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Reproductive and Developmental Toxicity of *Cryptolepis sanguinolenta* in Mice

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Abstract: *Cryptolepis sanguinolenta* (Periplocaceae), the herbal anti-malarial is a known cytotoxic and a DNA intercalator. Because cytotoxics can provoke adverse effects on developing foetuses, we studied the effect of the aqueous root extract of the plant (cryptolepis) on reproduction and foetal development in mice. Cryptolepis (62.5-1000 mg kg^{-1}) reduced female fertility from 100% in the control group to 0% at a dose of 1000 mg kg^{-1}. Cryptolepis (1000 mg kg^{-1}) also abolished pregnancy in 60% of mice treated during gestation from the onset of organogenesis. In addition, intrauterine growth inhibition was 37.0% and foetal mortality was 12.0%. Cryptolepis however, did not alter the gestation period or induce any malformation. In the dominant male lethal assay, cryptolepis (62.5-1000 mg kg^{-1}) did not induce significant increase in post implantation losses. Though, the present results cannot be directly extrapolated to man, the findings call for caution in the use of cryptolepis during pregnancy.

Key words: *Cryptolepis sanguinolenta*, reproduction, fertility, foetal development, mortality, genotoxicity

INTRODUCTION

Cryptolepis sanguinolenta is a plant used extensively in West African traditional medicine for the treatment of malaria (Sofowora, 1982). Cryptolepine, the major alkaloid in the aqueous root extract (Dwuma-Badu *et al*., 1978) is cytotoxic (Ansah and Gooderham, 2002; Bonjean *et al*., 1999) and is believed to cause apoptosis by intercalating DNA and inhibiting topoisomerase I (Bonjean *et al*., 1999; Dassonneville *et al*., 1999; Lisgarten *et al*., 2002). We estimated the LD_{50} of the aqueous root extract of the plant (cryptolepis) and found it to be well over 5000 mg kg^{-1} (unpublished), suggesting an apparent wide margin of safety. However, with the high incidence and debilitating nature of malaria in West Africa together with the high cost of conventional medications, the frequency of exposure to cryptolepis may be substantial though could be underestimated. For example, *Cryptolepis sanguinolenta* products have emerged in Ghanaian pharmacies and herbal shops for malaria treatment and are freely available to the general public including pregnant women and infants, who are particularly susceptible to malaria attacks. Cytotoxics are best avoided in pregnancy due to their tendency to cross the placenta, exerting adverse effects on the developing foetus (Cardonick and Iacobucci, 2004). Findings such as premature birth, low birth weight, major malformations, spontaneous abortions and foetal death particularly in the first trimester have been shown with cytotoxic administration during pregnancy (Leslie *et al*., 2005; Norgard *et al*., 2003; Zemlickis *et al*., 1992). *Cryptolepis* is reportedly cytotoxic (Ansah and Gooderham, 2002) and weakly mutagenic and/or clastogenic in mammalian assays (Ansah *et al*., 2005) but there is little information on its potential effect on pregnancy and the developing foetus. Paternal exposure to mutagens can also result in adverse outcomes on the survival and health of the offspring (Green *et al*., 1985; Russell and Shelby, 1985; Shelby, 1994). The effect of cryptolepis on reproduction and foetal development in mice is observed.

MATERIALS AND METHODS

Plant material: Dried *Cryptolepis sanguinolenta* roots were obtained from the Centre for Scientific Research into Plant Medicine, Mampong-Akwapim, Ghana, where it is routinely used as an antimalarial agent at the clinic. To simulate the traditional method of preparation, 1.0 kg of the dried roots was milled and extracted by boiling with 10 L of distilled water. The solution was filtered and the filtrate after cooling was freeze dried to obtain a yellowish brown powder referred to subsequently as cryptolepis. Routinely, cryptolepis was freshly prepared in water and administered by gavage to the experimental animals.

