cytotechnology

49. Stirpe, F., Barbieri, L. (1986). Symposium: Molecular mechanisms of toxicity, toxic lectins from plants. Human Toxicol. 5(2): 108-109. http://dx.doi.org/10.1177/096032718600500208

50. Sylva, M. (1998). Interspecies allometric scaling in pharmacokinetics of drugs. Acts Pharm Hung. 68 (6): 350-354.

51. Taur, D.J., Patil, R.Y. (2011). Effect of Abrus precatorius Leaves on milk induced leukocytosis and eosinophilia in the management of asthma. Asian Pacific J. Tropical. 1(1): 40-42. http://dx.doi.org/10.1016/S2221-1691(11)60119-6

52. Travis, D.C., White, R.K., Ward, R.C. (1990). Interspecies extrapolation of pharmacokinetics. J. Theoretical Biol. 142, 285 - 304. http://dx.doi.org/10.1016/S0022-5193(05)80554-5

53. Tripathi, S., Maith, T.K. (2005). Immunomodulatory role of native and heat denatured agglutinin from Abrus precatorius. Int. J. Biochem. Cell Biol. 37(13): 451-462. http://dx.doi.org/10.1016/j.biocel.2004.07.015 PMid:15474989

54. US Environmental Protection Agency (USEPA) (1986). Guideline for carcinogen risk assessment. Fed Regist 51: 3392-4003.

55. Wambebe, C., Amosun, S.L. (1984). Some neutromuscular effects of crude extracts of the leaves of Abrus precatorius. J. Ethnopharmacol. 11(1): 49-58. http://dx.doi.org/10.1016/0378-8741(84)90095-3

56. Watt, J.M., Breyer-Brandiwijk, A. (1962). The medicinal poisoning plants of Southern and Eastern Africa, 2nd ed., London: Livingstone publishers. PMCid:PMC1957435

57. Xiao, Z.H., Wang, F.Z., Sun, A.J. (2011). A new triterpenoid saponin from Abrus precatorius Linn. Molecules 17(1): 295-302. http://dx.doi.org/10.3390/molecules17010295 PMid:22210168

58. Yamba, O., Innocent, P.G., Odille, G.N. (2007). Biological and toxicological study of aqueous root-extract from Mitragyna inermis (Wild Okt) Rubiacea. Int. J. Pharmacol. 3(1): 80-85. http://dx.doi.org/10.3923/ijp.2007.80.85

Please cite this article as: Saganuwan S.A., Onyeyili P.A. The paradox of human equivalent dose formula: A canonical case study of Abrus precatorius aqueous leaf extract in monogastric animals. Mac Vet Rev 2016; 39 (1): 23-32. http://dx.doi.org/10.1515/macvetrev-2015-0061