Behavioral and neurotropic effects of an aqueous extract of *Euphorbia hirta* L. (*Euphorbiaceæ*)

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INTRODUCTION

This presentation treats of our pharmacological studies on an *Euphorbiaceæ* namely *Euphorbia hirta* L., a species which is found under the tropics. These studies are part of the general approach used in the Laboratory of Pharmacognosy at the University of Metz, whose aim is to establish an inventory of medicinal plants used in traditional pharmacopoeia and to select some experimental testing according to modern pharmacological technics (DOS SANTOS J. R., FLEURENTIN J., 1991). The goal is to establish their real action not only among indigenous populations but also for possible applications in modern medicine which is paying more and more attention to so called "soft" medication.

This ethnopharmacological approach requires several successive steps: first, a clear unambiguous botanical identification of the selected species. One must be sure that the therapeutic uses are well founded through comparisons between the oral and written tradition, that we call converging uses. Chemical, toxicological and also pharmacological studies previously carried out by other workers must be taken into account.

In our laboratory, the plant extracts are always prepared according to traditional medicine, but they are characterized chemically with modern identification technics such as chromatography, chemical reactions and so on. After characterization, these extracts are used for toxicological and pharmacological studies.

Euphorbia hirta is a well-known species in traditional medicine; for example, there are at least 183 identified vernacular names (LANHERS, 1988). It's largely used, and for a great variety of therapeutic indications; among them, we can cite the most important ones: the use in cardiac and respiratory troubles (asthma, bronchitis...), in gastro-intestinal (amœbiasis, diarrhea...), renal (stones...), hepatic (icterus...), genital (metrorrhagia, gonorrhea, urethritis...), ocular ailments (conjunctivitis...) as well as febrifuge effects and treatment of ailments of the skin and of the mucous membranes (scabies, boils, aphta, phlegmons...).

Investigation was undertaken to determine the possible sedative effects of *Euphorbia hirta*, effects otherwise suggested by CABALION P., following the observation of side-effects on people self-treating amœbiosis by *Euphorbia hirta* aquous extracts (New Caledonia and Vanatu).

Chemical composition of *Euphorbia hirta* has been described previously (LANHERS *et Coll.*, 1987).

Some pharmacological studies have already been carried out but most of them were relative to the action of *Euphorbia hirta* against amœbia, to its spasmolytic, cardiovascular and galactagogue properties.

To our knowledge, the sedative effects have never been confirmed experimentally. This fits very well with the themes of our laboratory which is specialized in vegetal with sedative and anxiolytic properties.

MATERIALS AND METHODS

All of these studies have been carried out on an aqueous extract obtained in the following manner: the whole plant is thrown in boiling water and let macerate for 24 hours. Throughout this presentation, the doses will be expressed in mg of dry plant per kilogramme of body weight.

The sedative effects have been investigated through two different procedures: non familiar environment tests and familiar environment tests.

Fig. 1

Influence of *Euphorbia hirta* and chlorazepate on general activity and rearing of mice in the activitest