Animals: ICR mice (20-30 g) were purchased from Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Accra, Ghana and maintained in the animal house of the Department of Pharmacology,

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College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana. They were housed in stainless steel cages (34×47×18 cm) with soft wood shavings as bedding and fed with normal commercial pellet diet (GAFCO, Tema, Ghana) and given water *ad libitum*. The animals were humanely handled throughout the experiment in accordance with internationally accepted principles for laboratory animal use and care. The experimental protocols were approved by the College of Health Sciences Ethics Committee.

Reproductive toxicity in female mice: Five groups of ICR mice (n = 20) were used in the study. Group I was the vehicle control and received distilled water only. Groups II, III, IV and V received 62.5, 100, 500 and 1000 mg kg^{-1} of cryptolepis daily for two weeks representing the pre-treatment phase. After the two weeks pre-treatment, animals were regrouped by subdividing each group into two to provide ten groups (n = 5) as follows: IA, IB, IIA, IIB, IIIA, IIIB, IVA, IVB, VA and VB. Two male mice were introduced into all the 10 groups. Groups IA and IB were maintained as control groups and continued to receive distilled water only. Treatment with cryptolepis was then discontinued in the A groups i.e., groups IIA, IIIA, IVA and VA. However, the B groups i.e., groups IIB, IIIB, IVB and VB continued to receive 62.5, 100, 500, 1000 mg kg^{-1} of cryptolepis till the end of gestation. Formation of vaginal plug was taken as evidence of successful mating. The effect of the extract on fertility, mating, litter number, litter size, life births and gestation period were assessed. Reproductive indices were then determined.

The dominant male lethality assay: The method used was as described (Green *et al*., 1985) with modifications. Twenty male ICR mice were grouped into four (n = 5). Group I was the vehicle control group and received distilled water only throughout the duration of the experiment. Groups II, III and IV received 62.5, 500 and 1000 mg kg^{-1} of cryptolepis daily dissolved in distilled water, respectively, throughout the duration of the experiment for 5 days. Individual animals in the groups were assessed on weeks 1, 2 and 5 after the treatment period by mating with two females. Successful mating was indicated by the formation of vaginal plugs. Females were then assessed on gestation day 14 and pregnant females were laprotomized for the determination of early death recognized as decidual tissue or moles.

Epididymal sperm assay: For epididymal sperm counts, the method described by Meistrich (1989) was used with slight modifications. Four groups of male mice (n = 5) were used in the study. Group 1 served as the vehicle control and received distilled only. The other three groups received 62.5, 500 and 1000 mg kg^{-1} of cryptolepis daily respectively for 2 weeks. Animals from each group were then euthanized by cervical dislocation and the wet weight of the left caudal epididymis and testis was taken.

For sperm analysis, the left caudal epididymis was minced and homogenized for 4 min in 10 mL of 0.9% $NaHCO_3$ solution containing 0.1% formalin. The homogenate was allowed to settle at 4°C, diluted to 50 mL and lightly stained with 40% eosin solution. After agitation of the stained samples, an aliquot was immediately dropped onto a haemocytometer and sperm heads were counted.

Developmental studies: Eighty female 1CR mice were kept together for three weeks to synchronize their oestrous cycle. The mice were then cohabited with males and observed for signs of mating by directly observing copulation or formation of vaginal plugs. Successful mated females were tagged and the day for mating recorded as gestation day 0. Mated mice were then grouped into four (n = 10) with Group 1 (vehicle treated control) receiving distilled water only. Groups II, III and IV received 62.5, 500 and 1000 mg kg^{-1} of cryptolepis from the 4th day of gestation to end of gestation. Mice were assessed on gestation day 14 and on gestation day 21 for signs of pregnancy indicated by maternal weight changes and evidence of litter at the end of gestation, respectively. Litter size, litter weight and life status were assessed.

Statistical analysis: Results for the experiments were analyzed using graph pad prism version 5. Results presented as mean±SD were analyzed by one way ANOVA using Bonferroni post test to compare columns. A value of $p<0.05$ was used as the criterion for statistical significance. Two way ANOVA using Bonferroni post-test was used to analyze post implantation between the weeks of treatment.

