Anti-inflammatory and antioxidant activities of *Lantana radula* Swartz and its phenylethanoid glycosides

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Many species from the genus *Lantana* (Verbenaceae) have been used in traditional medicine, and their anti-inflammatory and antioxidant activities demonstrated. *Lantana radula* Swartz has been reported to be rich in phenylethanoid glycosides, which have various biological properties. In order to evaluate the actions of this plant, studies were performed on anti-inflammatory activity of the aqueous phase resulting from the fractioning with HP-20SS resin (AP-20SS) of *L. radula* roots, as well as on antioxidant capacity of its isolated phenylethanoids. Anti-inflammatory activity of the AP-20SS (30, 100, and 300 mg/kg) was evaluated using carrageenan-induced paw edema and peritonitis models. Antioxidant activity of the AP-20SS and its phenylethanoid glycosides (1 to 100 μg/ml) was evaluated by quantification of nitric oxide radical generation and lipid peroxidation. The AP-20SS reduced paw edema (100 and 300 mg/kg, *p* < 0.01) and leukocyte influx (30, 100, and 300 mg/kg, *p* < 0.001). Nitric oxide radical generation was also inhibited by the AP-20SS (IC₅₀ value of 31.16 μg/ml). *L. radula* AP-20SS prevented Fe²⁺- or Fe²⁺ plus H₂O₂-induced lipid peroxidation (IC₅₀ values < 1.00 μg/ml). Raduloside, samioside and isonuomioside A significantly inhibited nitric oxide radicals generation (by approximately 13%) and lipid peroxidation (by 57 to 99%). The results of the present study suggest that the anti-inflammatory effects of the AP-20SS may be related, at least in part, to the antioxidant capacity of its phenylethanoids.

Key words: Leukocyte influx, lipid peroxidation, myeloperoxidase activity, nitric oxide radical scavenging activity, paw edema.

INTRODUCTION

Inflammation is a protective response that is initiated either after injury, physical and chemical damage, or infection by microorganism. It is correlated with oxidative processes, mainly because they are mediated by similar pathways (Kunsch and Medford, 1999). An increased free radical levels have been detected during many pathological conditions, such as cancer, ischemic disorders and dementia (Harput et al., 2012). Specific...
antioxidants have been demonstrated to be effective in decreasing tissue inflammation and injury in various experimental models (Conner and Grisham, 1996). Due to the importance of free radicals, many natural and synthetic antioxidants have been studied for use as potential therapeutic agents.

*Lantana* (Verbenaceae) is a neotropical genus that contains approximately 150 species, many of which exist in Brazil. Many species from the genus *Lantana* have been used in traditional medicine, and their anti-inflammatory, analgesic, anti-proliferative and antioxidant activities demonstrated (Silva et al., 2005; Julião et al., 2009; Melo et al., 2010). In a previous study, the chemical profile of *Lantana radula* Swartz was reported and this plant was rich in phenylethanoid and lignin glycosides (Sena-Filho et al., 2009). Some phenylethanoid glycosides had wide range of biological properties, including anti-inflammatory and antioxidant effects (He et al., 2000; Hausmann et al., 2007). Based on the considerations outlined, the objective of the present study was to evaluate the anti-inflammatory and antioxidant activities of the aqueous phase resulting from the fractioning with HP-20SS resin of *Lantana radula* roots, as well as the antioxidant capacity of its isolated phenylethanoids (raduloside, samioside, and isonuomioside A; Figure 1).

**MATERIALS AND METHODS**

**Plant collection and extraction**

*L. radula* was collected in Timbáuba in the state of Pernambuco, Brazil (07° 30’ 18” S, 35° 19’ 04” W), in January of 2006. The plant was identified by Prof. R. C. Pereira. A voucher specimen of *L. radula* was deposited at the Herbarium Dárdano de Andrade Lima (number 70004), in Empresa Pernambucana de Pesquisa Agropecuária (IPA) in the state of Pernambuco, Brazil. The dried and powdered roots (5.5 kg) were extracted using 95% ETOH (12 L, ×3) at room temperature. The solvent was evaporated at 40°C under reduced pressure, affording 454 g of the crude extract. The crude extract (250 g) was dissolved in H2O, defatted with hexane under reduced pressure, affording 454 g of the crude extract. The solvent was evaporated at 40°C ×3) at room temperature. The solvent was evaporated at 40°C

