



Diuretic activity of *Smilax canariensis*, an endemic Canary Island species

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ABSTRACT

Ethnopharmacological relevance: *Smilax canariensis* is an endemic species of the Canary Islands, popularly known as “Zarzaparrilla sin espinas”. This species has wide use in folk-medicine practice on the islands, especially as diuretic. So the aim of our study is to evaluate the diuretic activity of an aqueous and a methanol extract of this species.

Material and methods: Three infusions doses (250, 500 and 750 mg/kg) and two methanol extract doses (100 and 200 mg/kg) were orally administered to laboratory rats. Water excretion rate, pH, density, conductivity, and content of Na⁺ and K⁺ were measured in the urine of saline-loaded rats.

Results: Water excretion rates were significantly increased in a dose-dependent manner by both hot water infusions and the alcohol extract. The electrolytic excretion was also dose-dependent, although potassium excretion was markedly reduced when using the alcohol extract compared with that observed for the infusion.

Conclusions: *Smilax canariensis* presents a notable diuretic effect which appeared to be related both to its potassium content and to the presence of polar organic compounds. The present results provide a quantitative basis explaining the traditional folk-medicine use of *Smilax canariensis* as a diuretic agent by the Canary Island population.

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1. Introduction

Smilax (Liliaceae) plants are widely distributed in tropical and temperate regions throughout the world, especially in East Asia and North America. Many of them have been long used as medicinal herbs.

Smilax canariensis Willd. is an endemic species of the Canary Islands. It is popularly known as “Zarzaparrilla sin espinas” and it grows sporadically on various central islands, where humid soils support vegetative cover (Darias et al., 1986; Kunkel, 1992; Pérez-Paz and Hernández, 1999).

This species has wide use in folk-medicine practice on the islands due to the wide variety of medicinal properties attributed to it. The parts used as medicine are the rhizome, leaves and stem that habitually are employed as a hot water infusion administered orally. Traditionally this plant has been used as diuretic, laxative, depurative and hypoglycaemic (Jaén, 1984, 1989; Darias et al., 1986, 1989, 2001; Pérez-Paz and Hernández, 1999).

Until the present, no studies had been carried out on the chemical composition of this species. However, many *Smilax* species from other parts of the world such as *Smilax china* have been sub-

mitted to numerous chemical and biological studies due to their interesting properties. These species have been shown to contain steroidal saponins and phenolic compounds (Kubo et al., 1992; Sashida et al., 1992; Bernardo et al., 1996; Shu et al., 2002; Li et al., 2006; Sautour et al., 2006; Xu et al., 2006) and have demonstrated interesting anti-inflammatory, anti-conceptive, cytotoxic, antioxidant, immunomodulatory, anticancer, hypoglycaemic, uricosuric and antifungal activities (Giachetti et al., 1988; Suh et al., 1996; Fukunaga et al., 1997; Lee et al., 2001; Jiang and Xu, 2003; Cox et al., 2005; Kuo et al., 2005; Sautour et al., 2005; Thabrew et al., 2005; Xu et al., 2005; Chu and Ng, 2006; Huang et al., 2006; Wang et al., 2006; Li et al., 2007).

No formal studies have been made previously on the biological activities and medicinal properties of *Smilax canariensis*. The present study represents the first research into the diuretic effects of a water infusion and methanol extract of this plant employing laboratory mice and rats as test animals.

2. Materials and methods

2.1. Plant material

Smilax canariensis was harvested from La Palma Island in a place called Las Nieves, Canary Islands (Spain) at 265 m altitude above sea level, in June 2003, and labeled Exp. NE. UTM E228098-N3177053.

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It was identified by Dr. Pedro Pérez de Paz, Department of Plant Biology, University of La Laguna (Tenerife, Spain), where voucher specimens have been deposited (TFC 44393).

