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Toxicological Study of the Seed Extracts from *Dodonaea madagascariensis* Radlk (Sapindaceae), a Malagasy Medicinal Plant

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Abstract: This work was designed to study the seed toxicity of *Dodonaea madagascariensis* Radlk. (Sapindaceae), an endemic plant to Madagascar with multiple medicinal uses. Using different experimental models of animals, seed methanolic extract of *D. madagascariensis* (SMED) was found to be toxic to mice (LD50 of 36.12 mg/ kg by intraperitoneal route), chicks (*Gallus gallus domesticus*), juvenile fishes (*Cyprinus carpio*) (LC50 of 4.33 µg/mL) and frog tadpoles (*Ptychadena mascareniensis*) (LC50 of 5.41 µg/mL). Toxicity was ascribed to saponin group only. In mice, SMED developed different symptoms when administered by intraperitoneal, subcutaneous and oral routes. Trailing of the posterior limbs, low body posture, tremors, ataxia, abdominal breathing and at high dose, diarrhea were the most common occurring symptoms. In acute and subchronic administrations, SMED caused damages in the liver, kidneys, lungs, small and large intestines while brain, heart and stomach were not affected. No significant changes on serum concentration of ASAT, ALAT and creatinine were observed after oral subchronic exposure (30 days) to SMED at 12.71 mg/kg. SMED exerted a positive inotropic effect on isolated guinea pig atria at 12.5 µg/mL and had a hemolytic activity. In the light of these preliminary results, the toxicity of *D. madagascariensis* seeds could be used in the control of harmful cold blooded animals.

Keywords: *Dodonaea madagascariensis*, Seed Methanolic Extract, Saponins, Toxicity, Histopathological Lesions, Biochemical Parameters

1. Introduction

The study on *Dodonaea madagascariensis* is a part of a research program on toxic plants endemic to Madagascar [1-10].

Dodonaea is one of the 140 genera belonging to Sapindaceae. It is composed of about 60 species of evergreen shrubs and small trees. Plants of this genus grow wild in tropical and subtropical regions, in open forests and dry shrubs.

In Madagascar, *Dodonaea* is represented by *D. madagascariensis* and *D. viscosa* [11, 12]. The former, endemic to Madagascar has a limited distribution area while the latter is widespread in tropical and subtropical regions.

D. madagascariensis is a shrub or 2-8 m tree (Fig 1) growing in scrublands, mountains, rocky or poor soils and on the edge of forests. It is found in uplands (1500–2500 m) in Antananarivo (Analamanga, Vakinankaratra) and Toliary (Anosy) regions and in protected areas (Ambohitantely, Isalo, Kalambatritra). It is

cultivated in villages of the Analamanga region [13].

The available informations on the uses of *Dodonaea* members were limited to a few species.

D. viscosa, the most studied species, is the subject of many empirical uses [14]. Leaf infusion is used for the treatment of gout, hemorrhoids, bone fractures, snake bites [15], ulcer and pains of hepatic or stomach origin [16]. Leaf extract has antimicrobial [17, 18] and anthelmintic properties [15]. Isolated molecules from leaf have anti-inflammatory activity [19, 20, 21]. Leaf extracts have antihyperglycemic activity [14, 22]. In Pakistan, the plant is utilized for the treatment of various fungal skin diseases [23].

D. angustifolia has also a wide range of therapeutic applications against various diseases including malaria [24].

Many medicinal virtues are ascribed to *Dodonaea madagascariensis* [25, 26]. It has antibacterial, antiviral, diuretic and antihypertensive properties. Infusion of its root is used as cold remedy, its leaves have analgesic properties and are also chewed because of their stimulating effect. It is also used to heal fever, sore throats, chest pains, flu, stomach upsets and cancer. In Antananarivo, dry leaves are sold by herborists under the vernacular name *tsitoavina* for the treatment of stomach aches [25].

