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# Study of the Toxicity of Aqueous Extract of *Picralina nitida* Stapf (Fabaceae) in *Mus musculus* (Muridae) Mice

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**Abstract** **Original Research Article**

The toxicological study of *Picralima nitida* (Fabaceae) involved determining the acute toxicity of an aqueous extract of the plant's fruit on mice. This study was carried out by gavage (oral) and intraperitoneally, and enabled us to observe the symptomatic behaviour of single doses of this extract administered to mice and to determine toxicological parameter such as the 50% lethal dose (LD50, the dose that kills 50% of the experimental animals) with the 95% confidence limit. Acute toxicity results show that the aqueous fruit extract of Picralima nitida (EAPn) is non-toxic by gavage ($LD_{50}$ >5000 mg/kg Body Weight). By the intraperitoneal route, this extract has an $LD_{50}$ = 1166.6 mg/kg Body Weight. According to Diezi's classification, EAPn is of little or low intraperitoneal toxicity in rats. The oral route is therefore recommended for the administration of this plant.

**Keywords:** *Picralima nitida,* intraperitoneal toxicity, lethal dose, toxicity by gavage.



## INTRODUCTION

According to the WHO, in some developing countries in Asia, Africa, and Latin America, 80% of the population relies on traditional medicine, especially in rural areas, due to the proximity and accessibility of this type of care at an affordable cost (Békro *et al.*, 2010; Peter, 1998). Herbal medicine remains the most widely used means of improving access to healthcare for populations. However, the use of these plants is often described in popular culture but is not supported by clinical and experimental data (Salhi *et al.*, 2010). Thus, these traditional herbal treatments may pose toxicity or interaction problems and cause treatment failures or accidents (Hmamouchi, 1998). This study aims to investigate the toxicity of *Picralina nitida* for therapeutic management of populations.

## II- MATERIALS AND METHODS

### 1- MATERIALS

*Mus musculus* (Muridae) mice from homogeneous Swiss parent strains, weighing between 20 g and 25 g, were used to perform the toxicity tests.

### 2- METHODES

#### 2-1-Toxicity study by gavage

Acute oral toxicity study is performed on 30 mice divided into 6 groups of 5 mice, weighing between 20 and 25 g. This study is conducted in accordance with OECD Guideline 423 (OECD, 2001). Mice in the control group each receive 1 mL of distilled water. Animals in the test groups also receive a single 1 mL dose of the aqueous extract of *Picralina nitida* (EAPh).

Each mouse receives a single dose of 1 ml of EAPn, with predefined doses of 50, 300, 500, 2,000, and 5,000 mg/kg BW for 5 test batches. Experiment is conducted sequentially, batch by batch. First, the first

group of rats receives a single dose of 50 mg/kg BW. They are then placed under observation with special attention for 24 hours. The effects on the behavior of treated animals are observed and symptomatic disorders are noted. The number of dead mice is counted after 48 hours. The absence of mortality observed in the animals in this first batch allows the higher dose of 300 mg/kg BW to be administered to the second batch. And so on until the last batch receives the maximum dose of 5000 mg/kg BW.

During this observation period, emphasis is placed on toxicological effects such as changes in hair, somatomotor activity, and behavior. Particular attention is paid to food intake, tremors, convulsions, salivation, diarrhea, lethargy, sleep, coma, and death.

**2-2-Study of acute toxicity by intraperitoneal injection**

In this study, the sampling of mice is identical to that of the acute toxicity study by gavage. However, this toxicological study is carried out by first injecting different doses of EAPn intraperitoneally into five test groups of ten mice. Each mouse receives 0.5 mL of a single dose (evaluated in g/kg of body weight) of the substance. Mice in the control group also receive 0.5 mL of a 9‰ NaCl solution intraperitoneally. Mortality rates are determined after a 48-hour observation period. This first step consists of determining two limit doses of the extract: one causing 0% mortality and the other causing 100% mortality. Second step also involves making intermediate dilutions between these two limit substances and injecting 0.5 mL of a single dose of EAPn into each mouse in another series of 6 batches of 10 mice. The effects on the behavior of treated animals are also observed for 2 hours and symptomatic disorders are noted. The number of dead mice is counted 48 hours after injection of the substance. Each step of this second toxicological study is performed three times.

**2-3-Determination of toxicological parameters**

Toxicological parameter determined for each of the two acute toxicity studies is the lethal dose 50% ($LD_{50}$). The $LD_{50}$ is the dose of a substance that causes the death of 50% of the mouse population studied. It is determined by graphical method and by a calculation method.

