Pharmacodynamic interaction of the sedative effects of *Ternstroemia pringlei* (Rose) Standl. with six central nervous system depressant drugs in mice

José Luis Balderas a, Victoria Reza a, Martha Ugalde a, b, Laura Guzmán a, Miriam Isabel Serrano a, Abigail Aguilar c, Andrés Navarrete a, b,∗

a Facultad de Química, Departamento de Farmacia, Universidad Nacional Autónoma de México, Ciudad Universitaria, Coyoacán 04510, México, D.F., México
b Facultad de Estudios Superiores Zaragoza, Universidad Nacional Autónoma de México, J.C. Bonilla 66 y Calzada Ignacio Zaragoza, Colonia Ejército de Oriente, Iztapalapa 09230, México, D.F., México
c Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Av. Cuauhtémoc 330, Delegación Benito Juárez 06720, México, D.F., México

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**A B S T R A C T**

Ethnopharmacological relevance: The decoction of dried fruits of *Ternstroemia pringlei* (Rose) Standl. (Theaceae), commonly known as “Flor de Tila”, is used in the Mexican traditional medicine to diminish insomnia and fear.

**Aim of the study:** To examine the sedative effects of the dried fruits of *Ternstroemia pringlei* and investigate a possible synergistic pharmacodynamic interaction between the sedative effect of aqueous extract of this plant and six central nervous system (CNS) depressant drugs.

**Materials and methods:** The sedative effect was performed using the exploratory cylinder test in ICR mice. The extracts and drugs were intraperitoneally administered 30 min before testing in different doses, with exception of ethanol and buspirone which were administered 5 and 20 min before testing, respectively. An isobolographic analysis was used to characterize the interaction between *Ternstroemia pringlei* extract and six CNS depressant drugs.

**Results:** The intraperitoneal administration of the hexane, dichloromethane, methanol and aqueous extracts of *Ternstroemia pringlei* showed a dose-dependent sedative effect. *Ternstroemia pringlei* aqueous extract combined with buspirone, diazepam, diphenhydramine, haloperidol or pentobarbital exerted a super-additive (synergistic) sedative interaction. Whereas the combination *Ternstroemia pringlei* extract plus ethanol resulted in a sub-additive (attenuate) sedative interaction.

**Conclusions:** These findings are in agreement with the traditional use of *Ternstroemia pringlei* in the treatment of insomnia, however it is a plant that interacts in a complex form with CNS depressant drugs. It may represent an.advantage on the use of this plant concomitantly with other neuroactive drugs.

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# 1. Introduction

*Ternstroemia* is the largest genus in the Theaceae family with an estimated 130 species worldwide. The species are distributed almost equally between the eastern and western hemispheres and are tropical and subtropical in distribution (Boom, 1989). The species of *Ternstroemia* are very frequent in the cloud forest, oak forest of the “Sierra Madre Oriental”, “Serranías Meridionales”, and “Serranías Transístmicas” of México with elevations above 1000 m over the sea (Alcántara et al., 2002). It has been reported that nine species occur in México (Boom, 1989; Alcántara et al., 2002). Several species of *Ternstroemia* that grow in México, commonly known as “Flor de Tila”, are reputed to possess sedative, anxiolytic and anticonvulsant effects (Tortoriello and Romero, 1992; Aguilar-Santamaría and Tortoriello, 1996). Aqueous extracts of dried fruits of *Ternstroemia pringlei* (Rose) Standl., synonym *Ternstroemia lineata* DC (Kobuski, 1942; Bartholomew and McVaugh, 1997) and *Ternstroemia sylvatica* Schltdl. and Cham., which are the two major *Ternstroemia* species, are used as decoctions in the Mexican traditional medicine to diminish insomnia and fear (Molina et al., 1999). Pharmacological studies have showed that *Ternstroemia pringlei* (Aguilar-Santamaría and Tortoriello, 1996) and *Ternstroemia sylvatica* (Molina et al., 1999) produce sedative effects in rats. No chemical studies have been performed on these two species; however, from Asian species of *Ternstroemia* (principally *Ternstroemia japonica* and *Ternstroemia gymnanthera*) oleanane- and ursane-type triterpenoids, triterpenoid saponins,
carotenoids, monoterpenoids, tannins and other aromatic compounds have been identified (Kikuchi and Yamaguchi, 1974; Ikuta et al., 2003; Shin et al., 2003; Jo et al., 2005; Tori et al., 2005).

