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Diuretic activity of *Withania aristata*: An endemic Canary Island species

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Abstract

This study reports on the pharmacological evaluation of the diuretic activity of an infusion and a methanol extract of *Withania aristata* Ait. in laboratory rats. Water excretion rate, pH, density, conductivity, and content of Na^+, K^+ and Cl^- were measured in the urine of rats subjected to hypersaline conditions. Both the infusion and the methanol extract showed a significant diuretic effect compared with non-treated controls, with notable increases in the rates of water and sodium excretion. There was also a potassium retention effect. The diuretic effect did not appear to be related to the potassium content in the material tested, but did have some relation to its content of active polar compounds. The results justify the use of *Withania aristata* as a diuretic agent in folk medicine of the Canary Islands.

Keywords: *Withania aristata*; Diuretic activity; Medicinal plant; Urinary excretion; Rats; Folk medicine

1. Introduction

Withania aristata Ait. (Solanaceae) is an endemic species of the Canary Islands. It is popularly known as "orobal" or "sáquido" (Darias et al., 1986). The plant grows wild on many of the central islands, and is common in ravines and at the bases of mountains, in soils which are somewhat nitrified and humid. It is common in the thickets of thermophilic forests (Pérez-Paz and Hernández, 1999).

This species forms a bush with variegated foliage which can be tree-like in size, although not reaching over 4 m in height. Its bark is coarse and grey in color, and its fragile branches form a dense mass. The plant bears greenish flowers which arise from the axillae of the leaves on peduncles. The fruit is globose and orange-colored (initially green), fleshy, and enveloped in a thin, resistant calyx (Kunkel, 1992).

This species has wide use in folk medicine practice on the islands due to the wide variety of medicinal properties attributed to it; including its use as a scarring agent, antispasmodic, for rheumatic problems, eye problems and otitis, as well as for insomnia, constipation, and urinary pathologies. Ingestion of the fruit strongly stimulates urine production, making it useful against hydropesia (Jaén, 1984, 1989; Darias et al., 1986, 1989, 2001; Pérez-Paz and Hernández, 1999).

Partial studies on the chemical composition of *Withania aristata* have isolated withanolides – types of steroid lactones – including withaferine A and withanolide D, among other constituents (González et al., 1972, 1974). Other compounds found were phytosterols, oleoresins and withaminol (Valera and Santos, 2002). Other *Withania* species from other parts of the world such as *Withania somnifera* and *Withania coagulans* have been submitted to numerous chemical studies, also encountering withanolides which are compounds characteristic of the Solanaceae and in particular the genus *Withania* (Ganzera et al., 2003). These products have demonstrated interesting properties such as anti-inflammatory, immunosuppressive, anti-stress, anxiolytic, cicatrizant, fungicidal and trypanosomacidal effects (Al-Hindawi et al., 1992; Choudhary et al., 1995; Habtemariam, 1997; Manickam et al., 1997; Bhattacharya et al., 2000; Jayaprakasam and Nair, 2003; Abe et al., 2006; Machiah et al., 2006). Until the present, however, no formal studies had been made on the biological activities and medicinal properties of *Withania aristata*.

The present study, using laboratory mice and rats, is thus the first formal attempt to demonstrate the diuretic efficacy of hot water infusion and methanol extract of the plant.

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2. Materials and methods

2.1. Plant material

Withania aristata was harvested from the Santa Cruz Coast in a place called Taganana in Tenerife, Canary Islands (Spain) at 75 m altitude above sea level, in March 2003, and labeled Exp. NE. UTM E381093-N3160004. Voucher specimens were deposited in the La Laguna University Herbarium (TFC 44199).

2.2. Extracts preparation

The leaves of flowering and immature fruiting *Withania aristata* were air-dried in an oven at 40 °C for 4 days and then the dry plant was cut and ground to a powder mechanical milling.