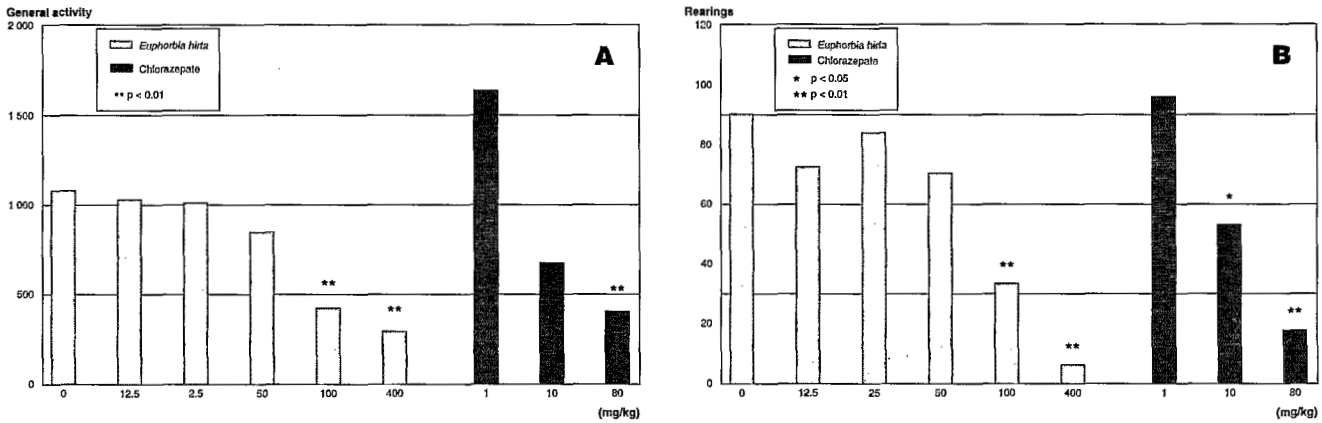
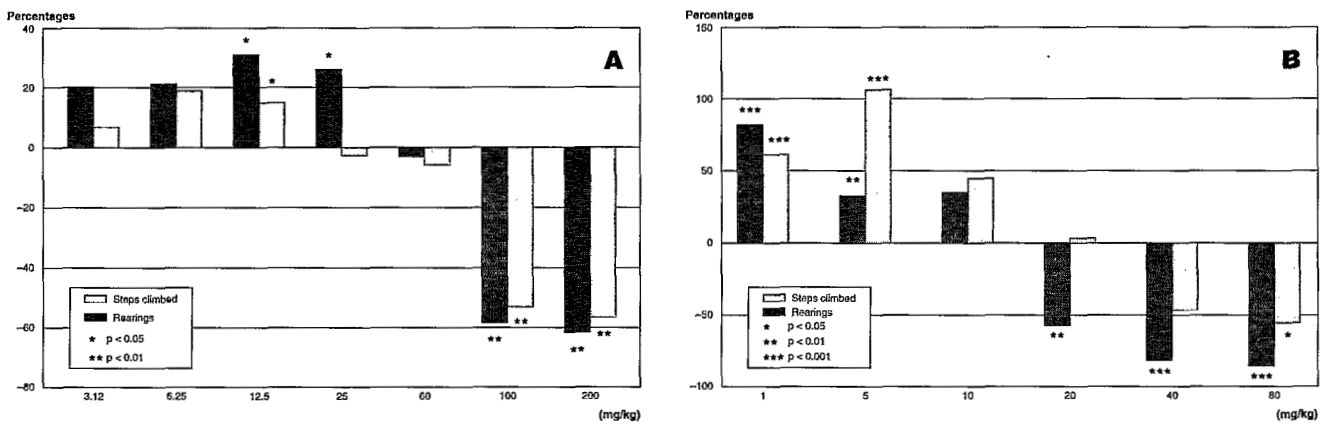


Fig. 2

Influence of *Euphorbia hirta* and chlorazepate on rearing and steps climbed by mice in the staircase test



In the first case, the animal (a mouse) is forced into an unknown environment without any familiar bearing and often strongly lit. Such a situation disturbs the emotional state of the animal and therefore its behavioral. We have thus used the activitest and the staircase test.

In a non-aversive situation such as in the two compartments test, the animal has free access to the unknown territory (without litter and food), but it can retire from it at will by returning to its familiar environment containing litter and food. This possibility to move back and forth from the known to the unknown territories allows the reduction of the emotional disturbance and therefore makes it possible to detect smaller sedative activity. Material and methods have been described previously (LANHERS *et coll.*, 1990).

RESULTS

1. Activitest

Activitest results are shown in Figure 1. We observed a dose-dependent decrease of the general activity and of the rearings of mice, which becomes significant at 100 mg/kg. The reduction compared to the untreated mice is above 60%.