**Animals**

Both male Wistar rats (120 to 170 g) and Swiss mice (20 to 30 g) from the breeding colony of the Central Animal House of the Federal University of Sergipe (São Cristóvão, Sergipe, Brazil) were used in accordance with the University Guidelines of the Ethics Committee for Animal Care and Use in Research (CEPA/UFS 89/2010). The animals were maintained at a controlled room temperature (21 ± 2°C) with free access to food and water. Prior to oral (p.o.) treatments, the animals were fasted for 12 h.

**Assessment of the carrageenan-induced inflammatory response in the rat hindpaw**

Carrageenan (1%, 0.1 ml) was administered into the subplantar regions of the right hindpaws of rats that had been treated (60 min prior, n = 6) with the AP-20SS (30 to 300 mg/kg, p.o.), dexamethasone [2 mg/kg, subcutaneous (s.c.)], or vehicle (saline, p.o.). Paw edema was measured plethysmographically (model 7150; Ugo Basile, Comerio, VA, Italy) at 1, 2, 3, and 4 h after carrageenan administration and was expressed in ml (Winter et al., 1962). The percentage of inhibition was calculated based on the area under the time-course curves (AUC_{0-4h}) using the trapezoidal rule. Myeloperoxidase (MPO) activity (indicator of neutrophil migration) was measured in the rat paw muscle tissue samples 4 h after carrageenan injection (Bradley et al., 1982). The tissue samples were homogenized (10 mg/ml) in phosphate buffer (50 mM, pH 6.0) containing 0.5% hexadecyltrimethylammonium bromide and incubated for 2 h at 60°C. The supernatants were mixed with o-dianisidine dihydrochloride (0.167 mg/ml) in 50 mM phosphate buffer containing H2O2 (0.005%), and the absorbances were read at 460 nm. The results were expressed as units of MPO (U/MPO)mg of tissue, where one U/MPo was defined as the amount of enzyme that degraded 1 μmol of H2O2 per min.

**Carrageenan-induced peritonitis in mice**

Peritonitis was induced by injecting carrageenan (1%, 250 μl) into the peritoneal cavities of mice that had been treated (60 min prior, n = 6) with the AP-20SS (30 to 300 mg/kg, p.o.), dexamethasone (2 mg/kg, s.c.), or vehicle (saline, p.o.). Following 4 h of peritonitis induction, the peritoneal cavities were washed with 3 ml of saline containing EDTA (1 mM). The total leukocyte counts were carried out using a Neubauer chamber. The results were expressed as the number of leukocytes/ml (Mendes et al., 2010).

**Determination of nitric oxide (NO) radical scavenging activity**

Sodium nitroprusside (20 mM) in phosphate buffer was mixed with 0.05 ml of the AP-20SS or its identified compounds (1, 2, and 3 at the concentrations of 1 to 100 μg/ml) and incubated at 37°C for 60 min (Green et al., 1982). The Griess reagent (2% sulfanilamide, 5% H3PO4, and 0.1% N-(1-naphthyl)ethylenediamine dihydrochloride) was then added to the samples. Ascobic acid (1 to 100 μg/ml) was used as a positive control. The absorbances were read at 540 nm, and the percentages of inhibition and IC50 values were calculated.

