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# AQUEOUS ROOT EXTRACT OF THE ANTIMALARIAL HERBAL *CRYPTOLEPIS SANGUINOLENTA* (LINDL.) SCHLTR DELAYS THE DEVELOPMENT OF PHYSICAL LANDMARKS AND SENSORIMOTOR SYSTEMS IN MICE

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**ABSTRACT:** We demonstrated previously that the aqueous root extract of *Cryptolepis sanguinolenta* (cryptolepis), with cryptolepine as the major constituent adversely affect reproduction and foetal development in mice. However, very little is known on the effect of prenatal exposure of cryptolepis on the post-natal life of surviving animals. Using murine models, we report here, the effects of prenatal exposure to cryptolepis on the growth and development of physical landmarks and sensorimotor systems. Prenatal cryptolepis (62.5, 100, 500 mg/kg; p.o) treatment of pregnant mice from gestation day 6 - 19 significantly caused a delay in eye opening and development of reflexes such as righting, mid-air righting, auditory startle and pinna reflex. Prenatal cryptolepis treatment also inhibited intrauterine growth but not post-natal growth. This study shows that prenatal cryptolepis treatment provokes functional toxicity by delaying the development of physical landmarks and sensorimotor systems in mice.

**INTRODUCTION:** According to the WHO, malaria is still endemic in Africa[1] despite considerable efforts towards its eradication. Malaria inflicts both social and economic burden on affected people and majority of malaria patients in developing countries depend heavily on herbal remedies.

The use of the aqueous extract of the root bark of *Cryptolepis sangunolenta* is popular in Ghana and other West and Central African communities [2] where it is used particularly as antimalarial, antidysentry and a febrifuge [2, 3].

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The plant is rich in indole alkaloids which are lead compounds in the search for new antimalarial drugs. Principal amongst its alkaloids is cryptolepine (Figure 1) [2].

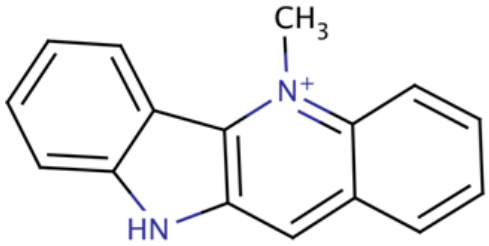


**FIGURE 1: CRYPTOLEPINE; THE MAIN ALKALOID FROM THE AQUEOUS ROOT EXTRACT OF *CRYPTOLEPIS SANGUINOLENTA*.**

Results from clinical studies provide scientific credence to the traditional use of the aqueous extract of the roots of *Cryptolepis sanguinolenta* as antimalarial medicine [4].

Although the aqueous extract of *Cryptolepis sanguinolenta* is not known to be teratogenic, it is reported to cause mortalities and intrauterine growth inhibitions in mice [5]. Presently, very little is known about surviving mice prenatally exposed to cryptolepis. Surviving mice may be morphologically and structurally identical to non-treated animals but may have functional deficiencies that may become apparent in adult life. Earlier research with cryptolepine showed that cryptolepine accumulates in tissues of the foetus particularly melanin containing tissues of the eye [6]. Since pregnant women and children below the age of five are more vulnerable to malaria and subsequent recurrent malaria attacks, it is essential to ascertain the safety of potential antimalarials in these susceptible groups. In the present study, we report on the effect of prenatal exposure to cryptolepis on the post natal life of surviving mice.

## MATERIALS AND METHODS:

**Plant material:** Dried *Cryptolepis sanguinolenta* roots were obtained and authenticated at the Centre for Scientific Research into Plant Medicine, Mampong-Akwapim, Ghana. At this research centre and herbal clinic, aqueous root extract of the plant is used for the management of malaria. The aqueous root extract was prepared in a similar manner to the method of preparation at the Centre. Briefly, dried cryptolepis roots (1 kg) was milled and extracted by boiling with 10 litres of distilled water for 30 minutes. The solution was filtered and the filtrate after cooling was freeze dried to obtain a yellowish-brown powder referred to subsequently as cryptolepis. The percentage yield was 9.3% w/w. The powder was stored at 4$^{o}$C immediately prior to use. In this study, 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, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana. The animals were maintained in stainless steel cages (34 x 47x 18 cm) with soft wood shavings as bedding. They were 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 (EEC Directive of 1986: 86/609 EEC). All animal experiments and protocols were approved by the departmental ethics committee.

