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The effects of resveratrol and quercetin administration in experimental pleural inflammation

Cristina Bidian[1], Adriana Filip[1], Adriana Albu[2], Adriana Florinela Cătoi[3], Mîndrilă Georgiana[4], Remus Moldovan[1], Nicoleta Decea[1], Daniela-Rodica Mitrea[1]
[1] *"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Department of Physiology*
[2] *"Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, 2nd Department of Internal Medicine*
[3] *"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Department of Pathophysiology*
[4] *"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, graduate*

Abstract

Background. Pulmonary diseases associated with inflammation are largely found in humans. The lungs are continuously exposed to oxidative stress, a process that, through the release of reactive oxygen species, leads to tissue damage and to an increase in the initial inflammatory reaction. Therefore, it is necessary to find a therapy that is able to counteract the noxious effects of reactive species and of inflammation. Resveratrol is a natural polyphenol with anti-inflammatory effects, having the capacity to limit the production of pro-inflammatory factors such as interleukins and prostaglandins. Quercetin, a flavonoid with known anti-inflammatory and antioxidant effects, inhibits phospholipase A2 and the enzymes of lipid peroxidation, reducing the synthesis of leukotrienes.

Aims. The antioxidant effects of resveratrol and quercetin were studied in an experimental model of carrageenan-induced pleural inflammation.

Methods. The study was performed using male rats, divided into 2 groups, each group containing a further 4 groups (control, administration of carrageenan, resveratrol and carrageenan, and quercetin and carrageenan, respectively). The oxidant/antioxidant balance was evaluated in the serum and in the lung tissue at 4 hours (groups I-IV) and at 24 hours (groups V-VIII).

Results. In serum, at 4 and at 24 hours after carrageenan administration, the malondialdehyde levels were decreased significantly by resveratrol and quercetin, and the ceruloplasmin concentration in the rats that were pre-treated with these chemicals was increased significantly, in comparison with the control and carrageenan groups. In lung homogenate, at 4 and at 24 hours, significant decreases of malondialdehyde in the groups that received antioxidants were recorded, compared to unprotected groups; increases of glutathione levels were recorded at 24 hours only in the resveratrol group.

Conclusions. In serum, both compounds, resveratrol and quercetin, presented antioxidant effects. In the lungs, at 24 hours, resveratrol had superior antioxidant effects.

Keywords: pleural inflammation, oxidative stress, carrageenan, resveratrol, quercetin.

Introduction

Inflammatory lung diseases are very common in the human population. Inflammation represents a nonspecific local response, as a defence mechanism of the body, triggered by different agents: chemical (toxic substances), biological (bacteria, viruses, parasites), physical (ionizing radiation, thermal variations, trauma) and immunological factors (***, 2019). During inflammation, several processes occur: local vasodilation with the increase of blood flow, increased capillary permeability, plasma extravasation into the interstitial space with fluid and protein accumulation, granulocyte and monocyte migration into the tissue, and cellular oedema in the lesion area.

Oxidative stress (OS) can be defined as a disequilibrium between oxidative substances and antioxidants, in favour of oxidative substances, leading to tissue destruction. The lungs are primarily exposed to OS caused by reactive oxygen species (ROS). In the lungs, ROS determine the amplification of the initial inflammatory-immune reaction through the mediators and the products of unsaturated free fatty acid peroxidation, and also through the concomitant destruction of the vessels' endothelium, with hyperpermeability and interstitial oedema (Genestra, 2007). Therefore, it is necessary to find a treatment that can counteract the noxious effects of free radicals and

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Address for correspondence: "Iuliu Hațieganu" University of Medicine and Pharmacy, 2nd Deparment of Internal Medicine, 2-4 Clinicilor Str., Cluj-Napoca, Romania
E-mail: albumed2@gmail.com
Corresponding author: Adriana Albu adriana.albu@umfcluj.ro
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inflammation. Antioxidants are endogenous or exogenous substances that protect the biological systems against the destructive action of ROS, inhibiting enzymatic reactions, blocking the synthesis of inflammatory mediators, or eliminating the products of excessive oxidation.

