Original Article
Resveratrol ameliorates cadmium induced renal oxidative damage and inflammation

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Abstract: Cadmium (Cd) is a common toxic environmental pollutants. People are exposure to Cd from air, drinking water and so on. Especially, tobacco smoking is another important way for people exposed to Cd. Kidney is the primary organ targeted by chronic Cd exposure. Resveratrol is a natural polyphenol and has the ability of ameliorating Cd-induced renal damages. However, the clearly involved mechanisms are still not fully elucidated. The aim of this study was to explore the possible mechanisms under the renal protective functions of resveratrol in zebrafish model induced by exposure to 1.5 mg/L CdCl2 in water for 72 h and in rat model induced by orally treated with 5 mg/kg/d CdCl2 for 4 weeks. It was found that resveratrol significantly attenuated Cd-induced zebrafish phenotype changes and rat renal injury. Resveratrol inhibited the renal collagen deposition, oxidative stress and inflammation, normalized enzymatic antioxidant status, regulated epithelial-mesenchymal transition (EMT) related factors and enhanced the expressions of nuclear related factor-2 (Nrf-2), heme oxygenase-1 (HO-1) and γ-glutamate cysteine ligase catalytic subunit (γ-GCLC). This study added the evidences that resveratrol prevented renal collagen deposition, oxidative stress and inflammation via regulating Nrf-2. It provided new insights for understanding the protective nature of resveratrol against Cd induced renal deficits.

Keywords: Cadmium, resveratrol, renal damages, oxidative stress, inflammation

Introduction

The rapid development of modern industry has brought increasingly serious environmental pollution problems, especially in the developing countries. Cadmium (Cd) is one of the most widely existed toxic environmental pollutants. Industrial production such as batteries manufacture, pigments generation and metal plating obviously enhances the risk for the contamination of Cd in the atmosphere, water and soil [1]. As a result, people are exposure to Cd from air, drinking water and so on. Especially, tobacco smoking is another important way for people exposed to Cd [2]. Cd with the status of non-biodegradable is not an essential element for human beings [3]. The biological half-life of Cd is long to 20-30 years [4]. So, Cd is easy to be accumulated in the body and highly toxic to nearly all organisms [1]. Briefly, acute intake of Cd leads to renal injury, anemia and osteoporosis [5]. It has been demonstrated that kidney has a preferential sensitivity to Cd and is the primary organ targeted by chronic Cd exposure [6]. The Cd accumulated in the kidney accounts for about 50% of the total Cd in vivo, and can finally results in the end-stage renal disease (ESRD) [4]. The exact mechanisms under the heavy metal pathogenesis have not been fully elucidated. A most recognized disturbance manner is metal caused oxidative stress [7]. Chronic exposure to Cd stimulates the production of reactive oxygen species (ROS) and contributes to oxidative stress in vivo [1, 4]. Additionally, inflammation is also a key indicator for Cd-induced tissue damages [6].

Natural polyphenols with antioxidant properties due to their chemical structure are suggested to have the beneficial functions of suppressing oxidative stress in human beings [5]. For example, grape seed contains an abundance of natural phenolic compounds and is demonstrated to can attenuate chronic Cd exposure induced
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renal injury by inhibiting the ROS generation and local inflammation. Its abilities of modulating the renal expressions of nuclear related factor-2 (Nrf-2) and several antioxidant genes are possibly responsible for these benefits [8]. Resveratrol is one of the mainly bioactive polyphenol in grape. Resveratrol has a variety of pharmacological effects including antioxidant, anti-inflammatory and anti-cancer [9]. Previous study revealed that daily treated with 20 mg/kg/d resveratrol inhibited the structural changes of kidney (disturbed glomeruli, increased collagen deposition and degenerated tubular) induced by exposure to Cd for 4 weeks [10]. In another animal model of acute renal injury induced by Cd, resveratrol ameliorated the Cd-induced lipid peroxidation and diminish in renal antioxidant status [11]. However, the clearly mechanisms under the renal protective functions of resveratrol against chronic Cd exposure are still not fully elucidated. This study was undertaken to investigate the possible mechanisms of resveratrol in zebrafish and rat model.