**2-3-1-Graphical method for determining the $LD_{50}$**

Method used to determine the maximum tolerated dose and the lethal dose 50% is that of Miller and Tainter (1944). In this method, the percentages of dead mice are used to plot the mortality curve as a function of the logarithm of the product concentration, expressed in mg/kg of body weight.

**2-3-2- Calculation method for determining the $LD_{50}$**

Dragsted and Lang (1957) calculation method is also used to determine the $LD_{50}$. This method is based on the following assumption:

- any animal that survives a given dose of a substance administered to it would survive any other lower dose of that substance;
- Similarly, any animal that has succumbed to a given dose of a substance administered to it would also succumb to any other higher dose.

Thus, the mortality percentage (M%) for a given dose of the substance administered is given by the number of specimens that died (Nm) at that dose, divided by the number of specimens that died plus the number of survivors (Nv):

$$M\ \% = Nm \times 100 / Nm + Nv$$

$LD_{50}$ is calculated using the Dragsted and Lang method by extrapolation, i.e., by finding the approximate value of the dose that corresponds to 50% mortality in an interval (X1-X2).

Standard formula is: $LD_{50} = [50(X2-X1)+(X1Y2-X2Y1)]/ [Y2-Y1]$

- X1: lower dose surrounding the $LD_{50}$;
- X2: higher dose surrounding the $LD_{50}$;
- Y1: mortality percentage corresponding to X1;
- Y2: percentage of mortality corresponding to X2.

## III-RESULTS AND DISCUSSION

**1-RESULTS**

**1-1-Study of the acute toxicity of EAPn in mice by oral administration Behavior of mice after oral administration of EAPn**

EAPn at predefined doses of 50, 300, 500, 2000, and 5000 mg/kg BW causes, for doses of 2000 and 5000 mg/kg BW, the mouse to move along the walls of the cage during the first 30 minutes after gavage. After that, the animals move around normally, drink water, and then eat normally. Doses of 50, 300, and 500 mg/kg BW did not alter the behavior of the treated mice.

**1-2- Mortality of mice after oral administration of EAPn**

Administration of EAPn at successive doses of 50, 300, 500, 2000, and 5000 mg/kg BW did not result in any mouse deaths.

**1-3- Study of acute toxicity in mice via intraperitoneal (IP) administration of EAPn**

In this study, EAPn is dissolved in 9‰ NaCl and administered intraperitoneally to mice at single doses ranging from 500 to 2500 mg/kg BW.

**1-3-1- Behavior of mice after IP administration of EAPn**

Intraperitoneal injection of EAPn at doses below 200 mg/kg BW does not cause any noticeable effects on the behavior of mice. Injection of EAPn at doses ranging from 500 to 2500 mg/kg BW causes,

within the first 12 minutes, the mouse to move along the walls of the cage with stretching of the trunk, followed by rubbing of the muzzle with the front paws.

During the 20 minutes following administration of EAPn, the mouse eats and drinks little.

After these periods, for non-lethal doses, the observed symptoms gradually disappear and the animal moves normally, drinks, and eats as before. However, lethal doses cause irregular breathing and decreased motor activity in mice, which remain huddled in a corner of the cage.

They no longer feed and show signs of fatigue. Death occurs between 45 minutes and 24 hours after intraperitoneal administration of EAPn.

**1-3-2- Mortality of mice after intraperitoneal administration of EAPn**

An initial series of tests on five groups of ten mice shows that injection of doses less than or equal to 500 mg/kg BW causes 0% mortality. Doses greater than or equal to 2500 mg/kg BW result in 100% mortality. Within this dose range (500 to 1700 mg/kg BW), the mortality rate of mice increases with the dose administered (Table 2).

| Lot | EAPn dose injected (mg/kg BW) | Number of mice tested | Number of mice dead | Mortality (%) |
|---|---|---|---|---|
| 1 | 0 (Control) | 10 | 0 | 0 |
| 2 | 500 | 10 | 0 | 0 |
| 3 | 750 | 10 | 1 | 10 |
| 4 | 1000 | 10 | 4 | 40 |
| 5 | 1500 | 10 | 7 | 70 |
| 6 | 1700 | 10 | 8 | 80 |
| 7 | 2500 | 10 | 10 | 100 |

**1-3-3- Determination of the lethal dose 50% ($LD_{50}$) of EAPn using the graphical method of Miller and Tainter (1944)**