RESULTS AND DISCUSSION

Cryptolepis has been used over the years as an antimalarial agent (Sofowora, 1982). Recent evidence suggests that cryptolepine, the major alkaloidal constituent in the extract is cytotoxic and a DNA intercalator (Ansah and Gooderham, 2002; Bonjean *et al*., 1999; Lisgarten *et al*., 2002). Cytotoxic agents have the propensity to provoke reproductive toxicity (Cardonick and Iacobucci, 2004). To date the possible effect of this popular antimalarial agent on reproduction has not been investigated. We therefore, sought to

Table 1: Comparison of reproductive indices for female mice pre-treated with cryptolepis for 14 days only prior to mating and female mice pre-treated with cryptolepis for 14 days prior to mating with continued treatment during gestation

Treatments	Group/dose of cryptolepis	No. of mated animals	No. of pregnant females	Deaths during pre-treatment	Mating index (%)	Fertility index (%)	Gestation period	Live Birth index	Weaning index
Pre-treatment for	1A (Control)	10	10	0	100	100	20.33±1.414	96.7	100
14 days only	IIA (62.5 mg kg^{-1})	9	9	1	100	100	20.22±0.666	97.3	100
followed by mating	IIIA (100 mg kg^{-1})	10	9	0	100	90	20.01±0.7071	98.0	98
	IVA (500 mg kg^{-1})	10	10	0	100	100	20.34±1.432	97.0	100
	VA (1000 mg kg^{-1})	7	7	3	100	100	20.23±0.365	100.0	100
Pre-treatment for	1B (Control)	10	10	0	100	100	20.11±0.833	100.0	100
14 days followed	IIB (62.5 mg kg^{-1})	10	4	0	100	40	21.23±1.118	94.1	42
by mating and	IIIB (100 mg kg^{-1})	10	6	0	100	60	20.78±1.568	86.4	94
continued treatment	IVB (500 mg kg^{-1})	10	3	0	100	30	21.56±0.711	70.0	85
during gestation	VB (1000 mg kg^{-1})	5	0	5	100	0	-	-	-

Mating Index (%), No. of mated females/number of females cohabited), Live Birth Index (%), No. of live offspring/number of offspring delivered), Weaning Index (%), No. of offspring at day 21/number of offspring delivered), Fertility index (% mated females/number of pregnant females)

Table 2: Reproductive performance of male mice following treatment with cryptolepis and its effect on fertility and total implants in untreated female mice

Post treatment period (week) in males	Dose	Female Fertility index	Total implants per female	Total live implants/ female	No. of deaths per female	Percentage of post implantation loss
One	Control	100	11.40±2.171	11.00±2.0000	0.400	3.51
	62.5 mg kg^{-1}	80	10.63±1.923	10.38±1.9230	0.250	2.35
	500 mg kg^{-1}	100	10.20±1.687	10.00±1.8260	0.200	1.96
	1000 mg kg^{-1}	70	11.00±2.380	10.71±2.4300	0.290	2.60
Two	Control	100	9.60±1.955	9.00±1.2470	0.600	6.25
	62.5 mg kg^{-1}	100	11.00±1.491	10.50±1.7800	0.500	4.95
	500 mg kg^{-1}	90	11.22±2.224	10.89±2.0880	0.330	4.41
	1000 mg kg^{-1}	80	8.50±2.828	8.250±2.493	0.250	2.94
Five	Control	100	10.30±1.130	9.80±1.3170	0.500	4.85
	62.5 mg kg^{-1}	100	10.20±1.814	9.80±1.6780	0.400	4.40
	500 mg kg^{-1}	90	10.11±2.028	10.00±2.0000	0.110	1.10
	1000 mg kg^{-1}	80	10.25±1.389	9.875±1.458	0.375	3.66

assess the effect of the aqueous extract routinely used for malaria therapy on reproduction and foetal development in mice.

