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Original

Effect of peppermint essential oil (*Mentha piperita L.*) in migraine-like responses in female rats

Laura de Oliveira Koren, Vanessa Bordenowsky Pereira Lejeune, Darciane Favero Baggio, Fernanda Mariano Ribeiro da Luz, Juliana Geremias Chichorro*

Department of Pharmacology, Biological Sciences Sector, Federal University of Parana, Curitiba, PR, Brazil.

Juliana Geremias Chichorro
juliana.chichorro@ufpr.br

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Marcelo Moraes Valença

Abstract

Migraine is a neurological disorder characterized by headache, photophobia, phonophobia, nausea and vomiting. It is considered the top cause of years lived with disability between the ages of 15–49, being two to three times more prevalent in women. Pharmacological treatment of migraine has advanced in the past years but is still considered unsatisfactory for a significant number of patients. There is growing evidence that essential oils may provide benefit for migraineurs. Herein it was tested the hypothesis that peppermint essential oil (*Mentha piperita L.*) could reduce migraine-related responses in rats. The model consisted in the injection of calcitonin-gene-related peptide (CGRP) in the trigeminal ganglion (TG) of female rats to induce the development of immediate periorbital cutaneous allodynia and late photosensitivity (24 h after CGRP). Inhalation of the peppermint essential oil during 15 minutes before CGRP injection in the TG did not reduce periorbital allodynia and photosensitivity. However, when the exposure occurred after CGRP injection, peppermint essential oil abolished the mechanical allodynia up to 2 hours and significantly reduced photosensitivity at 2 and 3 hours after the injection. Likewise, intranasal application of menthol, a major component of peppermint essential oil caused a significant reduction of periorbital allodynia at 2, 4 and 5 hours after CGRP injection. In conclusion, peppermint essential oil and menthol may represent a safe, low cost and noninvasive adjuvant abortive therapy for headache pain in migraine patients. However, further high-quality clinical studies are clearly warranted to determine efficacy, safety and to establish their best treatment regimen.

Keywords
Calcitonin-gene related peptide
Cutaneous allodynia
Photosensitivity
Menthol
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Introduction

Migraine is a disabling and chronic neurologic disorder characterized by recurring attacks with throbbing unilateral headache, often pulsating in quality, of moderate to severe intensity, associated with nausea and vomiting, sensory and cognitive dysfunctions, and aggravated by physical activity (1). It is estimated that migraine affects 15% of the general population, but has a female prevalence, which is still not fully understood (2, 3). Migraine is the number one cause of disability in women younger than 50 years (3). In the USA, migraine affect 18% of women and 6% of men, and the former present more debilitating symptoms, longer attacks and worse response to treatments (4).

Acute treatment of migraine attacks consists mainly of non-steroidal anti-inflammatory drugs (NSAIDs), which are considered effective for mild to moderate pain, and triptans, recommended as first-line for moderate to severe attacks (5). Triptans have strong evidence of efficacy but are not tolerated by some patients and contraindicated in patients with ischemic heart disease or previous myocardial infarction (6). NSAIDs therapy is also associated with increased cardiovascular risk, in addition to its frequent association with gastrointestinal and renal toxicity (7). Both classes of drugs have been associated to migraine chronification when used excessively (1, 5). Emerging therapies for acute migraine treatment include gepants, small-molecule CGRP receptor antagonists, and ditans, selective 5-HT1F receptor agonists, which, unlike triptans, lack vasoconstrictor activity (5). It has been suggested that gepants and ditans present low cardiovascular risk, but similar efficacy, compared to triptans (5, 8). However, further studies are warranted to compare the available drugs' efficacy, safety and explore long-term outcomes. It is also worth mentioning that newer drugs generally present high cost, lack of insurance coverage and limited availability. For instance, gepants and ditans are currently not commercialized in Brazil.

