Hypotensive Activity of Terpenes Found in Essential Oils

Igor A. C. Menezes, Carmélia M. N. Barreto, Ângelo R. Antoniolli,
Márcio R. V. Santos, and Damião P. de Sousa*

Departamento de Fisiologia, Universidade Federal de Sergipe, Av. Marechal Rondon,
s/n Jardim Rosa Elze, CEP 49.100-000, São Cristovão, SE, Brazil.
E-mail: damiao_desousa@yahoo.com.br

* Author for correspondence and reprint requests

The cardiovascular activity of essential oils has been reported. Some studies showed that the main chemical components of these oils contribute to their pharmacological activity. Therefore, the cardiovascular activity of four monoterpenes and one sesquiterpene was evaluated in the present work. In non-anaesthetized normotensive rats, (+)-α-pinene, (−)-β-pinene, (±)-citronellol and (±)-linalool (1, 5, 10, and 20 mg/kg, i.v.) induced hypotension [maximal effect: (−35 ± 3)%, (−46 ± 4)%, (−48 ± 2)% and (−40 ± 2)%, respectively; $n = 6$] and tachycardia [maximal effect: (13 ± 4)%, (16 ± 7)%, (21 ± 1)% and (19 ± 3)%, respectively; $n = 6$] while (−)-α-bisabolol (1, 5, 10, and 20 mg/kg, i.v.) induced hypotension [maximal effect: (−47 ± 8)%, $n = 6$] and bradycardia [maximal effect: (−57 ± 3)%]. In conclusion, these results demonstrated that all terpenes tested had hypotensive activity in rats and that the pharmacological effect of the terpene alcohols was more effective than that of the terpene hydrocarbons.

Key words: Essential Oils, Terpenes, Cardiovascular Activity

Introduction

Although a considerable number of antihypertensive drugs are available to treat hypertension, the search for new compounds as therapeutic alternatives increased, since the available antihypertensive drugs exert a wide range of side-effects. The pharmacological evaluation of medicinal plants and their chemical constituents in organic systems has contributed to the enrichment of the pharmacological arsenal used in the treatment of diseases and in the development of a scientific basis for their therapeutic application (Elizabetsky, 1986). Nevertheless, the discovery of a new drug in medicinal plants requires the pharmacological screening of their secondary metabolites through the rational investigation of their therapeutic potential.

Essential oils are natural products extracted from species of aromatic plants and exhibit a variety of biological properties (De Almeida *et al.*, 2009; Arruda *et al.*, 2006; Sadraei *et al.*, 2001; Camara *et al.*, 2003). These effects are attributed mainly to the terpenes, which are the major chemical components of these oils. The cardiovascular activity of essential oils has been reported (Interaminense *et al.*, 2005; Lahlou *et al.*, 2002;

Cunha *et al.*, 2004; De Siqueira *et al.*, 2006). Some studies showed that the main chemical components of these oils are bioactive (Interaminense *et al.*, 2005; De Siqueira *et al.*, 2006; Lahlou *et al.*, 2001, 2003).

For these reasons, it appeared possible that terpenes found in essential oils could also have cardiovascular activity. Therefore, our objective was to verify the potential hypotensive effect of representative terpenes present in medicinal plants. This study evaluated the activity of four monoterpenes, (+)-α-pinene, (−)-β-pinene, (±)-citronellol, and (±)-linalool, and one sesquiterpene, (−)-α-bisabolol (Fig. 1), on the blood pressure and heart rate in non-anaesthetized normotensive rats.

Material and Methods

Drugs

The following drugs were used: (+)-α-pinene (Aldrich, St. Louis, MO, USA), (−)-β-pinene (Aldrich), (±)-citronellol (Dierberger, Barra Bonita, SP, Brazil), (±)-linalool (Fluka, Milwaukee, WI, USA), and (−)-α-bisabolol (Puritta óleos essenciais, Torrinha, SP, Brazil). Sodium thiopental was purchased from Cristalia (São Paulo, Bra-

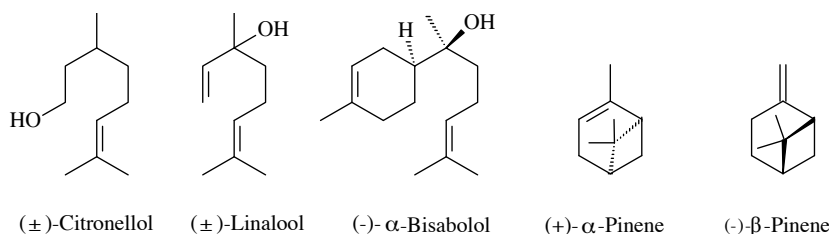(±)-Citronellol   (±)-Linalool   (-)-α-Bisabolol   (+)-α-Pinene   (-)-β-Pinene

Fig. 1. Chemical structures of the terpenes used in this study.

zil) and heparin sodium salt from Ariston (São Paulo, Brazil). Cremophor, a derivative of castor oil, and ethylene oxide, used to emulsify water-insoluble substances, were purchased from Sigma (St. Louis, MO, USA). Terpenes were dissolved in cremophor/saline solution (0.1%), while other drugs were freely dissolved in saline.