**Determination of lipid peroxidation**

Quantification of thiobarbituric acid reactive substances (TBARS) was used to measure the antioxidant capacity of the AP-20SS (Esterbauer and Cheeseman, 1990) and the ability of its isolated compounds to prevent FeSO4 (1.45 mM)-induced or FeSO4 (1.45 mM) plus H2O2 (0.4 M)-induced lipid peroxidation. The AP-20SS and the isolated phenylethanoids (1 to 100 μg/ml) were added to the phospholipid preparations (0.1% in 50 mM phosphate buffer, pH 7.4) and incubated for 1 h at 37°C. Then, 0.3 ml samples were added to 0.6 ml of trichloroacetic acid (20%) and the mixture centrifuged for 10 min at 10,000 × g and 4°C. A supernatant aliquot (0.5 ml) was mixed with thiobarbituric acid (TBA, 0.67%, 0.5 ml) and heated at 100°C for 30 min. Ascobic acid (1 to 100 μg/ml) was...
Figure 1. Chemical structures of compounds: raduloside (1), samioside (2), and isonuomioside A (3).

used as a positive control. The absorbance was read at 532 nm, the results were expressed as the percentage of inhibition, and IC<sub>50</sub> values calculated.

Statistical analyses

The anti-inflammatory activity is presented as the means ± SEM of n animals per group. The antioxidant activity assays were performed in triplicate, and the results are expressed as the mean values ± SD. Statistical evaluations of the data were performed using ANOVA followed by Bonferroni's or Newman-Keuls' post-hoc tests (version 4.0; GraphPad Prism Co., San Diego, CA, USA). *p < 0.05, **p < 0.01, and ***p < 0.001 were considered to be significant.

RESULTS

Role of the AP-20SS in inflammatory responses

Treatment of rats with the AP-20SS at 100 and 300 mg/kg reduced (p < 0.01) carrageenan-induced paw edema at the 3 and 4 h time points (Figure 2A). Likewise, the positive control group that had been treated with dexamethasone exhibited an inhibition (p < 0.05) of carrageenan-induced paw edema at all of the time points examined (Figure 2A). Based on the area under the curve (AUC<sub>0-4h</sub>) analyses, Figure 2B shows that treatment with the AP-20SS at 100 and 300 mg/kg inhibited the formation of paw edema (p < 0.01) compared with the vehicle-treated group. Four hours after the intraplantar injection of carrageenan in the rat hindpaws, a significant increase (14.7 ± 0.9 UMPO/mg tissue, p < 0.001) in MPO activity in the paw tissues was observed compared with the increase in MPO activity in control rats that had been injected with saline (0.1 ± 0.0 UMPO/mg tissue). At different doses (30, 100, and 300 mg/kg), the AP-20SS significantly inhibited (p < 0.001) carrageenan-induced increase in MPO activity compared with the vehicle-treated group (Figure 2C). Similarly, dexamethasone treatment reduced (p < 0.001) the carrageenan-induced increase in MPO activity in rat paw tissues after 4 h (Figure 2C). Figure 3 shows that significant increases in leukocyte number in the mouse peritoneal was observed 4 h after the intraperitoneal injection of carrageenan. Treatment with the AP-20SS (30, 100, and 300 mg/kg) significantly inhibited (p < 0.001) carrageenan-induced peritonitis (Figure 3). Dexamethasone treatment also significantly inhibited (p < 0.001) carrageenan-induced peritonitis (Figure 3).

Determination of the antioxidant activity

AP-20SS treatment inhibited sodium nitroprusside-generated NO radicals. The concentration of the AP-20SS required to achieve 50% inhibition (IC<sub>50</sub>) was 31.16 μg/ml, whereas ascorbic acid concentrations was less than 1.00 μg/ml. AP-20SS inhibited NO radicals generation in a concentration-dependent manner at 3, 10, 30, and 100 μg/ml (p < 0.05, Table 1). The AP-20SS
Figure 2. The effect of *L. radula* AP-20SS on rat paw edema and leukocyte influx. Animals were treated with vehicle, *L. radula* AP-20SS (30-300 mg/kg), or dexamethasone (Dexa, 2 mg/kg) before a carrageenan injection. (A) Response time curves of the paw edema formation (in ml) induced by carrageenan. (B) Area under the curves (AUC$_{0-4}$, in ml × h) of the paw edema after injection of carrageenan. (C) Myeloperoxidase (MPO) activity [in units of MPO (UMPO)/mg of tissue] in the rat paw muscle tissue samples 4 h after carrageenan injection. All values are means ± SEM. Statistical analysis by ANOVA followed by Bonferroni’s test. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ vs. vehicle-treated animals ($n = 6$/group).
of peritonitis. As expected, 4 h after carrageenan injection, a potent influx of leukocytes was observed in the peritoneal cavities of the mice. Additionally, the AP-20SS produced a marked inhibition of leukocyte counts in the peritoneal lavage of these animals. The mechanism of action of carrageenan on peritonitis involves the synergistic action of PG, leukotriene B4 and other chemotactic agents, which promotes increases in the vasodilatation, exudation and recruitment of leukocytes (Foster et al., 1986). Based on this knowledge, we can only speculate that the AP-20SS acts directly/indirectly to reduce the release of these mediators.

