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Phototherapy with blue and green mixed-light is as effective against unconjugated jaundice as blue light and reduces oxidative stress in the Gunn rat model

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ABSTRACT

Objective: Phototherapy using blue light-emitting diodes (LED) is effective against neonatal jaundice. However, green light phototherapy also reduces unconjugated jaundice. We aimed to determine whether mixed blue and green light can relieve jaundice with minimal oxidative stress as effectively as either blue or green light alone in a rat model.

Methods: Gunn rats were exposed to phototherapy with blue (420–520 nm), filtered blue (FB; 440–520 nm without < 440-nm wavelengths, FB50 (half the irradiance of filtered blue), mixed (filtered 50% blue and 50% green), and green (490–590 nm) LED irradiation for 24 h. The effects of phototherapy are expressed as ratios of serum total (TB) and unbound (UB) bilirubin before and after exposure to each LED. Urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) was measured by HPLC before and after exposure to each LED to determine photo-oxidative stress.

Results: Values < 1.00 indicate effective phototherapy. The ratios of TB and UB were decreased to 0.85, 0.89, 1.07, 0.90, and 1.04, and 0.85, 0.94, 0.93, 0.89, and 1.09 after exposure to blue, filtered blue, FB50, and filtered blue mixed with green LED, respectively. In contrast, urinary 8-OHdG increased to 2.03, 1.25, 0.96, 1.36, 1.31, and 1.23 after exposure to blue, filtered blue, FB50, mixed, green LED, and control, indicating side-effects (>1.00), respectively.

Conclusions: Blue plus green phototherapy is as effective as blue phototherapy and it attenuates irradiation-induced oxidative stress.

Practice implications: Combined blue and green spectra might be effective against neonatal hyperbilirubinemia.

1. Introduction

The fact that natural sunlight reduces neonatal jaundice was discovered in 1975 [1]. Cremer and colleagues then investigated the effective range of visible light and determined that bilirubin absorbs sunlight in the blue spectrum *in vitro* [2]. They developed a phototherapy device that emitted blue light superimposed upon white light for clinical applications [1,2]. Thereafter, blue light was considered more effective than white light [3]. Blue fluorescence light without the < 400-nm wavelength at the near ultraviolet end of the spectrum has been applied in Japan. However, a shorter wavelength that might damage cellular DNA [4] was still included in the blue fluorescence device. Thus, a device emitting green fluorescence was developed for phototherapy against jaundice [5,6] and this device has also been applied in Japan to treat neonatal jaundice. Green fluorescent light was initially considered to reduce serum total bilirubin to a level equivalent to that of blue light [5,6].

Durable, blue light-emitting diodes (LED) have recently been used predominantly to reduce electrical power consumption, and phototherapy with blue LED also has proven as effective as the use of blue fluorescent light [7–9].

Our retrospective study at Nara Medical University NICU found that entirely blue light with a narrow spectrum emitted by an LED together with a device emitting broad-spectrum green fluorescence with some blue component similarly mitigated neonatal unconjugated jaundice [10]. However, neither of these devices alone could treat serious jaundice caused by blood type incompatibility or accompanied by sepsis, whereas a combination of both was effective against unconjugated jaundice (unpublished data). In addition, we hypothesized that combined blue and green light might reduce total bilirubin in addition to oxidative stress resulted in on neonates by exposure to powerful blue light. The present study therefore aimed to confirm whether or not

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blue and/or green light emitted by customized LED devices can mitigate unconjugated jaundice in Gunn rats and whether or not various wavelengths impose changes in oxidative stress.

2. Materials and methods

2.1. Animals and environment

The models of unconjugated jaundice comprised 12 four-week-old homozygous male Gunn rats (Slc-j/j) (Nihon SLC Inc., Hamamatsu, Japan) that were acclimated for one week before the next three weeks trials. All experiments including control trials proceeded in the same room. This room was controlled facility at 23 °C and had no windows, and light cycle was controlled at the Laboratory Animal Research Center, Nara Medical University as follows: lights on, 08:00–20:00 h; lights off, 20:00–08:00 h (mimicking an artificial circadian rhythm of night-and-day). And even during phototherapy, we could not change the lighting because of the central control. The Ethics Committee at Nara Medical University approved the study protocol and the animals were handled and maintained according to institutional guidelines (Approval numbers: 10160 and 10489). They always could access to the CE-2CLEA rodent diet (CLEA Japan Inc., Tokyo, Japan) and water *ad libitum*. One of the 12 rats (No.9 rat; Table 1.) died while under anesthesia for shaving and venipuncture at six weeks of age. His data of the 5-weeks-old were involved in this analysis (Table 1.).