Due to partial efficacy and safety profile of the current pharmacological options for migraine treatment, alternative or adjunct interventions to enhance treatment outcomes are clearly warranted. In this sense, there is increasing evidence that essential oils from several plants may provide benefit for migraine patients (9, 10). The essential oil of Mentha piperita L. (peppermint) is one of the most used essential oils in the pharmaceutical and cosmetics industries. It is typically obtained through the steam distillation of aerial parts of the flowering plant. One of its major components is menthol, responsible for the specific taste and odor of the essential oil. In addition to menthol, it has menthone as another main component and a mixture of volatile metabolites that contribute to innumerous biological activities, such as antioxidant, antimicrobial and anti-inflammatory (11, 12). In migraine patients, two clinical trials showed that intranasal application of peppermint essential oil (1.5%) or application of a solution containing 10% menthol to the forehead and temporal area increased pain relief and reduced nausea and/or vomiting, and phonophobia and/or photophobia (13, 14). The results are promising, but still need validation. Therefore, the aim of the present study is to evaluate the effectiveness of peppermint essential oil via inhalation in an experimental model of migraine. The results will contribute to determine the efficacy of peppermint essential oil in responses associated with migraine (i.e., cutaneous allodynia and photophobia) following a standardized exposure in controlled conditions.

Methods

2.1. Animals

A total of 86 female Wistar rats, 2-month-old, weighing between 180 and 220 g, from the colony of Federal University of Paraná (UFPR) were used. The animals were housed 4 per cage and kept in a room with controlled humidity and temperature (22 ± 2 °C), in a 12-hour light-dark cycle (7 a.m.-7 p.m.). Water and food were freely provided to the animals during all experiments. The animals were acclimated in the laboratory for at least 48 hours before the beginning of the experiments. The tests were performed in quiet rooms with controlled temperature and humidity, during the light phase of the animal cycle (8 am to 6 pm). All protocols used in this study were approved by the Ethics Committee for the Use of Animals of the Biological Sciences Sector of the Federal University of Paraná (CEUA #1385 /BIO - UFPR) and followed the Brazilian guidelines of the National Agency for the Control of Animal Experimentation (CONCEA) and ARRIVE. The sample size was determined based on previous studies of our group (15, 16) and on a priori power analysis using the GPower 3.1 software standardizing F=0.5, power of 0.8 and α = 0.05 which determined a sample size of 8 rats per group.

2.2. Drugs

The calcitonin gene-related peptide (CGRP) (Sigma-Aldrich, St. Louis, MO, USA) was diluted in saline solution and administered into the trigeminal ganglion of the animals at 0.1 nmol or 380 ng/10 μL based on previous studies (15, 16). The essential oil of Mentha piperita L. (peppermint) and avocado vegetable oil were obtained from a commercial source (Quinari Fragrances and Cosmetics LTDA, Ponta Grossa, PR, Brazil) and diluted to 5% (v/v) in grain alcohol (Cloroquímica, Curitiba PR – Brazil) according to a previous study(17). (±)-Menthol (Santa Cruz Biotechnology, Dallas, TX, USA) and avocado vegetable oil were diluted to 1.5%/10 μL in grain alcohol for intranasal administration (14). The same batch of EO was used in all experiments, which was previously analyzed by gas chromatography mass spectrometry (GC/MS, supplied by the manufacturer – Quinari – PR – Brazil and performed at the Federal University of Minas Gerais UFMG) revealing 45% menthol

and 23.3% mentone as the main constituents, in accordance with the standards established by ISO-856:2006 and ISO-11024-2:1998. (18).

2.3. Intraganglionic injection

The animals were briefly anesthetized with halothane (4%) and O2 inhalation and received intraganglionic injections of CGRP or vehicle (saline) using a sterile long 27-G needle (0.4 - 30 mm). The needle was positioned at an angle of approximately 10° in relation to the midline of the animals' heads and then inserted into the zygomatic process through the infraorbital foramen until it reached the right trigeminal ganglion. After injecting 10 μL of the solution, the needle was carefully removed, and the animals were monitored until they recovered from anesthesia. This procedure has been extensively published by our group (15, 16, 19, 20).

2.4. Assessment of periorbital mechanical allodynia

The animals were individually placed in 30 cm3 acrylic observation boxes for a period of 2 hours for habituation. To avoid nonspecific responses, a baseline measurement was performed and only animals that did not respond to the application of the 8 g filament were included in the experimental groups. The mechanical threshold was measured in the periorbital region by applying von Frey filaments (Semmes-Weinstein, Stoelting, Wood Dale, IL, USA) to the midline of the forehead, close to the eyes of the animals. Each filament was applied three times, ranging from 0.04 to 8.0 g and the stimulation series began with the filament producing the lowest force and proceeded to the filament which evoked two positive responses, including reactions such as withdrawal of the head, escape, or sudden attack against the filament. The mechanical threshold was considered the filament that evoked two positive nociceptive responses (15, 16).