**Treatment of Animals:** Forty (40) female mice were cohabited with 20 male mice. Direct observation of copulation or formation of vaginal plugs were used as markers for mating. Successfully mated females were tagged and assigned to one of four groups (n=7). The day was recorded as gestation day 0. The mated animals received either aqueous cryptolepis (62.5, 100, 500 mg/kg; *p.o*) or distilled water from gestation day 6 to the end of gestation. On gestation day 16, dams were assigned to individual cages containing approximately 3cm depth of coarse saw dust and treatment continued until delivery. The day of birth (day 0) was determined by examining the cages twice a day; morning and evening. The duration of gestation, the number of pups per dam, weight of pups and crown-rump distance were measured. Pups were culled up to eight per dam.

**Effects of prenatal cryptolepis treatment on survival of pups and postnatal growth:** Pups (n=18) from each group (dose level) were monitored daily for the rate of growth and survival from postnatal day (PND) 0 to PND 14. All experiments involving weighing were carried out at 9.00 am.

**Effects of cryptolepis treatment on the time of attainment of physical landmarks:** Pups (n = 18) were selected from each group (dose level) and the time of acquisition of developmental landmarks including pinna detachment (pinna unfolding), incisor eruption, eye opening (pups are born blind with eyes shut), hair appearance, testis descent were noted [7].

**Effects of cryptolepis treatment on sensori-motor development:** Pups (n = 18) were selected from each dose level and assessed for the development of the following sensory motor systems.

1. **Rooting reflex on PND (1-3)-** A selected pup was induced to crawl forward, pushing its head in a rooting fashion when the snout was bilaterally between the thumb and forefinger [8].

2. **Vibrissae placing response PND (1-3) -** Pup was suspended by its tail and its vibrissae touched with a pencil, a positive result was when it raised its head and extended its forelimbs in order to grasp the object [8].

3. **Righting reflex PND (6) -** Pups were placed in a supine position on a plane surface and were no longer restrained. The time needed to recover to normal prone position (cut-off: 10 s) after they turn 180º around their longitudinal axis with all four paws in contact with the plane surface were noted [8, 9].

4. **Pinna reflex on (PND 11-13) -** The inner surface (near the concha) of the pinna was lightly touched with a filament. Any movement of the pinna (sudden twitch or flattening of the ear) made in response to the applied stimulus is recorded as positive. If the first ear tested did not respond to the stimulus, the opposite ear was tested [9].

5. **Auditory Startle Reflex (PND 11-13) -** Pup was placed in a beaker (1000 ml), with approximately 600 ml of bedding material and taken into the testing room. Litter mates remain outside the testing room in order to mitigate habituation to the auditory stimulus. A clicker was held directly above the beaker, but not touching it and the clicker stimulus was delivered. Any observable whole body response (e.g., flinching, jumping, and freezing of activity) meets the criterion for the startle response [9].

6. **Air righting reflex (PND 11-13) -** The air righting reflex is the ability of pups to land on all four paws when dropped from an inverted position. The pup was held in a supine position above a well-padded surface and then released. Pups were held 17 to 20 cm above the surface. The pup that landed on all four limbs met the criterion [9].

**Effects of Cryptolepis treatment on Motor activity:**

**Effects of cryptolepis on spontaneous locomotor activity at PND 30 -** On postnatal day 30, 5 female and 5 male mice of the $f_1$ generation prenatally treated to either distilled water only or cryptolepis (62.5, 100, 500 mg/kg *p.o*) from gestation day 6 till delivery were selected and tested for the effects of prenatal cryptolepis treatment on spontaneous locomotor activity. The spontaneous locomotor activity was measured with an automated mice activity cage (Model 7401, Milan, 19 x 23 x 35 cm). The movement of mice in the cage was detected by 29 stainless steel bars placed 1cm apart on the floor of the cage. Five (5) selected mice of the same group and sex were placed simultaneously into the cage. Ten minutes was allowed for habituation of the animals to the new environment. Activity was measured cumulatively every five minutes for thirty minutes.