Materials and methods

Chemicals and antibodies

The antibodies of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) were purchased from abcam, Inc. (Cambridge, Cambs, UK). The antibodies of Nrf-2 and heme oxygenase-1 (HO-1) were purchased from Proteintech Group, Inc. (Chicago, IL, USA). The antibody of γ-glutamate cysteine ligase catalytic subunit (γ-GCLC) were purchased from Boster, Co. Ltd. (Wuhan, Hubei, China). The commercial kits for the analysis of the blood urea nitrogen (BUN), serum creatinine (SCR), β-N-acetylglucosaminidase (NAG), malondialdehyde (MDA), total sulfhydryl (T-SH), total carboxyl (T-CO), glutathione/oxidized glutathione (GSH/GSSG), superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GPx) and nitric oxide (NO) were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, Jiangsu, China). The ELISA kit for the analysis of prostaglandin E2 (PGE2) was purchased from R&D System, Inc. (Minneapolis, MN, USA). Resveratrol (purity > 98%) was purchased from Aladdin Biochemical Technology Co. Ltd. (Shanghai, China). All other solvents and chemicals used in the study were of analytical grade and purchased from Sinopharm Chemical Reagent, Co, Ltd. (Shanghai, China).

Cd induced zebrafish (Danio rerio) embryos injury

Wild type zebrafish (AB strain) were applied in this study. The fish were maintained under a controlled tank (temperature 28°C and 14 h light: 10 h dark cycle). The embryos were obtained from natural spawning of male and female zebrafish in the tank overnight. The spawning was collected and induced in the next morning by the onset of white light at 28°C to 3 dpf for further analysis [12, 13]. Then, these zebrafish embryos were randomly divided into 8 groups (n = 11) in 24 well plates:

The vehicle control group: maintained in culture medium only; The 30, 10 or 1 μg/ml resveratrol control group: maintained in culture medium with 30 (in our previous study, the 72 h LD50 of resveratrol for zebrafish embryos was 35.08 μg/ml. So, 30 μg/ml was used as the high concentration in the present study), 10 or 1 μg/ml resveratrol; The Cd exposure group: maintained in culture medium with 1.5 mg/L CdCl2; The Cd + 30, 10 or 1 μg/ml resveratrol group: maintained in culture medium with 1.5 mg/L CdCl2 + 30, 10 or 1 μg/ml resveratrol; Half of the water was replaced with fresh prepared water with 1.5 mg/L CdCl2 (and/or resveratrol) each day. After 72 h of exposure, the fish were anesthetized and observed under a light microscope. The changes in dorsal and lateral phenotype (periocular and yolk sac edema) were recorded with a digital camera.

Rat model of Cd induced renal damage

Adult male Wistar rats weighing 200±20 g (10 weeks) were obtained from the Centers of Disease Control and Prevention of Hubei Province, China. The animals were housed at a controlled room (temperature 22±3°C, humidity 50±10% and 12 h light: 12 h dark cycle) and fed with standard diet and water ad libitum. After acclimatization to the laboratory conditions for 7 days, the animals were randomly divided into four groups (n = 8): the vehicle control group (vehicle), the resveratrol treated control group (resveratrol), the Cd exposure model group (Cd) and the resveratrol treated-Cd groups (resveratrol + Cd). The rats from Cd and
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**Table 1. The primer sequences**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Forward primer</th>
<th>Reverse primer</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-β1</td>
<td>5'-TATAGCAATTCCCGGTTACCT-3'</td>
<td>5'-GTCACCTCGACGTTGGGACTGA-3'</td>
</tr>
<tr>
<td>Twist</td>
<td>5'-GTCGCTGAACGAGGACTTTGAG-3'</td>
<td>5'-CCCCTCATCTCAGAAGC-3'</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>5'-CCCTACCAAGGCTGGATGAT-3'</td>
<td>5'-GAGCAAGGTCCTCCTGGTC-3'</td>
</tr>
</tbody>
</table>

Resveratrol + Cd groups were orally treated with 5 mg/kg/d CdCl₂ for 4 weeks [8]. The rats from vehicle and resveratrol groups were received the same volume of normal water. One hour after Cd treatment, the rats from resveratrol and resveratrol + Cd groups were intragastric administrated with 20 mg/kg/d resveratrol (the selection of this dose was analyzed in the Discussion) for 4 weeks, respectively. And the rats from vehicle and Cd groups were daily intragastric administrated with the same volume of normal water.

