







Evaluation of dermal and ocular safety of natural products based on *Murraya paniculata*, *Eucalyptus* sp. and *Indigofera suffruticosa* Mill. in New Zealand rabbits

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ABSTRACT

This study was conducted to evaluate the acute dermal and ocular irritant potential of three natural products obtained from medicinal plants *Murraya paniculata* (PNI), *Eucalyptus* sp. (PNII), and *Indigofera suffruticosa* Mill. (PNIII) for topical use in veterinary medicine. For the assessment of acute dermal and ocular irritability, methodologies from the Organization for Economic Cooperation and Development (OECD) were employed through guidelines 404 and 405, respectively, using New Zealand albino rabbits. The evaluated products showed no signs or symptoms of irritation/corrosion on the skin and eyes, exhibiting dermal and ocular irritation indices within the range of classification of non-irritating substances, according to the OECD Harmonized Integrated Classification System.

Keywords: acute dermal irritability, acute ocular irritability, *Murraya paniculata*, *Eucalyptus* sp., *Indigofera suffruticosa* Mill.

Evaluación de la seguridad dérmica y oftálmica de productos naturales a base de *Murraya paniculata*, *Eucalyptus* sp. e *Indigofera suffruticosa* Mill. en conejos Nueva Zelanda

RESUMEN

El presente trabajo se llevó a cabo para evaluar el potencial irritante agudo dérmico y ocular de tres productos naturales obtenidos de las plantas medicinales *Murraya paniculata* (PNI), *Eucalyptus* sp. (PNII) e *Indigofera suffruticosa* Mill. (PNIII) para su uso en la medicina veterinaria por vía tópica. Para la evaluación de la irritabilidad aguda dérmica y oftálmica, se aplicaron las metodologías de la Organización para la Cooperación y el Desarrollo Económico (OCDE) a través de las guías 404 y 405, respectivamente, empleando conejos albinos Nueva Zelanda. Los productos evaluados no evidenciaron signos ni síntomas de irritación/corrosión en la piel y los ojos, mostrando índices de

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irritación dérmica y ocular dentro del rango de clasificación de sustancias no irritantes, según el Sistema de Clasificación Integrado Armonizado de la OCDE.

Palabras clave: irritabilidad aguda dérmica, irritabilidad aguda oftálmica, *Murraya paniculata*, *Eucalyptus* sp., *Indigofera suffruticosa* Mill.

INTRODUCTION

In the field of veterinary medicine, the search for effective and safe therapeutic alternatives has led to a growing interest in the use of natural products. This interest is based on the premise that various botanical species and organisms harbor bioactive compounds with pharmacological and biological properties that can be applied in the treatment and prevention of diseases in animals (Guimarães *et al.* 2014). These compounds, derived from plant, animal, or mineral sources, have garnered the attention of researchers and veterinary medicine professionals due to their potential to offer novel therapeutic solutions (Reyna–Fuentes *et al.* 2021). Research in this area aims not only to provide alternatives to conventional therapies but also to understand and leverage the rich diversity of natural molecules to improve the quality of life and well-being of animals (Chaves 2020).

On the other hand, the incorporation of natural products in veterinary medicine is not without challenges, particularly concerning safety and toxicity. As new compounds are explored and developed, it is crucial to conduct comprehensive toxicological studies to evaluate their safety and establish safe dosages for administration in animals (Saganuwan 2017). These studies are essential to identify potential adverse effects, interactions with other drugs, and to determine the maximum exposure levels that are not harmful to animal health (Gupta 2019).

Natural products, despite their organic origins, may contain chemical components that could elicit toxic responses at inappropriate concentrations. Therefore, systematic toxicity evaluation becomes a critical step in the development and application of these products in veterinary medicine (Woodward 2008). Such studies, which may include tests for dermal and ocular irritation, acute, subchronic, and chronic toxicity, as well as assessments of genotoxicity and carcinogenicity, are essential to establish a safety and risk profile for each natural product under consideration (Ávila *et al.* 2020a). Furthermore, the inherent variability of each natural source and the chemical composition of the products add an additional layer of complexity to the safety evaluation (Aoki *et al.* 2005). It is important to recognize that the processes of extraction, purification, and formulation can also influence the toxicity and bioavailability of the compounds, underscoring the need for a comprehensive approach in toxicological studies (Salmerón–Manzano *et al.* 2020).