In the reproductive study (Table 1), we assessed the potential effect of cryptolepis in mice. Female mice aggressively resist mating in several phases of the oestrous cycle except within the pro-oestrous and oestrous phases. Alteration to the oestrous cycle in mice will most invariably affect mating as ovulation occurs during oestrous phase. In the presence of substances that inhibit ovulation, mating may occur but there will be no fertilization. COX-2, one of two isoenzymes of cyclooxygenase, is active in the ovaries during follicular development and COX-2 inhibition has major effects on ovulation, fertilization and implantation in rats as well as humans (Skomsvoll *et al*., 2005; Zanagnolo *et al*., 1996). Cryptolepine, the main alkaloid in the aqueous extract posses potent anti inflammatory properties (Olajide *et al*., 2009; Noamesi and Bamgbose, 1980) and has recently been suggested to inhibit COX-2. In the present study, cryptolepis reduced fertility considerably in female mice (Table 1) consistent with the action of COX-2 inhibitors. It is plausible that the observed reduction in fertility is related to the COX-2 effects of cryptolepis on ovulation. Additionally, cryptolepis terminated pregnancies in mice, which suggest that inhibition of ovulation may not be the only possible mechanism for the observed reduced fertility.

Cryptolepis causes G1 arrest in growing mammalian cells (Ansah and Gooderham, 2002), which can trigger apoptosis and induce foetal mortality following irreparable damage to the developing embryonic cells. Mortality at the very early stages of conception leads to resorption of the dead embryo and may present as reduced fertility.

Male mice received 62.5, 500 and 1000 mg kg^{-1} cryptolepis for 5 days and were mated serially on different weeks with two female mice. The impregnated females were kept until 14 days postcoitus. For each group, females were assessed according to the dominant lethal protocol (Green *et al*., 1985). There were no significant differences in post implantation losses between female groups assessed at week 1, 2 and 5 (Table 2). Treatment however, affected male fertility as reflected in decreased female fertility index at all doses of cryptolepis employed (Table 2). These effects persisted for up to week 5 after discontinuation of the treatment with cryptolepis albeit slight improvement in the fertility index (Table 2). Very few substances can be cytotoxic yet not genotoxic. *In vitro* studies by Ansah *et al*. (2005) showed that cryptolepine,

the main alkaloid in the extract was not genotoxic. However, the extract showed low genotoxicity at very high doses and attributed this observation to the possible presence of a minor genotoxic constituent. The results of the dominant lethality assay at present confirms that cryptolepis is at best weakly genotoxic, consistent with the *in vitro* report.

Left caudal epididymis and testes of mice exposed to cryptolepis or distilled water for 2 weeks were extracted and weighed and further subjected to sperm analysis as described by Meistrich (1989). The mean wet weights of the organs of the treated groups were reduced especially at 1000 mg kg^{-1} of cryptolepis although, it was not significant at $p<0.05$ compared to the control. However, sperm numbers decreased significantly ($p<0.05$) in all treated groups compared to the vehicle-treated group (Fig. 1). Significant weight losses, as high as 15% in some animals, occurred in all treated groups although, variability in susceptibility existed within animals of the same group.

Antimuscarinic activity (Rauwald *et al*., 1992), α-adrenoceptor antagonism (Bamgbose and Naomesi, 1981) and cytotoxicity (Ansah and Gooderham, 2002; Bonjean *et al*., 1999) are some of the pharmacological effects exhibited by cryptolepine and can adversely affect male fertility in rodents. Atropine and other antimuscarinic agents inhibit male fertility reversibly by an unknown mechanism (Sato *et al*., 2005; Ratnasooriya, 1984). Prazosin, phenoxybenzamine, tamsulosin all α- 1-adrenoceptor antagonists have a potent negative effect on fertility in male rodents by inhibition of sperm emission (Ratnasooriya and Wadsworth, 1994; Homonnai *et al*., 1984). The mechanism involves an inhibition on both the neurally-evoked contractions on vas deferens and sperm transport from the caudal epididymis to the distal vas deferens hence, reducing sperm numbers in the ejaculated semen (Solomon *et al*., 1997; Bradley and Doggrell, 1985; Doggrell, 1981). Subacute treatment of male animals for two weeks with cryptolepis resulted in a dose-dependent reduction in average sperm number in the head of the caudal epidimydis (Fig. 1). The combined wet weight of the left testes and epididymis, though not significant, was less than that of the control particularly at 1000 mg kg^{-1}. Cytotoxics have adverse effect on proliferating cells thus affecting male fertility by reducing the number of sperms, their morphology as well as the integrity of the organs involved (Klaassen *et al*., 1996). Administration of cryptolepis to pregnant mice before organogenesis (day 5-6) and throughout gestation caused termination of pregnancies in mice (Table 3). Terminations of pregnancies were between 40-60% of treated groups as against 0% for the control group (Table 3). Significant weight deficits (intrauterine growth inhibition) were high in litters born to cryptolepis treated mothers. Mortality