2.5. Assessment of photosensitivity

Twenty-four hours after the intraganglionic injection of CGRP or vehicle, the animals were placed in their housing boxes and exposed to a 5000-lux illumination for a period of 1 hour, using a 180 W directional lamp. Immediately after the exposure period, periorbital mechanical allodynia was measured, as previously described. This protocol is used for experimental assessment of migraine-associated photophobia(15, 16).

2.6. Experimental Design

For experiments 1 and 2, the animals were divided in the following groups: 1) Inhalation of vehicle plus intragaglionic injection of saline; 2) Inhalation of the EO plus intragaglionic injection of saline; 3) Inhalation of vehicle plus intraganglionic injection of saline; 4) Inhalation of the EO plus intragaglionic injection of CGRP. In experiment 1, the inhalation was performed 15 min before CGRP or saline injection in the TG to evaluate a potential prophylactic effect, while in experiment 2, the inhalation was performed 30 min after CGRP or saline injection in the TG, to assess a potential abortive effect. In both experiments, assessment of periorbital mechanical threshold was performed before the treatments and at 1h-intervals after the last treatment up to 4 hours.

The exposure to peppermint essential oil or vehicle was done individually in a cage box (41x32x16,5 cm), with a special device for standardized volatilization, allowing the animals to inhale the essential oil for 15 minutes. The animals were kept in separate rooms during the experiments so that the control group was not exposed to peppermint essential oil odor. Thus, the interference of the essential oil on the control group was avoided (17).

To investigate the effect of the essential oil on the reactivation of cutaneous allodynia by bright light exposure (photosensitivity), 24 hours after receiving intraganglionic injection of CGRP or saline the animals were exposed to an aversive light for 1 hour. The evaluation of periorbital mechanical threshold was performed before and at 1h-intervals after the light exposure up to 4 hours. The inhalation of the essential oil was not repeated (experiments 1 and 2).

Finally, the effect of isolated menthol on periorbital mechanical allodynia induced by CGRP was assessed (experiment 3). The animals received intraganglionic injection of CGRP or saline and after 30 minutes, 10 μL of 1.5% menthol solution or vehicle were dropped with the aid of a micropipette into the nasal cavity, ipsilateral to the injected TG. Assessment of periorbital mechanical threshold was performed before the intranasal treatments and at 1h-intervals up to 6 hours.

2.7. Statistical analysis

Two-way analysis of variance (ANOVA) with repeated measures (RM) followed by Bonferroni's post-hoc test was used to analyze cutaneous allodynia and photosensitivity. All data were expressed as mean ± standard error of the mean (SEM) for 6 to 9 animals per group. The results were considered statistically significant if $P < 0.05$. Statistical analysis was performed using GraphPad Prism version 9 for Windows (GraphPad Software, San Diego, CA, USA).

3. Results

Figure 1A illustrates the experimental design. Figure 1B shows that intraganglionic injection of CGRP in female rats caused a significant reduction of the periorbital mechanical threshold, indicating cutaneous allodynia, that was different from saline-injected rats from the first hour up to the fourth hour pos-injection. Rats exposed to the peppermint essential oil before saline or CGRP

injection in the TG did not show any change in the periorbital mechanical threshold (Figure 1B).

One day after CGRP or saline injection in the TG, the periorbital mechanical threshold had returned to baseline levels, but rats' exposure to a bright light reactivated the cutaneous allodynia only in the group previously treated with CGRP. There was no influence of the essential oil (administered before CGRP injection) in the development of periorbital cutaneous allodynia triggered by light (Figure 1C).