Research on natural products for veterinary use in Cuba has achieved significant progress in the control of parasitic diseases in animals. These formulations, derived from natural sources such as plant parts, essential oils, and other organic compounds, applied topically, have emerged as an alternative to conventional chemical products (Štrbac *et al.* 2023; Jamil *et al.* 2022). In Cuba, medicinal plants such as Muralla (*Murraya paniculata*), *Eucalyptus*

(*Eucalyptus* sp.), and Añil Cimarrón (*Indigofera suffruticosa* Mill.) possess repellent, insecticidal, antiseptic, antihyperpigmentary, antiparasitic, antibacterial, and astringent properties, which can help mitigate the infestation of external parasites in animals, such as fleas, ticks, lice, sarcoptic mange, and other ectoparasites.

Chemical studies on the extracts of these plants report the presence of tannins, carbohydrates, saponins, phenols, aldehydes, flavonoids, pyrethrin, phenolic acids, and coumarins (Akram *et al.* 2020; Ávila *et al.* 2020b; Chaves 2020; Mangas *et al.* 2020; Sánchez *et al.* 2006; Sarmiento and Velázquez 2021; Zamora and Toro 2021). Topical application of these products involves direct placement on the animal's skin or fur, exposing it to the cutaneous barrier and its underlying layers (OECD 2015). Since the skin is the primary contact and absorption point for these compounds, it is imperative to conduct dermal irritation studies to evaluate their potential to cause adverse skin reactions in treated animals (Monteiro-Riviere 2020). Similarly, the application of these products near the eyes of animals can cause damage to the delicate ocular anatomy, posing a risk to the visual health of the patient (Short 2021).

Consequently, evaluating the dermal and ocular safety of natural products is crucial to ensuring their safe topical application for the control of parasitic diseases in animals.

These studies provide valuable information on potential adverse effects on the skin and eyes, allowing for adjustments in formulations or dosages to minimize any potential risks (Camejo-Hernández *et al.* 2022). Moreover, they contribute to establishing clear guidelines for the

responsible and effective use of these products in veterinary practice, ensuring the health and well-being of both animals and their caregivers (Siska *et al.* 2017). For these reasons, the current study aims to evaluate the dermal and ocular irritation in New Zealand rabbits of three natural products based on extracts of *Murraya paniculata*, *Eucalyptus* sp., and *Indigofera suffruticosa* Mill. for therapeutic use in veterinary medicine.

MATERIALS AND METHODS

Substances under study

At the Center for Toxicology and Biomedicine (Toximed, for its acronym in Spanish), in Santiago de Cuba, a total of three natural products were evaluated, sourced from the Biological-Pharmaceutical Laboratory (Labiofam Business Group, Santiago de Cuba, Cuba). The PNI formulation, based on the plant *Murraya paniculata* (Lot: 210301); the PNII formulation, based on the plant *Eucalyptus* sp. (Lot: 210302); and the PNIII formulation, based on the plant *Indigofera suffruticosa* Mill. (Lot: 2008001), is composed by dark brown hydroalcoholic extracts with characteristic odor and taste. These extracts were maintained at a temperature of 25-30 °C and stored in plastic bottles.

Test animals

Adult female New Zealand White rabbits, weighing 2-3 kg, were provided by the National Center for Laboratory Animal Production (Cenpalab, Havana, Cuba). The animals were kept under conventional conditions with a relative humidity of 30-70%, a temperature of 22±3°C, and a 12-hour light/dark cycle with fluorescent

lighting. They were fed a conventional diet consisting of standard feed supplied by Cenpalab and had free access to water.