At the end of the experimental period, the animals were placed in metabolic cages to collect 24-hour urine for the measurement of NAG. Then, the blood samples were prepared for the analysis of BUN and SCR. The kidney samples were collected, weighted and excised. One part of the tissue was stored at -80°C for the subsequent western blot assay (renal levels of COX-2, iNOS, Nrf-2, HO-1 and γ-GCLC) and quantitative RT-PCR (qPCR) assay (renal levels of transforming growth factor-β1 (TGF-β1), twist and fibronectin). Another part of the tissue was fixed in 4% paraformaldehyde for 3 days and then embedded in paraffin and serially sectioned for the haematoxylin-eosin (HE) and masson staining. Stained areas of the sections were visualized and recorded using an optical microscope (Leica DMI8) at ×200. The rest tissue was made to the 10% tissue homogenate using ice cold physiological saline and then stored at -80°C.

All the animal experiments were performed in compliance with the Chinese legislation and in accordance with the ethical rules in the NIH Guidelines for the Care and Use of Laboratory Animals. The study was approved by the Institutional Animal Care and Use Committee at Puai Hospital, Tongji Medical College, Huazhong University of Science and Technology.

**Analysis for renal extent of oxidative stress and inflammation**

Renal extent of oxidative stress and inflammation was estimated using kidney tissue homogenate. Briefly, the renal level of oxidative stress was evaluated by measuring the levels of the oxidative stress indicators (MDA, GSSG, T-CO and T-SH), the non-enzymatic antioxidant (GSH) and the renal enzymatic antioxidant status (SOD, CAT, GR and GPx). The renal level of inflammation was assessed by detecting the levels of inflammatory-related factors (PGE₂ and NO). All the procedures were performed according to the manufacturer's instructions of the commercial available kits.

**Analysis for renal expressions of COX-2, iNOS, Nrf-2, HO-1 and γ-GCLC**

The renal expressions of COX-2, iNOS, Nrf-2, HO-1 and γ-GCLC were evaluated by western blot analysis using tissue samples. Tissue protein samples were separated by 10% SDS-polyacrylamide gel electrophoresis and then transferred to a PVDF membrane by electrophoretic transfer. Transferred membranes were blocked for 1 h at 37°C with 5% nonfat milk in Tris-buffered saline, and then incubated overnight at 4°C with different primary antibodies (1:500 for COX-2, or 1:1000 for iNOS, Nrf-2, HO-1 and γ-GCLC). After washed with TBST, the membranes were incubated with horseradish peroxidase-conjugated secondary antibodies in TBST with 3% nonfat milk for 1 h at room temperature. Quantification of bands was determined by integrated optical density analysis using Gel-Pro Analyzer software after immunoblots. The expressions of total proteins were normalized using β-actin (1:8000) as an internal control. And the expression of nucleic protein Nrf-2 was normalized using Lamin B (1:1000) as an internal control.

**Analysis for renal levels of TGF-β1, twist and fibronectin**

After ground in liquid nitrogen, the total RNA was extracted from each sample using Trizol reagent and quantified using gel electrophoresis. The qPCR was performed in the real-time PCR system using a fast qPCR master mix kit according to the manufacturer’s protocol. Post-
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PCR melt curve analysis was used to control the PCR product specificity. Relative levels were calculated using the equation $2^{-\Delta\Delta Ct}$ [14]. The primer sequences of TGF-β1, Twist and fibronectin were showed in Table 1. GAPDH was used as the internal standard.