**Effects of cryptolepis on motor coordination at PND 40 -** The effects of prenatal cryptolepis treatment on motor coordination were assessed with the rotarod apparatus on postnatal day 40. The rotarod apparatus (Model 7600, Ugo Basile, Milan, Italy) consist of a base platform and a rotating rod (3cm diameter) with a non-skid surface. The rod, 50 cm high, is divided into five equal sections by six disks allowing for the testing of five mice simultaneously. In this experiment, the rotarod apparatus was set to rotate constantly at 12 rpm. Motor performance was measured as the latency to fall from an accelerating rotarod. Five (5) male mice treated at the same dose level were placed on the rod and the latency to fall off the rod or the endurance time was recorded. Each animal was given four successive trials and the mean of the last two trials was determined. The experiment was repeated using five (5) female mice. A maximum cut off time of 300 s was set.

**RESULTS AND DISCUSSION:** The objective of the present study was to ascertain the effect of prenatal cryptolepis on neonatal life. Growth and development of sensorimotor systems are essential for the interaction of an organism with its environment and a necessity for survival. In previous studies, we demonstrated that prenatal treatment of mice with cryptolepis resulted in embryo and foetal mortalities[5]. In this study prenatal cryptolepis also reduced postnatal survival. Most deaths occurred before postnatal day 6. Mortality was significantly high at 62.5 and 100 mg/kg of cryptolepis treatment when compared with control. Interestingly, this observation was not dose-dependent as postnatal mortalities at 500 mg/kg of cryptolepis treatment were not significantly different from control (**Figure 2**).

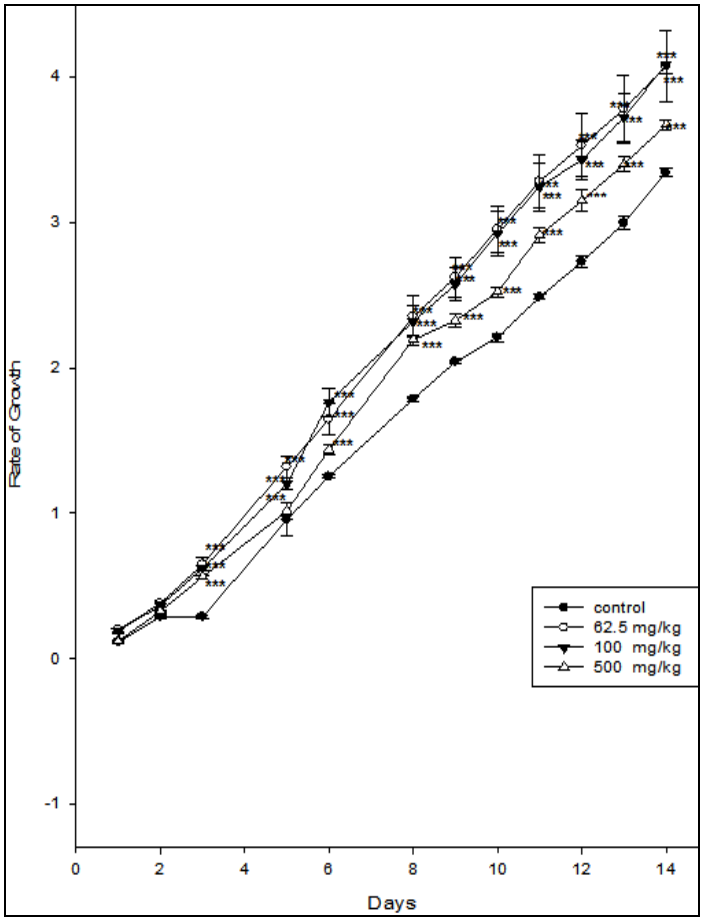


**FIGURE 2. EFFECTS OF PRENATAL CRYPTOLEPIS TREATMENT ON POSTNATAL GROWTH.** Statistical analysis was by two way anova using Bonferroni's post hoc test. * means $p < 0.05$, ** means $p < 0.01$,*** means $p < 0.001$.

