Hypotensive and antihypertensive effects of a hydroalcoholic extract from *Senecio nutans* Sch. Bip. (Compositae) in mice: Chronotropic and negative inotropic effect, a nifedipine-like action

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**Abstract**

**Ethnopharmacological relevance:** *Senecio nutans* Sch. Bip. (Compositae) is an endemic plant of South America used in the management of acute mountain sickness in the Andean communities. Currently, the direct effects of hydroalcoholic extract from *S. nutans* on the cardiovascular system are unknown. The aim of this study was to determine the effects and mechanism of action of *S. nutans* on cardiovascular function in normotensive and Angiotensin II (1 μg/mL) hypertension mice models.

**Material and methods:** Blood pressure and ECG measurements were simultaneously carried out on the mice and rats. The isolated right atrium, papillary muscle of the left ventricle and isolated heart of rat were used to study the cardiac functions and mechanisms.

**Results:** *S. nutans* (40 mg/Kg) induced a 30% and 12% significant (*p* < 0.05) reduction of the mean arterial pressure (MAP) in normotensive and hypertensive mice respectively. This decrease was as a result of decrease in heart rate (HR) in normotensive (25%) and hypertensive model (31%). It also decreased the sinus rhythm in isolated right atrium of rat. Compared with Losartan, a known anti-hypertensive, *S. nutans* caused a dose-dependent negative inotropic effect (dP/dtmax) on Langendorff isolated heart system. While Losartan, decreased the MAP by 30% but had no effect on heart rate. The calcium blocker nifedipine had similar effects as *S. nutans*, decreasing the beat frequency of isolated right atrium and contractility of papillary muscle of the left ventricle of rat.

**Conclusion:** The results suggest an important clinical function in hypertension therapy, as *S. nutans* could decrease the blood pressure in hypertensive mice by decreasing the HR and contractility, leading to a reduction in myocardial oxygen demand.

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1. Introduction

*Senecio nutans* Sch. Bip. (synonyms: *Senecio graveolens* Wedd., *Senecio graveolens* var. *Psiloachaenius* Cabrera) belongs to the family Compositae. *Senecio nutans* is a species that aggregates with a family of medicinal plants that are called “chachacoma”. *Senecio nutans* is a perennial shrub about 20–60 cm high, that grows in habitat with heights fluctuating between 3500–5000 m above sea level in the Andes Chile, Argentina, Peru and Bolivia. It is a medicinal plant widely used by the communities living in these areas (Villagrán et al., 2003).

**Sesquiterpenes** derived from *p*-hydroxyacetophenones, benzofurans, benzopyrans, monoterpenoids, eremophilanes and germacrano derivatives of shikimic acid are reported constituents of *Senecio nutans* (Dupré et al., 1991; Loyola et al., 1985; Morales et al., 1996).

Dihydroeuparin from *S. nutans* is reported to have hypotensive effect in rats (Gallardo and Araya, 1982b), *p*-hydroxyacetophenone, a hypotensive effect in frog and iguana (Gallardo and Araya, 1982b), sesquiterpenes vasodilate the corpus cavernosum of Guinea pig (Hnatyszyn et al., 2003), while Loizzo et al (2009) reported that the flavonoids compounds show a inhibitory activity of angiotensin converting enzyme *in vitro* bioassay.

The branches and leaves from *S. nutans* are taken in the Andes of northern Chile as a tea to lower blood pressure, in a bid to counteract the effects of acute mountain sickness (Giberti, 1983;
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Table 1

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<tr>
<th></th>
<th>Normotensive</th>
<th>Hypertensive</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Sn</td>
</tr>
<tr>
<td>SBP, mmHg/s</td>
<td>111 ± 1</td>
<td>86 ± 3**</td>
</tr>
<tr>
<td>DBP, mmHg/s</td>
<td>73 ± 1</td>
<td>48 ± 1**</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>38 ± 2</td>
<td>37 ± 4</td>
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Values are mean ± standard error of the mean of 5 experiments in mmHg. Statistically significant differences: **p < 0.01 vs. Control; ***p < 0.001 vs. Control; ****p < 0.001 vs. Ang II.

Pérez et al., 1999; Serra, 2001).