Mortality rates obtained following intraperitoneal administration of EAPn were used to plot the curve in Figure 1, which shows the average variation in the mortality rate of mice as a function of the dose of extract injected. The resulting curve (Trevan curve, 1927) is a sigmoid curve (Figure 1-A). This dose-response curve is linearized (Bliss probit transformation, 1938) by plotting the mortality curve, expressed as a probit value, against the logarithm of the EAPn concentration (Figure 1-B). On the linearized curve, the lethal dose 50% ($LD_{50}$) is determined. Thus, this toxicological parameter, determined using the graphical method developed by Miller and Tainter (1944), is as follows: $LD_{50}$ = 1176 mg/kg BW

**1-3-4- Determination of the 50% lethal dose of EAPn using the calculation method developed by Dragsted and Lang (1957)**

Dragsted and Lang calculation method was used to determine the following lethal dose 50% for three series of experiments: $LD_{50}$ = 1166.6 ± 200 mg/kg BW.

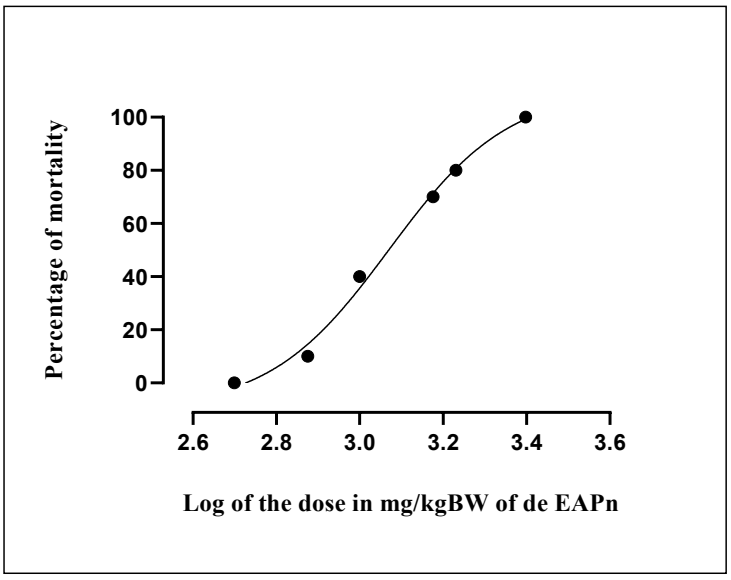


**Figure 1A: Variation in mouse mortality as a function of the dose of aqueous extract of Picralima nitida (EAPn) injected (Trevan, 1927)**

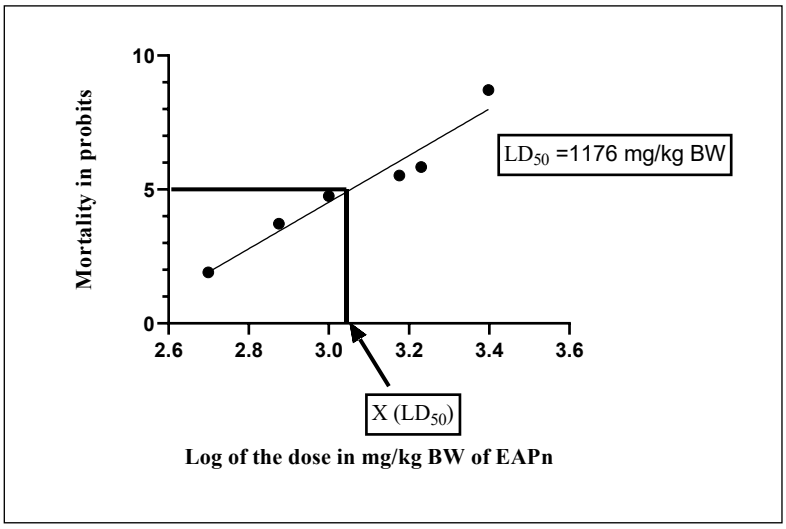


**Figure 1 B: Variation in mouse mortality as a function of the dose of aqueous extract of *Picralima nitida* (EAPn) injected (Bliss, 1938)**