Animals

Male Wistar rats (200–300 g) were used for all experiments. Animals were housed under conditions of controlled temperature [(25 ± 1) °C] and lighting (light on: 06:00–18:00 h) and had free access to food and tap water. All procedures described in the present work are in agreement with the rules of the Animal Research Ethics Committee of Universidade Federal de Sergipe.

Direct measurement of blood pressure and heart rate in non-anaesthetized normotensive rats

For measurement of mean arterial pressure (MAP) and heart rate (HR), rats were anaesthetized with sodium thiopental [45 mg/kg, intraperitoneal (i.p.)]. A polyethylene catheter was inserted into the abdominal aorta via the left femoral artery for pressure recordings. Another catheter was inserted into the lower vena cava via the left femoral vein for administration of the drugs. Both catheters were filled with heparinized saline and led under skin to exit between the scapulae. 24 h after surgery, rats were placed in large individual cages and experiments were performed in non-anaesthetized rats.

The arterial catheter was connected to a pre-calibrated pressure transducer (Edwards Life-science, Irvine, CA, USA), and pressure outputs were recorded in an amplifier-recorder (Model BD-01, BioData, João Pessoa, PB, Brazil) connected to a personal computer equipped with an analog-to-digital converter board (BioData). For each cardiac cycle, the computer calculated the MAP and pulse interval (referred to as HR).

Effect of terpene compounds on MAP and HR in non-anaesthetized normotensive rats

After haemodynamics parameters had stabilized, MAP and HR were recorded before (baseline values) and after administration of randomized doses of (+)-α-pinene, (−)-β-pinene, (±)-citronellol, (±)-linalool, and (−)-α-bisabolol [1, 5, 10, and 20 mg/kg, intravenous (i.v.)], separately. Successive injections were separated by a time interval sufficient to allow full recovery of haemodynamics parameters.

Statistical analysis

Values are expressed as means ± SEM. ANOVA "one way" with Turkey post-test were conducted in order to evaluate the significance of differences between means. All statistical analyses were done using Graph Pad Prism™ version 3.02 software.

Results

In non-anaesthetized normotensive rats, baseline values of MAP and HR were (118 ± 1) mmHg and (376 ± 10) bpm, respectively, and cremophor/saline solution (0.1%) had no effect when administered intravenously to these animals (data not shown).

As can be seen in Fig. 2, the intravenous bolus injections of (+)-α-pinene and (−)-β-pinene (1, 5, 10, and 20 mg/kg) induced a transitory hypotension [(−10 ± 2), (−11 ± 2), (−20 ± 3) and (−35 ± 3)%, and (−3 ± 2), (−19 ± 2), (−27 ± 3) and (−46 ± 4)%, respectively; $n = 6$] associated with tachycardia [(4 ± 1), (2 ± 2), (6 ± 6) and (13 ± 4)%, and (1 ± 1), (3 ± 3), (2 ± 2) and (16 ± 7)%, respectively; $n = 6$)]. (−)-β-Pinene was significantly ($p < 0.05$) more efficacious than (+)-α-pinene.
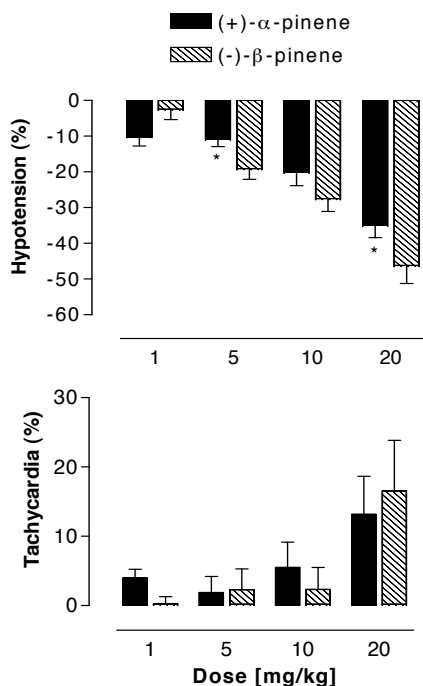
Fig. 2. Hypotensive and tachycardic effects induced by (+)-α-pinene and (−)-β-pinene (1, 5, 10, and 20 mg/kg, i.v.) on non-anaesthetized normotensive rats. Values are means ± SEM of six experiments. * *p* < 0.05 *vs.* (−)-β-pinene.
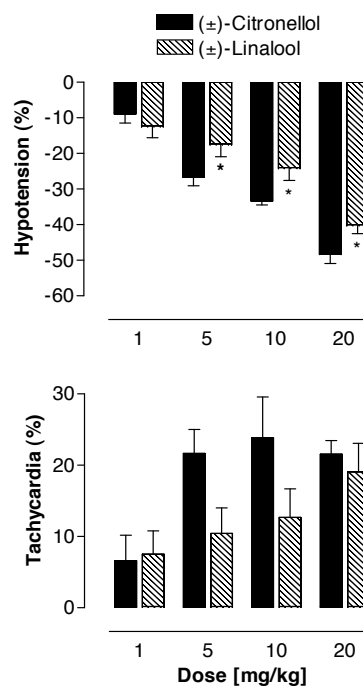
Fig. 3. Hypotensive and tachycardic effects induced by (±)-linalool and (±)-citronellol (1, 5, 10, and 20 mg/kg, i.v.) on non-anaesthetized normotensive rats. Values are means ± SEM of six experiments. * *p* < 0.05 *vs.* (±)-citronellol.