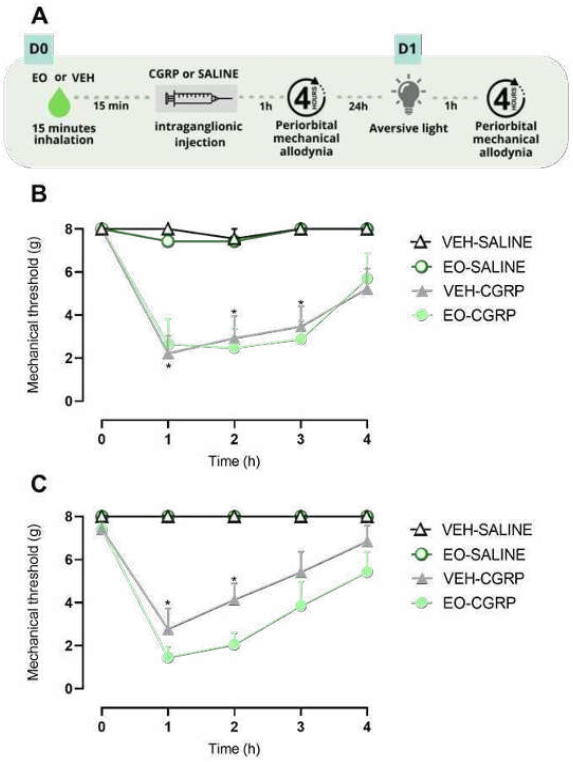


Figure 1- Effect of peppermint essential oil inhalation before migraine induction in female rats. Rats were exposed to peppermint essential oil (EO) or vehicle (VEH) inhalation 15 minutes before intraganglionic injection of saline or CGRP, as illustrated in (A). (B) Periorbital cutaneous allodynia assessment before (0) and at 1-h intervals up to 4 h after intraganglionic injections. (C) One day after CGRP or saline injections, rats were exposed to a bright light and the periorbital cutaneous allodynia was assessed before (0) and at 1-h intervals up to 4 h after photosensitivity induction. Data are expressed as mean ± SEM (n=9 for each group treated with saline, n=8 for each group treated with CGRP). *P < 0.05 when compared to the VEH-SALINE group. Two-way ANOVA with repeated measures followed by Bonferroni post hoc test.

Figure 2 shows the effect of peppermint essential inhalation after migraine induction, according to the experimental design illustrated in Figure 2A. In this exposure protocol the essential oil abolished the development of cutaneous allodynia (Figure 2B). The antinociceptive effect of the essential oil was observed during the whole period that the female rats showed allodynic responses, i.e., from 1 to 3 hours after CGRP injection in the TG. Inhalation of the essential oil did not change the mechanical threshold of the control group (saline-injected rats, Figure 2B). Moreover, when administered after migraine induction, but 24 hours before the exposure to the bright light, the essential oil significantly reduced the periorbital mechanical allodynia, but did not change the mechanical threshold of saline-injected rats (Figure 2C).

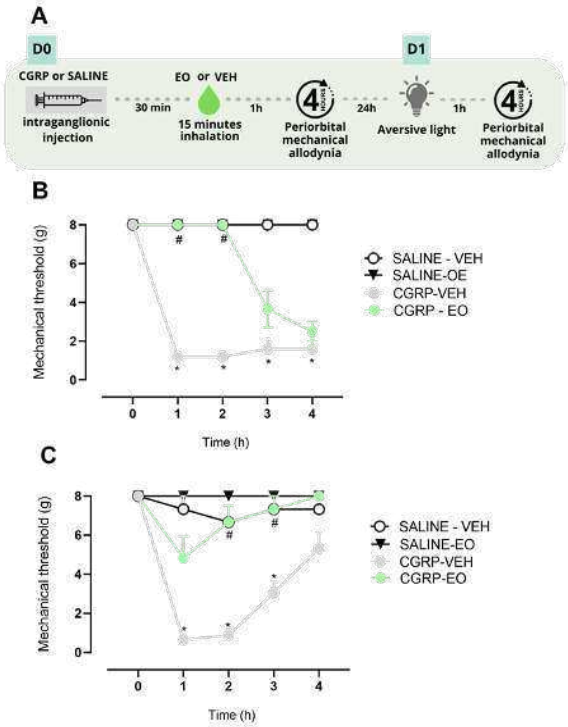


Figure 2- Effect of peppermint essential oil inhalation after migraine induction in female rats. Rats received intraganglionic injection of saline or CGRP and 30 min later were exposed to peppermint essential oil (EO) or vehicle (VEH) inhalation, as illustrated in A. (B) Periorbital cutaneous allodynia assessment before (0) and at 1-h intervals up to 4 h after intraganglionic injections. (B) One day after CGRP or saline injections, rats were exposed to a bright light and the periorbital cutaneous allodynia was assessed before (0) and at 1-h intervals up to 4 h after photosensitivity induction. Data are expressed as mean ± SEM (n=6 rats each group). *P < 0.05 when compared to the SALINE-VEH group and #P < 0.05 when compared to the CGRP-VEH group. Two-way ANOVA with repeated measures followed by Bonferroni post hoc test.