2.2. Wavelength and intensity of LED units

The following (P4630) LED units (Ushio Inc., Tokyo, Japan) were custom-built for this study. The wavelength ranges (with peak emissions; color) were 420–520 (450; blue), 440–520 (455; filtered blue: FB), 440–590 (bimodal peak, 455, 515; mixed), and 490–590 (515; green) nm (Fig. 1). The mean energy of light intensity was 669, 671, 336, 671, and 738 μW/cm^2 for the blue, filtered blue, filtered blue at 50% intensity (FB50), mixed, and green LED, respectively. Spectral intensity was obtained by integrating each spectrum as a function of wavelength measured using a calibrated HR4000 spectrometer (Ocean Optics, Dunedin, FL, USA) at a distance of 12.5 cm. During phototherapy, the LED unit was suspended in a canopy 12.5 cm above 3700M071 metabolic cages (Tecniplast, Buguggiate, Italy).

Table 1
Light-emitting diodes and laboratory data at start of phototherapy.
Schedule of phototherapy. Serum TB and UB levels at start of phototherapy and urinary 8-OHdG at 6 h thereafter did not significantly differ among rats (Student's *t*-test). Rat No. 9 died while under anesthesia for shaving and venipuncture at six weeks of age. TB, serum total bilirubin; UB, serum unbound bilirubin.

LED TB, UB and 8-OHdG at start of phototherapy			
Rat no.	5-weeks old	6-weeks old	7-weeks old
1	Green 4.8, 0.75, 628.52	Mixed 4.7, 0.76, 335.99	Filtered blue 4.1, 0.63, 351.32
2	Mixed 5.1, 0.7, 486.26	Filtered blue 5.9, 0.76, 1817.46	Green 4.5,0.74, 827.67
3	Filtered blue 5.4, 0.88, 469.93	Green 5.5,0.78, 643.99	Mixed 4.4, 0.68, 197.65
4	Green 5.2, 0.7, 775.48	Mixed 6.0, 0.93, 633.40	Filtered blue 5.5, 0.80, 388.83
5	Mixed 4.9, 0.7, 453.99	Filtered blue 5.0,0.77, 555.98	Green 5.1, 0.74, 254.95
6	Filtered blue 5.0/0.79: 172.20	Green 5.4/0.85: 163.35	Mixed 5.1/0.79: 161.80
7	Control NT NT 557.17	FB50 4.3, 0.66, 593.56	FB50 4.5,0.82, 868.95
8	FB50 6.2, 0.96, 557.17	Control NT NT 681.42	FB50 5.3, 0.81, insufficient sample volume
9	FB50 4.7, 0.76, insufficient sample volume	Dead	Dead
10	Blue 5.8, 0.89, 472.81	Blue 6.2, 0.90, 492.53	Blue 4.9, 0.82, 364.59
11	Blue 7.2, 1.10, 216.88	Blue 5.4, 0.83, 213.94	Blue 6.1, 0.98, 146.51
12	Control NT NT 598.86	Control NT NT 634.80	Control NT NT 485.96

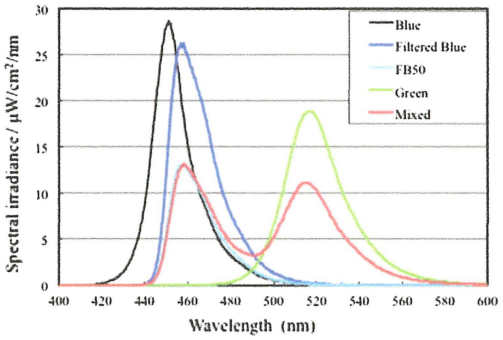
LED, light-emitting diode; NT, not tested; TB (mg/dL), UB (μg/dL); serum obtained by venipuncture at 0 h phototherapy. 8-OHdG (μg/g Creatinine); urine collected between 0–6 h of phototherapy (pre-phototherapy).