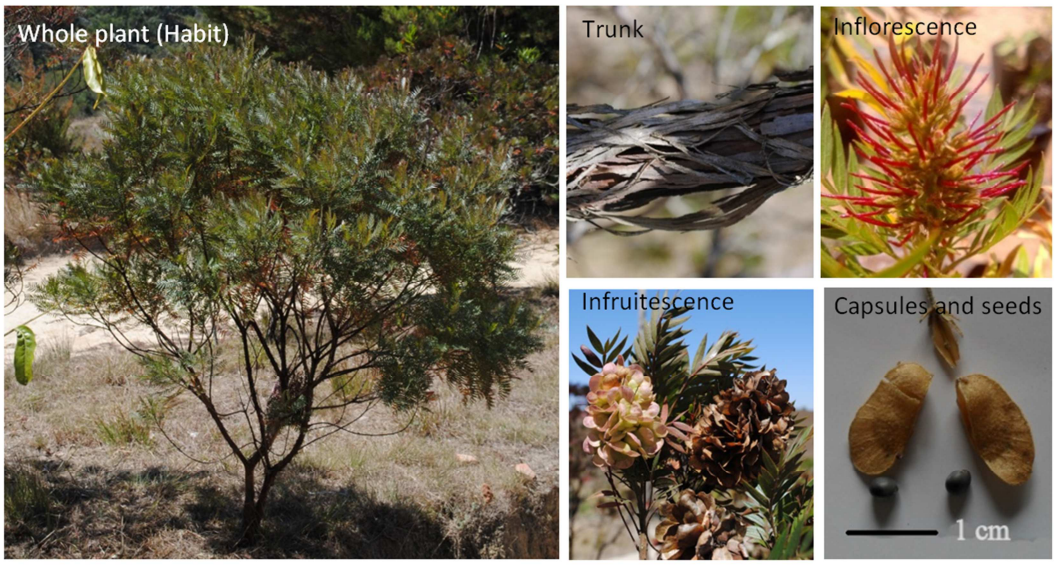

Figure 1. *Dodonaea madagascariensis Rdlk. Source: the authors.*

According to our surveys of village residents in the vicinity of our harvesting site (Ambohitantely forest), *D madagascariensis* leaves were used to protect crops against harmful insects.

D. madagacariensis has other non-medicinal uses: timber, firewood, ornamental and shade tree and in agroforestry for protection and improvement of soils. It is also used in silkworm rearing (*Borocera madagascariensis*) and valued by beekeepers for its flowers [26].

With the exception of botanical studies, the only known works carried out on *D. madagascariensis* were those of Trotin *et al*. [25, 27] on the phytochemistry and some pharmacological properties of leaf extracts. They found flavonoids, alkaloids and saponins as main compounds and low antibiotic and slight antispasmodic activities. The lethal dose for mice by intraperitoneal route was about 6 g of leaves per kg of body weight.

It was somewhat surprising to note that *D. madagascariensis* seeds, although found in high amounts on the plant, were not used in traditional medicine. This could account for the lack of researches on this organ of the plant.

Our preliminary work revealed the toxic effect of the seed extract on mice. This result encouraged the deepening of the study. So, the aim of this work mainly consisted of a better assessment and characterization of the toxicity and the identification of the chemical group responsible of the toxic effects on animals in SMED.

2. Experimental

2.1. Plant Materials

Seeds were harvested around Ambohitantely forest located 140 km northwest of Antananarivo, in the district of Ankazobe.

About 72 seeds weigh 1 g. After washing and drying in the shade, seeds were ground into a fine powder.

2.2. Animals

OF-1 strain Albino mice (*Mus musculus*), weighing 25±2 g, came from the Pasteur Institute of Madagascar (IPM) breeding farm.

Guinea pigs were provided by Malagasy Institute of Applied Research (IMRA).

One day old chicks (*Gallus gallus domesticus*) were furnished by AVITEC farm.

Carp alvins (*Cyprinus carpio*), Royal strain, 2-4 cm size, were provided by an approved fish farmer.

Apode frog tadpoles (*Ptychadena mascareniensis*) were harvested from the ponds in the vicinity of the Antananarivo

University site. Fishes and tadpoles were allowed to acclimatize to the aquarium conditions for three days after their arrival in laboratory.

2.3. Extract Preparations

2.3.1. Seed Methanolic Extract (SMED) Preparation

Seed powder was delipidated with hexane during 36-48 hours. After filtration using a Whatman filter, the resulting material was air-dried, then extracted with methanol by maceration under stirring, during 24 h at room temperature. After filtration through a cotton-wool, SMED was obtained after methanol evaporation.