The same effect was observed with (±)-citronellol and (±)-linalool (1, 5, 10, and 20 mg/kg) that induced transitory hypotension [(−9 ± 2), (−26 ± 2), (−33 ± 1) and (−48 ± 2)%, and (−12 ± 3), (−17 ± 3), (−24 ± 3) and (−40 ± 2)%, respectively; *n* = 6)] associated with tachycardia [(7 ± 3), (21 ± 3), (24 ± 5) and (21 ± 2)%, and (7 ± 3), (10 ± 3), (12 ± 4) and (19 ± 3)%, respectively; *n* = 6)] (Fig. 3). Statistical analyses of the maximal responses demonstrated that there was no significant difference in their efficacy.

On the other hand, (−)-α-bisabolol (1, 5, 10, and 20 mg/kg) induced transitory hypotension [(−9 ± 3), (−37 ± 8), (−40 ± 9) and (−47 ± 8)%, respectively; *n* = 6)] associated with bradycardia [(−4 ± 5), (−51 ± 7), (−52 ± 5) and (−57 ± 3)%, respectively; *n* = 6)] (Fig. 4).

Discussion

Because these terpenes are common in many plant species, and are used in cosmetic, non-

cosmetic, and pharmaceutical preparations, as well as in the food industry, it is interesting and important to know their potential pharmacological effects. Several studies have reported effects of essential oils on the rat cardiovascular system (Lahlou *et al.*, 1999, 2000, 2001, 2002; Cunha *et al.*, 2004; De Siqueira *et al.*, 2006). However, there are few studies on the bioactive compounds that contribute to the pharmacological activity of these oils. We report in this comparative study the findings on the hypotensive activity of four monoterpenes, (+)-α-pinene, (−)-β-pinene, (±)-linalool, and (±)-citronellol, and one sesquiterpene, (−)-α-bisabolol, on the mean arterial pressure and heart rate of non-anaesthetized normotensive rats.

The evaluation of the effects of terpenes on the cardiovascular system was performed in non-anaesthetized rats to avoid the influences of anaesthesia and post-surgical stress. On the one hand, in these animals, (+)-α-pinene, (−)-β-pinene, (±)-citronellol, and (±)-linalool were able to in-

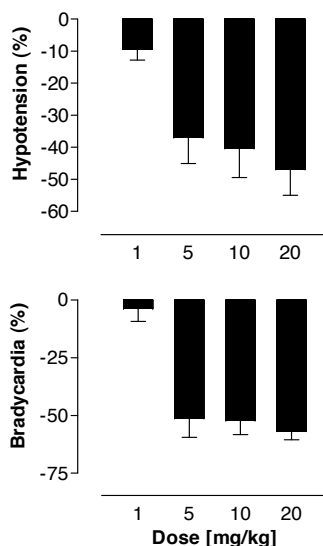Fig. 4. Hypotensive and bradycardic effects induced by (–)-α-bisabolol (1, 5, 10, and 20 mg/kg, i.v.) on non-anaesthetized normotensive rats. Values are means ± SEM of six experiments.