On the other hand, drug–drug interactions and drug–dietary supplements, including herb–drug interactions are emerging as important issues to consider in the evaluation of new drug candidates. However, herb–drug interaction studies are very limited (Fugh-Berman and Cott, 1999; Fugh-Berman and Ernst, 2001; Huang and Lesko, 2004). There is a dearth of well-documented data in this area and there are few studies that have specifically evaluated herb–drugs interactions (Rotblatt and Ziment, 2002).

Both preclinical and clinical studies of the drug interactions have been performed using the isobolographic analysis. This analysis offers a rigorous evaluation of the interactions between two drugs that act together to produce overtly similar effects (Tallarida, 2000). The effect of the combination may be a simple addition of the individual effects (additivity). In contrast, the effect of the combination can be exaggerated or even attenuated. The exaggerated effect is termed super-additive or synergistic, whereas the attenuated effect is termed sub-additive (Tallarida et al., 1997).

Several commercial products contain mixtures of the Ternstroemia species that grow in México, however there are no studies related to the potential interaction between these products and central nervous system (CNS) depressant drugs. Therefore in continuation with our studies on the potential pharmacological interaction between Mexican medicinal plants with reputed CNS depressant effect and commonly prescribed CNS depressant drugs (Ugalde et al., 2005), this study was designed to investigate a possible synergistic pharmacodynamic interaction between the sedative effect of aqueous extract of *Ternstroemia pringlei* and six CNS depressant drugs (diazepam, ethanol, pentobarbital, buspirone, haloperidol and diphenhydramine) by use of an isobolographic analysis in the exploratory cylinder test, a model to test sedative effect in mice (Ugalde et al., 2005; González-Trujano et al., 2006).

2. Materials and methods

2.1. Plant material

The dried fruits of *Ternstroemia pringlei* were acquired from a local market (Mercado de Sonora, México City) in January 2004. The homogeneity and authenticity of the plant material were certified by one of the authors (A. Aguilar), botanist from the Herbarium of the Instituto Mexicano del Seguro Social. A sample was deposited in this herbarium with the voucher number IMSSN117.

2.2. Extraction and isolation

After grinding, using a manual miller, 443 g of fruits were extracted at room temperature with hexane (3 × 2 L, 24 h each), then with CH<sub>2</sub>Cl<sub>2</sub> (3 × 2 L, 24 h each) and finally with MeOH (3 × 2 L, 24 h each); evaporation of the solvents in vacuum gave 0.94 g (0.21% yield), 2.1 g (0.47% yield) and 152.7 g (34.46% yield) of syrupy residues, respectively. Aqueous extract was prepared with 10 g of dried and powdered fruits by boiling in 90 ml of distilled water for 10 min. Afterwards, the extract was filtered by gravity and concentrated through air current at room temperature (22 ± 2 °C) obtaining 1.52 g (15.2% yield) of a breakable reddish solid.

2.3. Drugs

Haloperidol, diphenhydramine, buspirone and Tween 80 were purchased from Sigma Co. (Sigma St. Louis, MO). Absolute ethanol was of HPLC grade (Fisher Scientific). Sodium pentobarbital (Anestesal™) was purchased from Pfizer S.A. de C.V., México, as a pharmaceutical solution for veterinary use.

2.4. Animals

All experiments were performed on adult male ICR mice (25–34 g; Centro UNAM-Harlan, Harlan México, S.A. de C.V.). Procedures involving animals and their care were conducted in conformity with the Mexican Official Norm for Animal Care and Handling (NOM-062-ZOO-1999) adopted in our laboratory, and in compliance with international rules on care and use of laboratory animals.

The experimental groups consisted of six (interaction study) or ten animals (calculus of ED<sub>50</sub> of individual drug). They were maintained at constant room temperature (22 ± 2 °C) and submitted to a 12 h light/dark cycle with free access to food and water. All behavioral evaluations were carried out between 10:00 and 14:00 h.

Diazepam (Roche S.A.) and the organic extracts were suspended in 0.5% Tween 80 in saline solutions, all other compounds, including the aqueous extract, were dissolved in saline solution (0.9%). The drugs were freshly prepared each time and intraperitoneally injected in a volume of 0.1 ml/10 g body weight. Control animals received the same volume of vehicle (0.5% Tween 80 in saline or saline solution only).

2.5. Procedure

The apparatus consisted of a glass cylinder (30 cm in height, 11 cm in diameter, with wall of 3 mm). The cylinder is placed on filter paper in a room with constant lighting and isolated from external noise (Hiller and Zetler, 1996; Oliva et al., 2004; Ugalde et al., 2005).