NO, an essential bioregulatory molecule that is required for several physiological processes is a potentially toxic agent that displays free radical characteristics, and is responsible for many physiologic and pathologic events. NO radicals are also implicated in diabetes, inflammation, cancer and other pathological conditions (Moncada et al., 1991). Therefore, inhibitors of NO release may be considered for use as therapeutic agents in the treatment of inflammatory diseases. In addition to its anti-inflammatory activity in the rodent hindpaw and peritoneum (peritonitis), the AP-20SS also displays antioxidant activity. NO radicals generation and lipid peroxidation were both found to be inhibited by the AP-20SS. Free radicals are also known to act on lipids. Lipid prevented Fe²⁺-induced lipid peroxidation at all the concentrations used (86 to 88%, p < 0.001, Table 1), with IC₅₀ values < 1.00 µg/ml, which were similar to ascorbic acid (IC₅₀ < 1.00 µg/ml). Additionally, the AP-20SS inhibited (by 53 to 66%, p < 0.001) lipid peroxidation that was induced by the co-incubation of Fe²⁺ with H₂O₂ at all the concentrations tested (IC₅₀ < 1.00 µg/ml, Table 1). Similarly, ascorbic acid reduced Fe²⁺ plus H₂O₂-induced lipid peroxidation in all the concentrations (IC₅₀ < 1.00 µg/ml, p < 0.001, Table 1). Compounds 1, 2, and 3, isolated from the AP-20SS, significantly inhibited NO radicals generation at all the concentrations tested (p < 0.05, Table 1). The reference drug ascorbic acid inhibited NO generation by more than 80% at all the concentrations tested (p < 0.001, Table 1). The compounds significantly (p < 0.001) inhibited (by 57 to 99%) lipid peroxidation in a concentration-dependent manner in both the Fe²⁺ and Fe²⁺ plus H₂O₂ assays at all the concentrations tested in this study (Table 1).

**DISCUSSION**

The present study revealed that the AP-20SS significantly ameliorated the inflammatory response in rodent models, thus suggesting that the AP-20SS may contain promising active compounds that could be used for the development of potential pharmacological agents to treat inflammatory processes. The anti-inflammatory effects of the AP-20SS were investigated using classical
Table 1. Antioxidant activity of L. radula AP-20SS and its phenylethanoids isolated.