S. nutans is reported to possess cytotoxicity activity which is enhanced in hypoxia (Echiburú-Chau et al., 2014), antibacterial activity (Belaunde et al., 2007) and antioxidant activity (Lizarraga et al., 2012; Rojo et al., 2009). It is also reportedly used in the treatment and management of colds, bronchitis, whooping cough, asthma, stomach pain, tiredness (Carod-Artal, Vázquez-Cabrera 2007; Giberti, 1983).

To our best knowledge the direct effect of hydroalcoholic extract of Senecio nutans on hypertension and heart function have not been examined previously. This study is designed to study the antihypertensive and cardiovascular properties of S. nutans, and the possible mechanism(s) of action using in vivo and in vitro methods on normotensive and hypertensive models.

2. Material and methods

2.1. Plant material

The branches, leaves and inﬂorescences from Senecio nutans Sch. Bip. (chachacoma) were collected in Toconce (22°15’11.16” S 68°5’44.68” O; a 3.788 m.s.n.m.), North of Chile, II Región of Antofagasta. The specimen was identified by Dr. Roberto Rodríguez, Departamento de Botánica, Facultad de Ciencias Naturales y Oceanográficas. Universidad de Concepción, Concepción, Chile. A specimen was deposited for collection of herbarium (registration number CONC 139,929).

2.2. Extract preparation

Aerial parts: the plant material was spread and dried in the shade at room temperature, and with the help of a mechanical mill was finely ground. A mass of 2.0 Kg of dry and powdered plant was deposited into a cotton bag with 4 L of a mixture EtOH: H2O (1:1) for 72 h inside a glass beaker. Then, the resulting solution was filtered (Whatman No. 4 filter paper) and concentrated on a rotary evaporator (50°C) to a quarter of the initial volume. This procedure was repeated several times, until the final solution was colorless. The concentrate obtained was freeze-dried using a 4.5 FreeZone, Labconco lyophilizer. The lyophilized hydroalcoholic extract was stored at 4°C until use. The yield of extraction was 19%.

2.3. Animals

Male CF-1 mice (6–8 weeks of age, 35–45 g), male Sprague-Dawley rats (6–8 weeks of age, 180–300 g) for Langendorff, atrium and papillary muscle experiments from the breeding colony at the Antofagasta University were used for this study. All animals were housed in a temperature-controlled, light-cycled (08:00–20:00 h) room with ad libitum access to drinking water and standard rat chow (Champion, Santiago). In this study 20 mice were randomly allocated into four groups (n = 5) and 10 rats into two groups (n = 5), respectively; and after 1 h, both of these groups with Ang II (1 μg/Kg). The method of Jimenez-Ferrer et al. (2010) was followed in the model of hypertensive mice (Jiménez-Ferrer et al., 2010). In addition, two groups of rats were used for experiments on isolated right atrium, papillary muscle (n = 5), and Langendorf isolated heart system (n = 5). To evaluate the traditional use of the plant, three groups of rats were used for experiments on blood pressure and ECG. The first group was rats treated with vehicle (Control; n = 4), the second group of rats was treated with of S. nutans (40 mg/Kg; n = 4) for 10 days, and the third group of rats was injected with intravenous bolus of S. nutans (40 mg/Kg; n = 4).

The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication revised 2013), and the local animal research committee approved the experimental procedure used in the present study (number CEIC REV/2013).

Fig. 1. Original tracings showing the antihypertensive effect of Senecio nutans (Sn) and losartan (Los) on the blood pressure and electrocardiogram (ECG). The systolic blood pressure (SBP), diastolic blood pressure (DBP), time dilatation of pulse pressure (Td), HR and the QT interval of the ECG were measured. The blood pressure (A) and ECG (B) were recorded simultaneously in anesthetized mice, and measurements were made 20 s after administration of the drug, during maximum effect. Sn (40 mg/Kg) and Los (10 mg/Kg) were administrated intravenously, 1 h prior to Ang II (1 μg/Kg).
2.4. Measurement of blood pressure

Blood pressure and ECG measurements were simultaneously carried out on the mice and rats, described by our laboratory (Cifuentes et al., 2009; Cifuentes et al., 2015). Briefly, the animals were anesthetized with ketamine (42 mg/Kg, i.p.) and xilazin (5 mg/Kg, i.p.). A catheter of polyethylene PE-50 tubing (Clay Adams, Sparks, Md) filled with heparinized saline (100 UI/mL) was placed in the carotid artery for the measurement of blood pressure. The arterial was connected to pressure transducer (DA100B, TSD 120 Biopac Systems), and blood pressure was measured using the AcqKnowledge III computer program. An interval of 15 to 30 min was allowed for the blood pressure to stabilize before the baseline blood pressure parameters were recorded.

