INTRODUCTION

Ultraviolet (UV) rays are categorized as short wave (200-280 nm, UVC), medium wave (280-320 nm, UVB), and long wave (320-400 nm, UVA) according to their wavelength. Many studies have reported that human skin exposure to a certain dose of UVB radiation may result in sunburn, inflammation, and aging and may ultimately result in cancer. We investigated whether phloroglucinol (1,3,5-trihydroxybenzene), by enhancing the expression and activity of 8-oxoG DNA glycosylase 1 (Ogg1), had an effect on the capacity of UVB-exposed human HaCaT keratinocytes to repair oxidative DNA damage. Here, the effects of phloroglucinol were investigated using a luciferase activity assay, reverse transcription-polymerase chain reactions, western blot analysis, and a chromatin immunoprecipitation assay. Phloroglucinol restored Ogg1 activity and decreased the formation of 8-oxoG in UVB-exposed cells. Moreover, phloroglucinol increased Ogg1 transcription and protein expression, counteracting the UVB-induced reduction in Ogg1 levels. Phloroglucinol also enhanced the nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) as well as Nrf2 binding to an antioxidant response element located in the Ogg1 gene promoter. UVB exposure inhibited the phosphorylation of protein kinase B (PKB or Akt) and extracellular signal-regulated kinase (Erk), two major enzymes involved in cell protection against oxidative stress, regulating the activity of Nrf2. Akt and Erk phosphorylation was restored by phloroglucinol in the UVB-exposed keratinocytes. These results indicated that phloroglucinol attenuated UVB-induced 8-oxoG formation in keratinocytes via an Akt/Erk-dependent, Nrf2/Ogg1-mediated signaling pathway.

Key Words: Phloroglucinol, Ultraviolet B, 8-oxoguanine DNA glycosylase 1, NF-E2-related factor 2, Protein kinase B, Extracellular signal-regulated kinase

INTRODUCTION

Ultraviolet (UV) rays are categorized as short wave (200-280 nm, UVC), medium wave (280-320 nm, UVB), and long wave (320-400 nm, UVA) according to their wavelength. Many studies have reported that human skin exposure to a certain dose of UVB radiation may result in sunburn, inflammation, aging, and eventually cancer (Bridgeman et al., 2016; Wu et al., 2018; Lin et al., 2019; Kim et al., 2020). One of the reasons for these effects is probably UVB radiation-induced oxidative stress, resulting in DNA base modification and 8-oxoguanine (8-oxoG) production (Gunaseelan et al., 2017; Takemori et al., 2017). 8-oxoG is considered a cellular marker for both oxidative stress and DNA damage (Ba and Boldogh, 2018). During DNA replication, 8-oxoG residues frequently pair incorrectly with adenine, ultimately resulting in G-to-T and C-to-A substitutions (Bruner et al., 2000; Hyun et al., 2000, 2003). 8-OxoG DNA glycosylase 1 (Ogg1) excises the 8-oxoG base, leaving behind an abasic site, which is then restored to guanine by the base excision repair (BER) machinery (Boiteux and Radicella, 2000; de Souza-Pinto et al., 2001; Ba and Boldogh, 2018). Imbalances in the redox state have been associated with NF-E2-related factor 2 (Nrf2), a transcription factor that activates the antioxidant response element, upregulating the activity of Nrf2. Akt and Erk phosphorylation was restored by phloroglucinol in the UVB-exposed keratinocytes. These results indicated that phloroglucinol attenuated UVB-induced 8-oxoG formation in keratinocytes via an Akt/Erk-dependent, Nrf2/Ogg1-mediated signaling pathway.
the expression of a variety of downstream antioxidant genes (Nguyen et al., 2004; Kensler et al., 2007; Surh et al., 2008; Sinha et al., 2012). The Ogg1 promoter contains a binding site of transcription factor considered for Nrf2, known for antioxidant response elements (Dhénaut et al., 2000; Merrill et al., 2002; Singh et al., 2013). Akt and Erk1/2 are major signaling enzymes involved in cell protection against oxidative stress and are upstream regulators of Nrf2 (Piao et al., 2011).