Resveratrol, a natural polyphenol identified in grapes, berries or nuts, has anti-inflammatory effects, limiting the release of pro-inflammatory factors (interleukins or prostaglandins), reducing chemotaxis and immune cell recruitment at the inflammation site (Lançon et al., 2016). Resveratrol inhibits the synthesis of: eicosanoids, activator protein-1 (AP-1), cyclooxygenases (COX-1, COX-2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) (Das and Das, 2007). Resveratrol has protective effects in respiratory diseases such as acute pulmonary lesions, asthma, chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis (Conte et al., 2015). This polyphenol also has antioxidant potential through three mechanisms: competition with coenzyme Q in the decrease of oxidative chain complex activity (the mechanism that generates ROS), removal of reactive oxygen species synthesized in mitochondria, and inhibition of lipid peroxidase (de la Lastra and Villegas, 2005).

Quercetin, part of a group of pigments named flavonoids, produces the colour of many fruits, flowers and vegetables. Food sources with a high content of flavonoids include: citrus fruits, onion, parsley, berries, green tea and red wine. Quercetin has anti-inflammatory, antioxidant, anti-allergic, antiviral and anti-carcinogenic effects (Middleton et al., 2000). It inhibits the metabolism of eicosanoids acting directly on the enzymatic cascades: phospholipase A_2 and lipid peroxidation enzymes are inhibited, and the synthesis of leukotrienes is reduced (LT).

Carrageenan, a high molecular weight sulphated polysaccharide, extracted from red seaweeds, has been largely used over the last decade in studies performed in animals. Carrageenan may induce acute inflammation, and many models of inflammation were developed to test the efficiency of anti-inflammatory drugs (Duarte et al., 2016).

Objectives

The present research studied the antioxidant effects of resveratrol and quercetin on a carrageenan-induced pleural inflammation model.

Material and methods

a. Place of the research

The research was performed in the Experimental Research Laboratory of the Physiology Department, at “Iuliu Haţieganu” University of Medicine and Pharmacy, Cluj-Napoca. Adult male Wistar rats with weights between 150-160 g, provided by the University Biobase were used. The rats were kept in cages in the same room, at 21°C degrees, with 12 h light/12 h dark cycle, with access to food and water *ad libitum*. The tests were carried out under the guidelines of Directive 89/609/EEC and of the Ethical Committee of “Iuliu Haţieganu” University of Medicine and Pharmacy, Cluj-Napoca (nr. 444/31.07.2015).

b. Chemicals

All reagents were acquired from Sigma-Aldrich, Germany. Resveratrol and quercetin were dissolved in carboxymethyl cellulose 0.5% (CMC 0.5%).

c. Experimental design

The research was performed using white male Wistar rats, with weights between 150-160 g, divided into 2 groups, each group containing a further 4 groups with 8 animals/group (control, administration of carrageenan, resveratrol and carrageenan, and quercetin and carrageenan, respectively).

The experimental groups were the following:

- groups I and V (control groups): 0.5 ml CMC 0.5% by oral gavage for three days; on the fourth day, 0.2 ml physiological salt, in intrapleural injection
- groups II and VI: 0.5 ml CMC 0.5% by oral gavage for three days; on the fourth day, 0.2 ml carrageenan 1% in intrapleural injection
- groups III and VII: 10 mg/kg/day resveratrol dissolved in 0.5 ml CMC 0.5% by oral gavage for three days; on the fourth day, 0.2 ml carrageenan 1% in intrapleural injection
- groups IV and VIII: 10 mg/kg/day quercetin dissolved in 0.5 ml CMC 0.5% by oral gavage for three days; on the fourth day, 0.2 ml carrageenan 1% in intrapleural injection

At 4 hours (groups I, II, III and IV) and at 24 hours (groups V, VI, VII and VIII) after carrageenan administration, venous blood (from the retro-orbital sinus) and lung tissue were taken. The surgical procedure was performed under general anaesthesia with ketamine 10% and xylazine 2% by intramuscular injection. An incision was made through the sixth intercostal space, the subjacent musculature was sectioned, and inside the pleural cavity 0.2 ml carrageenan 1% were injected. The incision was closed after surgery (adapted technique from Petronilho et al., 2010).