2.5. Electrocardiogram (ECG) and Heart rate variability (HRV) analysis

The needle electrodes for ECG were placed subcutaneously in bipolar configuration (DII). The ECG100C Electrocardiogram Amplifier (BIOPAC) was used to record the electrical activity. The QT interval is the time from the beginning of the QRS complex formation to the end of the T wave. The RR interval is time elapsed between two consecutive maxima of the R waves. The corrected
QT interval (QTc) was calculated in accordance with the formula: QTc = QTc/(RR)1/2 (Hayes et al., 1994).

Heart rate variability (HRV) is the examination of physiological rhythms that exist in the beat-to-beat interval of an ECG. HRV was evaluated through frequency analysis of Lead II ECG in mice. HRV was assessed from each 1-minute ECG recording using HRV software (AcqKnowledge 3.9). Changes in the short-term variability of heart rate were calculated by averaging five successive values. The individual RR intervals and RR variations from ECG were evaluated. The frequency bands used were: total power (P: 0 to 3 Hz), low frequency (LF: 0.75 to 3.0 Hz), and high frequency (HF: 0.75 to 3.0 Hz). Sympatovagal balance was calculated as the LF to HF ratio (LF/HF) (Pagani et al., 1988).

2.6. Langendorff isolated heart system

Sprague–Dawley rats were anesthetized with ketamine (90 mg/Kg, i.p.) and xilazin (10 mg/Kg, i.p.) and then heparinized (800 IU/Kg, i.p.) for 5 min. The heart was quickly removed and mounted on the Langendorff system apparatus, and perfused with constant flow 10 ml/min of Krebs–Henseleit buffer (KHB containing (in mM): 4.7 KCl, 1.2 KH2PO4, 118 NaCl, 25 NaHCO3, 1.2 MgSO4, 1.75 CaCl2, 0.5 EDTA and 8 D-glucose (pH 7.4; 37 °C; 95% O2 and 5% CO2). A ball of polyvinyl chloride in the left ventricle was used to determine contractile function. The balloon is filled with saline (0.9% NaCl), and end diastolic pressure between 4–10 mmHg. Heart rate was held constant at 360 bpm by electrical stimulation of right atrium (5 V pulse of 1 ms duration, 6 Hz). Data were recorded by using PowerLab system (ADInstruments, Australia). HR, left ventricular pressure and the first derivative of pressure intraventricular (dp/dtmax and dp/dtmin) were registered continuously using the Chart for Windows 4.2. After mounting the heart in the Langendorff system it was subjected to stabilization and perfusion with KHB for 10 min, then the hearts were perfused with S. nutans (1, 10, 100, 1000 pg/ml), which was diluted in KHB and the concentration gradually increased every 5 min.

2.7. Frequency of isolated right atrium and contractility of left ventricular papillary muscle of the rat

Then the heart was quickly excised and placed in a cold (4 °C) physiological Krebs–Ringers buffer (KRB) containing (in mM): 4.2 KCl, 1.19 KH2PO4, 120 NaCl, 25 NaHCO3, 1.2 MgSO4, 1.3 CaCl2, and 5 D-glucose (pH 7.4; 37 °C; 95% O2 and 5% CO2). A ball of polyvinyl chloride in the left ventricle was used to determine contractile function. The balloon is filled with saline (0.9% NaCl), and end diastolic pressure between 4–10 mmHg. Heart rate was held constant at 360 bpm by electrical stimulation of right atrium (5 V pulse of 1 ms duration, 6 Hz). Data were recorded by using PowerLab system (ADInstruments, Australia). HR, left ventricular pressure and the first derivative of pressure intraventricular (dp/dtmax and dp/dtmin) were registered continuously using the Chart for Windows 4.2. After mounting the heart in the Langendorff system it was subjected to stabilization and perfusion with KHB for 10 min, then the hearts were perfused with S. nutans (1, 10, 100, 1000 pg/ml), which was diluted in KHB and the concentration gradually increased every 5 min.

