Review of: "Toxicological evaluation of aqueous extracts of Clematis hirsuta and Rhamnus prinoides"

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Potential competing interests: No potential competing interests to declare.

Article revision

Developing countries rely on traditional herbal medicine to meet their primary healthcare needs. This traditional herbal medicine has quickly grown to the point of becoming popular due to its ease of use, low cost, proven effectiveness, and decreased perceived side effects. Nevertheless, the safety of herbal medicine still needs to be proven. Popular belief states that all traditional medicines are harmless to the health of consumers. This is not always true because the difference between medicine and poison is the dose. The authors, therefore, conducted this study to verify the toxicological effects of *Clematis hirsuta* leave and *Rhamnus prinoides* roots on Wistar rats.

The authors conducted two experimental studies. Acute oral toxicity according to OECD guideline 423. In this study, the authors determined the LD50 and the effects of treatment with different extracts on the body weight variation, water and food intake and some behavioral parameters of 21 rats.

Repeated oral toxicity for 28 days still following the OECD guideline. The authors used female rats to verify the toxic effects of the different extracts at doses of 25, 75 and 225 mg/kg on the evolution of weight and on some hematological and biochemical parameters.

The authors report that the present study investigated the safety of aqueous extracts of*Clematis hirsuta* leaves and *Rhamnus prinoides* roots in rats. Toxicological data on aqueous extracts of*C. hirsuta* leaves were mixed. For example, in the acute toxicity study, rats given 2000 mg/kg aqueous extract of *C. hirsuta* leaves gained weight relative to rats in the control group without physical signs of toxicity after 24 hours or 14 days. Ironically, rats treated with *C. hirsuta* had lower food and water consumption rates than rats in the control group. In subacute toxicity, there were no significant changes in weight gain, hematological or biochemical parameters between *Clematis hirsuta*-treated rats and controls.

Administration of aqueous root extract of*R. prinoides* to Wistar rats did not cause any physical signs of toxicity during the first 24 hours or after 14 days and was associated with significant weight gain compared to the control. However, food and water consumption in rats treated with *R. prinoides* was lower than that of rats in the control group. Moreover, there were no significant differences in weight gain, hematological or biochemical parameters between rats and controls treated with the aqueous extract of the roots of *R. prinoides*.

This study did not evaluate the effects of aqueous extracts of*C. hirsuta* leaves and *R. prinoides* roots on major organs in

Wistar rats as well as their phytochemical composition and pharmacological properties. The authors plan to do this in future work.

The authors concluded that aqueous extracts of *C. hirsuta* leaves and *R. prinoides* roots are safe when administered orally to Wistar rats.

General observations:

The report is conceptually important in its approach and attempts to justify the empirical use of these plants in traditional medicine.

However, some points of concern should be raised here to bring more clarity and understanding to the conclusions drawn by the authors:

In acute toxicity: the authors must:

1- Give the number of animals per group;

2- Give the evaluation protocol of the different parameters. It is not enough to quote them, for the need of reproduction it is necessary to say how they were measured;

3- Explain the OECD guideline 423 they used. The authors state that they used 21 rats for this experiment. According to this protocol and in the absence of death, the number of animals is 15 (3 rats for the control group, 3 rats for the test group and 3 rats for the satellite group. In the absence of death after 48 hours, 2000 mg/kg is administered at 6 other rats which makes 15 rats) how the authors managed to have the 21 rats this does not appear in the document;

4- The authors do not provide any information on the method of evaluation of the behavioral parameters. Were the animals observed individually or in groups? Was the observation made by the experimenter or by a team or using cameras? the authors must provide details for a better understanding.

In subacute toxicity: the authors must:

1- Give the number of animals per group and justify the sex of the animals if possible;

2- Give the blood sample collection protocol;

3- Provide supporting documents for the choice of the different doses

General comment

1- This precision "(mean ± SEM, n = 5)" in Tables 1 and 2 must also be present in the legend of the figures;

2- There are pasted words in the text, for example, the first and third line of section 3.1.3 “of clementis” and “between C. hirsuta”

3- What does “a”, “b” and “c” present in Table 2 mean? it must be specified in the legend;

4- In the result section, the titles are too simple and do not allow to understand the effect of plant extracts on the parameters. Indeed, when reading the tire, we must have an idea of the conclusion of the effect of plant extracts on the parameters. For example, in the acute toxicity study, “the aqueous extract of the *R. prinoides* roots caused body weight gain”.

5- In view of the toxic effects noted by the authors, a microscopic study on the detoxification organs to confirm the absence of toxicity is the major shortcoming of this study. If organs such as the liver, kidneys and lungs are fixed, I recommend making histological sections of these organs to give more credit to the work.

Conclusion :

In the end, I accept the article subject to correction