2.2. Extract preparation

Rhizomes, leaves and stems (20:40:40) of *Smilax canariensis* were air-dried in an oven at 40 °C for 4 days and then the dry plant was cut and ground to a powder by mechanical milling. Three infusions doses, at 250, 500 and 750 mg/kg body weight (bw) with respect to dry initial plant material, were freshly prepared in distilled boiling water just prior to administration, by mean traditional method applied in Canaries (aqueous extract yield 15.2%).

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 17.17% 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 to the guidelines of the European Community Council Directive 86/609, for the handling and use of laboratory animals.

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 g were used for administration of the infusion and MeOH extract of *Smilax canariensis*. The animals had free access to standard commercial diet and water *ad libitum* in a 12-h light/12-h dark cycle at 22 °C. Increasing doses of the infusion up to 2.5 g/kg bw (0.4 ml/20 g bw) and MeOH extract up to 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-h light/12-h 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 each infusion dose of *Smilax canariensis*, two groups of rats were orally administered 5 ml/kg bw of the methanol extract at 100 and 200 mg/kg of weight, respectively, and other two groups of rats were orally administered 5 ml/kg bw of HCTZ at 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⁺) 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 meq./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⁺. 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 ± SEM (standard error of mean). The statistical evaluation was carried out by analysis of variance (ANOVA) followed by Student's *t*-test for multiple comparisons. When comparing with control groups, values of *P* less than 0.05 were considered significant.

Table 1

Effect of oral administration of the infusion and the methanol extract of *Smilax canariensis* on urinary volume and electrolyte excretion

Group	n	Urine volume (ml/100 g/8 h)	Diuretic index ^a	Na ⁺ (meq./100 g/8 h)	K ⁺ (meq./100 g/8 h)	Saluretic index ^b		Na/K
						Na	K	
Control	16	4.37 ± 0.17	–	0.53 ± 0.02	0.19 ± 0.02			2.79
HCTZ (10 mg/Kg)	4	6.14 ± 0.23**	1.39	0.70 ± 0.07**	0.29 ± 0.07***	1.32	1.53	2.41
HCTZ (25 mg/Kg)	4	6.07 ± 0.07**	1.40	0.69 ± 0.04**	0.27 ± 0.01***	1.30	1.42	2.56
<i>Smilax canariensis</i> (250 mg/kg)	4	4.97 ± 0.83	1.14	0.50 ± 0.06	0.19 ± 0.06	0.94	1.00	2.63
<i>Smilax canariensis</i> (500 mg/kg)	4	5.37 ± 0.82	1.23	0.52 ± 0.09	0.24 ± 0.02	0.98	1.26	2.16
<i>Smilax canariensis</i> (750 mg/kg)	4	5.77 ± 0.35*	1.32	0.58 ± 0.04*	0.29 ± 0.02***	1.09	1.53	2.00
<i>Smilax canariensis</i> (MeOH, 100 mg/Kg)	4	5.29 ± 0.41	1.21	0.60 ± 0.03	0.16 ± 0.02	1.13	0.84	3.75
<i>Smilax canariensis</i> (MeOH, 200 mg/Kg)	4	6.21 ± 0.28**	1.42	0.72 ± 0.02**	0.18 ± 0.02	1.36	0.95	4.00

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

^a Diuretic index = volume problem group/volume control group.

^b Saluretic index = meq. problem group/meq. control group.

Table 2
Effects of oral administration of the infusion and the methanol extract of *Smilax canariensis* on conductivity, pH and density