**A**-Dose-response curve (Trevan sigmoid curve, 1927)

**B-** Linearized curve (Bliss probit transformation, 1938)

## 2- DISCUSSION

Acute toxicity study by oral administration of the aqueous extract of *Picralima nitida* (EAPn) shows that this extract administered by gavage does not cause any mouse deaths at doses up to 5000 mg/kg BW. The fact that EAPn is not lethal at the maximum dose of 5000 mg/kg BW indicates that its $LD_{50}$ is well above this value. Thus, EAPn, whose $LD_{50}$ is undeniably greater than 5000 mg/kg BW, is non-toxic when administered orally. Furthermore, the aqueous extract of Picralima nitida, at these doses, does not cause any significant changes in the behavior of treated mice. This reinforces the idea that EAPn, administered orally, does not cause visible damage in mice. This route of administration could be recommended for the use of EAPn. These results are similar to those of Asiimwe (2015), who showed that *Pseudarthria hookeri* essential oil administered orally is non-toxic because its $LD_{50}$ is equal to 5506 mg/kg BW. The results obtained following administration of the aqueous extract of *Picralima nitida* by intraperitoneal injection show that doses of this extract ranging from 500 to 2500 mg/kg BW cause a decrease in mobility in mice. Lethal doses (≥750 mg/kg BW) also cause a decrease in respiratory activity. These effects of EAPn suggest a probable action of this extract on locomotion and the nervous system when administered intraperitoneally. Doses of EAPn greater than or equal to 750 mg/kg BW are lethal to mice when administered intraperitoneally. In this dose range, the mortality rate increases in a dose-dependent manner, with 100% mortality achieved at a dose of 2500 mg/kg BW. This dose corresponds to the lethal dose 100% ($LD_{100}$). The curve showing the percentage of mice that died per batch (mortality) as a function of the logarithm of the injected dose of EAPn (Trevan curve, 1927) has a sigmoid shape. This confirms that the effect of EAPn is dose-dependent and suggests that its activity may involve receptor activation (Miller and Tainter, 1944). Graphical method developed by Miller and Tainter (1944) allows the $LD_{50}$ for EAPn (IP) to be determined as 1166.6 mg/kg BW. The calculation method developed by Dragsted and Lang (1957) also allows us to determine an $LD_{50}$ of 650 mg/kg BW for this extract. $LD_{50}$ values for EAPn, determined using two methods: graphical (1676 mg/kg BW) and calculation (166.60 mg/kg BW), are fairly similar (non-significant difference, $P > 0.05$). This indicates that the results are consistent and that the methods used in this toxicological study are credible. $LD_{50}$, a quantitative indicator of a substance's toxicity, measures the short-term toxic potential (acute toxicity) of a substance. According to Diezi (1989), the $LD_{50}$ value allows a substance to be classified according to its degree of toxicity. For this author, substances with $LD_{50}$ values of: greater than 5000 mg/kg BW are considered non-toxic; between 5000 mg/kg bw and 500 mg/kg BW, are in the range of substances that are slightly or weakly toxic; between 500 mg/kg BW and 50 mg/kg BW are toxic substances; between 50 mg/kg BW and 5 mg/kg BW, are highly toxic substances; between 50 mg/kg BW and 5 mg/kg BW, are highly toxic substances and less than 5 mg/kg BW are classified as extremely toxic substances. Based on this classification, EAPn, with an $LD_{50}$ of 1166.6 mg/kg BW, is slightly or mildly toxic when administered intraperitoneally. As a result, mice have a high tolerance to this drug. The comparative study of acute toxicity in mice shows that the aqueous extract of *Picralima nitida* is non-toxic when administered by gavage, but is slightly or mildly toxic when administered intraperitoneally. When administered via gavage, the active ingredients in the extract pass through the liver during digestion, where they are partially transformed (or even eliminated) before being distributed throughout the body to exert their effects. However, when administered intraperitoneally, the active ingredients enter the

bloodstream and reach the target organs or cells directly without undergoing the action of the digestive system and the first-pass effect of the liver, which could delay and attenuate the effect of these active ingredients. In this case, the active ingredients are more bioavailable than when taken orally, and the speed of action and/or the amount of medication that takes effect is greater. The study of the acute toxicity of the aqueous extract of *Picralima nitida* on mice showed that this extract is non-toxic when administered by gavage, but slightly or mildly toxic when administered intraperitoneally. This extract could therefore be recommended for pharmacological studies. However, intraperitoneal administration should be carried out with caution, particularly taking into account its maximum tolerated dose, which is the maximum dose of this extract injected into animals without causing toxic effects.

## CONCLUSION

At the end of this investigation, acute toxicity studies revealed that the aqueous extract of *Picralima nitida* fruit (EAPn) is non-toxic when administered by gavage ($LD_{50}$ >5000 mg/kg BW). This extract, administered intraperitoneally, has an $LD_{50}$ = 1166.6 mg/kg BW. According to Diezi's classification, EAPn is slightly or mildly toxic when administered intraperitoneally to rats.

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