Then three aqueous extracts at 5, 10 and 15% from the dried powdered plant material were prepared by mean traditional method applied in Canaries. Amounts of 5, 10 and 15 g, respectively of pulverized plant material were each placed in 100 ml distilled boiling water and left at room temperature 15 min to infuse, and then were filtered. Five millilitres per kilogram body weight (bw) of each infusion was then given orally to individual rats (equivalent to doses of 0.25, 0.50 and 0.75 g/kg). The infusions were freshly prepared just prior to administration. In a second test procedure, the dried powdered plant material was submitted to a continuous extraction in a soxhlet extractor for 5 days using 100% methanol as a solvent. The solvent was then eliminated by vacuum distillation in a rotary vacuum evaporator (Buchler Corp.), representing a yield of 10.39% of the dry material extracted. The methanol residue obtained was dissolved in distilled water just before administration, and administered at doses of 100 and 200 mg/kg bw in a volume of 5 ml/kg bw.

2.3. Animals

Male albino Sprague-Dawley rats (180–210 g) and male and female albino Swiss mice (20–24 g) obtained from the Central Animal House, University of La Laguna, were used for the experiments, according with the guidelines of the European Community Council Directive 86/609.

2.4. Drugs

Hydrochlorothiazide (HCTZ; Sigma Chemical Co.) was used as a reference diuretic drug.

2.5. Acute toxicity test

Groups of 10 mice, 5 male and 5 female weighing 20–24 were used for administration of the infusion and MeOH extract of *Withania aristata*. The animals had free access to standard commercial diet and water *ad libitum* in a 12/12 h light–dark cycle at 22 °C. The test infusion at 2.5 g/kg bw (0.4 ml/20 g bw) and MeOH extract at 1 g/kg bw, respectively, were administered orally by means of a gastric catheter. Food was withdrawn 16 h before the start of the experiment. The mice were observed for symptoms of toxicity for 15 days in terms of weight loss, and autonomic and neurobehavioral alterations. On the 15th day, the animals were sacrificed and their vital organs were individually observed for overt pathology.

2.6. Diuretic activity

Diuretic activity was determined following the methods of Kau et al. (1984), with minor modifications. Male rats were divided into seven groups of eight animals each, in laboratory cages. They were fed laboratory diet *ad libitum* and allowed free access to drinking water. They were exposed to a 12/12 h light–dark cycle at 22 °C. Eighteen hours before testing, the animals were fasted overnight, with free access to tap water only. Then all animals were given an oral loading of normal saline (5% bw). Subsequently, three groups of rats were orally administered 5 ml/kg bw of the 5, 10 and 15% infusions of *Withania aristata,* two groups of rats were orally administered 5 ml/kg bw of the methanol extract at doses 100 and 200 mg/kg of weight, respectively, and other two groups of rats were orally administered 5 ml/kg bw p.o. of HCTZ at doses 10 and 25 mg/kg, respectively. Control rats received the same amount of deionised water (5 ml/kg bw). Immediately after administration, the rats were paired and placed in metabolism cages. Urine was collected in a graduated cylinder and its volume was recorded at 2 h intervals for 8 h. Cumulative urine excretion was calculated in relation to body weight and expressed as ml/100 g bw. Electrolyte (Na^+, K^+, Cl^-) concentrations, pH, density and conductivity were estimated from a pooled urine sample of each pair of rats at the end of the experiment (8 h) and expressed as mequiv./100 g bw.

2.7. Analytical procedures

Na^+ and K^+ concentrations were measured using a Jenway Corp. model PFP7 flame photometer. The instrument was calibrated with standard solutions containing different concentrations of Na^+ and K^+. Cl^- concentrations were determined by direct potentiometry, using an ion-selective chloride electrode (Orion 9417B) and an Ag/AgCl reference electrode with a double junction (Orion 90-02). The potentials were measured with an Orion Ionalyzer 901. KNO_3 2 M was used as a standard in all the determinations; pH and conductivity were directly determined on fresh urine samples using a HI-8424 Hanna Instruments pH-meter and a LF-320 WTF conductivity meter, respectively. Density estimation was made by weighing with a Mettler AE163 (±0.1 mg) analytical balance on urine volume measured with a Nichiryo micropipette.