Pups prenatally treated with cryptolepis had reduced weight as well as length depicted by the crown and rump distance (Table 1). Contrary to intrauterine growth, prenatal treatment did not inhibit postnatal growth at the doses of cryptolepis tested but rather it appeared to stimulate growth. Animals in the low dose group became significantly heavier than the controls from postnatal day 6 to postnatal day 14.

It is possible that the high postnatal growth rate seen in pups prenatally treated with cryptolepis is a compensatory mechanism as a result of prolonged intrauterine growth inhibition.

Similar observations were made in mice exposed to prenatal stress by Morley-Fletcher *et al.*, (2003) [10], where prenatally stressed mice were consistently bigger than controls.

Prenatal treatment with cryptolepis caused a delay in the attainment of certain key physical and developmental landmarks. For pinna unfolding however, prenatal cryptolepis exposure seamed to enhance unfolding, significant ($p < 0.05$) at 500 mg/kg of treatment (**Table 1**).

**TABLE 1: EFFECTS OF CRYPTOLEPIS TREATMENT ON THE TIME OF ATTAINMENT OF PHYSICAL LANDMARKS**

| Dose | Control | 62.5mg/kg | 100mg/kg | 500mg/kg |
|---|---|---|---|---|
| Birth weight | 1.472±0.060 | 1.462±0.157 | 1.228±0.111*** | 1.350±0.133* |
| Crown rump distance (cm) | 3.45±0.038 | 3.267±0.095 | 2.980±0.051** | 2.894±0.085*** |
| Pilation | 3.89±0.076 | 3.778±0.101 | 4.06±0.056 | 3.94±0.5556 |
| Pinna Unfolding | 3.94±0.055 | 4.000±001 | 3.78±0.101 | 3.61±0.1182* |
| Incisor eruption | 10.39±0.118 | 10.33±0.1143 | 10.56±0.121 | 10.61±0.1182 |
| Eye opening | 14.11±0.076 | 14.06 ±0.098 | 14.89±0.159*** | 14.61±0.1182** |
| Testicular decent | 23.00±0.365 | 22.50±0.224 | 23.67±0.421 | 23.17±0.3073 |

The unit of measurement is per litter. Statistical analysis is one way anova using Neuman- Keuls post hoc test to compare means to control. * $p < 0.05$,**$p<0.001$, ***$p<0.0001$.

Eruption of incisors and testicular descent were not affected by prenatal cryptolepis treatment. Eye opening was delayed by treatment significantly at 100 and 500 mg/kg. In developmental studies a delay in eye opening is a clear indication of an inhibition in the formation and development of the neural tube suggesting alteration in neurogenesis [8]. Furthermore, earlier studies with cryptolepine, the main alkaloid of the aqueous extract, in pregnant mice showed that it accumulations in foetal tissues particularly melanin containing tissues of the eye [6]. It is therefore possible that the delay in eye opening in the pups prenatally treated with cryptolepis could be linked to the affinity of cryptolepine for the tissues of the eye. However, it is known that intrauterine growth inhibitions in pups correlates with delays in appearance of key physical landmarks [8] suggesting that the alterations seen in this study may be a consequence of intrauterine growth inhibitions.