2.3.2. Extraction of Total Alkaloids

A 10% chlorhydric acid solution (30mL) was added to delipidated seed powder (10g) mixed with methanol (100mL). The mixture was macerated under stirring at room temperature for 24 hours. After filtering through cotton-wool, methanol was removed from the filtrate by evaporation. This methanol extract was partitioned in a mixture of dichloromethane and distilled water (50:50, v/v). After decantation and separation of the two phases, the resulting aqueous solution containing total alkaloids in salt form was alkalinized with NH_4OH (25%) to render them in base form. Then, total alkaloids were extracted 3 times with dichloromethane (3x10 mL). After decantation, the total alkaloids in the organic phase, were washed three times with distillated water (pH 7) and dehydrated with Na_2SO_4. Finally the total alkaloids in the organic phase, was obtained after dichloromethane evaporation.

2.3.3. Extraction of Total Saponosides

Saponosides were extracted from SMED. The dry evaporation residue of SMED was dissolved in methanol. The resulting solution was poured dropwise into a mixture of acetone/diethyl ether (50/50, v/v) at 0°C. Total saponosides precipitated. The precipitate was harvested by centrifugation and the supernatant was submitted to the same treatment until there was no more precipitation. All the precipitates were gathered then dissolved in water and solvents were removed by evaporation under reduced pressure to obtain dry residue.

2.4. Phytochemical Screening

All the reactions of chemical group detection were those developed by Fong *et al.* [28] and Marini-Bettolo *et al.* [29].

2.5. Experiments on Animals

All the methods used in the study of extracts on animals (toxicity assessment, organ section preparation, effect measurement on isolated atria, physiological functions and hemolytic test), but not described here, were detailed in previous papers [4, 5, 7-10].

2.5.1. Measurement of Blood Biochemical Parameters

One group of 3 female mice was daily treated with SMED (12.72 mg/kg of body weight) by oral route during 30 days. At the end of experiment, 1 mL of venous blood was collected. All the blood samples, without anticoagulant, were centrifuged (13000 rpm for 10 minutes at 4°C, with Biofuge fresco, Heraeus Instruments). The sera, stored at -20°C, were used for the assessment of aminotransferase (ALAT), aspartate aminotransferase (ASAT) and creatinine rates.

2.5.2. Histopathological Examination

Organ damages caused by acute intoxications were examined. Three groups of 5 mice were used. A sublethal dose of SMED (36.53 mg/kg) was intraperitoneally injected to 4 mice of each group. The 5th mouse served as control. At different times (6, 12 and 24 hours), 1 animal of each group was sacrificed and the organs were collected.

All the organs were preserved in BOUIN solution. The preparation of the organ sections for histopathological examinations was carried out as described in [7].

3. Results

3.1. Chemical Study

Phytochemical analysis was carried out on the seed powder and SMED. Both seed preparations generally contained the same compounds although, in some cases, amounts were slightly different. Alkaloids, saponins, triterpenes, insaturated sterols were found in high amounts and tannins, iridoids and quinones were missing (Table 1).

Table 1. *Phytochemical screening of seed preparations of D. madagascariensis (powder and SMED).*

Chemical groups	Tests	Seed powder	SMED
Alcaloid	Mayer	++	++
	Wagner	++	++
	Dragendorff	++	++
	Confirmatory test (solubility in ethanol)	+	+
Flavone	Willstätter	±	++
Iridoid	Hot HCl	-	-
Leucoanthocyanin	Bate-Smith	±	-
Saponins	Foam test	+++	+++
Steroids	Liebermann-Burchard	±	±
Triterpenes		++	+
Insaturated sterols	Salkowsky	+++	±
Coumarin		+	-
Tannins	Gelatin 1%	-	-
	Gelatin-salt 10%	-	-
	$FeCl_3$	-	-
Polyphenols		+	+
Quinones	Borntrager	-	-

+: positive test; -: negative test

3.2. Toxicological Study

3.2.1. Toxic Effects of SMED on Mice

(i). Symptoms Developed and LD50 value

The effects of intraperitoneal, subcutaneous and oral routes were assessed at three doses (46.27, 600.8 and 2228.76 mg/kg) (Table 2). The first dose (46.27 mg/kg) was the DL100 by intraperitoneal route. At this dose, no symptom was yet observed by subcutaneous and oral routes. At doses up to 13 times higher (600.8 mg/kg), the mortality rate was 100% by

subcutaneous route while by oral route only slight symptoms began to appear but disappeared the next day. At a dose 48 times higher (2228.16 mg/kg) the mortality rate was yet 60% by oral route.