Dermal irritation assay

The assay was conducted according to the OECD guideline 404. Three animals per group were used for each product (PNI, PNII, and PNIII). The animals were shaved on both flanks (10% of body surface area) 24 hours before product application. The skin was washed with sterile water and allowed to rest for 24 hours. Patches with 0.5 mL of the product were applied to an area of approximately 6 cm² on one flank, while the other flank was used as a control. The animals were exposed to the product for four hours, after which the patches were removed, and the application area was washed with sterile water. Observations were recorded at 1, 24, 48, and 72 hours after removing the patches (OECD 2015).

Behavior, general condition, posture, and reflexes, as well as attitude towards food, water, and hygiene, were evaluated. Their weights were recorded and compared at the beginning and end of the study. An assessment of edema and erythema was performed, and the dermal irritation index

(DII) was calculated using the following formula:

$$DII = \frac{\text{Sum of erythema and edema scores}}{\text{Number of animals} \times \text{Number of observations}}$$

The extracts were classified according to the scale proposed by Draize (1944) (table 1) and following the guidelines for the assessment of chemicals issued by the OECD, a methodology used to determine the degree of acute dermal irritation/corrosion (OECD 2015).

Ocular irritation assay

The OECD guideline 405 was employed to determine the degree of ocular irritation/corrosion (OECD 2023). A total of three rabbits per test group underwent a rigorous examination of ocular structures: cornea, iris, and conjunctiva. Following OECD regulations, 60 minutes before instillation of the natural products, 0.01 mg/kg of buprenorphine was administered subcutaneously to provide systemic analgesic effect, and two drops of topical ocular anesthetic (0.5% proparacaine hydrochloride) were applied to each eye 5 minutes before product application. The eye receiving no product but treated with topical anesthetic served as the control. After 60 minutes had elapsed,

TABLE 1. Dermal irritation score ranges established by Draize (1944), for the classification of substances with irritant effect on the skin

Ranges of dermal irritation Score	Classification of dermal irritability
0 < DIS < 0.4	Non- irritant
0.4 ≤ DIS < 2.0	Slightly irritating
2.0 ≤ DIS < 5.0	Moderately irritating
5.0 ≤ DIS ≤ 8.0	Severely irritating

Source: own elaboration.

a volume of 0.1 mL of each product was instilled into the lower conjunctival sac of the right eye, with the eyelids held together for the following 20 minutes. Both eyes of each animal were examined at the initial time point and at 24, 48, and 72 hours, always by the same specialist. Corneal damage was determined in a dark room by applying a 2% solution of sodium fluorescein and physiological saline solution to remove excess instilled revealing solution. Finally, ultraviolet light was used for structure observation. Observations were made for up to five days to assess the reversibility of effects, and at the end of the study, the animals were weighed to compare variations in this parameter.

The ocular irritation index (OII) was determined using the following formula (OECD 2023):

$$OII = \frac{\sum \text{Individual observations}}{\text{Number of animals} \times \text{Number of observations conducted}}$$

The obtained value was compared with the ranges defined in table 2 to determine approval or rejection results, according to the Cuban method proposed by García-Simón, defined as approval limits of OII from 0 to 19 and rejection from 20 to 110 (García-Simón *et al.* 1988).

Ethical considerations

The experimental design was reviewed and approved by the Ethics Committee for Research at Toximed N.º 8 and the Quality Assurance Unit, according to Protocol Toximed/UGC/010404. It complied with the conditions of the Good Laboratory Practices of the Food and Drug Administration (FDA), as well as the guidelines established by the National Institutes of Health (NIH, USA).

RESULTS AND DISCUSSION

Dermal irritation

For all three animals, the mean score for erythema/eschar formation at 24, 48, and 72 hours was 0.00 for each product at each evaluated time point. No aberrant results were observed on the skin of any control animal (removal of dressing, gauze patch, and test item) at 1, 24, 48, and 72 hours, following treatment. On the treated skin of the rabbits, the natural products did not induce any discoloration or corrosive effects (figure 1).