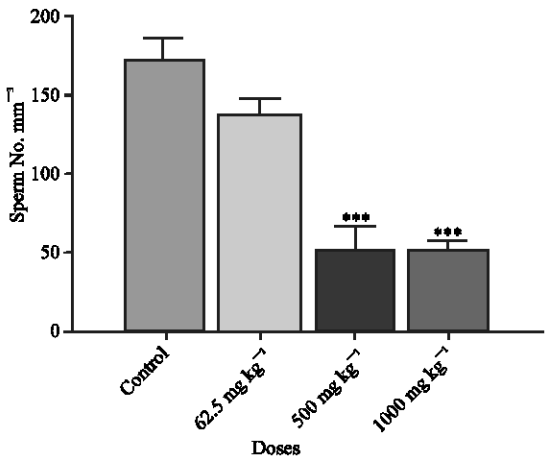

Fig. 1: Effect of cryptolepis on cauda epididymal sperm number. Male mice were treated with either cryptolepis (62.5-1000 mg kg^{-1}) or distilled water for 2 weeks. The left caudal epididymis was then processed for sperm heads count as described in the method using a haemocytometer. Sperm number is presented as mean±SD (n = 5). ***indicates significance from vehicle treated control ($p<0.001$) using one-way ANOVA followed by Bonferroni's post hoc test

Table 3: Effect of cryptolepis on pregnancy and foetal development in mice

Doses	Pregnant females (%)	Foetal mortality (%)	Mean litter weight
Control	100	0.5	1.450±0.124
62.5 mg kg^{-1}	50	3.0	1.361±0.168
500 mg kg^{-1}	60	5.5	1.251±0.249*
1000 mg kg^{-1}	40	12.0	1.200±0.324**

Mean litter weight is presented as mean±S.D (n = 20). *indicates significance from vehicle treated control ($p<0.05$) and **indicates significance from vehicle treated control ($p<0.01$) using one-way ANOVA followed by Bonferroni's post hoc test

amongst offspring was 12% at 1000 mg kg^{-1} of cryptolepis as against 0.5% of the control although, no anatomical malformations in limbs, palate and spine were observed. For a toxic outcome, the timing of exposure is very important as different phases of foetal development have varying susceptibility (Klaassen *et al*., 1996; Wilson, 1973). The ability of cryptolepis to terminate pregnancies may suggest that its embryonic toxicity occur around the very early stage of development. Indeed most developmental toxicants, which induce growth deficits and death without malformation exert their effects during the early stage before organogenesis (Klaassen *et al*., 1996). This has been demonstrated for DDT, nicotine or methyl methane sulfonate (Klaassen *et al*., 1996; Fabro *et al*., 1984) and the same effect were seen with cryptolepis. The embryo around the fourth day is a fluid filled cavity with only a few of the cells (inner mass of

cells) present developing into the organism. The cells are undifferentiated with great restorative potential (Snow and Tam, 1979), hence can regenerate if the damage is not overwhelming to lead to malformations and death.

CONCLUSION

Cryptolepis sanguinolenta extract reduces fertility in male and female mice. It terminates pregnancies, when introduced before organogenesis. It also induces foetal mortality and intrauterine growth inhibition in developing mice. Although, the present findings cannot be directly extrapolated to humans caution needs to be taken in the use of cryptolepis especially during pregnancy.

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