2.8. Statistical analyses

Results are expressed as the mean values ± S.E. (standard error of mean) of four pairs of rats. The statistical evaluation was carried out by analysis of variance. The difference between the means of treated groups and the non-treated control groups was evaluated by the Student's unpaired *t*-test.

Table 1
Effect of oral administration of the infusion and the methanol extract of *Withania aristata* on urinary volume excretion

Group	*n*	Urine volume (ml/100 g/8 h)	Diuretic index[a]
Control	16	4.37 ± 0.17	–
HCTZ 10 mg/kg	4	6.14 ± 0.23*	1.39
HCTZ 25 mg/kg	4	6.07 ± 0.07*	1.40
Withania aristata (infusion 5%)	4	5.08 ± 0.54	1.16
Withania aristata (infusion 10%)	4	5.56 ± 0.35**	1.27
Withania aristata (infusion 15%)	4	6.08 ± 0.98**	1.39
Withania aristata (MeOH) 100 mg/kg	4	6.10 ± 0.51*	1.40
Withania aristata (MeOH) 200 mg/kg	4	6.35 ± 0.81*	1.45

The results show the mean values and standard errors; *n* = number of pairs used in each group. *$p < 0.01$ and **$p < 0.05$ compared with the control group (Student's unpaired *t*-test).
[a] Diuretic index = volume problem group/volume control group.

Table 2
Effects of oral administration of the infusion and the methanol extract of *Withania aristata* on urinary electrolyte excretion

Group	*n*	Na^+ (mequiv./100 g/8 h)	K^+ (mequiv./100 g/8 h)	Cl^- (mequiv./100 g/8 h)	Saluretic index[a]			Na/K
					Na	K	Cl	
Control	16	0.53 ± 0.02	0.19 ± 0.00	1.06 ± 0.03			2.79	
HCTZ 10 mg/kg	4	0.70 ± 0.07**	0.29 ± 0.01*	1.37 ± 0.06*	1.32	1.53	1.29	2.41
HCTZ 25 mg/kg	4	0.69 ± 0.04**	0.27 ± 0.01*	1.51 ± 0.18*	1.30	1.42	1.42	2.56
Withania aristata (infusion 5%)	4	0.59 ± 0.05**	0.18 ± 0.03	0.96 ± 0.08	1.48	0.96	1.23	3.28
Withania aristata (infusion 10%)	4	0.62 ± 0.08	0.26 ± 0.01*	1.06 ± 0.06	1.55	1.37	1.36	2.38
Withania aristata (infusion 15%)	4	0.73 ± 0.03***	0.39 ± 0.02*	1.24 ± 0.00***	1.83	2.05	1.59	1.87
Withania aristata (MeOH) 100 mg/kg	4	0.64 ± 0.02***	0.18 ± 0.00	1.30 ± 0.09**	1.21	0.96	1.48	3.56
Withania aristata (MeOH) 200 mg/kg	4	0.65 ± 0.05***	0.25 ± 0.01**	1.57 ± 0.05*	1.23	1.32	1.23	2.60

The results show the mean values and standard errors; *n* = number of pairs used in each group. *$p < 0.001$, **$p < 0.01$ and ***$p < 0.05$ compared with the control group (Student's unpaired *t*-test).
[a] Saluretic index = mequiv. problem group/mequiv. control group.

3. Results

3.1. Diuretic activity

The different parameters analyzed for the infusion and for the methanol extract of *Withania aristata* in the test animals, as well as the HCTZ and control groups, are included in Tables 1–3.

Table 1 lists the urinary volume results (ml/100 g/8 h) and Table 2 the electrolyte (Na^+, K^+, Cl^-) content (mequiv./100 g/8 h) in the urine of animals treated with *Withania aristata* infusion, methanol extract, HCTZ and control groups. Other parameters related to excretion such as the density, pH, and conductivity of the urine samples are also presented in Table 3.