<table>
<thead>
<tr>
<th>Sample (concentration [μg/ml])</th>
<th>NO radical scavenging activity</th>
<th>TBARS (FeSO₄)</th>
<th>TBARS (FeSO₄ + H₂O₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP-20SS (1) 3.44 ± 0.85</td>
<td>87.48 ± 4.26***</td>
<td>53.33 ± 2.65***</td>
<td></td>
</tr>
<tr>
<td>AP-20SS (3) 5.10 ± 0.30*</td>
<td>88.25 ± 2.86***</td>
<td>64.58 ± 0.52***</td>
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</tr>
<tr>
<td>AP-20SS (10) 20.18 ± 1.04***</td>
<td>88.44 ± 1.63***</td>
<td>65.42 ± 3.54***</td>
<td></td>
</tr>
<tr>
<td>AP-20SS (30) 53.95 ± 0.44***</td>
<td>86.71 ± 3.06***</td>
<td>66.25 ± 4.43***</td>
<td></td>
</tr>
<tr>
<td>AP-20SS (100) 75.71 ± 0.52***</td>
<td>86.71 ± 2.08***</td>
<td>65.83 ± 0.72***</td>
<td></td>
</tr>
<tr>
<td>Isonuomioside A (1) 7.91 ± 1.22**</td>
<td>85.87 ± 2.31***</td>
<td>97.96 ± 1.45***</td>
<td></td>
</tr>
<tr>
<td>Isonuomioside A (3) 8.75 ± 0.91**</td>
<td>98.55 ± 1.57***</td>
<td>94.76 ± 1.89***</td>
<td></td>
</tr>
<tr>
<td>Isonuomioside A (10) 9.24 ± 2.48**</td>
<td>97.46 ± 1.13***</td>
<td>98.98 ± 1.77***</td>
<td></td>
</tr>
<tr>
<td>Isonuomioside A (30) 9.95 ± 0.12**</td>
<td>93.48 ± 0.94***</td>
<td>94.00 ± 1.60***</td>
<td></td>
</tr>
<tr>
<td>Isonuomioside A (100) 13.06 ± 4.77***</td>
<td>95.38 ± 3.96***</td>
<td>98.21 ± 0.88***</td>
<td></td>
</tr>
<tr>
<td>Samioside (1) 5.94 ± 0.97**</td>
<td>88.51 ± 2.97***</td>
<td>73.94 ± 5.90***</td>
<td></td>
</tr>
<tr>
<td>Samioside (3) 5.52 ± 1.54*</td>
<td>95.40 ± 2.22***</td>
<td>78.48 ± 1.41***</td>
<td></td>
</tr>
<tr>
<td>Samioside (10) 6.43 ± 1.70**</td>
<td>96.06 ± 5.55***</td>
<td>89.90 ± 1.52***</td>
<td></td>
</tr>
<tr>
<td>Samioside (30) 7.52 ± 0.56**</td>
<td>91.95 ± 3.46***</td>
<td>93.27 ± 1.11***</td>
<td></td>
</tr>
<tr>
<td>Samioside (100) 8.73 ± 0.22***</td>
<td>96.88 ± 2.43***</td>
<td>96.93 ± 1.24***</td>
<td></td>
</tr>
<tr>
<td>Raduloside (1) 6.38 ± 0.92***</td>
<td>64.86 ± 0.99***</td>
<td>78.83 ± 1.25***</td>
<td></td>
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<tr>
<td>Raduloside (3) 6.25 ± 0.13***</td>
<td>88.57 ± 0.99***</td>
<td>84.27 ± 4.25***</td>
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<tr>
<td>Raduloside (10) 6.86 ± 0.87***</td>
<td>88.00 ± 1.71***</td>
<td>98.79 ± 1.21***</td>
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<tr>
<td>Raduloside (30) 5.86 ± 0.74***</td>
<td>80.57 ± 1.02***</td>
<td>78.63 ± 3.04***</td>
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<tr>
<td>Raduloside (100) 7.87 ± 0.15***</td>
<td>85.43 ± 8.49***</td>
<td>57.66 ± 6.84***</td>
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<tr>
<td>Ascorbic acid (1) 82.27 ± 0.12***</td>
<td>60.27 ± 2.52***</td>
<td>78.94 ± 0.31***</td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid (3) 82.27 ± 0.24***</td>
<td>64.11 ± 2.52***</td>
<td>75.04 ± 1.40***</td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid (10) 83.38 ± 0.55***</td>
<td>73.62 ± 5.36***</td>
<td>77.70 ± 0.53***</td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid (30) 85.11 ± 0.32***</td>
<td>76.13 ± 1.16***</td>
<td>78.58 ± 0.31***</td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid (100) 85.87 ± 0.55***</td>
<td>79.30 ± 1.76***</td>
<td>78.05 ± 0.31***</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as means ± SD (triplicate). * p < 0.05, ** p < 0.01, and *** p < 0.001 vs. respective system values (ANOVA and Newman-Keuls's post hoc test).