TABLE 2. Ocular irritation score ranges established according to the Cuban method for classification of eye irritation/corrosion

Ranges of ocular irritation Score	Classification of eye irritability
0 < OIS < 10	Non-irritant
10 ≤ OIS < 20	Slightly irritating
20 ≤ OIS < 30	Moderately irritating
30 ≤ OIS ≤ 110	Severely irritating

Source: own elaboration.

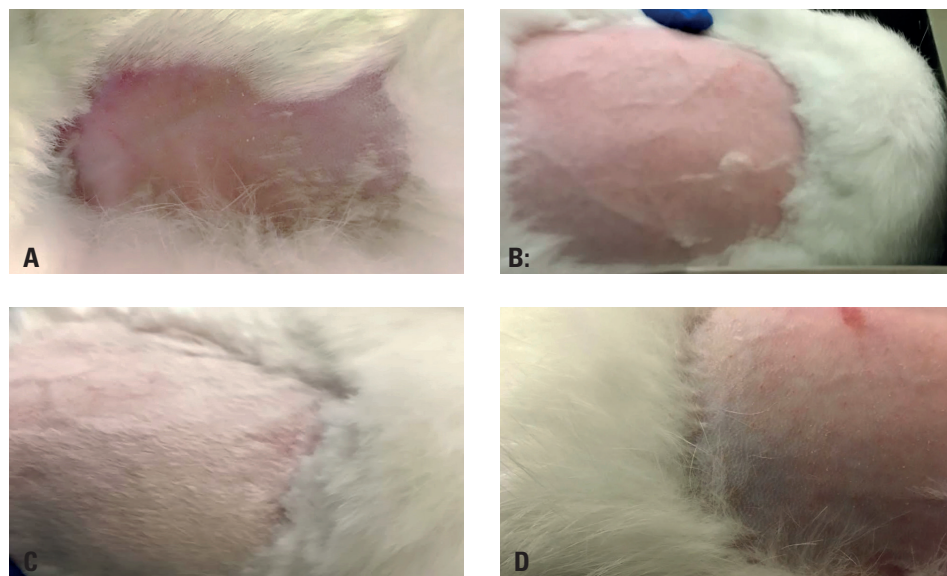


FIGURE 1. Absence of corrosion in the skin of rabbits after completion of the dermal irritancy test. A: Control group; B: PNI; C: PNII; D: PNIII.

Source: own elaboration.

In the dermal irritation evaluation assay, it was found that the increase in body weight during the experimental period (table 3) was within the usual range of variation for this species according to its age (Alemán *et al.* 2020).

The results obtained allowed the calculation of the primary dermal irritation index (DII) for the three plant-based

products tested, which was, in all cases, equal to 0.00. Therefore, they are classified as “non-irritants” to rabbit skin, according to the Harmonized Integrated Classification System.

Ocular irritation

At the conclusion of the ocular irritation assay, ocular responses were recorded at 1,

TABLE 3. Body weight behavior in New Zealand rabbits during the dermal irritancy test

Animals	Sex	PNI		PNII		PNIII	
		Initial weight	Final weight	Initial weight	Final weight	Initial weight	Final weight
01	Female	2.83	3.00	2.61	2.84	2.66	2.81
02	Female	3.00	3.07	2.80	2.87	2.68	2.84
03	Female	3.00	3.09	2.78	2.83	2.70	2.89

Source: own elaboration.

24, 48, and 72 hours. For each animal, a mean score was obtained for corneal opacity, iris, conjunctival redness, and chemosis, for the three products evaluated at each observation time, resulting in a total of 17, 0, 16, and 14, respectively (table 4).

Throughout the experimental stage, the treated eye of each animal appeared normal. During the acclimatization and post-treatment periods, no clinical symptoms of toxicity were found in any of the animals. It was observed that all body weights of the animals were within the usual range of variation observed in the species and age group (Alemán *et al.* 2020), with a normal increase observed in each case (table 5).

These results allowed the determination of the ocular irritation indices (OII) for each product, reaching values below 10:

PNI (1.41), PNII (1.33), PNIII (1.16), therefore, they were classified in all cases as “non-irritants” for rabbit eyes, according to the OECD Harmonized Integrated Classification System.