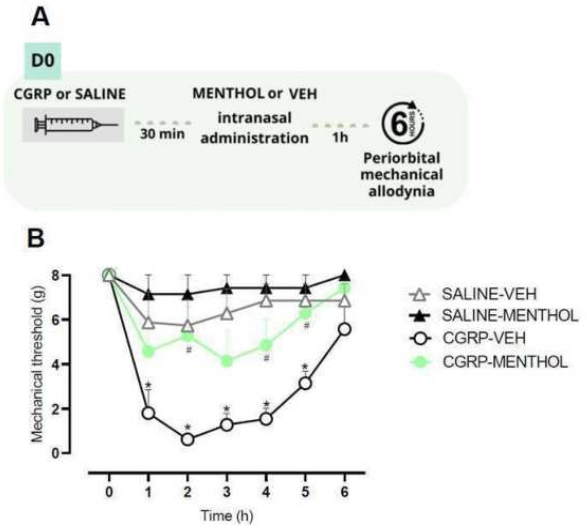


Figure 3 – Effect of menthol intranasal application after migraine induction in female rats. Rats received intraganglionic injection of saline or CGRP and 30 min later were treated with vehicle (VEH) or menthol as illustrated in (A). (B) Periorbital cutaneous allodynia assessment before (0) and at 1-h intervals up to 6 h after intraganglionic injections. Data are expressed as mean ± SEM (n=7 rats each group). *P < 0.05 when compared to the SALINE-VEH group and #P < 0.05 when compared to the CGRP-VEH group. Two-way ANOVA with repeated measures followed by Bonferroni post hoc test.

4. Discussion

There is growing evidence that mechanisms operated by CGRP in the TG play a fundamental role in migraine physiopathology. CGRP is expressed by 50% of TG small neurons (C-fibers), while its receptor is present in 40% of TG medium-sized neurons (Aδ fibers) and satellite glial cells (21, 22). Activation of CGRP receptors in the TG causes the release of mediators from neurons and satellite glial cells, which mediate neuron-glia communication and contribute to sensitization of trigeminal afferents (23, 24). We have previously demonstrated that injection of CGRP into the TG of rats induces periorbital mechanical allodynia, photosensitivity and anxiety-like behavior in male and female rats (15). Females were more sensitive to CGRP effects, presenting longer-lasting mechanical allodynia compared to males, but treatment with sumatriptan reduced the nociceptive responses in both sexes (15). Due to the higher prevalence of migraine in females, herein only female rats were evaluated, which represents a limitation of the study.

The results of the present study showed that inhalation of peppermint essential oil before migraine induction in female rats failed to change periorbital cutaneous allodynia. However, when the animals were exposed do the essential oil after intraganglionic injection of CGRP, the treatment prevented the development of periorbital cutaneous allodynia. In migraine patients, intranasal application of peppermint essential oil (1.5%) reduced the severity and duration of the migraine crisis similarly to lidocaine (14). Interestingly in this study, the patients were instructed to pour two drops of the essential oil as soon as they realized that the headache was starting. The intensity of the headache was reduced in over 40% of the migraineurs, briefly after the intranasal application (around 5 min). The intranasal route of administration has many advantages compared to the oral route, including rapid onset of action, less drug degradation, high rate of absorption, and direct nose to brain delivery (25). Moreover, this route may increase patient compliance, especially among migraineurs, due to nausea and other gastrointestinal symptoms, such as gastric stasis, that may delay oral absorption of drugs and complicate the treatment (26). Likewise, the inhalation of essential oils allows a safe, simple, non-invasive, and low-cost therapeutic alternative that may be useful during migraine attacks. Through this route, the essential oil may have a rapid direct effect on peripheral trigeminal afferents, as well as a rapid transportation from the nasal mucosa to the brain through the olfactory and trigeminal nerves (27).