An individual naïve mouse was put on the filter paper-covered floor of the glass cylinder; the number of rears performed over a 5-min period was recorded. The inner side of the apparatus and floor were cleaned with alcoholic solution and filter paper was changed between each animal test session (Oliva et al., 2004). The crude organic and aqueous extracts were tested for activity at different doses (10–1000 mg/kg i.p.) in the exploratory cylinder assay. The aqueous extract showed the major sedative activity. Therefore, the aqueous extract was used in the interaction study and it was freshly prepared each time in the same day of the experimentation. The aqueous extract and drugs were administered 30 min before testing in different doses, with exception of ethanol and buspirone which were administered 5 and 20 min before testing, respectively (Ugalde et al., 2005). When drugs were given in combination, aqueous extracts were injected first in the right side of the peritoneum, followed by the injection of the test drug in the left side. When only one of the drugs was given, the missing drug injection was substituted with the injection vehicle. During observation, the experimenter stood next to the apparatus always at the same place. The observations were made without prior knowledge of the experimental conditions applied to the animal. Reduced exploratory rearing showed by naïve mice after placement in an unfamiliar environment reveals a sedative effect (Rolland et al., 1991; Hiller and Zetler, 1996; Oliva et al., 2004).

Dose–response curves were constructed to assess the sedative effect of *Ternstroemia pringlei* extracts and the other CNS depressant drugs using ten animals at each of at least five doses. The ranges of doses used of the CNS depressant drugs were: diazepam (0.3–7.5 mg/kg), ethanol (1000–4000 mg/kg), pentobarbital (2.5–40 mg/kg), buspirone (0.15–10 mg/kg), haloperidol (0.1–3 mg/kg) and diphenhydramine (10–25 mg/kg). The dose that produced 50% of sedation (ED<sub>50</sub>) 50% of reduction in the rears
number with respect to control group) and its associated 95% confidence intervals were calculated using standard linear regression analysis of the log dose–response (Tallarida, 2000).

2.6. Analysis of the interaction

An isobolographic analysis was performed to characterize the interaction between Ternstroemia pringlei extract with diazepam, ethanol, pentobarbital, buspirone, haloperidol and diphenhydramine. The theoretical additive doses ($Z_{add}$) with their S.E.M. for each combination in the same component ratio (1:1) were computed from the median effective doses (ED$_{50}$) of the single drugs, according to the method described by Tallarida (1992) to satisfy the equation:

$$Z_{add} = fA + (1 - f)B$$

where $A$ was the ED$_{50}$ of Ternstroemia pringlei extract and $B$ was the ED$_{50}$ of the CNS depressant drug. For a 1:1 fixed ratio, $f$ in this case was 0.5 and $(1 - f)$ was also 0.5. The value $fA = a$ represents the fraction of the ED$_{50}$ of the Ternstroemia pringlei extract in the combination and $(1 - f)B = b$ represents the fraction of ED$_{50}$ of the CNS depressant drug in the combination (Tallarida, 2000). $Z_{add}$ represents a total additive dose of the drugs, theoretically providing a 50% reduction in the rear number with respect to the control group. $Z_{exp}$ is an experimentally determined total dose of a mixture of two component drugs, which was administered at a 1:1 fixed-ratio combination sufficient to reduce the number of rearings by 50% with respect to the control group. The $Z_{exp}$ values (with their 95% confidence limits) were determined from the respective drug–dose effect curves of combined drugs, according to standard linear regression analysis of the log dose–response curve (Tallarida, 2000), and subsequently, the 95% confidence limits were transformed into S.E.M. Experimentally determined $Z_{exp}$ was statistically compared with the theoretically calculated $Z_{add}$ doses with the use of Student’s $t$-test, according to procedures previously described by Tallarida et al. (1989), who has proposed the use of this statistical test for analyzing the data in isobolography. $Z_{exp}$ values that were lower than $Z_{add}$ value, with a $p < 0.05$ for the differences in both the $X$ and $Y$ directions, were interpreted as a significant super-additive interaction. Values of $Z_{exp}$ that were higher than $Z_{add}$ values, with a $p < 0.05$ for the differences in both the $X$ and $Y$ directions, were interpreted as a significant sub-additive interaction. When there were no statistical differences between the values $Z_{exp}$ and $Z_{add}$, this was interpreted as no interaction and an additive relationship (additivity) was established in the combination (Tallarida, 2000).