acute inflammatory models, including paw edema and peritonitis (Mendes et al., 2010; Thomazzi et al., 2010). The carrageenan-induced inflammatory response in the rodent hindpaw is mediated by multiple processes: the first phase, which lasts up to 2 h, involves the participation of histamine, serotonin (5-HT) and bradykinin (BK), while the second phase, which lasts from 3 to 4 h, is sustained by prostaglandin (PG) and NO release (Di Rosa, 1972; Seibert et al., 1994). In the present study, the intraplantar injection of carrageenan in the rat hindpaw causes a significant and time-dependent edema formation that peaked at 4 h. Moreover, at the 4 h point the accumulation of MPO levels, used as an indicator of neutrophils, are significantly elevated in the paw tissue, showing that, in addition to plasma extravasation, a significant influx of leukocytes occurred in the hindpaw. However, by treating the animals with the AP-20SS, a significant reduction of both paw edema and increased MPO activity evoked by carrageenan was seen. These data suggest that the AP-20SS can act to inhibit increased microvascular permeability (edema) and leukocyte influx; however, the action mechanisms involved should be further investigated.

To further confirm the role that the AP-20SS plays in leukocyte migration (mainly neutrophils), experiments were carried out in a carrageenan-induced animal model peroxidation can be defined as a cascade of biochemical events that results from the action of free radicals on the unsaturated lipids in cell membranes, producing mainly alkyl, peroxyl and alkoxyl radicals. This process can lead to the destruction of membrane structures, metabolite exchange mechanism failures, and, in extreme conditions, cell death (Srinivasan et al., 2007). Phenylethanoid glycosides are found in small amounts in plants and only a limited number of phenylethanoid glycosides have been studied. Some authors have shown that phenylethanoid glycosides exhibit antioxidant activities. Compound 2, which was isolated from the aerial parts of Phlomis samia L. (Laminaceae), demonstrated scavenging properties toward 2,2-diphenyl-
1-picyrlyhydrazyl (DPPH) radicals (Kyriakopoulou et al., 2001). Compound 3, which was isolated from Ruellia tuberosa L. (Acanthaceae), exhibited radical scavenging activity using the oxygen radical absorbance capacity (ORAC) assay (Phakeovilay et al., 2013). However, the antioxidant activity of 1 has not been demonstrated to date.

In the present study, we demonstrated for the first time that 1, a phenylethanoid that was isolated from L. radula roots, displays antioxidant activity. We also showed that 2 and 3 displayed NO radical scavenging properties and the ability to inhibit lipid peroxidation, in addition to the DPPH scavenging and oxygen radical absorption activities that were demonstrated in previous studies. However, the inhibition in free radicals generation by these compounds was found to be much less than that observed with the AP-20SS. This suggests that the main active compounds present in the AP-20SS could not be identified and isolated. The antioxidant capacity of many substances confers a therapeutic potential with anti-inflammatory property (Li et al., 2002; Librowski et al., 2005). Evidence accumulated has pointed to significant connections between inflammation and oxidative stress, both processes contributing to fuel the other one, thereby establishing a vicious cycle able to perpetuate and propagate the inflammatory response (Lugrin et al., 2014).

Phenylethanoids prevent the formation of cytokines and essential cell messengers, the activation of important enzymatic systems, such as phosphatases and transcription factor activation pathways, and inflammatory protein gene expression (Kunsch and Medford, 1999). Several studies have shown that phenylethanoids inhibit NO release in the lipopolysaccharide-induced J774. A1 murine macrophage cell line (Julião et al., 2009). For example, verbascoside (syn. acteoside) was shown to possess wound-healing activity and anti-inflammatory potential (Akdemir et al., 2011), and it ameliorates intestinal inflammation during dextran sodium sulfate-induced colitis in mice (Hausmann et al., 2007).

**Conclusion**

Our findings reveal for the first time that the anti-inflammatory activity of L. radula Swartz is consistent, at least in part, with the use of members of the genus *Lantana* in popular medical practices. The AP-20SS from L. radula displayed both anti-inflammatory and antioxidant properties. Additionally, its phenylethanoid glycosides demonstrated antioxidant actions. Therefore, the observed antioxidant activity of L. radula compounds may be responsible for some of its medicinal effects. L. radula contains promising active compounds that may be used for the development of pharmacological agents to treat inflammatory processes.

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**Conflict of interest**

The authors report no declarations of interest.

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