The results in the tables showed that the reference diuretic HCTZ induced excretion values for water of nearly 40%, and between 30 and 50% for the excretion of Na^+ and K^+, when compared with the untreated control group. It should also be noted that maximum excretion was observed in animals receiving the lowest doses of the HCTZ (Tables 1 and 2).

Excretion followed a dose-dependent relation in tests of the *Withania aristata* infusions, with values from between 15 and 40% compared with the control group, suggesting that this phytodiuretic had important effects on the excretion of water. This effect was repeated in rats receiving the methanol extract, where values of 40 and 45% were obtained for the 100 and 200 mg/kg doses, respectively, and which were comparable to the effects of HCTZ.

Table 3
Effects of oral administration of the infusion and the methanol extract of *Withania aristata* on the conductivity, pH, and density of the urine

Group	*n*	Conductivity	pH	Density
Control	16	15.04 ± 0.37	6.27 ± 0.13	0.9566 ± 0.006
HCTZ 10 mg/kg	4	17.60 ± 0.26**	7.26 ± 0.13**	0.9855 ± 0.002
HCTZ 25 mg/kg	4	17.76 ± 0.34**	7.10 ± 0.12*	0.9828 ± 0.008
Withania aristata (infusion 5%)	4	16.12 ± 0.76**	7.24 ± 0.20*	0.9907 ± 0.001
Withania aristata (infusion 10%)	4	16.12 ± 0.53*	7.02 ± 0.53*	0.9861 ± .0030
Withania aristata (infusion 15%)	4	16.36 ± 0.04*	6.87 ± 0.09*	0.9900 ± 0.002
Withania aristata (MeOH) 100 mg/kg	4	14.15 ± 0.49	7.35 ± 0.12**	0.9539 ± 0.006
Withania aristata (MeOH) 200 mg/kg	4	15.50 ± 0.26	7.18 ± 0.14**	0.9505 ± .0060

The results show the mean values and standard errors; *n* = number of pairs used in each group. *$p < 0.05$ and **$p < 0.01$ compared with the control group (Student's unpaired *t*-test).

Electrolyte excretion induced by *Withania aristata* showed that both the infusion and the methanol extract gave equivalent results for the excretion of water. These results also demonstrated a dose-dependent relation for the excretion of Na^+ and K^+, although the results were lower than those produced by the HCTZ, with the only exception noted when using the 15% infusion which produced results higher than those obtained from the group receiving the HCTZ. Here, it was observed that both the infusion and the methanol extract showed significantly reduced potassium excretion, both inferior to that induced by the HCTZ and less than or equal to values in the control group. The only exception was the result from the 15% infusion (Table 2). Reduced potassium excretion was noted from the saluretic index of the infusion and the methanol extract, the values of which for the experimental groups were between 0.96 and 1.37, with 1.0 for the control group and 1.42 for the HCTZ groups.

The conductivity, which is an indirect measure of ion content of the urine, showed a dose-dependent increase in all the treated groups in comparison with the control group. In all cases the response was less for the *Withania aristata* treatments than with the HCTZ.

The pH values were higher in the treated groups than in the controls, showing a decrease in effect with increase in the dosage of the *Withania aristata* materials. There were no statistically valid differences in urine density among treated and control values.

3.2. Acute toxicity

Neither the infusions nor the methanol extract used in the tests produced acute toxicity in the mice tested, as evidenced by the absence of mortality in the animals during the study period. No macroscopic alterations were noted in the viscera of the treated mice.

4. Discussion and conclusions

HCTZ produced its maximum diuretic effect at a dose of 10 mg/kg, in agreement with values given in the literature (Kawashima et al., 1985). The results showed a marked excretory effect on both water and ions, typical of saluretic diuretics of the HCTZ type.

Results from the *Withania aristata* infusion and extract showed a clear and significative dose-dependent diuretic effect, with values very similar to those of the HCTZ. These results confirmed therefore the popular use as diuretic agent of this species (Pérez-Paz and Hernández, 1999; Darias et al., 2001).