Phloroglucinol (1,3,5-trihydroxybenzene; PG) is a naturally occurring secondary metabolite produced by certain plant species. It is derived from edible seaweeds and is a purely natural antioxidant (Shibata et al., 2004). PG and its derivatives are widely applied in the pharmaceutical, cosmetic, and textile industries; they have been developed as anticancer, antidepressant, antimicrobial, anti-protozoal, anti-spasmodic, antiviral, and anti-Parkinson’s disease compounds (Singh et al., 2009; Ryu et al., 2013). PG attenuates oxidative stress and inflammation in RAW 264.7 cells (Kim and Kim, 2010). Moreover, PG reduces lipid peroxidation and reverses the decrease in glutathione levels observed in HepG2 lung cancer cells (Quégineur et al., 2012). We previously showed that PG exerts cytoprotective effects, attenuating the oxidative stress and senescence induced by gamma or UV radiation via the direct scavenging of reactive oxygen species (ROS) as well as the upregulation of antioxidant enzymes in skin keratinocytes and lung fibroblasts (Kang et al., 2006, 2010; Kim et al., 2012; Piao et al., 2012, 2014). We also found that PG protects mouse skin against UVB-induced oxidative stress and DNA damage (Piao et al., 2014, 2015). In recent years, some studies have addressed the mechanism by which PG inhibits DNA damage (Piao et al., 2014, 2015; Park et al., 2019). However, the effect of PG on the DNA repair enzyme, Ogg1, has not yet been addressed. Here, we investigated the mechanism by which PG reduced the levels of UVB-induced 8-oxoG in human HaCaT keratinocytes.

MATERIALS AND METHODS

Cell culture and UVB exposure

Human skin keratinocytes, HaCaT, were maintained at 37°C in an incubator containing a humidified atmosphere of 5% CO2, and were cultured in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum, streptomycin (100 µg/mL), and penicillin (100 units/mL). The cells were seeded at a density of 2×10^4/cm² and exposed to UVB radiation. A CL-1000 M UV Crosslinker (UVP, Upland, CA, USA) was used as the UVB source and delivered a UVB energy spectrum of 280-320 nm.

Reagents and antibodies

PG, avidin-tetramethylrhodamine isothiocyanate (avidin-TRITC), and anti-actin antibody were purchased from Sigma Chemical Company (St. Louis, MO, USA). The antibodies against Ogg1, Nrf2, Erk, and phospho-Erk were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). The antibodies against phospho-Akt, Akt, and histone 3 were purchased from Cell Signaling Technology (Danvers, MA, USA). The antibody against TATA-binding protein (TBP) was purchased from Abcam (Cambridge, UK). Thiazolyl blue tetrazolium bromide (MTT) and dimethyl sulfoxide (DMSO) were purchased from Amresco LLC (Solon, OH, USA).

Analysis of 8-OHdG formation

Cellular DNA was isolated using a Wizard® genomic DNA purification kit (Promega Corporation, Madison, WI, USA) and quantified using a Qubit™ dsDNA HS assay kit (Invitrogen, Eugene, OR, USA). The amount of 8-hydroxy-2-deoxyguanosine (8-OHdG, a nucleoside of 8-oxoG) in the DNA was measured using a Bioxytech 8-OHdG ELISA kit (OXIS Health Products, Portland, OR, USA). The amount of 8-OHdG reflected the level of 8-oxoG. The cells were fixed and permeabilized with ice-cold methanol for 15 min and incubated with avidin-conjugated TRITC at room temperature for 1 h. Fluorescence images showing the highly specific binding of avidin and 8-OHdG were obtained using an Olympus Fluoview FV1200 Laser Scanning Confocal Microscope (Olympus Life Science, Tokyo, Japan).

Analysis of Ogg1 activity

The cells were seeded in 24-well plates at a density of 2×10^4/cm², pretreated with 10 µM PG for 30 min, exposed to 30 mJ/cm² UVB, and incubated at 37°C for 24 h. The 8-oxoG-containing oligonucleotide 5’-FAM-GCACTOAAGC-GCCGCACGCATGTCCGCAGCTTCACTGC-DAB-3’ (O; 8-oxoG) was synthesized by Bioneer Corporation (Daejeon, Korea) with 30 mJ/cm² UVB, and incubated at 37°C for 24 h. The 8-oxoG-containing oligonucleotide 5’-FAM-GCACTOAAGC-GCCGCACGCATGTCCGCAGCTTCACTGC-DAB-3’ (O; 8-oxoG) was synthesized by Bioneer Corporation (Daejeon, Korea)