**Statistical analysis**

The values were presented as mean ± S.D. Results were analyzed statistically by one-way ANOVA followed by Tukey’s multiple comparison using SPSS software. Differences were considered as significant at $P < 0.05$.

**Results**

Effects of resveratrol on Cd-induced changes in dorsal and lateral phenotype

Exposure to Cd for 72 h leads to periocular and yolk sac edema in zebrafish. The edema rate of Cd exposure group (70.56±4.19%) was significantly ($P < 0.01$) enhanced when compared to the vehicle control (0±0%). Co-treated with 1, 10 or 30 μg/ml resveratrol obviously decreased the edema rate to 49.01±15.53% ($P < 0.05$), 42.59±8.49% ($P < 0.01$) or 31.21±4.67% ($P < 0.01$) when compared to the untreated Cd exposure group, respectively. However, there was no significant difference ($P > 0.05$) among the 1, 10 and 30 μg/ml resveratrol. Additionally, 1, 10 or 30 μg/ml resveratrol alone did not increased ($P > 0.05$) the edema rate when compared to the vehicle control.

Effects of resveratrol on body weight, kidney weight and food intake in rats exposure to Cd

The changes on body weight, kidney weight and food intake are showed in Table 2. Four weeks Cd exposure led to significant reduction in the body weight gaining, kidney weight and food intake when compared to the vehicle control. Co-treated with 20 mg/kg/d resveratrol for 4 weeks significantly increased the body weight gaining and kidney weight when compared to the Cd model. There was no significant difference ($P > 0.05$) on body weight gaining, kidney weight and food intake between vehicle control and resveratrol group.

Effects of resveratrol on the levels of BUN, SCR and NAG in rats exposure to Cd

Figure 1 represents that orally treated with 5 mg/kg/d Cd for 4 weeks causes significant enhancement in the levels of BUN, SCR and NAG.

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial body weight (g)</th>
<th>Final body weight (g)</th>
<th>Body weight change (g)</th>
<th>Kidney weight (g)</th>
<th>Kidney index (%)</th>
<th>Initial food intake (g/100 g/d)</th>
<th>Final food intake (g/100 g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>224.12±18.19</td>
<td>357.12±27.60**</td>
<td>133.38±39.04**</td>
<td>2.06±0.18**</td>
<td>0.575±0.016</td>
<td>11.76±0.64</td>
<td>10.75±0.41**</td>
</tr>
<tr>
<td>Cd</td>
<td>219.38±14.88</td>
<td>300.25±23.60**</td>
<td>80.88±21.29**</td>
<td>1.67±0.16**</td>
<td>0.555±0.013</td>
<td>12.17±1.51</td>
<td>7.49±0.83**</td>
</tr>
<tr>
<td>Cd + resveratrol</td>
<td>223.38±13.51</td>
<td>342.75±20.21**</td>
<td>119.37±16.45**</td>
<td>1.94±0.17**</td>
<td>0.566±0.021</td>
<td>12.17±1.51</td>
<td>9.12±0.77</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>220.75±13.48</td>
<td>347.12±23.33**</td>
<td>126.38±29.84**</td>
<td>2.01±0.16**</td>
<td>0.578±0.023</td>
<td>11.86±1.54</td>
<td>9.52±0.87**</td>
</tr>
</tbody>
</table>

**P < 0.01 compared to the vehicle control, *P < 0.05 compared to the Cd model, **P < 0.01 compared to the Cd model.
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NAG when compared to the vehicle control. Resveratrol obviously inhibited these Cd-induced increased levels of BUN, SCR and NAG when compared to the untreated Cd model. And 20 mg/kg/d resveratrol alone did not change the kidney function ($P > 0.05$) when compared to the vehicle control.

**Effects of resveratrol on renal morphologic changes and collagen deposition in rats exposure to Cd**

**Figure 2** shows that Cd exposure contributes to the shrinkage of glomerulus (solid arrow) and dilation of tubules (dovetail arrow), as well as the deposition of collagen (dotted arrow) when compared to the vehicle control group. Resveratrol ameliorated these morphologic changes and suppressed the renal collagen deposition when compared to the model control.

