TOXINS OF VETERINARY INTEREST: EVALUATION OF THE IMMUNOTOXICITY, NEUROTOXICITY AND TERATOGENICITY IN RODENTS AND GOATS

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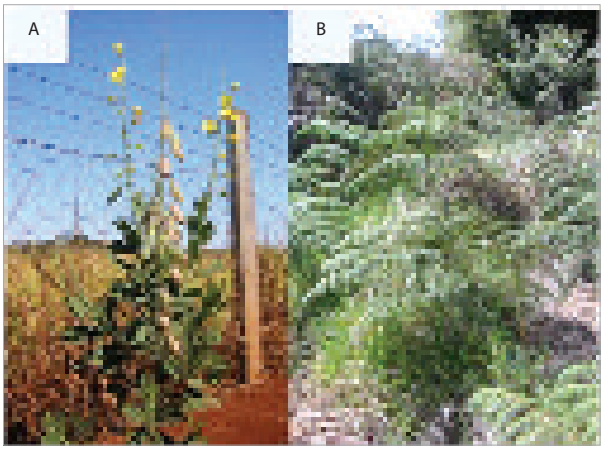


A) Crotalaria spectabilis. *B)* Pteridium aquilinum. *In Górniak, S.L. Poisonous plants of agronomical interest. Spinosa, H.S, Górniak, S.L., Palermo-Neto, J (eds) Manole, Barueri, 2008.*

Poisonous plants and mycotoxins are two of the main causes of economic losses to Brazilian animal livestock industry. Besides animal death losses, other consequences from the prolonged exposure to toxins are the reduced animal body weight gains and production, reproductive impairments, abortions, birth defects, and immunossupression with sub-clinical or short-term illness. Furthermore, plant-associated toxins may negatively impact food safety and contaminate human food.

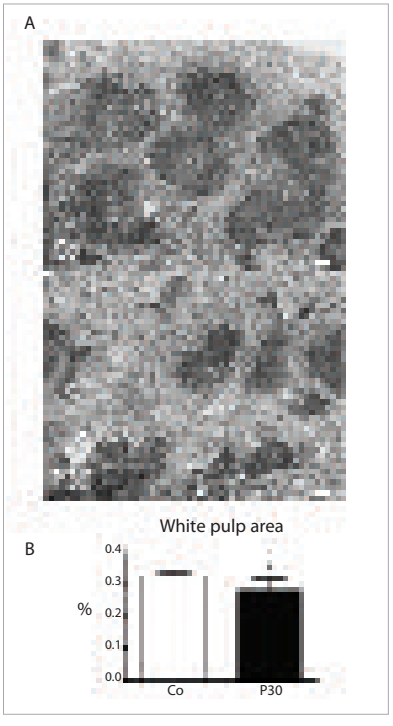
The immune system is pivotal in host defense against infectious agents and neoplasia, which is a highly integrated network of cells. Xenobiotics that alter immune cells functions, can also potentially injure these cells, disrupting the immune responses and altering host resistance. The aims of the present study includes the evaluation of the potential immunotoxicity and teratogenic effects of some plants and mycotoxins to both livestock and human health. In addition, we propose to improve current immune and teratogenic test protocols employed by regulatory agencies of risk assessment.

Pteridium aquilinum is a plant founded worldwide and epidemiological studies have revealed a higher risk of cancer in people who consume this plant directly or indirectly through milk from animals that are feeded with this plant species. In cattle, it has been showed that chronic exposure induces urinary bladder carcinomas and carcinomas of the upper alimentary tract. There are evidences of association between these carcinomas and chronic intoxication by *P. aquilinum* ingestion and bovine papilloma virus infection. Thus, it is plausible that the observed increasing in cancers diseases could be related to induction of an overall immunossuppression by this plant. Considering this, our study has evaluating the immunosuppressive effects of *P. aquilinum* in mice.

Monocrotaline (MCT) is a pyrrolizidine alkaloid found in a variety of plants, including *Crotalaria spp*, which are largely distributed in Brazil. The main symptoms of MCT toxicities in livestock are related to hepato- and nephrotoxicity. Although studies have shown that MCT can cause effects on cellular functions that would be critical to lymphocytes/macrophages during a normal immune response, no immunotoxicological study on MCT have been performed yet. Thus, the aim of the present study is to evaluate MCT effect on different branches of the immune system using mice as animal model.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Histological analyses of C57BL/6 mice administered with *P. aquilinum* extracts revealed a significant reduction in spleen white pulp area. A variety of immune response were analyzed in these animals including delayed-type hypersensitivity (DTH) and decreased IFNÁ production by NK cells during TH1 priming. The innate response in these hosts, assessed by analysis of NK cell cytotoxic functionality was also diminished in comparison to control animals in the assay. These results have confirmed the expected immunosuppressive effects of *P. aquilinum*. Thus, many of the modulated immune responses can contribute to the increased risk of cancer in exposed hosts.



Effects in spleens of mice treated with 30 (P30) g/kg BW of P. aquilinum *and supplemented with B1 vitamin in water (10 mg/ml) for 14 days. A) Representative spleen sections from the control group and from the P30 group. Observe smaller white pulp area in spleens from the P30 group. Bar = 100µm. B) Morphometric analyses showed a significant reduction in white pulp area in spleens from the P30 group (p = 0.004, Mann-Whitney test). Data are expressed as the mean ± SD (n = 9). Latorre et al.,* in press

Rats treated with MCT have their lymphoid organs, acquired immune responses, and macrophage (MO) activity evaluated. No significative changes in the relative weight of lymphoid organs were observed. However, it was observed a decrease in the bone marrow cellularization in rats treated with MCT. Treatments with MCT caused no significant alterations in phagocytic function or in hydrogen peroxide production, however, the MCT causes compromised nitric oxide release by these cells. In conclusion, these results have shown that MCT causes myelotoxic effects and interferes in the formation of at least one product critical to the inflammatory process. Future experiments will be conducted to determine which bone marrow cell lines are affected by MCT, and the roles of iNOS and NO in the inflammatory process. We will also analyze if the effects of this compound, on alveolar macrophages, could be a factor in the pulmonary hypertension known to be induced by this alkaloid.

MAIN PUBLICATIONS

Hueza IM, Benassi JC, Raspantini PCF, Raspantini LER, Sá LRM, Haraguchi M, Górniak SL. 2009. Low doses of monocrotaline in rats cause diminished bone marrow cellularity and compromised nitric oxide production by peritoneal macrophages. *Journal of Immunotoxicology*. **6**: 11-8.

Latorre AO, Sakai M, Fukumasu H, Hueza IM, Furlan, MS, Haraguchi M, Górniak SL. 2009. Immunomodulatory effects of *Pteridium aquilinum* on natural killer cell activity and select aspects of the cellular immune response of mice. *Journal of Immunotoxicology*. **6**: 104-114.

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