Group	n	Conductivity	pH	Density
Control	16	15.04 ± 0.37	6.27 ± 0.13	0.9566 ± 0.06
HCTZ (10 mg/Kg)	4	17.60 ± 0.26**	7.26 ± 0.13**	0.9855 ± 0.02
HCTZ (25 mg/Kg)	4	17.76 ± 0.34**	7.10 ± 0.12*	0.9828 ± 0.08
<i>Smilax canariensis</i> (250 mg/kg)	4	15.40 ± 0.31	7.24 ± 0.20**	0.9907 ± 0.01
<i>Smilax canariensis</i> (500 mg/kg)	4	16.04 ± 0.38	7.71 ± 0.38**	0.9947 ± 0.03
<i>Smilax canariensis</i> (750 mg/kg)	4	16.27 ± 0.17	7.91 ± 0.29**	0.9974 ± 0.06
<i>Smilax canariensis</i> (MeOH, 100 mg/Kg)	4	15.55 ± 0.68	6.80 ± 0.22	0.9612 ± 0.01
<i>Smilax canariensis</i> (MeOH, 200 mg/Kg)	4	15.65 ± 0.10	6.50 ± 0.27	0.9705 ± 0.06

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).

3. Results

3.1. Diuretic activity

The different parameters analyzed for the infusion and for the methanol extract of *Smilax canariensis* in the test animals, as well as the electrolytes (Na^+ and K^+) content of the three infusion samples used, are included in Tables 1–3.

Table 1 shows the urinary volume (ml/100 g/8 h) and the electrolyte (Na^+ , K^+) content (meq./100 g/8 h) in the urine of animals treated with *Smilax canariensis* extracts, HCTZ and control groups, and Table 2 other parameters related to excretion such as the conductivity, pH and density.

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 (Table 1).

Table 1 also shows that the *Smilax* infusions induced an important degree of urinary excretion beginning with the lowest dose administered; the three doses administered produced increase excretion levels ranging from 14% to 32% of those measured in the untreated controls. This effect was repeated in rats receiving the methanol extract, where values of 21% and 42% were obtained for the 100 and 200 mg/kg doses, respectively, the latter dosage producing a similar effect to that obtained with HCTZ.

Electrolyte excretion induced by *Smilax canariensis* showed a dose-dependent increase for both the infusion and the methanol extract when compared to the control group, in parallel with the urinary excretion (Table 1).

The 750 mg/kg *Smilax canariensis* infusion dose produced a moderately significant increase in the Na^+ excretion, when compared with the control group (* $p < 0.05$); potassium excretion was much more intense than that of sodium, and particularly significant at this highest dose with a highly significant value which was equal to the effect obtained using HCTZ, saluretic reference drug (** $p < 0.001$).

On the other hand, the methanol extract showed an interesting increase in sodium excretion, especially significant at 200 mg/kg (** $p < 0.01$), with values higher than that of the groups receiving HCTZ (36% and 32%, respectively) but, unlike the result with the infusion, there was a very reduced potassium excretion, which was even less than values for the control

Table 3
 Na^+ and K^+ content of the *Smilax canariensis* infusion samples

Plant samples	Na^+ (meq./l)	K^+ (meq./l)
<i>Smilax canariensis</i> (250 mg/kg)	15.72	12.33
<i>Smilax canariensis</i> (500 mg/kg)	26.21	30.68
<i>Smilax canariensis</i> (750 mg/kg)	52.42	62.86

group, and indeed much lower than that induced by the HCTZ.

There was a weak increase in the urine conductivity of the rats treated with the *Smilax* infusions and methanol extract in relation to control data. The pH values were higher in the treated groups than in the controls and there were no statistically significant differences in urine density among treated and control values (Table 2).

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

Both the *Smilax canariensis* infusion and methanol extract showed a dose-dependent increase in urine excretion, which turned out to be significant at the higher doses tested. With respect to the infusion, the most notable increase of urinary excretion was produced at 750 mg/kg with value of 32% compared with the control group; and at the highest dosage of the methanol extract (200 mg/kg), there was an increase of 42% compared with the control group, which was even slightly higher than the result obtained using the HCTZ.