**TABLE 2: EFFECTS OF PRENATAL CRYPTOLEPIS TREATMENT ON SENSORI-MOTOR DEVELOPMENT**

| Behaviour | Day | CONTROL | : | $\chi^2$ | 100 mg/kg | $\chi^2$ | 500 mg/kg | $\chi^2$ |
|---|---|---|---|---|---|---|---|---|
| Rooting | 1 | 7 | 8 | 0.06 | 5 | 0.53 | 6 | 0.06 |
| | 2 | 14 | 11 | 2.00 | 12 | 0.72 | 10 | 3.94* |
| | 3 | 15 | 18 | 2.50 | 16 | 0.10 | 17 | 0.10 |
| Vibrissae placing response | 1 | 5 | 9 | 3.39 | 8 | 1.73 | 6 | 0.07 |
| | 2 | 13 | 15 | 0.62 | 11 | 0.62 | 13 | 0.07 |
| | 3 | 15 | 17 | 0.90 | 13 | 0.90 | 15 | 0.10 |
| Righting reflex | 4 | 5 | 6 | 0.07 | 1 | 3.39 | 2 | 1.73 |
| | 5 | 10 | 11 | 0.06 | 4 | 6.806** | 7 | 1.41 |
| Mid air righting | 11 | 9 | 10 | 0.06 | 7 | 0.50 | 4 | 4.50* |
| | 12 | 17 | 14 | 6.62* | 13 | 12.97*** | 13 | 12.97*** |
| | 13 | 16 | 15 | 0.141 | 14 | 0.26 | 15 | 0.14 |
| Auditory startle | 12 | 14 | 14 | 0.08 | 9 | 6.55* | 11 | 2.01 |
| | 13 | 17 | 18 | 0.53 | 14 | 6.61* | 18 | 0.53 |
| Pinna reflex | 11 | 10 | 12 | 0.51 | 6 | 2.76 | 13 | 1.41 |
| | 12 | 16 | 18 | 1.27 | 9 | 23.74*** | 18 | 1.27 |

Each group represents the number of pups eliciting sensori-motor behaviour on a specified day. Differences between the control group and cryptolepis groups (62.5 mg/kg *p.o*) were tested by the Chi square test. * means significant at $p < 0.05$, ** means significant at $p < 0.01$ and *** means significant at $p < 0.001$.

Prenatal treatment with cryptolepis also affected sensori-motor development. The rooting reflex and the vibrissae placing response, are grasping behaviours and are related to eating behaviour. Suckling pups have to display rooting and grasping reactions in order to successfully reach for the dam's teats. Treatment with cryptolepis had minimal effect on these behaviours, suggesting that poor postnatal nutrition could not account for the differences in growth and appearance of developmental landmarks.

Prenatal cryptolepis treatment delayed the development of righting reflex, auditory startle, midair righting, pinna reflex. Pinna reflex is effected by the 7th cranial nerve. Auditory startle depicts the integrity of the middle ear. In mice, vestibular structures undergo differentiation on gestation day 14 [11]. Prenatal cryptolepis treatment caused a delay in righting and mid air righting reflexes; two motor assays of vestibular and proprioceptive origin [12].

The 8th cranial nerve or the vestibulochochlea nerve inputs sensory signals of proprioception from the vestibule and the semicircular canals to medulla and the cerebellum of the brain for interpretation. A delay in this process shows alteration in neurogenesis. This study shows that prenatal cryptolepis treatment can affect the development of nervous structures during post natal life.

On PND30 mice treated prenatally with distilled water or cryptolepis (62.5, 100, 500 mg/kg) were assessed for spontaneous locomotor activity. Animals treated with cryptolepis were hyperactive compared to control (**Figure 3**). Hyperactivity was highest in animals in the 100 mg/kg cryptolepis-treated group.