Both the infusion and methanol extract showed an electrolyte excretion clearly in proportion to the water excretion, in a dose-dependent manner. Thus it seems reasonable to think that the diuretic effect of *Withania aristata* was of the saluretic type, and similar to that produced by HCTZ, in contrast to the aquaretic type typical of most phytodiuretic agents.

On the other hand, it was also noted that, beginning with the initial dose and both for the infusion and the methanol extract, there was a weak excretion of potassium (0.18 mequiv.), which was lower than in the control group (0.19 mequiv.) and notably less than that of the HCTZ group (0.29 mequiv.); this suggested an interesting K^+-saving effect with the use of *Withania aristata*. This effect disappeared when a higher concentration (15%) of the infusion was employed, causing 0.39 mequiv. of potassium to be excreted, and also exceeding the results obtained with HCTZ. Nevertheless, it should be noted that the 15% *Withania aristata* infusion level was unusually high, and not normally achieved in typical household preparations. In fact, typical preparation of the infusion in Canary Island households is about 2.5–5%.

Quantitative determinations of the ions present in the *Withania aristata* infusion revealed the presence of very low amounts of potassium salts, suggesting that diuretic effect does not seem to be due to the potassium content in the infusion samples. It is well known that potassium overloading, which occurs when the kidney tubules are incapable of absorbing it, produces urinary excretion of the osmotic type (Loew et al., 1991). Our (unpub.) data has shown that an aqueous solution of KCl (1.06 mmol/l), of similar potassium concentration as that occurring in the 15% *Withania aristata* infusion, did not increase diuresis in the test animals.

Regarding to the methanol extract, we should point out that, in contrast to the infusion in whose water preparation it occurs a removal of salts, with the methanol this salts removal does not generate. Thus the notable diuretic effect produced by the methanol extract reaffirmed the concept that the diuretic activity of *Withania aristata* was not due to its content of potassium salts. For this reason it is more appropriate to assume the occurrence of a diuretic effect which was not of the osmotic type; this was evident with the methanol extract and even more probable for the infusion.

We therefore suggest that the diuretic effects of *Withania aristata* are fundamentally due to the presence of naturally active polar compounds, among which we have cited the withanolides (González et al., 1972, 1974); these are the main active components in this species, although until now there has been no literature found containing conclusive data concerning the diuretic activity in these products.

There was a significant increase in the conductivity in the urine of the rats in both treatment with the *Withania* infusion and methanol extract in relation to the data from the controls. Since the conductivity value is an indirect measure of the electrolyte concentration in the urine, the diuretic effect of the *Withania aristata* was again concluded to be (as above) saluretic rather than aquaretic, the latter being the typical effect of diuretics of plant origin. This was to be expected, as it coincides with the above-mentioned concept of the lightly saluretic characteristic of *Withania aristata* products, although these results are not comparable with the important saluretic effect of the HCTZ.

The absence of acute toxicity confirmed the safe nature of the ingestion of this plant since doses of up to 10× the typically used dosage in folk medicine failed to elicit any toxic symptoms in the test rodents.

In summary, *Withania aristata* produces a notable effect of the saluretic type, not due to an osmotic mechanism related to the salts contained within the plant, and with a diuretic profile different from the HCTZ, due to the interesting potassium-saving

effect showed at 5 and 10% infusion and 100 and 200 mg/kg methanol extract. Also, *Withania aristata* was very safe, and within the rodent model, failed to exhibit any toxicity.

The present results provide a quantitative basis explaining the traditional folk medicine use of *Withania aristata* as a diuretic agent by the Canary Island population. The fact that the simple infusions provided diuretic effects comparable to the more difficult to obtain methanol extract, suggested that the traditional folk medicine infusions need not be replaced by more costly chemically processed products.

Additionally, this species may be of use in treatment of bacterial urinary infections through the action of "therapeutic lavage" (when taken with a sufficient quantity of liquid), based on its content of certain active compounds such as the withanolides (steroid lactones), which may exhibit a certain degree of antibacterial activity (Arora et al., 2004).

In the future more studies are required to further define the diuretic value of extracts of this plant, particularly the role of its active components such as the withanolides.

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