duce hypotension associated with tachycardia, which could be suggestive of an effect on the peripheral vascular resistance with consequent baroreflex response. On the other hand, the administration of (–)-α-bisabolol induced hypotension associated with intense bradycardia, which would suggest a different mechanism of action, possibly involving a decrease of cardiac output. The antihypertensive activity of some plants has been related to the presence of terpenes. Extracts and diterpenoids of *Salvia* species have shown cardiovascular activity, such as ferruginol and 7-oxo-abieta-9,12,14-triene (Ulubelen, 2003). In an other work, in normotensive anaesthetized rats, the cardiovascular effect of the essential oil of *Mentha* x *villosa* and its main constituent, piperitenone oxide, suggests that hypotensive activity may result from its vasodilatory effects directly upon vascular smooth muscle (Lahlou *et al.*, 2001). These reports, together with our findings, show the importance of this natural chemical class as good candidates for antihypertensive drugs.

Comparing the hypotensive effect of (+)-α-pinene and (–)-β-pinene, the monoterpene (–)-β-pinene was significantly more potent than its isomer (+)-α-pinene, indicating that the exocyclic double bond contributes more to the pharmaco-

logical effect than the endocyclic double bond. The difference in stereochemistry of the chiral centers at carbon atoms 1 and 5 in these molecules can also influence the hypotensive effect. The cardiovascular activity of pinenes shown in this study demonstrates that non-oxygenated terpenes present in cardioactive essential oils may contribute to this activity. Indeed terpene hydrocarbons are the main chemical constituents of some essential oils that have hypotensive activity, *e.g. trans*-caryophyllene and limonene in the leaf and fruit essential oils of *Ocotea duckei* (Lauraceae), respectively (Barbosa-Filho *et al.*, 2008).

Similarly, the comparison between the hypotensive activities of the acyclic monoterpenes (±)-citronellol and (±)-linalool showed that the (±)-citronellol, a primary alcohol, was significantly more efficacious than (±)-linalool, a tertiary alcohol. However, (–)-α-bisabolol, a tertiary alcohol, was more efficacious than (±)-linalool, but not significantly different to (±)-citronellol. The effect displayed by (–)-α-bisabolol indicates that it is associated to a possible decrease of cardiac output in consequence of the intense bradycardia. It is described in the literature that the monoterpene tertiary alcohol terpinen-4-ol produces hypotensive effect in rats. Terpinen-4-ol is the main constituent of the essential oil of *Alpinia zerumbet* (Pers.) B. L. Burtt. & R. M. Sm. (Zingiberaceae). Lahlou *et al.* (2003) showed that the hypotensive effects of the essential oil of *Alpinia zerumbet* are partially attributed to the actions of terpinen-4-ol, which was more potent than this oil. In an other study, Barbosa-Filho *et al.* (2008) showed that the essential oils from stem and root of the plant *Ocotea duckei* have hypotensive activity. The main chemical constituents of these oils are the terpene alcohols β-eudesmol and elemol, respectively. Therefore, our data are in agreement with those obtained in studies with structurally similar terpenes.

Furthermore, studies have demonstrated that some of these terpenes have depressant properties in other organic systems. Sadraei *et al.* (2001) and Camara *et al.* (2003) showed that both, (+)-α- and (–)-β-pinene, relax rat and guinea-pig ileum, respectively. Other studies have shown that (±)-linalool promotes the spasmolytic effect in guinea-pig ileum mediated by cAMP (Lis-Balchin and Hart, 1999), and recently Tanida *et al.* (2006) demonstrated that the inhalation of (±)-linalool reduces the blood pressure mediated by the cen-

tral nervous system in rats. Therefore, the hypotensive activity could originate from vasodilatory effects induced by these compounds. This possible mechanism of action was demonstrated in citronellol, which lowers blood pressure by a direct effect on the vascular smooth muscle leading to vasodilation (Bastos *et al.*, 2010).

In conclusion, the results from the present study show that all terpenes tested have hypotensive activity in rats. In general, the terpene alcohols are more effective than the hydrocarbon terpenes, and the position of the hydroxy group in the respective terpene structures influences the efficacy of their hypotensive activity.

Acknowledgements

Arruda T. A., Antunes R. M. P., Catão R. M. R., Lima E. O., De Sousa D. P., Nunes X. P., Pereira M. S. V., Barbosa-Filho J. M., and Cunha E. V. L. (2006), Preliminary study of the antimicrobial activity of *Mentha × villosa* Hudson essential oil, rotundifolone and its analogues. Rev. Bras. Farmacogn. **16**, 307–311.

Barbosa-Filho J. M., Cunha R. M., Dias C. S., Athayde-Filho P. F., Silva M. S., Cunha E. V. L., Machado M. I. L., Craveiro A. A., and Medeiros I. A. (2008), GC-MS analysis and cardiovascular activity of the essential oil of *Ocotea duckei*. Rev. Bras. Farmacogn. **18**, 37–41.