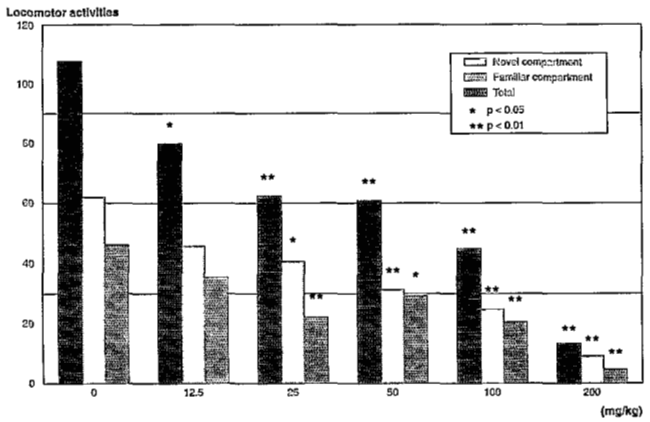
A similar profile was obtained with chlorazepate dipotassic in the activitest, a typical benzodiazepine, the sedative effects appearing from 10 mg/kg.

2. Staircase test

The results obtained in the staircase test are shown in Figure 2. At higher doses (100 and 200 mg/kg), we observed a decrease

Fig. 3

Influence of *Euphorbia hirta* on locomotor activities of mice in the two compartments test



of the number of rearings and of steps climbed by treated mice, a decrease which corresponds to a powerful sedative effect.

A similar profile was obtained with chlorazepate dipotassic in the staircase test, a benzodiazepine, the sedative effects appearing from 20 mg/kg on, mearings and from 40 mg/kg on climbed steps.

3. Two compartment test

When the mouse is placed in a less aversive situation, such as in the two compartment test, the sedative activity appears at doses much lower, namely 12.5 mg/kg (Figure 3).

In this procedure, we observed a dose-dependent decrease of the behavioral parameters (the total locomotor activity, the locomotion recorded in the novel compartment and the locomotion recorded in the familiar compartment).

4. Anxiolytic effects

We have continued investigations looking for possible anxiolytics effects which are often associated to sedative effects. We have thus used non familiar environment tests such as the staircase test and the light/dark choice situation test.

The main difference between this latter test and the staircase test resides in the fact that the mouse can escape to the aversive situation by taking refuge in an unknown compartment but dark and therefore more securizing. The administration of an anxiolytic compound can reduce or even eliminate the behavioral perturbations induced by the aversive situation.

The staircase test results are shown in Figure 2. At lower doses, we observed an increase of the number of rearings and of steps climbed by the mouse, which is significant at 12.5 and 25 mg/kg. This increase corresponds to an anxiolytic effect, but it remains small as compared to the reference benzodiazepine tested at the active doses of 1 and 5 mg/kg.

In the light/dark choice situation test (Figure 4), an anxiolytic effect is obtained at 25 mg/kg, dose which increases significantly the time spent by the mouse in the lit box.

5. Sleep induction

After showing that *Euphorbia hirta* exhibits dose-dependent sedative effects, associated to a small anxiolytic action, we have tried to determine whether it was a main or a side effect. Indeed, many psychotropic substances such as hypnotics, neuroleptics, antidepressants and minor tranquilizers can also exhibit secondary sedative effects.

We have not been able to confirm the existence of hypnotic effects *per se*, but we have clearly shown the activity of the plant extract toward barbiturate sleep, both in terms of potentiation and of induction.

The results obtained toward pentobarbital sleep potentiation (barbiturate being used at an hypnotic dose) show a dose-dependent increase of the sleeping time in treated mice. This effect becomes significant from 400 mg/kg on (Figure 5*a*).

The aqueous extract is also active toward an infra-hypnotic dose of pentobarbital, by inducing the sleep in treated mice (Figure 5*b*). This sleep induction is dose-dependent and becomes significant at 50 mg/kg and onward. A similar profile was obtained with chlorazepate dipotassic tested at the active doses of 5 and 20 mg/kg.