**Effects of resveratrol on renal oxidative stress in rats exposure to Cd**

**Figure 3** reveals that 4 weeks exposure to Cd results in renal oxidative stress characterized by much higher levels of MDA, T-CO, GSH, GSSG and SOD when compared to the vehicle control. Treated with 20 mg/kg/d resveratrol for 4 weeks alleviated these alterations. Co-treated with resveratrol obviously decreased the levels of MDA, T-CO and GSSG, increased the levels of T-SH and GSH, and enhanced the activities of SOD, CAT, GPx and GR when compared to the untreated Cd model group.
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Effects of resveratrol on renal inflammation in rats chronic exposure to Cd

The effects of resveratrol on the levels of inflammatory-related factors are showed in Figure 4. Cd exposure resulted in significantly enhanced renal expressions of COX-2 and iNOS, as well as obviously increased levels of PGE\(_2\) and NO when compared to the vehicle control. Treatment with 20 mg/kg/d resveratrol for 4 weeks contributed to noticeably lower levels of COX-2, iNOS, PGE\(_2\) and NO when compared to the untreated Cd model group.

**Effects of resveratrol on renal EMT factors in rats exposure to Cd**

Figure 5 describes the effects of resveratrol on modulating the renal levels of TGF-β1, twist and fibronectin. Significantly increased levels of

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*Figure 4.* Effects of resveratrol on renal expressions of COX-2 and iNOS, as well as the levels of PGE\(_2\) and NO in rats exposure to Cd. **\(P < 0.01\) compared to the vehicle control, \#\(P < 0.05\) compared to the Cd exposure model, ###\(P < 0.01\) compared to the Cd exposure model.

*Figure 5.* Effects of resveratrol on the renal levels of TGF-β1, Twist and fibronectin in rats exposure to Cd. *\(P < 0.05\) compared to the vehicle control, **\(P < 0.01\) compared to the vehicle control, #\(P < 0.05\) compared to the Cd exposure model, ###\(P < 0.01\) compared to the Cd exposure model.
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TGF-β1, twist and fibronectin were found in the rats chronic exposure to Cd when compared to the vehicle control group. Daily administered with 20 mg/kg resveratrol significantly attenuated the over-generation of TGF-β1, twist and fibronectin when compared to the Cd model group.

Effects of resveratrol on renal levels of Nrf-2, HO-1 and γ-GCLC in rats exposure to Cd

As indicated in Figure 6, Cd exposure decreases the renal expressions of Nrf-2, HO-1 and γ-GCLC when compared to the vehicle control group. Resveratrol treatment increased the expressions of Nrf-2, HO-1 and γ-GCLC when compared to the Cd group.

Discussion

ESRD is the eventual terminus of varies kinds of chronic kidney diseases including Cd-induced renal injury, and has produced a huge amount of medical costs [4, 15]. The zebrafish is a freshwater tropical vertebrate with a small body. It has highly similar physiological and genomic profiles to human [12]. As a result, it is widely using in the estimate of environmental toxicology and drug activity recently. Zebrafish model is an important method for investigating renal toxicity via observing local edema [16]. In this study, Cd exposure induced periocular and yolk sac edema in zebrafish. Resveratrol at the doses of 1, 10 and 30 μg/ml obviously decreased the Cd-induced zebrafish edema rate. However, there was no significant difference (P > 0.05) among the 1, 10 and 30 μg/ml doses co-treated groups. Additionally, previous studies indicated that the dose of 20 mg/kg/d for rats showed nicely beneficial effects on kidney and is a safe dose [10, 11, 17]. So, this dose was applied in the present study.