Bastos J. F. A., Moreira I. J. A., Ribeiro T. P., Medeiros I. A., Antoniolli A. R., De Sousa D. P., and Santos M. R. V. (2010), Hypotensive and vasorelaxant effects of citronellol, a monoterpene alcohol, in rats. Basic Clin. Pharmacol. Toxicol. **106**, 331–337.

Camara C. C., Nascimento N. R., Macedo-Filho C. L., Almeida F. B., and Fonteles M. C. (2003), Antispasmodic effect of the essential oil of *Plectranthus barbatus* and some major constituents on the guinea-pig ileum. Planta Med. **69**, 1080–1085.

Cunha R. M., Farias S. R. Q., Duarte J. C., Santos M. R. V., Ribeiro E. A. N., and Medeiros I. A. (2004), Cardiovascular effects induced by the essential oil of *Ocotea duckei* Vattimo (LAURACEAE). Biol. Geral Exper. **5**, 12–18.

De Almeida R. N., Araújo D. A. M., Gonçalves J. C. R., Montenegro F. C., De Sousa D. P., Leite J. R., Mattei R., Benedito M. A. C., Carvalho J. G. B., Cruz J. S., and Maia J. G. S. (2009), Rosewood oil induces sedation and inhibits compound action potential in rodents. J. Ethnopharmacol. **124**, 440–443.

De Siqueira R. J., Magalhaes P. J., Leal-Cardoso J. H., Duarte G. P., and Lahlou S. (2006), Cardiovascular effects of the essential oil of *Croton zehntneri* leaves and its main constituents, anethole and estragole, in normotensive conscious rats. Life Sci. **78**, 2365–2372.

Elizabetsky E. (1986), New directions in ethnopharmacology. J. Ethnobiol. **6**, 121.

Interaminense L. F., Leal-Cardoso J. H., Magalhães P. J., Duarte G. P., and Lahlou S. (2005), Enhanced hypotensive effects of the essential oil of *Ocimum gratis-simum* leaves and its main constituent, eugenol, in DOCA-salt hypertensive conscious rats. Planta Med. **71**, 376–378.

Lahlou S., Leal-Cardoso J. H., Magalhaes P. J., Coelho-de-Souza A. N., and Duarte G. P. (1999), Cardiovascular effects of the essential oil of *Croton nepetaefolius* in rats: role of the autonomic nervous system. Planta Med. **65**, 553–557.

Lahlou S., Leal-Cardoso J. H., and Magalhaes P. J. (2000), Essential oil of *Croton nepetaefolius* decreases blood pressure through an action upon vascular smooth muscle: studies in DOCA-salt hypertensive rats. Planta Med. **66**, 138–143.

Lahlou S., Carneiro-Leao R. F., Leal-Cardoso J. H., and Toscano C. F. (2001), Cardiovascular effects of the essential oil of *Mentha × villosa* and its main constituent, piperitenone oxide, in normotensive anaesthetised rats: role of the autonomic nervous system. Planta Med. **67**, 638–643.

Lahlou S., Figueiredo A. F., Magalhães P. J., and Leal-Cardoso J. H. (2002), Cardiovascular effects of 1,8-cineole, a terpenoid oxide present in many plant essential oils, in normotensive rats. Can. J. Physiol. Pharmacol. **80**, 1125–1131.

Lahlou S., Interaminense L. F., Leal-Cardoso J. H., and Duarte G. P. (2003), Antihypertensive effects of the essential oil of *Alpinia zerumbet* and its main constituent, terpinen-4-ol, in DOCA-salt hypertensive conscious rats. Fundam. Clin. Pharmacol. **17**, 323–330.

Lis-Balchin M. and Hart S. (1999), Studies on the mode of action of the essential oil of lavender (*Lavandula angustifolia* P. Miller). Phytother. Res. **13**, 540–542.

Sadraei H., Asghari G. R., Hajhashemi V., Kolagar A., and Ebrahimi M. (2001), Spasmolytic activity of essential oil and various extracts of *Ferula gummosa* Boiss. on ileum contractions. Phytomedicine **8**, 370–376.

Tanida M., Niijima A., Shen J., Nakamura T., and Nagai K. (2006), Olfactory stimulation with scent of lavender oil affects autonomic neurotransmission and blood pressure in rats. Neurosci. Lett. **398**, 155–160.

Ulubelen A. (2003), Cardioactive and antibacterial terpenoids from some *Salvia* species. Phytochemistry **64**, 395–399.