3. Results

3.1. Senecio nutans and losartan induce hypertensive and anti-hypertensive effects in mice and rats

To determine whether the findings of this study may have clinical implications, we measured in vivo different cardiovascular parameters in mice and rats. We found differences in systolic and diastolic blood pressure in normotensive and hypertensive mice treated with S. nutans. Table 1 summarizes systolic (SBP) and diastolic (DBP) blood pressures, and pressure pulse (PP) between normotensive and hypertensive mice. In normotensive mice treated with S. nutans, SBP and DBP decreased significantly 23% (p < 0.001) and 35% (p < 0.001), respectively. But in the hypertensive mice, only the DBP decreased significantly (17%; p < 0.01) in presence of extract. As shown Table 1, S. nutans (40 mg/Kg) did not decrease the PP in normotensive and hypertensive mice; whereas, losartan decreased significantly the PP in hypertensive group.

We observed that S. nutans decreased the MAP, and heart rate (HR) in normotensive and hypertensive mice (Fig. 1). As shown in Fig. 2A, the MAP was 86 ± 2 mmHg in Control versus 61 ± 1 mmHg in extract-treated normotensive mice (p < 0.001); and 113 ± 2 mmHg with Ang II versus 99 ± 4 mmHg in extract-treated hypertensive mice (p < 0.05). The HR was 204 ± 14 bpm in Control versus 153 ± 8 bpm in extract-treated normotensive mice (p < 0.05); and 240 ± 8 bpm in Ang II group versus 164 ± 11 bpm in extract-treated hypertensive mice (p < 0.001; Fig. 2B). However, losartan decreased the MAP in the Ang II group (79 ± 5 mmHg; p < 0.001), but did not change the HR.

To evaluate the hypothesis associated with the traditional use (oral administration), the S. nutans (40 mg/Kg) was administered orally and intravenously in normotensive rats. As shown in Fig. 7A, S. nutans administrated orally decreased the MAP (111 ± 4 mmHg in Control versus 103 ± 4 mmHg by oral administration), but these decreases were not significant. The intravenous administration significantly p < 0.001 decreased the MAP (79 ± 4 mmHg). HR was not changed by oral administration (320 ± 4 bpm in Control versus 298 ± 9 bpm; Fig. 7B), however intravenous administration caused a significant p < 0.001 decrease in heart rates (226 ± 8 bpm).

3.2. Senecio nutans prolongs the QTc interval of the ECG in normotensive and hypertensive mice

To provide some information as to the possible cause of the decrease of HR by S. nutans, the QTc interval of the ECG and the HRV were determined in anesthetized mice. The results showed a
prolonged QTc interval in both groups, normotensive (456 ± 20 ms in Control versus 593 ± 28 ms with S. nutans; p < 0.01) and hypertensive (455 ± 22 ms in Ang II versus 558 ± 31 ms with S. nutans + Ang II; p < 0.05; Fig. 3A) mice treated with S. nutans, also resulted in a significant prolongation of time dilatation (Td) of the pressure pulse (49% with S. nutans, p < 0.01; and 70% S. nutans + Ang II, p < 0.001; Table 2). In hypertensive mice, losartan did not change QTc interval or Td. Moreover, S. nutans and losartan did not alter spectral components of HRV (LF/HF ratio) in normotensive and hypertensive mice (Fig. 3B).

To test whether atrial frequency are involved in the action of S. nutans on the HR, we measured the functional activity of the rat isolated right atrium. As shown in Fig. 4, 300 μg/mL S. nutans decreased significantly the frequency beating of rat right atrium (269 ± 4 bpm in Control versus 239 ± 1 bpm with S. nutans; p < 0.01).