6. Other pharmacological investigations

Concerning neuroleptic effects, no protective action was obtained toward group toxicity at 200 and 800 mg/kg induced

Fig. 4

Influence of *Euphorbia hirta* on time passed by mice in the lit box in the light/dark choice situation test

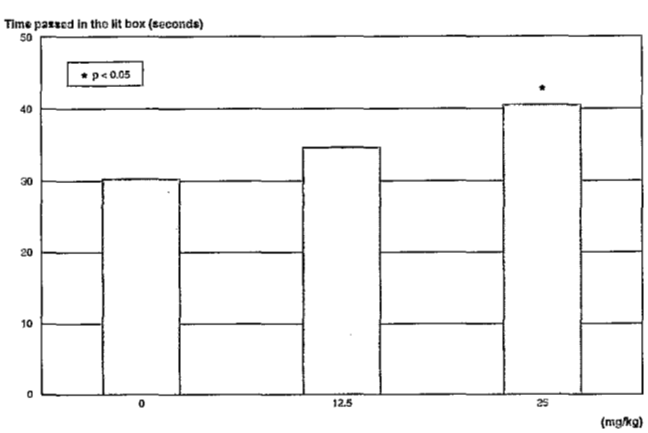
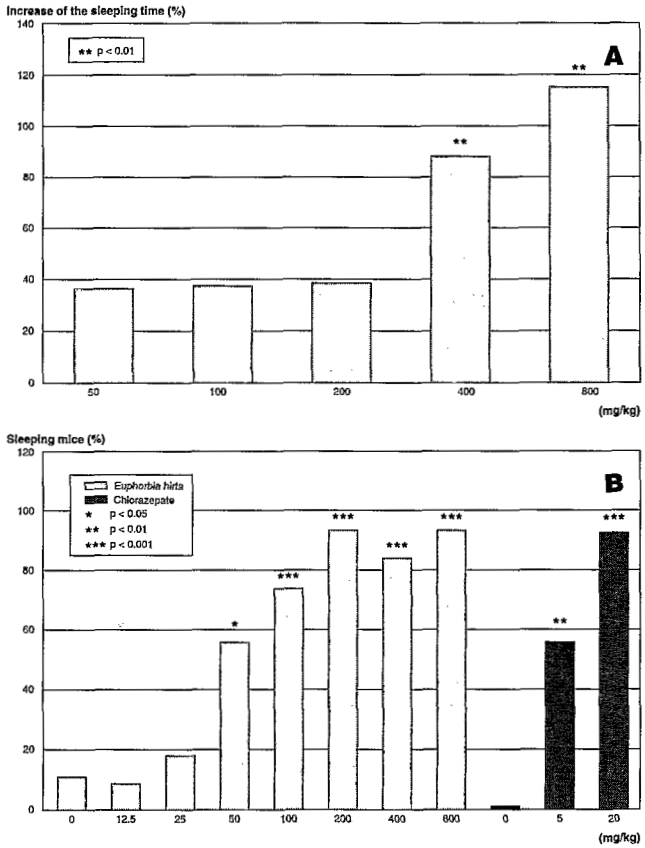


Fig. 5

Influence of *Euphorbia hirta* on the sleeping time of mice after pretreatment with pentobarbital at hypnotic dose (A) or infra-hypnotic dose (B)



in mice by the dexamphetamine; no characteristic cataleptic effect was observed in rats at 100 and 400 mg/kg; and eventually, the aqueous extract didn't antagonize amphetaminic stereotypes, but on the opposite it induced a slight strenghtening with the doses of 100 and 400 mg/kg.

Antidepressant properties have been studied by the research of characteristic antireserpine and anticholinergic activities (Table 1).

Concerning the reserpinic effects, only a slight antagonism of the ptosis has been observed with *Euphorbia hirta* at 400 mg/kg. The others parameters (akinesia, hypothermia) not being affected.The same dose produced a slight antagonism of the cholinergic hypothermia, other parameters (shivers, salivation, lacrimation) not being affected (Table 1).