Fig. 1. Phloroglucinol (PG) attenuates UVB-induced 8-oxoguanine (8-oxoG) formation in HaCaT cells. (A) The cells were exposed to 30 mJ/cm² UVB radiation after treatment with 10 µM PG. The content of 8-oxoG was measured using the 8-OHdG kit. *Significantly different from the control cells (p<0.05); #significantly different from the UVB-exposed cells (p<0.05). (B) The formation of 8-oxyG was evaluated under a confocal microscope using avidin-conjugated TRITC dye (Olympus Life Science, Tokyo, Japan); the fluorescence intensity is shown. *Significantly different from the control cells (p<0.05); #significantly different from the UVB-exposed cells (p<0.05).
Phloroglucinol (PG) increases Ogg1 expression at both the mRNA and protein levels. (A) Lipofectamine reagents were used to transfect the cells with plasmid vectors containing the luciferase gene under the control of the Ogg1 promoter. Transfected cells were exposed to 30 mJ/cm² of UVB radiation after treatment with 10 μM PG. Ogg1 gene transcription was examined by Ogg1 gene promoter luciferase assay. *Significantly different from the control cells (p<0.05); **significantly different from the UVB-exposed cells (p<0.05). (B) The cells were exposed to 30 mJ/cm² of UVB radiation after treatment with 10 μM PG and incubated for 12 h. The Ogg1 mRNA level was analyzed by RT-PCR. (C) The cells were exposed to 30 mJ/cm² of UVB radiation after treatment with 10 μM PG and incubated for 24 h. Ogg1 protein expression was analyzed by western blotting.

**Fig. 3.** Phloroglucinol (PG) increases Ogg1 expression at both the mRNA and protein levels. (A) Lipofectamine reagents were used to transfect the cells with plasmid vectors containing the luciferase gene under the control of the Ogg1 promoter. Transfected cells were exposed to 30 mJ/cm² of UVB radiation after treatment with 10 μM PG. Ogg1 gene transcription was examined by Ogg1 gene promoter luciferase assay. *Significantly different from the control cells (p<0.05); **significantly different from the UVB-exposed cells (p<0.05). (B) The cells were exposed to 30 mJ/cm² of UVB radiation after treatment with 10 μM PG and incubated for 12 h. The Ogg1 mRNA level was analyzed by RT-PCR. (C) The cells were exposed to 30 mJ/cm² of UVB radiation after treatment with 10 μM PG and incubated for 24 h. Ogg1 protein expression was analyzed by western blotting.
transferred onto nitrocellulose membranes. The membranes were incubated with the appropriate primary antibodies, followed by incubation with horseradish peroxidase-conjugated secondary antibodies. The protein bands were visualized using an Amersham ECL western blotting detection reagent (GE Healthcare, Buckinghamshire, UK).

**Chromatin immunoprecipitation (ChIP) assay**

The cells were seeded at a density of 2×10^4/cm^2 in 4-well culture dishes, pretreated with 10 µM PG for 1 h, exposed to 30 mJ/cm^2 UVB radiation, and incubated at 37°C for 20 h. ChIP experiments were performed based on the instructions of the SimpleChIP™ enzymatic chromatin IP kit, as previously described (Piao et al., 2011). The Oggt1 gene promoter spanned the positions from −938 to −701 of the Oggt1 gene sequence from the transcription start site. The primers for the Oggt1 gene promoter were: sense, 5′-GGCTGAGGCAGGAGAATCGT-3′; antisense, 5′-TCTTCCCTTCTGGAGGATGGC-3′.

**Small interfering RNA (siRNA) transfection**

The cells were seeded in 60 φ dish culture plates at a density of 2×10^4/cm^2 and allowed to reach approximately 50% confluence on the day of transfection. The employed siRNA constructs were mismatched siRNA control (siControl; Santa Cruz Biotechnology) and Nrf2-specific siRNA (siNrf2; Bioneer). The cells were treated with 10 µM PG for 1 h, exposed to 30 mJ/cm^2 UVB radiation, and incubated for 24 h at 37°C. Then, 50 µL of MTT stock solution (2 mg/mL) were added to each well. After 4 h, the formazan crystals were dissolved with 350 µL of DMSO and the absorbance at 540 nm was measured on a VersaMax ELISA microplate reader (Molecular Devices, Sunnyvale, CA, USA) (Zhen et al., 2019).