3.3. Senecio nutans and losartan decrease the cardiac contractility during systole, and increase the cardiac relaxation during diastole in hypertensive mice

In order to gain insight into the potential role of S. nutans on cardiac function, the first derivative of the pressure pulse was calculated in normotensive and hypertensive mice. The maximal values of the ascending and descending limb of the pulse pressure, dP/dtmax and dP/dtmin respectively, are presented in Table 2. In hypertensive mice, S. nutans and losartan decreased significantly the inotropic effect in systolic function (21% with S. nutans and 23% with losartan vs. Control), and increased significantly the myocardium relaxation in diastolic function of left ventricle (45% with S. nutans and 37% with losartan vs. Control). According to these data, the time dilatation (Td) increased only in presence of S. nutans in normotensive (48%) and hypertensive mice (70%) compared to the Control group or the Ang II group, respectively (Table 2).

To study the direct effect of administration of S. nutans on cardiac contractility, Langendorff isolated heart system was used. In this protocol of the Langendorff, the HR remained constant at 360 bpm, while cardiac contractility was the dependent variable to be measure. We confirmed that S. nutans caused a dose-dependent negative inotropic effect on the isolated rat hearts. Although the maximal rate of increase (dP/dtmax) of left ventricular pressure did not decrease significantly with 100 μg/mL S. nutans (Fig. 5B), nor did the dP/dtmin increased significantly (Fig. 5C), the left ventricular pressure (LV pressure) was drastically reduced with the same dose (81 ± 8 mmHg/s Basal vs. 33 ± 15 mmHg/s with 100 μg/mL S. nutans; p < 0.05; Fig. 5A). Moreover, 1000 μg/mL S. nutans significantly decreased the contractility (dP/dtmax) and left ventricular pressure, and also increased the relaxation of the ventricle during diastole (dP/dtmin).

Regarding the above findings with S. nutans, we decided to compare the cardiovascular effect antihypertensive drug. As shown in Fig. 6, the calcium blocker nifedipine had a similar effect to S. nutans, decreasing the beat frequency of isolated right atrium and contractility in isolated papillary muscle of the left ventricle of rat. The effects of the S. nutans (1000 μg/mL) and the losartan (10⁻⁶ M) on the atrial or papillary muscle were reversed after washing (data not shown).

4. Discussion

Our study for the first time demonstrated the hypotensive properties of the hydroalcoholic extract of Senecio nutans when administered intravenously in normotensive animals, and also its antihypertensive effects on hypertensive animal models. S. nutans administration significantly decreased the MAP in both normotensive and hypertensive models of animal experiments. This decrease was as a result of decreases in HR and cardiac contractility.

The decreases in HR and bradycardia occurred among many factors including but not limited to a prolongation of the corrected QT (QTc) electrocardiogram, in both groups of mice. The QTc prolongation could be attributed to decreased influx of extracellular calcium through L-type calcium channel (Weiner, 1986). Bradycardia could also have occurred through a reduction in the frequency of sinus node beats by S. nutans in experiments of isolated right atrium of normotensive rats.

Another factor that regulates the HR is sympathovagal balance (Hall, 2010). Considering that the HRV is considered an indirect sympathovagal balance parameter (Stein et al., 1994), HRV as LH/HF ratio was determined in ECG. We observed that S. nutans did not decrease HRV in normotensive mice compared to control, and neither reversed the sympathovagal imbalance (HRV) induced by Ang II in the model of hypertensive mice. The increased Ang II-induced sympathovagal imbalance (HRV) would be explained by increased sympathetic activity and an attenuation of baroreflex control of HR (Guo and Abboud, 1984; Mace et al., 1985; McMullan et al., 2007). Therefore, the above results suggest that the effect of S. nutans on HR is mainly due to an electrical disturbance of cell automatic sinus node, which is manifested in a prolongation of...
QTc, rather than an imbalance sympathovagal (Chattipakorn et al., 2007). It is not surprising that plant extracts with potential cardiovascualr protective effect have no beneficial effect on the sympathovagal balance in normotensive animals (Supakul et al., 2014). However, in the model of spontaneously hypertensive rats and hypertension induced with L-NAME that have a sympathovagal imbalance (Chaswal et al., 2012), substances such as clonide (El-Mas and Abdel-Rahman, 2003), resveratrol or grape juice have been reported to reverse the imbalance sympathovagal (Dillenburg et al., 2013).