The increases in diuresis induced by both the infusion and the alcohol extract were reflected in similar manners in ionic excretion, producing dose-dependent increases when compared with controls. Nevertheless, ion excretion patterns differed between the infusion and the methanol extracts. The infusion produced little or no sodium excretion compared with the control group, but did indeed induce at the highest dose a notable excretion of potassium, with values similar to those produced by the HCTZ (53%). The methanol extract produced sodium excretion values higher than those of the infusion, equalling or exceeding, at the highest dose (200 mg/kg), the values obtained when using HCTZ (36% vs 32%). However, in contrast with results from the infusion, potassium excretion associated with this extract was very low, and even lower than in the control group.

This difference in effect between the infusion and the methanol extract can be noted by observing the Na/K ratio which reached, at the 200 mg/kg methanol extract dosage, a value of 4.0, much higher than that for the 750 mg/kg infusion which gave a value of only 2.0, and even higher than the value obtained using HCTZ which was

from 2.41 to 2.56 for the two doses used of this drug. Thus these data demonstrate a notable reduction of potassium excretion by the methanol extract.

The different results obtained on electrolytic excretion by the two extracts suggested a difference in their comparative diuretic profile. It is probable that the important infusion effect on excretion of potassium, at the highest dosage, was due to a high content of potassium salts in the plant sample. In fact, quantitative determinations of the ions present in the *Smilax canariensis* infusion revealed the presence of high amounts of potassium salts (Table 3), suggesting that the diuretic effect of the infusion was due in part to its potassium content. It is well known that potassium overloading produces urinary excretion of the osmotic type and this occurs when the kidney tubules are incapable of absorbing it (Loew et al., 1991). Studies from our group have shown that oral administration of an aqueous solution of KCl, of similar potassium concentrations as that contained in the infusion doses used, produced at the highest concentration only a slight diuretic effect in the test animals (data not shown).

Nevertheless the high degree of potassium excretion was not observed when administering the lowest dose of the infusion (250 mg/kg), which is the dosage normally used in Canary Islands folk-medicine. The 750 mg/kg infusion level is unusually high, and is not normally obtained in typical household preparations.

Then the osmotic mechanism due to the potassium salts does not appear to be the sole reason for the diuretic effect of this plant species, since the minor infusion doses and the methanol extract maintain the diuretic effect. Moreover, the methanol extract water excretion cannot be due to potassium salts because, in contrast to the infusion in whose preparation it occurs a removal of salts, with the methanol this salts removal does not generate. Preliminary phytochemical studies have confirmed the presence of flavonoids and steroidal saponins in the plant, promoting the hypothesis that these types of polar compounds may be also responsible for the diuretic effects. It is known that these types of compounds increase renal circulation, and thus the rate of glomerular filtration which promotes increased urine formation (Loew et al., 1991).

In short the notable diuretic effect shown by the methanol extract with regard to water excretion as well as having an interesting effect on the conservation of potassium supports the hypothesis of a non-osmotic diuretic effect, which is an interesting property in a phytodiuretic.

The specific conductivity, which is an indirect measure of the ionic content of the urine, was increased in a dose-dependent manner in all the *Smilax canariensis* aqueous and methanol extract treated groups when compared with the controls. In all cases, the results were quite lower for the *Smilax canariensis* treatments (between 15.40 and 16.77) than those produced by the HCTZ (17.60 and 17.76; ** $p < 0.01$), probably related with its slight ionic excretion.

The pH values of urine from rats treated with the infusions were higher than in the controls, possibly due to the presence in this aqueous extract of alkaline salts not present in the methanol extract.

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, we can conclude that *Smilax canariensis* produces a notable diuretic effect which appeared to be related both to its potassium content and to the presence of polar organic compounds. Also for the methanol extract, this activity was comparable to that produced by the reference diuretic HCTZ, although with the advantage of an interesting potassium-saving effect.

The present results provide a quantitative basis explaining the traditional folk-medicine use of *Smilax canariensis* as a diuretic agent by the Canary Island population (Pérez-Paz and Hernández, 1999; Darias et al., 2001). 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. Further research is underway in our laboratory to determine the mechanism of this diuretic action, and particularly the role of active polar compounds present in this species.

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