d. Biochemical determinations

Biochemical determinations were performed in the Oxidative Stress Research Laboratory of the Physiology Discipline, at “Iuliu Haţieganu” University of Medicine and Pharmacy Cluj-Napoca. Oxidative stress and antioxidant protection were investigated in serum and lung tissue based on malondialdehyde (MDA) (technique of Conti et al., 1991), reduced glutathione (GSH) (Hu method, 1994) and ceruloplasmin (Cp) (Ravin method, 1961).

e. Data analysis

The obtained results were analysed using GraphPad Prism version 5.03 for Windows, GraphPad Software, (San Diego, California, USA), by performing one-way ANOVA followed by the Bonferroni post-test. The significance level was set at $p<0.05$ ($p<0.001$ noted with ***; $p<0.01$ with ** and $p<0.05$ with *).

Results

a. Comparative statistical analysis among the groups, in serum

✓ *at 4 hours*

In serum, the MDA level presented significant increases in the rats that received only carrageenan (group II) in comparison with the control group (I), and also in comparison with the groups that received resveratrol or quercetin (groups III or IV) as protection. Significant increases of MDA were seen in the control group (I), compared to the group pre-treated with resveratrol (III).

Serum GSH presented significant increases in the rats

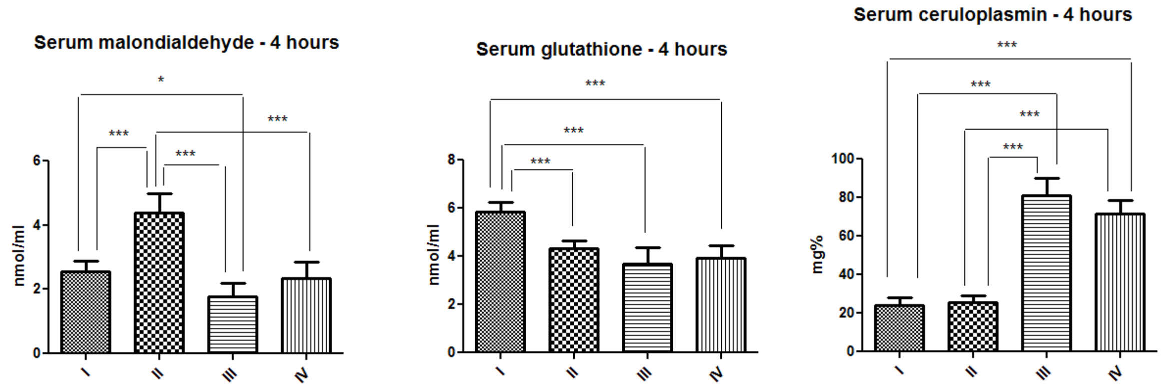

Figure 1. Serum levels of malondialdehyde, glutathione and ceruloplasmin, at 4 hours.

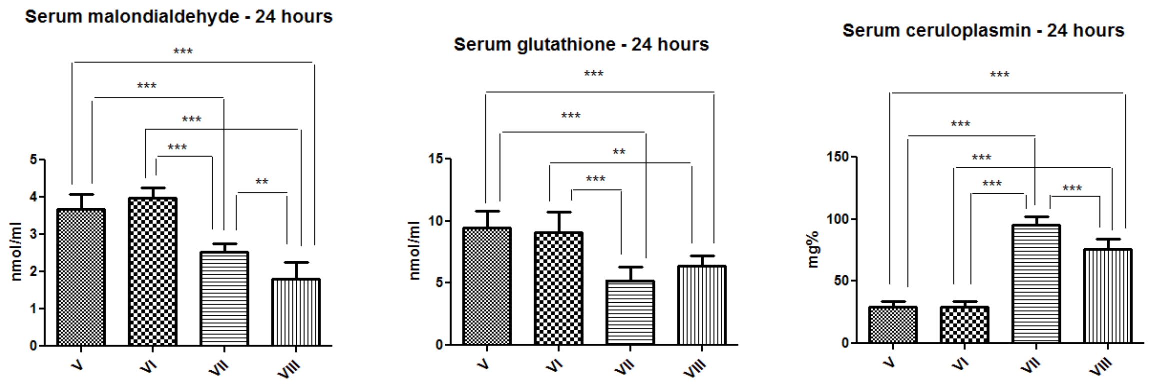

Figure 2. Serum levels of malondialdehyde, glutathione and ceruloplasmin, at 24 hours.