In fact, the antidepressant effects remain small both quantitatively (*i.e.*, as activity-wise) and qualitatively (*i.e.*, in terms of parameters affected). Imipramine was used as an antidepressant references.

Finally, we completed this study of psychotropic activites by the research of a possible benzodiazepine-like activity profile, since minor tranquilizers such as benzodiazepines are known for their sedative and anxiolytic properties.

To this aim, we have looked for characteristic activities, such as hypothermic, anticonvulsant and muscle relaxant activities, as well as possible affinity for the benzodiazepine receptor sites. We have thus detected a moderate and transient hypothermic activity with the dose of 400 mg/kg.

On the other hand, no anticonvulsant activity was observed until 3,200 mg/kg.

As for muscle relaxant activity, the plant extract tested at 200, 400 and 800 mg/kg didn't modify the muscular strengh of treated mice, in the suspension test. The same doses were active in the rota-rod test by reducing their sense of balance, but no in a dose-dependent way.

At last, a benzodiazepine receptor antagonist, flumazenil, didn't inhibit the in vivo sedative effects of the plant extract (Figure 6).

Table 1

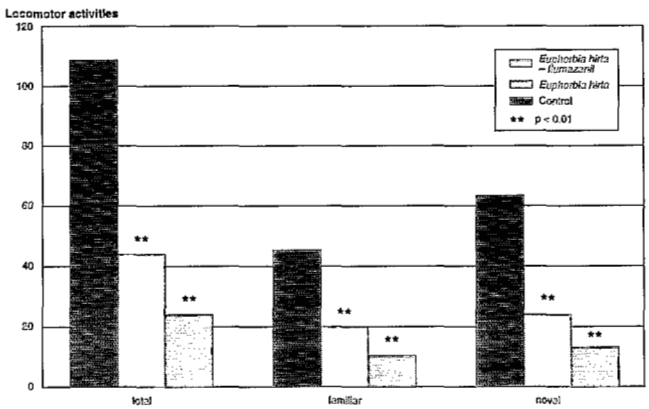
Influence of *Euphorbia hirta* on Reserpine-induced ptosis and on cholinergic hypothermia, in mice

Groups	ptosis		temperature variations (°C) as compared to rectal temperature recorded just before oxotremorine injection		
	30 min	2 hours	30 min	60 min	120 min
Control	7.6 ± 0.3	7.7 ± 0.2	–5.5	–7.4	–6.8
Imipramine	4.7 ± 0.4***	5.9 ± 0.7*	–2.3**	–4.9*	–3.0**
E. hirta 400 mg/kg	6.8 ± 0.2*	6.8 ± 0.3*	–4.0	–4.8*	–2.0*

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

Fig. 6

Influence of *Euphorbia hirta* and *Euphorbia hirta* + flumazenil on the locomotor activities of mice in the two compartments test



CONCLUSION

All of these results allow us to conclude that the activity profile of *Euphorbia hirta* is different from that of benzodiazepines.

The research carried out on a nontoxic aqueous extract of *Euphorbia hirta* allows us the following conclusions:

– The most important result is relative to the central depressant effect for which we observed a strongh sedative activity, thus confirming traditional indicationsand observations done by CABALION P.

– Some anxiolytic effects, that were never been described before, were also recorded.

– Usually, sedative and anxiolytic effects are routinely observed for benzodiazepines, but we haven't been able to confirm the existence of an activity profile similar to that of these minors tranquilizers.

– Finally, no hypnotic and no neuroleptic properties were recorded and if some small anti-reserpinic and anti-cholinergic effects were obtained toward certain reserpinic actions, such as ptosis, and toward certain cholinergic actions, such as hypothermia, we haven't detected any essential antidepressant properties.

Several other pharmacological works are under way, as well as chemical fractionations of this plant extract, in order to complete the activity profile of *Euphorbia hirta.*

This research activity is part of a larger framework concerning ethnopharmacology and is geared toward improving therapeutic skills in developed and underdeveloped countries.

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