**Statistical analysis**

All measurements were performed in triplicate (n=3), and the values are expressed as the mean ± standard error. Tukey’s test was used to analyze the variance. The threshold for statistical significance was set at p<0.05.

**RESULTS**

**Phloroglucinol attenuated the DNA base oxidation induced by UVB exposure**

The level of 8-OHdG was higher in the cells exposed to 30 mJ/cm^2 UVB (226 pg/µL DNA) than in the untreated cells (57 pg/µL DNA), as determined by ELISA assay (Fig. 1A). Pretreatment with 10 µM PG for 1 h before UVB exposure significantly decreased the level of 8-OHdG to 125 pg/µL DNA. The intracellular formation of 8-OHdG was also investigated using TRITC fluorescent dye tagged to avidin, which binds to 8-OHdG molecules, as shown in Fig. 1B. UVB exposure induced red fluorescence, corresponding to 43 arbitrary units of

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**Fig. 4.** Phloroglucinol (PG) increases Nrf2 nuclear translocation and binding to the Oggt1 promoter. The cells were exposed to 30 mJ/cm^2 of UVB radiation after treatment with 10 µM PG. (A) The nuclear proteins were harvested after 24 h of exposure to UVB radiation. The protein levels in the nuclear extracts were analyzed by western blotting using antibodies against Nrf2 and TBP. TBP was used as a nuclear loading control. (B) Confocal image showing the location of Nrf2 (green color). DAPI staining indicates the location of the nucleus (blue color), and the merged image indicates the nuclear localization of Nrf2. (C) Cells were transected with siNrf2, treated with 10 µM PG, and incubated for 24 h. Western blotting was performed using antibodies against Nrf2, Oggt1, and actin. (D) ChIP analysis with antibodies against Nrf2 and histone 3 and primers for the amplification of the Oggt1 promoter region. The Nrf2 bands reflect Nrf2 binding to the Oggt1 promoter.
8-OHdG, in the exposed cells, whereas only 17 arbitrary units were found in the control HaCaT cells. However, cell pretreatment with 10 μM PG for 1 h before UVB exposure resulted in the production of 25 arbitrary units of 8-OHdG (Fig. 1B). On the basis of these results, we concluded that pretreatment with PG reduced the amount of 8-OHdG and attenuated UVB-induced oxidative stress in HaCaT cells.

**Phloroglucinol restored Ogg1 activity in cells exposed to UVB**

Exposure of HaCaT cells to UVB significantly reduced the Ogg1 activity (Fig. 2A). In cells that were only exposed to UVB, the FITC fluorescence was significantly reduced to 2.1 foci per cell. However, when PG treatment preceded the UVB exposure, the Ogg1 activity increased to 3.2 foci per cell (Fig. 2A). The fluorescence emission of beacon-transfected cells containing 8-oxoG was analyzed by flow cytometry (Fig. 2B).

In the control cells, fluorescence emission corresponded to 630 arbitrary units, whereas in the PG-treated cells, 935 arbitrary units of fluorescence were detected. Moreover, UVB exposure substantially reduced the fluorescence (169 arbitrary units) compared to that in the control cells; however, PG pretreatment before UVB radiation yielded 245 arbitrary units. On the basis of these data, it was concluded that UVB exposure reduced Ogg1 activity in HaCaT cells, whereas PG pretreatment restored Ogg1 activity.

**Phloroglucinol increased Ogg1 expression**

Ogg1 transcription was higher (by 2.3-fold) in the PG-treated cells than in the untreated cells (Fig. 3A). Furthermore, Ogg1 transcription was reduced by 50% in the UVB-exposed cells compared to that in the controls; however, pretreatment with PG before UVB exposure substantially restored Ogg1 transcription. As shown in Fig. 3B, the level of Ogg1 mRNA was lower in the UVB-exposed cells than in the control cells, as determined by RT-PCR. However, pretreatment with PG before UVB exposure increased the levels of Ogg1 mRNA compared to that in the cells that had only been exposed to radiation. The results of Ogg1 protein expression analysis were consistent with the above-described findings (Fig. 3C). On the basis of these data, it can be concluded that Ogg1 expression was stimulated by PG pretreatment in the UVB-exposed cells, both at the mRNA and protein levels.