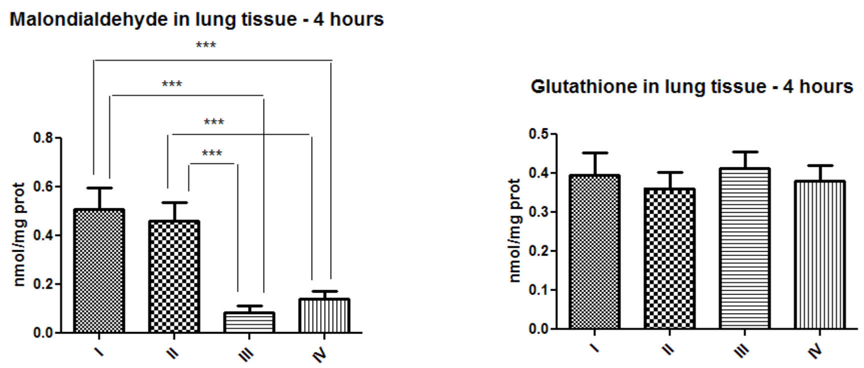

Figure 3. Malondialdehyde and glutathione in lung tissue, at 4 hours.

of the control group (I) compared to the other groups of rats (II, III and IV).

Cp increased significantly in the serum of rats that received antioxidants (groups III and IV), in comparison with both the control group (I) and the carrageenan group (II) (Figure 1).

✓ *at 24 hours*

Serum MDA, at 24 hours after intrapleural carrageenan administration, increased significantly in the control (V) and carrageenan (VI) groups, compared to the groups that received antioxidants as pre-treatment (groups VII and VIII). MDA presented significant differences between the groups that received antioxidants, with higher values in rats pre-treated with resveratrol (VII), in comparison with the quercetin group (VIII).

GSH decreased significantly in the serum of rats that received resveratrol (group VII) and quercetin (group VIII) compared to the control group (V) and the carrageenan group (VI).

Cp registered significant increases in the rats that received resveratrol (group VII) or quercetin (group VIII), compared to the rats of the control (V) and carrageenan (VI) groups. Significant differences were seen between the groups of rats that received antioxidants, with the highest values of Cp in the serum of rats with resveratrol as pre-treatment (group VII) (Figure 2).

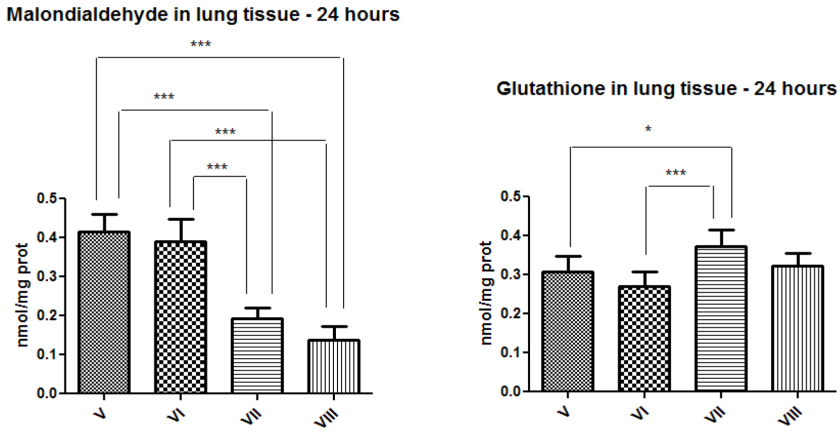

Figure 4. Malondialdehyde and glutathione in lung tissue, at 24 hours.

b. Comparative statistical analysis among the groups, in lung tissue

✓ *at 4 hours*

In lung homogenate, MDA presented significant increases in the control (I) and carrageenan (II) groups, in comparison with the groups pre-treated with antioxidants (groups III and IV).

GSH did not present any significant variations among the groups, in lung tissue (Figure 3).