Photophobia is commonly associated with migraine, but it is still poorly understood. Among the several proposed mechanisms, it has been suggested that CGRP actions on peripheral and central sites contribute to this phenomenon (28). Previous results from our group demonstrated that CGRP priming causes sensitization to light in male and female rats, but females present longer lasting periorbital mechanical allodynia (15). Herein it was demonstrated that inhalation of peppermint essential oil before migraine induction did not affect the development of photosensitivity, assessed 24 hours after intraganglionic injection of CGRP. However, when the animals were exposed do the essential oil after intraganglionic injection of CGRP, the treatment prevented the reactivation of periorbital cutaneous allodynia by light. To our knowledge the effect of peppermint essential oil has not been tested against other migraine related symptoms besides pain, however in patients with episodic migraine, the topical application of a 10% menthol solution to the forehead and temporal area caused significant reduction of photophobia, as well as phonophobia, nausea and vomiting (13). Altogether, these results suggest a potential for menthol and peppermint essential oil in the relief of photophobia associated with migraine, but further studies are needed to validate these findings.

Menthol is a major component of peppermint essential oil and has been used as a non-opioid pain reliever since ancient times (10). In the clinical setting, cutaneous application of menthol solution decreased by 50%

the intensity of headache and was superior to placebo on 2-h pain free, 2-h pain relief, sustained pain free and sustained pain relief endpoints (13). This finding is corroborated by the demonstration that topical menthol 6% gel application to the skull base within 2 h of headache onset caused a significant improvement of pain in episodic migraineurs (29). In line with this idea, in the present study it was demonstrated that intranasal application of menthol significantly reduced periorbital mechanical allodynia induced by intraganglionic administration of CGRP in female rats. Thus, it is possible to suggest that menthol contributes to the antinociceptive effect of peppermint essential oil. Several mechanisms have been proposed for the analgesic effect of menthol that may influence migraine, for instance activation of TRPM8 receptors; blockade of voltage-gated calcium and sodium channels, resulting in decreased neuronal excitability and blockade of spontaneous synaptic transmission; desensitization of nociceptive C-fibers, the sensitization of which is associated with cutaneous allodynia (30-33). When applied topically, menthol is considered generally well tolerated although a burning sensation on the skin and increased lacrimation are reported by some patients (13). Current evidence on efficacy and safety of menthol in the treatment of migraine should motivate further studies on this topic.

Finally, it is important to highlight that both treatments were effective after migraine induction, which is consistent with clinical findings. It has been demonstrated that activation of TRPM8 receptors can result in pro- and antinociceptive effects. Several studies, including in migraine models, suggest that activation of TRPM8 alone is pro-nociceptive, however when TRPM8 is activated in the presence of other stimuli, the result is anti-nociceptive (34). It has been proposed that the inhibition of nociceptive afferent signaling by TRPM8-expressing fibers can be either via direct inhibition of TG nociceptor central terminals or by activation of inhibitory interneurons at the first synapse level (34). This idea may explain the lack of effect of peppermint essential oil applied before migraine induction, but its efficacy when applied in the presence of ongoing activation of trigeminal afferents.

5. Conclusion

The current study demonstrated that inhalation of peppermint essential oil or menthol after migraine induction caused a significant reduction in periorbital mechanical allodynia and photosensitivity induced by intraganglionic CGRP injection in female rats. Peppermint essential oil may represent a safe, low cost and noninvasive adjuvant abortive therapy for headache pain in migraine patients. However, further high-quality clinical studies are clearly warranted to determine efficacy, safety and to establish the best treatment regimen for menthol and/or peppermint essential oil in migraine patients. It is noteworthy that herbal products do not follow the rigorous pharmaceutical industry regulation, thus the use of quality products from trustful sources is highly recommended.

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Laura de Oliveira Koren
Vanessa Bordenowsky Pereira Lejeune
Darciane Favero Baggio
Fernanda Mariano Ribeiro da Luz: https://orcid.org/0009-0007-8986-1980
Juliana Geremias Chichorro: https://orcid.org/0000-0001-5345-141X

Authors' contribution: to the study: Koren, Lejeune and Chichorro stablished the experimental procedures, analyzed the data, and prepared the manuscript. Koren, Lejeune, Baggio and da Luz performed the experiments. All authors revised and approved the manuscript in its current version.

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