**Phloroglucinol upregulated Nrf2 expression and translocation to the nucleus**

It was reported that the Ogg1 promoter contains a region for the specific binding of Nrf2 transcription factor, and that Ogg1 transcription is controlled by Nrf2 (Dhénaut et al., 2000; Merrill et al., 2002; Singh et al., 2013). The nuclear localization of Nrf2 was significantly reduced in the UVB-exposed cells, compared to that in the control cells, as shown by western blot analysis (Fig. 4A). Notably, the proportion of nuclear Nrf2

![Fig. 5. Phloroglucinol (PG) increases Ogg1 expression via an Akt and Erk signaling-dependent, Nrf2-mediated mechanism. (A) After treatment with 10 μM PG for 1 h, the cells were exposed to 30 mJ/cm2 UVB radiation and incubated for 6 h. The levels of phosphorylated Akt and Erk were analyzed by western blotting. Total Akt and total Erk2 were the loading controls. (B) Western blot analysis of nuclear Nrf2 expression. The cells were transfected with a Nrf2 promoter construct and examined by western blotting. Total TBP served as a loading control.](https://doi.org/10.4062/biomolther.2020.059)

![Fig. 6. Phloroglucinol (PG) protects the cells from the effects of UVB exposure through Akt and Erk signaling. (A-D) Cell viability was determined using the MTT method. *Significantly different from the control cells (p<0.05); **significantly different from the UVB-exposed cells (p<0.05).](https://doi.org/10.4062/biomolther.2020.059)
was significantly restored in UVB-exposed cells that had been pretreated with PG (Fig. 4A). Immunocytochemical analysis with an antibody against Nrf2 yielded similar results (Fig. 4B). To explore the effect of Nrf2 on the level of Ogg1 protein, Ogg1 expression was determined by western blotting in HaCaT cells transfected with siNrf2 and treated with PG. As shown in Fig. 4C, in siNrf2-transfected cells, PG induced the expression of both Nrf2 and Ogg1. However, in siNrf2-transfected cells, PG had no effect on the expression of either proteins. The hybridized nuclear lysates, cross-linked with transcription factor and nucleotide, were immunoprecipitated with Nrf2 antibody and subjected to PCR using primers containing the Nrf2 binding regions in the Ogg1 promoter. The binding of Nrf2 to the Ogg1 promoter was reduced by UVB exposure but restored by cell pretreatment with PG (Fig. 4D). In conclusion, PG pretreatment promoted the nuclear translocation of Nrf2, resulting in increased Nrf2-dependent Ogg1 transcription.

Phloroglucinol promoted Ogg1 expression through an Akt and Erk signaling-dependent, Nrf2-mediated pathway

Akt and Erk are major signal transduction enzymes involved in the protection of cells from oxidative stress via Nrf2 (Luo et al., 2017). Akt and Erk phosphorylation was higher in the UVB-exposed cells pretreated with PG than in those only exposed to radiation (Fig. 5A). To elucidate the upstream events regulating Nrf2/Ogg1 activation, cell pretreatment with an Akt inhibitor (AKTI) or an Erk inhibitor (U0126) was followed by treatment with PG, and then by UVB exposure. Western blot confirmed that the nuclear localization of Nrf2 was reduced by UVB exposure and restored by pretreatment with PG. However, Nrf2 localization to the nucleus was clearly suppressed by treatment with either the Akt or the Erk inhibitor (Fig. 5B). These results indicated that the effect of PG was mediated by Nrf2 and depended on Akt and Erk signaling.

Phloroglucinol preserved the viability in UVB-exposed cells via Akt and Erk signaling

UVB radiation causes cell death by inducing oxidative stress and DNA damage, including 8-oxoG production. To determine the role of the Akt and Erk enzymes in the ameliorating effects of PG in the UVB-exposed cells, we first confirmed the effect of PG on UVB-induced cell damage. PG protected the cells from UVB-induced death (Fig. 6A). However, treatment with the PI3K or Akt inhibitors (LY294002 or Akt inhibitor) prevented the restoration of cell viability by PG in the UVB-exposed cells (Fig. 6B, 6C). Similar results were obtained with the Erk inhibitor (U0126; Fig. 6D). In conclusion, PG preserved the viability of cells exposed to UVB radiation through the activation of the Akt and Erk signaling pathways.