2.3. Phototherapy procedures

The flanks and backs of five to seven-week-old Gunn rats weighing 60–170 g were shaved, then blood and urine samples were collected before and after exposure to continuous phototherapy for 24 h. The rats were allowed to breed normally for six days and were then exposed to different wavelengths for 24 h. Phototherapy with blue LED, filtered blue LED, FB50 LED, mixed LED, and green LED was applied to rats bred from the first until the last exposure to phototherapy for three weeks. Control rats were not exposed to illumination. All experiments including control trials proceeded consecutively from 06:00 h to 06:00 h on the following day in the same room and under the light cycle environment that mentioned "Animals and environment". Table 1 shows the phototherapy schedule and the measured parameters (serum total bilirubin (TB), unbound bilirubin (UB), and 8-OHdG; 8-hydroxy-2′-deoxyguanosine) at the start of phototherapy. All rats underwent three 24-h phototherapy sessions. None of the measured parameters were influenced by prior studies (TB: 5 weeks old vs. 6 weeks old, $p = 0.79$; 6 weeks old vs. 7 weeks old, $p = 0.13$; UB: 5 weeks old vs. 6 weeks old, $p = 0.48$; 6 weeks old vs. 7 weeks old, $p = 0.57$; 8-OHdG: 5 weeks old vs. 6 weeks old, $p = 0.38$; 6 weeks old vs. 7 weeks old, $p = 0.20$; Student's *t*-test), confirming that the six-day interval between studies was sufficient.

2.4. Serum total and unbound bilirubin analysis

Concentrations of TB and UB were determined from blood (0.05 mL) collected from tail veins under inhaled isoflurane anesthesia into sodium heparinized micro-hematocrit capillary tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) at 0 and 24 after starting phototherapy. Serum was immediately separated by centrifugation for 5 min at 11,800 ×*g* (Kubota Corp., Tokyo, Japan) and then TB and UB were



		Blue	Filtered Blue	FB 50	Mixed	Green
Total irradiance	(/μW/cm²)	669	671	336	738	671
Wavelength	(nm)	420-520	440-520	440-520	440-590	490-590
Peak wavelength	(nm)	450	455	455	455, 515	515

Fig. 1. Emission spectra of light-emitting diode (LED) devices used for phototherapy. Irradiance of each device was adjusted to minimize differences except for FB50 which was filtered blue light with 50% intensity achieved by omitting wavelengths < 440 nm. Mixed refers to LED device comprising half filtered blue and half green lamps and it has bimodal peak.

measured using the peroxidase oxidation method [11] using a UB A1 Analyzer (Arrows Co. Ltd., Osaka, Japan).

2.5. Urinary 8-OHdG measurements

The oxidatively damaged nucleoside, 8-hydroxy-2′-deoxyguanosine (8-OHdG), might be a repair product of DNA or the nucleoside pool. It is excreted in urine without undergoing further metabolism and being chemically quite stable [12]. It has been widely used as a marker of oxidative stress *in vivo*.

We evaluated whether phototherapy causes oxidative damage to DNA by comparing levels of 8-OHdG in urine from rats that were exposed to phototherapy and from control rats that were not ($n = 5$). Urine collected from chambers installed in the metabolic cages at 6 h (pre-sample; during 0–6 h of phototherapy) and 24 h (post-sample; during 12–24 h of phototherapy) were stored at −80 °C. Urine samples (1.5 mL) were thawed and clarified by centrifugation at 1870 ×*g* (Hitachi Koki Co., Ltd., Tokyo, Japan) for 10 min. Ascorbic acid and anionic species were removed from supernatants (0.9 mL) using a US-001 8-OHdG pretreatment kit (Tanita Corp., Tokyo, Japan) [13,14]. Urinary 8-OHdG concentrations were determined by electrochemical high-performance liquid chromatography (HPLC) detection using Develosil C_{30}^{TM} (Nomura Chemical Co. Ltd., Tokyo, Japan) column-switching and an LC-10A HPLC system (Shimadzu Corp., Kyoto, Japan). The column for the HPLC analysis of 8-OHdG and the guard column were 5 μm (4.6 × 250 mm) and 3 μm (1.0 × 4.0 mm) in size, respectively. The flow rate was 1.0 mL/min, and 15 μL was injected into the HPLC system. Urinary creatinine concentrations were simultaneously determined using enzyme assays (0.1 mL). The 8-OHdG concentrations in urine samples are expressed as μg/g creatinine.

2.6. Evaluation of phototherapeutic effects

The effects of phototherapy are expressed as ratios of pre- and post-phototherapy TB and UB values. Adverse effects of phototherapy were evaluated as an increase of > 1.0 in the ratio of urinary 8-OHdG after correction for creatinine.

2.7. Statistical analysis

Data were statistically analyzed by Student's *t*-test and the Mann–Whitney *U* test using StatFlex ver. 6 for Japanese Windows (Artec Inc., Osaka, Japan). Data in Figs. 2–3 are presented as medians ± standard error. The level of significance was set at $p < 0.05$.