Graphical representation of the observed interactions in the shape of isoboles (iso-effect curves or isobologram), which is a simple form of visualization of interactions, facilitated the interpretation of interactions between Ternstroemia pringlei extract and each CNS depressant drug studied. The isobologram was constructed by connecting the ED$_{50}$ of Ternstroemia pringlei extract on the abscissa with ED$_{50}$ of the combined CNS depressant drug on the ordinate.

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>ED$_{50}$ (mg/kg, i.p.)</th>
<th>CL 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane extract</td>
<td>446.68</td>
<td>307.70–648.3</td>
</tr>
<tr>
<td>Dichloromethane extract</td>
<td>345.93</td>
<td>150.20–795.6</td>
</tr>
<tr>
<td>Methanol extract</td>
<td>232.80</td>
<td>178.40–304.1</td>
</tr>
<tr>
<td>Aqueous extract</td>
<td>77.58</td>
<td>50.21–124.1</td>
</tr>
<tr>
<td>Buspirone</td>
<td>1.04</td>
<td>0.73–1.46</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1.22</td>
<td>0.97–1.49</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>17.05</td>
<td>15.70–18.53</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1938.83</td>
<td>1617.65–2323.77</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.42</td>
<td>0.30–0.55</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>11.86</td>
<td>10.53–13.34</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Combination</th>
<th>$Z_{add}$ (mg/kg)</th>
<th>$Z_{exp}$ (mg/kg)</th>
<th>Magnitude of the interaction$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ternstroemia pringlei extract:buspirone</td>
<td>39.31 ± 5.82</td>
<td>20.85 ± 5.38</td>
<td>0.52$^d$</td>
</tr>
<tr>
<td>Ternstroemia pringlei extract:diazepam</td>
<td>39.40 ± 5.82</td>
<td>22.76 ± 3.61</td>
<td>0.57$^d$</td>
</tr>
<tr>
<td>Ternstroemia pringlei extract:diphenhydramine</td>
<td>47.32 ± 5.83</td>
<td>20.65 ± 1.98$^b$</td>
<td>0.43$^d$</td>
</tr>
<tr>
<td>Ternstroemia pringlei extract:ethanol</td>
<td>1008.21 ± 63.45</td>
<td>1938.83 ± 167.96</td>
<td>1.92$^a$</td>
</tr>
<tr>
<td>Ternstroemia pringlei extract:haloperidol</td>
<td>39.00 ± 5.82</td>
<td>16.33 ± 1.21$^c$</td>
<td>0.41$^d$</td>
</tr>
<tr>
<td>Ternstroemia pringlei extract:pentobarbital</td>
<td>44.72 ± 5.83</td>
<td>21.06 ± 2.40$^a$</td>
<td>0.44$^d$</td>
</tr>
</tbody>
</table>

$^a$ $Z_{exp}$ value was statistically lower than $Z_{add}$ value with a $p < 0.05$.

$^b$ $Z_{exp}$ value was statistically higher than $Z_{add}$ value with a $p < 0.05$.

$^c$ According to the relation: $a/A + b/B$, (see Section 2).

$^d$ Super-additive interaction $a/A + b/B$ was statistically $>1.0$ ($p < 0.05$).

$^e$ Sub-additive interaction $a/A + b/B$ was statistically $<1.0$ ($p < 0.05$).
Fig. 2. Isobolograms for the intraperitoneal co-administration of *Ternstroemia pringlei* aqueous extract with central nervous system depressant drugs. (A) *Ternstroemia pringlei*: buspirone; (B) *Ternstroemia pringlei*: diazepam; (C) *Ternstroemia pringlei*: diphenhydramine; (D) *Ternstroemia pringlei*: ethanol; (E) *Ternstroemia pringlei*: haloperidol; (F) *Ternstroemia pringlei*: pentobarbital. The individual ED\textsubscript{50} values in each combination (■), the theoretical calculated ED\textsubscript{50} for an additive effect (Z\textsubscript{add}) in a fixed ratio 1:1 (●), and the experimentally found ED\textsubscript{50} values (Z\textsubscript{exp}, ▲) are represented in the graphs. Horizontal and vertical bars indicate S.E.M. The values of Z\textsubscript{exp} were close to Z\textsubscript{add}, indicating an additive relationship for all the combinations studied.

ordinate to obtain the additivity line (Tallarida, 2000). The amounts of each component in combination (experimental (Z\textsubscript{exp}) and theoretical additive (Z\textsubscript{add}) doses) were also plotted in the same graph. The theoretical additive point lies on a line connecting the ED\textsubscript{50} values of the individual drugs. Experimental values that lie below and to the left of this additive line are considered to be synergistic or super-additive, whereas values that lie above and to the right of the line demonstrate an attenuated or sub-additive interaction.