DISCUSSION

Many kinds of phlorotannins have been reported to possess antioxidant properties, as they upregulate antioxidant

![Fig. 7. Schematic diagram of the mechanism by which phloroglucinol prevents UVB-induced oxidative damage via the activation of the Nrf2/Ogg1 signaling pathway. Phloroglucinol induces Akt and Erk phosphorylation, and activated Akt and Erk promote Nrf2 translocation to the nucleus. Nrf2 binds to the Ogg1 promoter, thus increasing Ogg1 expression and activity, which ultimately leads to the removal of UVB-induced 8-oxoG.](www.biomolther.org)
enzymes or directly scavenge ROS or reactive nitrogen species (Shibata et al., 2008; Manandhar et al., 2019). These compounds are also known to protect cells and tissues from other types of stress (e.g., UV radiation or gamma-ray) (Li et al., 2011; Steinhoff et al., 2012). PG, a typical and basic structural phlorotannin, derives from brown algae such as Ecklonia (Shibata et al., 2004). PG exerts a protective action against gamma rays and hydrogen peroxides via the upregulation of antioxidant enzymes, and exhibits ROS scavenging activity in lung fibroblasts, as we previously reported (Kang et al., 2006, 2010). Furthermore, we previously found that PG attenuates UVB-derived oxidative stress and senescence by directly absorbing the UVB radiation and inhibiting the transcription of activator protein-1 in human keratinocytes (Kim et al., 2012; Piao et al., 2012).

8-OxoG is a well-known oxidized guanine DNA base, and oxidative stress may induce its formation in nuclear and mitochondrial DNA (Bruner et al., 2000; de Souza-Pinto et al., 2001). The modification of guanine to 8-oxoG adversely affects DNA preservation. UVB, one of the photons generated from solar light, was reported to induce DNA damage through both indirect and direct mechanisms (Cadet et al., 2015). A typical type of indirect DNA damage induced by UVB exposure is the oxidation of DNA bases, such as that leading to the formation of 8-oxoG. Ogg1, the primary enzyme responsible for 8-oxoG excision, attenuates the genetic mutation oxidized guanine base by exposure of oxidative stresses. Ogg1 activity analyzed with the transfection of 8-oxoG contained beans which could be emitting the fluorescence when they were cut by Ogg1.

In this study, PG showed cytoprotective ability against UVB-induced 8-oxoG formation and oxidative stress, by promoting the expression and activity of the BER enzyme, Ogg1, in human keratinocytes. PG decreased the level of UVB-induced intracellular 8-oxoG and restored Ogg1 activity. Interestingly, the Ogg1 promoter contains a binding region for Nrf2, a transcription factor controlling antioxidant enzymes (Dhénaut et al., 2000; Merrill et al., 2002; Singh et al., 2013). We here demonstrated that UVB exposure suppressed Nrf2 binding to the Ogg1 promoter in HaCaT cells, while pretreatment with PG restored this interaction. It was reported that the activation of PI3K/Akt or Erk induces Nrf2 nuclear translocation or promotes Nrf2 stability, ultimately increasing Nrf2 activity (Wang et al., 2008; Luo et al., 2017). HaCaT cell treatment with PG enhanced Akt and Erk phosphorylation, counteracting the effects of UVB exposure (Fig. 5A). Moreover, Nrf2 silencing prevented PG-induced Ogg1 upregulation (Fig. 4C). Therefore, we concluded that Ogg1 expression was controlled by Nrf2 and that PG protected human HaCaT keratinocytes from UVB-induced oxidative damage by activating the Nrf2/Ogg1 pathway downstream of Akt and Erk signaling (Fig. 7). The protective effect of PG was due to the enhanced activity of the antioxidant enzyme, Ogg1. In vivo experiments will have to be performed to further verify these results. Our data provide an important basis for the development of new effective agents for skin protection.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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