The global pet market is currently one of the fastest-growing markets worldwide. This market positioning is accompanied by a growing concern among pet owners about the health of their animals, both in terms of nutrition and the use of medications with less severe side effects, including the prevention and treatment of infestations by parasites such as fleas and ticks, as well as public health regarding the transmission of pathogens from animals to humans (Chaves 2020). For these reasons, over the years, there has been an increasing demand from society for alternative pest control products that

TABLE 4. Determination of the number of ophthalmic affectations as a consequence of the application of natural plant-based products in New Zealand rabbits

Hours	PNI				PNII				PNIII			
	1H	24H	48H	72H	1H	24H	48H	72H	1H	24H	48H	72H
Conjunctiva	5.00	2.00	0.00	0.00	2.00	2.00	2.00	0.00	2.00	2.00	0.00	0.00
Iris	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Cornea	5.00	5.00	0.00	0.00	5.00	5.00	0.00	0.00	5.00	0.00	5.00	0.00

Source: own elaboration.

TABLE 5. Body weight behavior in New Zealand rabbits during the ophthalmic irritancy test

Animals	Sex	PNI		PNII		PNIII	
		Initial weight	Final weight	Initial weight	Final weight	Initial weight	Final weight
01	Female	2.68	2.88	2.66	2.83	2.71	2.87
02	Female	2.67	2.87	2.67	2.85	2.70	2.88
03	Female	2.69	2.88	2.69	2.84	2.71	2.87

Source: own elaboration.

do not cause negative impacts on human and animal health, the environment, and natural resources. Botanical insecticides are products derived from plant parts, which have been suggested as possible alternatives to the use of conventional synthetic insecticides, presumably because extracts and essential oils have a lesser impact on human health and the environment (Isman *et al.* 2011).

The natural products based on hydroalcoholic extracts evaluated meet safety requirements for use in veterinary medicine for topical application, based on the results obtained in the present research. *Murraya paniculata*, the main component of PNI, has been evaluated in acute and subacute toxicity studies (Joshi & Gohil 2023), showing no signs of toxicity for single doses of 2,000 and 5,000 mg/kg, nor for doses of 100, 200, and 400 mg/kg in repeated doses for 28 days (Gautam *et al.* 2012; Menezes *et al.* 2015). Furthermore, studies conducted on a formulation containing a species from the same family such as *Murraya koenigi* showed it to be non-dermal irritant and mildly ocular irritant in New Zealand albino rabbits (Krishnaraju *et al.* 2010).

In the case of *Eucalyptus*, a component of PNII, it has been extensively studied for topical use, primarily in the cosmetic industry. From the species *Eucalyptus globulus*, six components were evaluated for cosmetic use, with safety studies conducted showing that they posed no risks to consumers (Becker *et al.* 2023).

On the other hand, the plant *Indigofera suffruticosa* Mill., the main ingredient in the formulation of product PNIII, has shown signs of acute toxicity such as agitation, irritation, piloerection, and spasms when administered in aqueous extracts at high doses (2,400 mg/kg) intraperitoneally in

mice (Vieira *et al.* 2012). Meanwhile, the methanolic extract applied by the same route and in the same experimental model showed an LD50 of 1,600 mg/kg (Almeida *et al.* 2013). Despite the low toxicity of the plant, and the fact that PNIII is proposed for topical use, precautionary measures should be considered to prevent ingestion of the product by treated animals (Campos *et al.* 2018).

These studies contribute to determining the safety of the topical use of the evaluated formulations, allowing the availability of new natural products based on medicinal plants for the control of parasitic diseases to be provided to pet owners and owners of economically important animals.

CONCLUSIONS

The natural products based on medicinal plants evaluated (PNI, PNII, PNIII) can be classified as potentially non-irritating according to OECD guidelines 404 and 405, which assess the degree of acute dermal and ocular irritation/corrosion, respectively.

CONFLICT OF INTEREST

We declare that there is no commercial or personal interest within the scope of the research that would lead to the production of the submitted manuscript.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE

We declare that we did not use artificial intelligence.

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