To obtain a value describing of the magnitude of the interaction, a fractional analysis was performed for each combination, using the ED\textsubscript{50} of the *Ternstroemia pringlei* extract, the CNS depressant drug and their combination according to:

\[
a \cdot \frac{A}{a} + b \cdot \frac{B}{b}
\]

where A and B are the ED\textsubscript{50} when each drug (*Ternstroemia pringlei* extract and CNS depressant drug) acts alone and a and b are the amounts when each drug acts in the combination. These total fraction values measure the divergence between the experimental dose (Z\textsubscript{exp}) of the combination and the theoretical (Z\textsubscript{add})
additive dose (Tallarida, 2000). Statistical difference demonstration ($p < 0.05$) of 1 for the relation $a/A + b/B$ was interpreted as super-additive interaction if $a/A + b/B$ was $<1.0$ and as sub-additive interaction if $a/A + b/B$ was $>1.0$; the absence of a statistical difference ($p > 0.05$) was interpreted as additive effect (Tallarida, 2000).

3. Results

Intraperitoneal administration of the organic and aqueous extracts of Ternstroemia pringlei fruits resulted in a dose-dependent decrease of the number of rearings in the exploratory cylinder model (Fig. 1). The order of sedative effect for these extracts was (ED$_{SO}$): aqueous (77.58 mg/kg$>$) methanol (232.80 mg/kg$>$) dichloromethane (345.93 mg/kg$>$) hexane (446.68 mg/kg). The CNS depressant drugs also showed a dose-dependent sedative effect in this model. The values of the effective dose $50$ (ED$_{50}$) and $95\%$ confidence limits (CL$_{95}$) for the dependent sedative effect in this model. The values of the effective dose $50$ (ED$_{SO}$) and $95\%$ confidence limits (CL$_{95}$) for Ternstroemia pringlei extracts and the other drugs appear in Table 1. The interaction study between this plant and the CNS depressant drugs was performed only with the aqueous extract since it was the most active sedative extract. All drug combinations were applied at dose-fixed ratios of 1:1. Theoretical ($Z_{theor}$) and experimental ($Z_{exp}$) ED$_{50}$ values for each combination tested are given in Table 2. The $Z_{exp}$ values when Ternstroemia pringlei aqueous extract was simultaneously administered with buspirone, diazepam, diphenhydramine, haloperidol or pentobarbital were statistically lower ($p < 0.05$) than $Z_{add}$ value. In addition, the fractional analysis for these combinations demonstrated that the relation $a/A + b/B$ was statistically $<1.0$ ($p < 0.05$), indicating a super-additive or synergistic interaction for each one of these combinations (Table 2). In contrast, for the simultaneous injection of Ternstroemia pringlei aqueous extract plus ethanol the $Z_{exp}$ value (1938.83 mg/kg) was significantly higher ($p < 0.05$) than the $Z_{add}$ value (1008.21 mg/kg) and the relation $a/A + b/B$ was statistically $>1.0$ ($p < 0.05$), indicating a sub-additive interaction for this combination (Table 2).

The isobolograms of the simultaneous injection of Ternstroemia pringlei aqueous extract + buspirone (Fig. 2A), Ternstroemia pringlei aqueous extract + diazepam (Fig. 2B), Ternstroemia pringlei aqueous extract + diphenhydramine (Fig. 2C), Ternstroemia pringlei aqueous extract + haloperidol (Fig. 2D) and Ternstroemia pringlei aqueous extract + pentobarbital (Fig. 2E) depict also a super-additive interaction because the experimental points lay below the additive line (Tallarida, 2000). Whereas the combination Ternstroemia pringlei aqueous extract + ethanol gave an experimental point lying in the sub-additive region (Fig. 2F) and the sub-additive interaction was statistically demonstrated ($p < 0.05$) based on the comparison of theoretical and experimental data as stated above.

From the methanol extract of Ternstroemia pringlei a white amorphous powder was spontaneously precipitated (mp 243–245 °C); after crystallization from a methanol/hexane mixture) that was identified as epi-ursolic acid by comparison of their IR (film) and proton NMR (400 MHz, CDCl$_3$ + DMSO-d$_6$) spectroscopy and MS (EI) data with those reported for this triterpene (Mukherjee et al., 1982; Jo et al., 2005). This compound was suspended in 0.5% Tween 80 in saline solutions and tested at 100 mg/kg, i.p. in the exploratory cylinder model in mice ($n = 8$), however it did not show sedative effect.