Table 2. *Effect of SMED on male mice according to the administration route.*

DOSE (mg/kg)	Mortality rate (%)		
	Intraperitoneal	Subcutaneous	Oral
46.27	100	0	0
600.8	100	100	0
2228.16	100	100	60

Regardless the administration route (intraperitoneal, subcutaneous and oral) and the doses tested, the symptoms caused by SMED in mice were almost the same. They could be grouped in nervous system disorders (Trailing of the posterior limbs, low body posture, slight body tremors, hiccups, piloerection, ataxia, prostration, exophthalmos), respiratory disorders (hyperpnea, dyspnea, increase in respiratory rate), cardiovascular (ear vasodilatation) and other disorders (abdominal contortion, ears extended backwards, loose and mucous stools). However, these symptoms took much more time and required higher doses to appear by subcutaneous and oral routes.

The signs of the nervous system disorders were the earliest and most often observed.

The LD50 (24h) of SMED was assessed at 36.12 mg/ kg body weight by intraperitoneal route.

(ii). Comparison of the Toxicity of Different Parts of D. Madagascariensis

The toxicity of SMED was compared to that of methanolic extracts of other parts of *D. madagascariensis*. Two doses, 300 and 1200 mg/kg, about 6.5 and 26 times higher than the DL100 of SMED (46.27 mg/kg) were intraperitoneally injected to mice. As shown in Table 3, all organ extracts were much less toxic than SMED. With capsule extract, no toxic effects were noted at the tested doses.

Table 3. *Effects of the methanolic extracts of different parts of D. madagascariensis intraperitoneally administered to mice.*

Dose (mg/kg)	Mortality rate (%)			
	Capsule	Stem bark	Leaf	Seed
300	0	67	0	100
1200	0	100	33	100

(iii). Effects on Blood Biochemical Parameters

No significant changes of serum concentration of ASAT, ALAT and creatinine were noted in mice after 30 days of treatment with a SMED subchronic dose (12.72 mg/kg) (Table 4).

Table 4. *Effect of subchronic dose of SMED on biochemical parameters in mice after 30 days of continuous treatment by oral route.*

Biochemical parameters	Non treated animals	Treated animals with SMED (12.7 mg/Kg)
ASAT (UI/l)	476.33 ± 66.08	440.00 ± 103.87
ALAT (UI/l)	35.67 ±5.44	52.75 ± 20.72
Creatinine (mg/L)	2.95 ± 0.48	3.77 ± 0.06

(iv). Histopathological Lesions

No macroscopic lesion was observed. In all experimental conditions, heart, brain and stomach remained histologically normal. For lungs, liver, kidneys, small and large intestines, lesions varied according to exposure time. At the tested dose (36.53 mg/kg) and after a time exposure of 6 hours purifier organs (lungs and liver) were the most concerned. Histologic damages resulted in vasodilatation, neutrophil polymorphonuclears and sometimes necrotic zones, (Fig 2). In kidneys lesions were visible only after 12 hours.