✓ *at 24 hours*

In lung tissue, at 24 hours after carrageenan administration, MDA level was increased significantly in the control (V) and carrageenan (VI) groups, compared to the groups that received antioxidants as protection (VII and VIII).

Significant increases of GSH levels in the lung homogenate were seen at 24 hours after intrapleural carrageenan administration only in the rats that received resveratrol (group VII), in comparison with the rats of the control (V) and carrageenan (VI) groups (Figure 4).

Discussions

Our study evidenced the presence of OS in serum at 4 and also at 24 hours after intrapleural carrageenan administration.

MDA levels presented significant increases in the rats that did not receive antioxidants, compared to the rats pre-treated with resveratrol or quercetin. The pro-inflammatory action of carrageenan was observed at 4 hours after inflammation induction, through significantly increased levels of MDA in the rats that received only carrageenan, compared to the rats of the control group, which received only physiological salt. The differences between these groups were not observed at 24 hours after carrageenan inflammation.

Cp presented significant increases in the rats that were treated with resveratrol and quercetin, in comparison with the unprotected rats, showing the antioxidant effects of these substances in inflammation, at 4 and at 24 hours after inflammation induction.

The serum GSH level decreased significantly at 4 hours after carrageenan administration in both groups pre-treated with antioxidants, compared to the control groups. The decrease of GSH was also recorded at 24 hours, a long-term decrease of this parameter being observed.

OS was revealed in the lung tissue at 4 and at 24 hours after carrageenan administration, MDA levels being significantly increased in the rats that did not receive antioxidants, compared to the rats pre-treated with resveratrol or quercetin. At 24 hours after carrageenan inflammation, GSH level in lung homogenate presented significant increases only in the rats that received resveratrol.

Donnelly et al. (2004) studied the anti-inflammatory effects of resveratrol and quercetin on epithelial cells of the respiratory pathways and observed their inhibitory effects on NF-kB activation, AP-1 dependent transcription, cAMP response element-dependent transcription, effects that were stronger than the effects of dexamethasone. Their study showed that in human primary airway epithelial cells, resveratrol inhibited nitrite synthesis by reducing the expression of cytokine-stimulated inducible nitric oxide synthase, inhibited COX-2 expression, granulocyte-macrophage colony-stimulating factor, and IL-8 release.

In their study performed in 2014, Zhang et al. tested the effects of resveratrol on OS in endotoxemia-induced acute lung injury and presented the beneficial effects of this antioxidant that inhibited OS, decreasing pro-oxidant biomarkers (MDA and H_2O_2) and increasing antioxidant biomarkers (GSH, catalase - CAT and superoxide dismutase - SOD).

Yeh et al. (2014) presented the protective effects of resveratrol on mitochondrial biogenesis in lungs with ischemia-reperfusion injury. Pulmonary inflammation and OS were investigated through leukocyte and MDA determinations. Their study showed that in the lung with ischemia-reperfusion injuries, OS was increased, but treatment with resveratrol protected the lung against these lesions, reducing OS and leukocyte infiltration.

Özdemir et al. (2014) studied the biochemical and histopathological effects of resveratrol in newborn rats with hyperoxia-induced lung injuries and demonstrated that this polyphenol had a protective role through its anti-inflammatory and antioxidant effects.

Wang et al. (2017) studied the analgesic and anti-inflammatory effects of resveratrol on different experimental models. Their results showed that in acetic acid-induced pleural effusion in rats, resveratrol significantly inhibited leukocytes and decreased exudate, decreased nitric oxide (NO) synthesis and increased SOD activity in serum, being a potential drug in the treatment of pain and inflammation.

Hamza and El-Shenawy (2017) studied the anti-inflammatory and antioxidant effects of resveratrol on nicotine-induced pulmonary modifications in an experimental model of male rats and showed that nicotine administration significantly increased lipid peroxidation and significantly reduced the activity of lung antioxidant enzymes. The levels of IL-2, IL-6, α-fetoprotein and tumour necrosis factor alpha (TNF-α) increased in animals exposed to nicotine, while resveratrol administration followed by nicotine exposure ameliorated pulmonary lesions and was associated with an enhancement of all the mentioned parameters, demonstrating the protective effect of this antioxidant through OS modulation and antioxidant defence (enzymatic/non-enzymatic) amelioration.