4. Discussion

The present study revealed clearly that Ternstroemia pringlei extracts exerted sedative effect. The activity of the extracts was increasing with the polarity of the solvents used to prepare such extracts, the aqueous extract being the most active of them with an ED$_{50}$ value of 77.58 mg/kg. Aguilar-Santamaría and Tortoriello (1996) reported the sedative effect for this plant using the prolongation of sleep induced by pentobarbital as sedative model; however, no ED$_{50}$ value was provided in that study to compare with the value obtained in the present work. The validity of the exploratory cylinder model for testing sedative drugs is well established (Rolland et al., 1991; Hiller and Zetter, 1996; Oliva et al., 2004; Ugalde et al., 2005). In this model the rearing numbers decrease with an increase of the doses of sedative drugs, and allows the construction of dose–response curves and the calculus of effective doses for individual drugs and in combination (Ugalde et al., 2005).

It is logical to think that a CNS depressant drug may potentiate the effect of other depressant drugs. However, we found an attenuation of the sedative effect for the case of the combination of ethanol with Ternstroemia pringlei extract (Table 2; Fig. 2F). This sub-additive effect is difficult to explain; however, the existence of triterpene saponins has been reported in other species of Ternstroemia genus (Shin et al., 2003). It is known that these kinds of compounds have activity in the central nervous system (Ren et al., 2006), and also that they are able to modify the activity of some isofoms of cytochrome P450 enzymes (Henderson et al., 1999); thereafter the ethanol metabolism alteration should not be discarded as a possible explanation in the attenuation of the sedative effect of ethanol observed by the co-administration of Ternstroemia pringlei extract. This observation requires experimental support to give a convincing explanation of these facts.

The super-additive effect shown by the simultaneous administration of Ternstroemia pringlei extract with pentobarbital (Fig. 2F) is in agreement with the report of Aguilar-Santamaría and Tortoriello (1996) that showed a prolongation of the pentobarbital-induced sleeping time in rodents.

The present study is the first work that investigates the effect on the sedative activity of the simultaneous administration of Ternstroemia pringlei extract with buspirone, diazepam, diphenhydramine, ethanol and haloperidol, therefore there are no previous works to contrast our results. Also the absence of phytochemical studies of this plant does not allow establishing a correlation between the components and the activities reported for them. In relation with this, the major component isolated from methanol extract, the epi-ursolic acid, showed no sedative effect, but the major activity showed by the aqueous extract suggests that the active compound or compounds should have more polarity than epi-ursolic acid. The analysis of the aqueous extract of this plant by thin layer chromatography demonstrated that epi-ursolic acid is not present in this extract. So the identification of the active principle remains to be defined in this plant.

Considering all the above-mentioned facts, it is clear that this plant has hard non-predictive interactions with CNS depressant drugs; thereafter the combination of this plant with CNS depressant drugs should be avoided. The use of Ternstroemia pringlei should be regulated by health authorities, since several herbal preparations contain extracts made from the crude drug. Those commercial products are promptly accessible in the cities of Mexico where the use of CNS depressant drugs by medical prescription is possible. The plant–drug interactions are less important in rural and indigenous regions where the concomitant use of medicinal plants and drugs are less frequent.

A final point to highlight is that the common name as “Flor de Tila” for this plant is frequently confounded with European Tilia that in Spanish have the same name, and the latter correspond to another genera and another botanical family (Tilia sp.; Family Tiliaceae). In addition, in the labels of some commercial products it is declared that they contain Tilia sp. when in reality they contain Ternstroemia sp. Therefore it is important that National Health Authorities notify to local consumers as well as to national...
and international traders about the potential risk of using this plant concomitantly with CNS depressant drugs.

5. Conclusions

The intraperitoneal administration of organic and aqueous crude extracts of fruits of *Ternstroemia pringlei* showed sedative effect in the exploratory cylinder model in mice. Through an isobolographic analysis it was observed that the co-administration of the aqueous extract of *Ternstroemia pringlei* fruits potentiate the sedative effect of buspirone, diazepam, diphenhydramine, haloperidol or pentobarbital and produce an attenuation of the sedative effect of ethanol. According to the results obtained, *Ternstroemia pringlei* is a plant that interacts in a complex form with CNS depressant drugs and it may represent an advertisement on the use of this plant concomitantly with other neuroactive drugs.

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