In renal local, the over-generated ROS and diminished antioxidant enzymes induced by Cd lead to uncontrolled oxidative stress. Oxidative stress stimulates the damages of DNA, lipids, proteins and other cellular biomolecules, as well as promotes the interruption of cellular redox homeostasis, the cellular apoptosis and the abnormal activation of signaling pathways [18, 19]. Subsequently, numbers pathological progresses are initiated [1]. Cd causes disturbances in body weight and kidney weight, reduces the glomerular filtration and enhances the levels of BUN and SCR due to Cd-induced oxidative damage to the renal tubular cells [7, 8]. Furthermore, Cd has a higher electron affinities for the thiol than antioxidants (like GSH)
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and enzymes (such as SOD and GPx). As a result, Cd can deplete these antioxidants via chelating their thiol groups [3, 7, 18]. They are the key defenses against oxidative stress and convert free radicals into harmless O₂ and H₂O [13]. The renal levels of MDA and carbonyl protein in animal exposed to Cd are obviously enhanced [7, 8]. MDA is a lipid peroxidation product from polyunsaturated fatty acids and commonly used to be an indicator for oxidative damages in cellular and organic functions [13, 20]. Increased levels of carbonyl compounds suggest that proteins are subjected to free radical damages [8].

Additionally, inflammation often complicates pathologic processes by associating with oxidative stress. ROS can trigger the activation of macrophage and then elicit immune responses [21]. In immune system, iNOS and COX-2 are early response genes for inflammation and are commonly used as inflammatory markers [13]. The iNOS belongs to the NOS family and is an inducible enzyme. When activated by Cd, iNOS promotes the production of NO and stimulates inflammatory responses [22]. NO also interacts with ROS to deplete GSH in Cd induced oxidative damage [20]. COX-2 is a pivotal enzyme involved in inflammatory responses. The expression of COX-2 is enhanced when exposure to Cd [6]. PGE₂ functioned as a mediator for inflammatory and immunomodulatory. The synthesis of PGE₂ is accelerated through the catalyze of COX-2 [13, 22].

Chronic Cd exposure may induce changes in renal extracellular matrix (ECM) and promote EMT [23]. Previous animal studies demonstrated that 30 days, 6 weeks or 12 weeks Cd exposure led to varied extent of renal collagen deposition [14, 24]. It has been observed that EMT markers of twist and fibronectin were up-regulated by Cd [23]. EMT is a crucial mediator of wound healing and closely associated to organ fibrosis. The process of EMT is controlled by transcription factors including twist [25]. Fibronectin is an early indicator for renal interstitial fibrosis [24]. TGF-β1 is a key factor in varies of fibrotic diseases. During the inflammation and oxidative damage, the activation of TGF-β1 will accelerate the synthesis and deposition of ECM, promote the differentiation of myofibroblasts, increase the apoptosis of tubular, stimulate the replacement of intrinsic renal cells by fibrotic tissue, and eventually increase the development of glomerulosclerosis and tubulointerstitial fibrosis [14, 24, 26]. In this study, resveratrol inhibited Cd-induced oxidative stress, enhanced renal activities of antioxidant enzymes, decreased the levels of inflammatory-related factors COX-2, iNOS, PGE₂ and NO, as well as attenuated the over-generations of EMT related factors TGF-β1, twist and fibronectin. Ultimately, resveratrol ameliorated the disturbances in body weight, kidney weight and structural changes of kidney.

Nrf-2 is a transcription factor that belongs to the Cap’n’ Collar basic leucine zipper transcription factor family [27]. It plays an important role in the maintenance of cellular homeostasis and has the function of protecting cells and tissues against oxidative stress. Renal expression of Nrf-2 will be decreased by exposed to Cd [8]. Then, the productions of several antioxidants (such as HO-1 and γ-GCLC) are inhibited. HO-1 plays an essential part in antioxidant defense against toxic free radicals [28]. Additionally, the expression of HO-1 is showed to be negatively correlated with the expression of iNOS [21]. Increased level of γ-GCLC contributes to an enhanced intracellular concentration of GSH and the maintaining cellular thiol redox status [28].

The whole findings showed that resveratrol can ameliorate Cd-induced renal oxidative damage and inflammation via regulating Nrf-2. This study added positive evidence for the benefits of resveratrol in Cd-induced chronic renal injury. It also provided new insights for understanding the protective nature of resveratrol against Cd induced renal deficits.

Acknowledgements

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Disclosure of conflict of interest

None.
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