Cardiac contractility (dP/dtmax, dP/dtmin) may be assessed as the change in the slope of the pulse wave over time (Mason et al., 1971). In hypertensive mice, MAP reduction by *S. nutans* occurs by a decrease in HR as mentioned above, and also by decreased cardiac contractility (dP/dtmax), followed by an increase in diastolic relaxation (dP/dtmin). In contrast to the decrease of contractility by *S. nutans* in hypertensive mice, the lack of variation in the contractility observed in normotensive mice would suggest that there might be *in vivo* mechanisms masking or counterbalancing the negative inotropic effect of *S. nutans*. This hypothesis is supported by the observation that, in experiments of Langendorff isolated heart system in normotensive rats, *S. nutans* decreased significantly the left ventricular pressure (LVP) and ventricular contractility (LV dP/dtmax), and increased the relaxation and compliance of LV. Reports in literature showed that the negative inotropic effect of calcium channel blockers is often compensated by reducing afterload by arterial vasodilation (Davies et al., 1991; Parmley, 1992).

Losartan is a nonpeptide antagonist of type 1 Ang II receptor (AT1R), used to treat essential hypertension (Ramasubbu et al., 2007). Although Losartan was not able to decrease the HR in hypertensive mice unlike *S. nutans*, it significantly reduced the PP and cardiac contractility (dP/dtmax). Similar results in hypertensive mice with L-NAME would indicate that the decreased peripheral resistance is mediated by nitric oxide (NO) (Sigmon and Beierwaltes, 1993). In fact, losartan reduces vasoconstriction and simultaneously causes endothelial vasodilation via NO, and cyclic Guanosine monophosphate (cGMP) (Batenburg et al., 2005; Xu et al., 2009). The dilation time (Td) of the pulse wave in hypertensive mice was significantly longer with *S. nutans* than losartan. Whereas losartan reduces the Td of the left ventricle (LV) in rats with postinfarction (Loennechen et al., 2002), while *S. nutans* through a slower mechanism (high Td). In previous experiments in vascular reactivity, we note that *S. nutans* slowly vasodilates rat aorta, human mammary artery and radial artery by a mechanism independent of the endothelium and NO, involving blockade of calcium influx (data not shown). Interestingly, the cardiovascular effect of *S. nutans* was similar to that of a calcium blocker such as nifedipine, which decreases the frequency of beats of the right atrium and papillary muscle contractility of the left ventricle of rat.

Although the results on hypotensive and anti-hypertensive

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**Fig. 5.** Effects of *S. nutans* (Sn) on cardiac function of Langendorff isolated heart system. The Figures show a decrease of the left ventricular (LV) pressure (A), the ventricular contractility (dP/dtmax) (B) and relaxation of the ventricle during diastole in presence of Sn (C). Values are mean ± standard error of the mean of 5 experiments expressed as percentage bpm. Statistically significant differences: *p < 0.05, **p < 0.01, ***p < 0.001 vs. Basal.
The effect of *S. nutans* in mice were significant, their extrapolation to traditional use must be evaluated with caution and for comparative purposes with another mammalian. As mentioned above, the traditional use of extracts of *S. nutans* consist in oral administration, as a tea. To evaluate the limitation of our study on intravenous administration, we researched the hypotensive effect of *S. nutans* in normotensive rats by oral administration. We found that *S. nutans* decreased the MAP by 10 mmHg, but this decreases were not significantly, while intravenous administration caused a significant decrease in the MAP.

Since oral administration decreases the MAP, it is a first step of ethnopharmacology significance of our findings. Further studies currently going on in our laboratory would focus on intravenous administration of this extracts, its absorption and metabolism kinetics, as well as fractionation and profiling of the chemical compounds responsible for such effects. Results will help in the development of a phytomedicine and drug composition.

In conclusion, the intravenous administration of *S. nutans* decreases the blood pressure in hypertensive mice with Ang II, in part, by decreasing the HR and reduced contractility. In normotensive mice, the hypotensive effect of *Senecio nutans* is mainly because of the decrease in HR. These findings have potential clinical effect for the therapy of hypertension, especially in patients undergoing hypoxic episodes (e.g., ischemia or acute mountain sickness), because the decrease of HR and contractility lead to a reduction in myocardial oxygen demand, in the same way as do calcium blockers (Hackett and Roach, 2001).

**Conflict of interest statement**

The authors declare no conflict of interest.

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