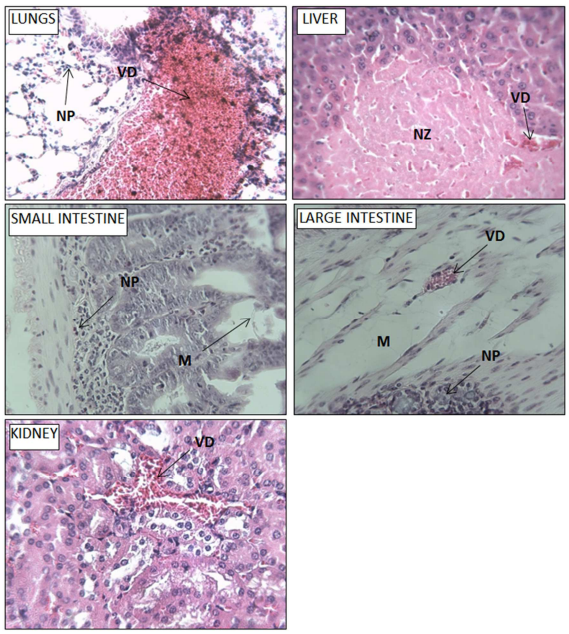

Figure 2. *Main lesions induced by SMED (36.53 mg/kg) on lungs, liver, small and large intestines after 6 hours and kidney after 12 hours (magnification factor x 40) M: Mucus; NP: Neutrophil polymorphonuclears; NZ: Necrotic zone; VD: Vasodilatation.*

3.2.2. Effects on Isolated Guinea Atria

The SMED effects on the number of beats per minute or chronotropy and the magnitude of the contraction or inotropy were evaluated on the isolated guinea pig atria.

SMED did not significantly change the number of atrial beats per minute up to a concentration of 25 µg/ml (Fig. 3a). On the other hand, at 12.5 µg/ml and after 5 min of contact, it caused a significant increase in the amplitude of cardiac contraction ($p < 0.02$). But at 25 µg/ml, this effect was not statistically significant (Fig. 3b).

3.2.3. Effects on Other Animals

As shown in Table 5, SMED had no effect on chicks at mice LD100 dose (46.27 mg/kg) but it was toxic to the frog *Ptychadena mascareniensis* tadpoles and the fish *Cyprinus carpio* alvins.

3.2.4. Effects of SMED Main Chemical Groups on Mice

In order to determine the chemical group(s) responsible of the SMED toxicity, the effects of saponins, alkaloids and others were assessed on mice. At 46.27 mg/kg (SMED DL100) and 185.28 mg/kg, a dose 4 times higher, were intraperitoneally injected. Saponins exhibited the same

toxicity as SMED, while with alkaloids and other chemical groups, only slight symptoms were observed after extract administration which disappeared after 21 hours.

4. Discussion

4.1. Chemistry

Saponins were the major compounds in SMED. These compounds exhibit a number of physical, chemical and biological properties, only a few of which are common to all members [30]. In addition, given the endemicity of *D. madagascariensis,* its seed saponins might be new.

The phytochemical screening revealed the presence in *D. madagascariensis* seeds of secondary metabolites known to be of pharmacological interest as alkaloids, flavonoids and triterpenes.

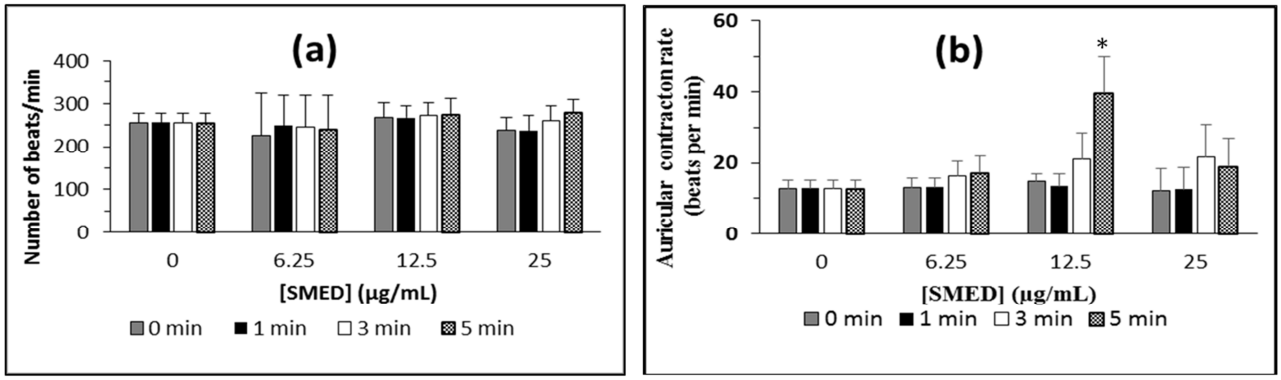

Figure 3. *Effect of different concentrations (µg/ml) and contact time (in minutes) of SMED on the amplitude of contraction (a) and the number of beats per minute (b) of the isolated guinea pig atria (n=4); *: p<0.02.*