In a recent study, Fan et al. (2019) showed that amurensin H, a resveratrol dimer derived from *Vitis amurensis Rupr.*, reduced the lung inflammatory modifications caused by cigarette smoke, decreasing the levels of IL-6, TNF-α and interferon-γ (IFN-γ) in bronchoalveolar lavage fluid. Amurensin H may ameliorate the inflammation of respiratory passageways *in vivo* and *in vitro* and may be useful in the treatment of inflammation in COPD.

Xu et al. (2019) studied the anti-inflammatory effects of resveratrol and dexamethasone in prevention of ischemia-reperfusion injuries in rats with transplanted lung and demonstrated that the levels of IL-6 and TNF-α in serum and in the bronchoalveolar lavage fluid were reduced in the groups pre-treated with resveratrol or dexamethasone, compared to the control group.

Çiftçi et al. (2016) investigated the efficiency of resveratrol and quercetin in experimental spinal cord lesions and showed a significant increase of the total antioxidant capacity and paraoxonase activity in groups that were treated with resveratrol, quercetin, or with both antioxidants, without significant differences among the groups.

Tripathi et al. (2019) studied in rats the effect of quercetin administration in different doses before exposure to hypobaric hypoxia and observed that the optimal dose was 50 mg/kg administered 1 hour before exposure, a dose that determined the inhibition of OS (ROS and MDA), a concomitant increase of antioxidants (GSH, glutathione peroxidase - GPx and SOD), a decrease of pro-inflammatory cytokines (TNF-α and IFN-γ), and a significant reduction of pulmonary oedema.

Zhang et al. (2018) established in a study performed *in vitro* on human embryonic pulmonary fibroblasts and *in vivo* on an experimental mouse model that quercetin ameliorated bleomycin-induced pulmonary fibrosis, inhibiting sphingosine kinase 1 and sphingosine-1-phosphate signaling.

Huang at al. (2015) studied the effects of quercetin in pulmonary lesion induction and found that this flavonoid decreased the MDA level and increased the activity of SOD, CAT and GPx in rats with lipopolysaccharide administration.

A different study performed on rats evaluated the protective capacity of melatonin and quercetin against pulmonary lesions induced by carbon tetrachloride (CCl_4). The level of MDA was increased significantly in the rats exposed to CCl_4 compared to the rats that received antioxidants. GSH level was significantly increased in the rats treated with melatonin or quercetin, compared to the rats that were only exposed to CCl_4 (Taslidere et al., 2014).

Yang et al. (2012) studied the antioxidant and anti-inflammatory effects of quercetin in prevention of chronic respiratory diseases induced by cigarette smoke. The results demonstrated the role of quercetin in mitigating the increased mucin synthesis induced by cigarette smoke, inhibiting OS and inflammation, thus presenting a great potential for treating chronic respiratory diseases.

Komaravelli et al. (2015) investigated the protective role of resveratrol and quercetin in metapneumovirus infection and observed significant decreases in oxidative cellular lesions, in inflammatory mediator production and viral replication, supporting the use of food antioxidants as an efficient treatment in modulation of oxidative lesions and of inflammation in metapneumovirus infection.

The present study registered results that are concordant with those presented in the literature on different experimental models of pulmonary inflammation and showed the positive effects of resveratrol and quercetin. These antioxidants could be used in inflammatory lung diseases as an alternative or as an adjuvant medication, without the adverse reactions of the usual anti-inflammatory drugs.

Conclusions

1. In serum, both natural compounds had antioxidant actions. At 4 hours and at 24 hours after carrageenan administration, resveratrol and quercetin significantly reduced MDA and significantly increased Cp levels in the serum of rats that received these substances, compared to the rats of the control and carrageenan groups.
2. In lung homogenate, at 4 hours and at 24 hours, MDA decreased significantly in the rats that were pre-treated with antioxidants compared to the untreated rats. At 24 hours, at the pulmonary level, resveratrol presented higher antioxidant effects than quercetin, evidenced by significant increases of GSH only in the resveratrol group.
3. Our results support the use of these substances in the treatment of inflammatory lung diseases.

Conflicts of interest

There are no conflicts of interest.

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