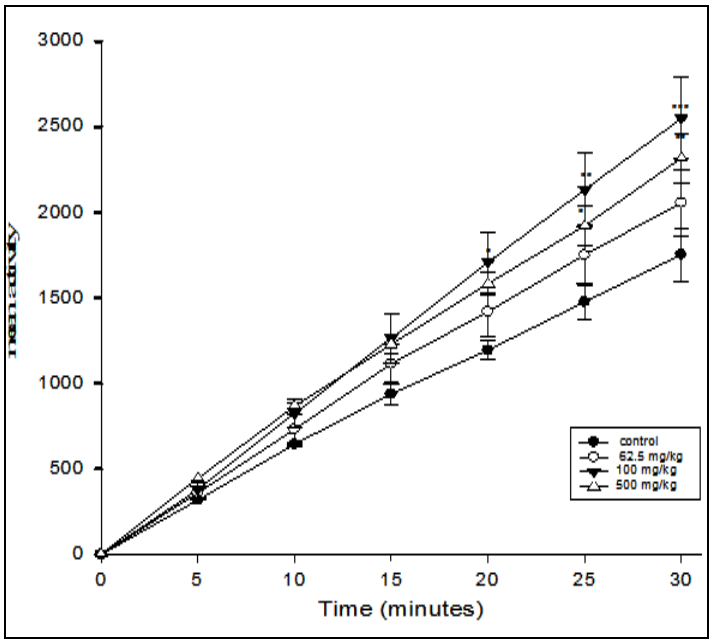


**FIGURE 3: EFFECTS OF PRENATAL CRYPTOLEPIS TREATMENT ON SPONTANEOUS LOCOMOTOR ACTIVITY ON PND 30.** Statistical analysis is by two way anova using Neuman keuls post hoc to compare means. * $p < 0.05$,**$p<0.01$, ***$p<0.001$

In the rotarod experiment, it was evident that prenatal cryptolepis treatment showed some sex specificity. Female animals had higher latencies to stay on the rotarod than controls at all doses of treatment though the results were not statistically significant (**Table 4**).

In males however, a reduction in latencies of falling from the rotarod was observed (Table 4). This was significant at all doses of treatment. Male animals prenatally exposed to cryptolepis had altered motor coordination.

**TABLE 4: EFFECTS OF PRENATAL CRYPTOLEPIS TREATMENT ON MOTOR COORDINATION**

| DOSE | FEMALE | MALE |
|---|---|---|
| Control | 132.2 ± 45.87 | 43.33 ± 9.208 |
| 62.5 mg/kg | 152.1 ± 52.57 | 5.00 ± 1.722 *** |
| 100 mg/kg | 225.5 ± 39.10 | 8.58 ± 2.850 *** |
| 500 mg/kg | 118.0 ± 40.44 | 16.40 ± 3.374 ** |

Statistical analysis is by one way anova using Neuman-Keuls post hoc test to compare means to control (n=5). ** p < 0.01,***p<0.001.

Cryptolepis can elicit these effects in several ways. One possible pathway is the interaction with the Wnt signaling pathway which is critical during foetal development. During primary neurulation, the ectoderm divides into three components; neural tube, epidermis and neural crest. The neural tube has four distinct areas each developing into portions of the CNS. Cryptolepis appears to delay the development of the neural tube indicated by a delay in eye opening [8]. The dorsal part of the neural tube which develops into the spinal cord controls the development of sensation whilst the ventral controls motor coordination [13].

Wnt proteins are signalling molecules playing very active roles in the development of sensation and sensory systems in the spinal cord of the foetus. Wnt also exerts inhibitory effects on molecules such as the sonic hedgehog (Shh) on the ventral side of the spinal cord controlling motor development and motor coordination [14]. In addition to its action in the spinal cord, Wnt canonical signaling induces neural dorsal identities in other regions of the developing CNS such as the forebrain and the eye [15, 16, 17]. Their activities depend on prostaglandin activity and substances that interfere with prostaglandins will affect the pathway and alter the development of sensory systems[18].

Cryptolepis and cryptolepine antagonise the activity of COX 2 [19, 20, 21, 22] and cryptolepine inhibits the activity of prostaglandin $E_2$ [23]. This strongly suggests that inhibition of prostaglandins synthesis could account for the altered sensori-motor development observed in the present study.

In conclusion, prenatal treatment of mice with aqueous extract of Cryptolepis delays the development of physical landmarks and sensorimotor systems in mice. Though the present observation cannot be directly extrapolated to humans, caution should be taken in the routine use of cryptolepis in the management of malaria during pregnancy.

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