Table 5. *Toxicity of SMED on different animal species.*

Animal class	Species	LD50 or LC50	Observations
Mammals	Mouse	36.12 mg/kg	
Birds	*Gallus gallus domesticus* (chicks)		A dose corresponding to LD100 on mice had no effect by intraperitoneal and oral routes
Amphibians	*Ptychadena mascareniensis* (apode frog tadpoles)	5.41 µg/mL	
Fishes	*Cyprinus carpio* (alvins)	4.33 µg/mL	

4.2. Toxicological Properties

With the exception of fruit capsule, all the organs of *D. madagacariensis* so far examined contained saponins. It has been shown that SMED toxicity was attributed to these compounds. This toxicity was much higher than the toxicity of extracts of other parts of the plant. These results suggested that either toxic seed saponins were different from those of other parts or toxic saponins were the same but in small amounts in other organs.

The great variety of medicinal uses of the *D. madagascariensis* leaf extract could at least be due to its low toxicity. On the contrary, the low toxicity of SMED by oral route could not explain its non-use unless human species is more sensitive to SMED than mouse. The unpleasant bitterness due to saponins (in high amounts) and alkaloids and the unavailability of seeds throughout the year might be involved.

The high toxicity of SMED to cold-blooded animal could be exploited to combat harmful animals as insects. As already mentioned above, the seeds of *D. viscosa* has insecticide and anthelminthic activities. In addition, *D. madagascariensis* leaves are used as insect crop pest. Experiments on the SMED effects on insects are ongoing in our laboratory.

In comparison with the toxicity of other species of the Sapindaceae family by intraperitoneal route in mouse, SMED (LD50 of 36.12 mg/kg) was less toxic than *Blighia unijugata* butanol leaf extract (LD50 of 5.26 mg/kg) [31], but more toxic than *Paullinia pinata* ethanolic leaf extract (LD50 of 1131 mg/kg) [32]. Compared to other seed extracts, the toxicity of which was assessed under similar conditions [7], SMED was as toxic as seed methanolic extract of *Albizia aurisparsa* (36.30-38.76 mg/kg) and *Albizia androyensis* (LD50 of 35.27-41.55 mg/kg), more toxic than *Albizia bernieri* (LD50 of 52.23-55.00 mg/kg) but much less toxic than *Albizia greveana* (LD50 of 1.13-2.30 mg/kg) and *Albizia tulearensis* (LD50 of 2.9-3.2 mg/kg).

The main lesions found in all organs, were generally those frequently observed in intoxications by saponins [4, 5, 7-10]. The high toxicity of SMED to cold blooded animals and its hemolytic activity were also attributed to saponins.

The only positive effect of the extract on the two auricular parameters studied was the positive inotropic effect obtained at 12.5 µg/ml and after 5 min of contact. It was certainly secondary to the increase of the intracellular calcium pool in the origin of the auricular contraction. Among the positive inotropic substances, the digitalis, with their steroid pharmacophores, are the most potent. They are known as inhibitors of the pump Na+/ K+-ATPase. SMED contained traces of steroids that could be at the origin of this positive inotropic effect. It could also contain a molecule(s) able to inhibit the phosphodiesterase type III enzyme. PDE-3 inhibitors, like a milrinone, were endowed with a positive inotropic effect without significant chronotropic effect as SMED did.

The biochemical parameters did not increase in subchronic

exposure condition to SMED. That meant that, at the dose used and during 30 days, SMED did not cause an important destruction of liver cells resulting in release of the transaminases (ASAT and ALAT) into the bloodstream. It did not also impair the kidney function in the control of the serum creatinine.

5. Conclusion

The results obtained from the present work brought the first scientific data on *D. madagascariensis* seeds and highlighted their toxicity. They contributed to a better knowledge of the Malagasy endemic plants particularly poisonous plants.

Bearing in mind the importance and the great variety of the pharmacological properties of saponins, investigations are ongoing for exploring other properties of *D. madagascariensis* seed saponins.

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