3. Results

Twelve Gunn rats were exposed to 29 sessions of phototherapy (Table 1) using blue ($n = 6$), filtered blue ($n = 6$), FB50 ($n = 5$), mixed ($n = 6$), and green ($n = 6$) LED. The control group for urinary 8-OHdG measurements comprised five rats. Body weight, water intake, urinary excretion during phototherapy (data not shown), serum TB and UB at the start of phototherapy, and urinary 8-OHdG at 6 h after phototherapy did not significantly differ among the rats (TB: 5 weeks old vs. 6 weeks old, $p = 0.79$; 6 weeks old vs. 7 weeks old, $p = 0.13$; UB: 5 weeks old vs. 6 weeks old, $p = 0.48$; 6 weeks old vs. 7 weeks old, $p = 0.57$; 8-OHdG: 5 weeks old vs. 6 weeks old, $p = 0.38$; 6 weeks old vs. 7 weeks old, $p = 0.20$; Student's *t*-test). Values for 8-OHdG, TB, and UB measured one week before and immediately after phototherapy did not significantly differ (Student's *t*-test), confirming that the interval between studies was sufficient.

3.1. Effects of phototherapy on TB and UB

Fig. 2 shows that the ratio of pre- and post-phototherapy TB did not differ after exposure to green LED, but was significantly more decreased after phototherapy with filtered blue ($p < 0.01$), mixed ($p < 0.01$), and blue ($p < 0.05$) than with green LED light. The UB levels were also significantly reduced after phototherapy with blue and mixed than with green LED light ($p < 0.01$).

3.2. Urinary 8-OHdG levels

The rate of the increase in urinary 8-OHdG levels was highest after exposure to blue LED (Fig. 3), whereas filtered blue light did not significantly affect these levels. Urinary 8-OHdG levels were higher after phototherapy with blue LED compared with controls ($p < 0.01$), FB50, mixed and green LED ($p < 0.05$).

4. Discussion

We confirmed that phototherapy using blue and filtered blue LED decreases serum bilirubin levels. In contrast, green LED did not effectively reduce these levels, although the peak wavelength of green LED was shifted only 50 nm towards the longer wavelength than those of the blue and filtered blue LED. Nevertheless, in this study, the curative effects of mixed FB50 LED (low mitigating effect at half the intensity) plus half the intensity of green LED (completely ineffective) were notably equivalent effects of the blue and filtered blue LED. It seemed that green light drew the ability of blue light to reduce serum bilirubin. We considered that this phenomenon was associated with the applied spectrum and photo-isomerization to bilirubin. The insoluble natural bilirubin isomer ZZ-bilirubin, reversibly changes upon exposure to blue light near 450 nm, to ZE- and EZ-bilirubin that are water-soluble, geometric photoisomers that promptly and irreversibly change to the structural photoisomer EZ-cyclobilirubin (lumirubin). This photoisomer is mostly excreted in the urine and stools of human neonates. In addition, this reaction is promoted by green light irradiation at around 510 nm [15]. Although Gunn rats mainly excrete ZE-bilirubin, they also produce and excrete lumirubin [16].

We previously found that green fluorescence emitted by a lamp mitigates jaundice, whereas the green LED in the present study did not. The total irradiance of the green fluorescence emitted by the lamp comprised 10% blue light (400–480 nm), whereas that of the green LED was 490–590 nm, with a peak at 515 nm, and no emissions were near 450 nm. We surmised that the mixed LED reduced jaundice through a similar mechanism as the green fluorescence lamp. That is, the blue portion of the visible spectrum (around 450 nm) must be included for phototherapy units to be clinically functional.

We considered that the mixed LED comprising a filtered blue (low mitigating effect at half the intensity) and green (completely ineffective) LED was effective because photoisomerization of the geometric photoisomers ZE- and EZ-bilirubin elicited by blue light changed to the irreversible structural photo-isomer, lumirubin and was easily excreted.

We measured urinary 8-OHdG, a marker of oxidation status as a side effect of phototherapy. Previous findings have indicated that exposure to near-ultraviolet light (400–450 nm) causes DNA strands to break and the generation of toxic photoproducts [17–19]. Therefore, we prepared a filtered blue LED device without near-ultraviolet light spectra < 440 nm and a device emitting blue-light that included spectra < 440 nm. Although the rate at which urinary 8-OHdG increased did not significantly differ between these blue devices, the median of the blue LED device was about 1.5-fold higher than that of the filtered blue LED device. Moreover, the blue LED elicited a high oxidative stress reaction that significantly differed between exposure to FB50, mixed, and green ($p < 0.05$) LED and the control ($p < 0.01$).

In addition, the different wavelengths and irradiance generated these results, and they were not associated with differences among individuals or ages (data not shown).

The present study confirmed that simultaneous phototherapy with blue and green light can mitigate jaundice in a manner similar to that

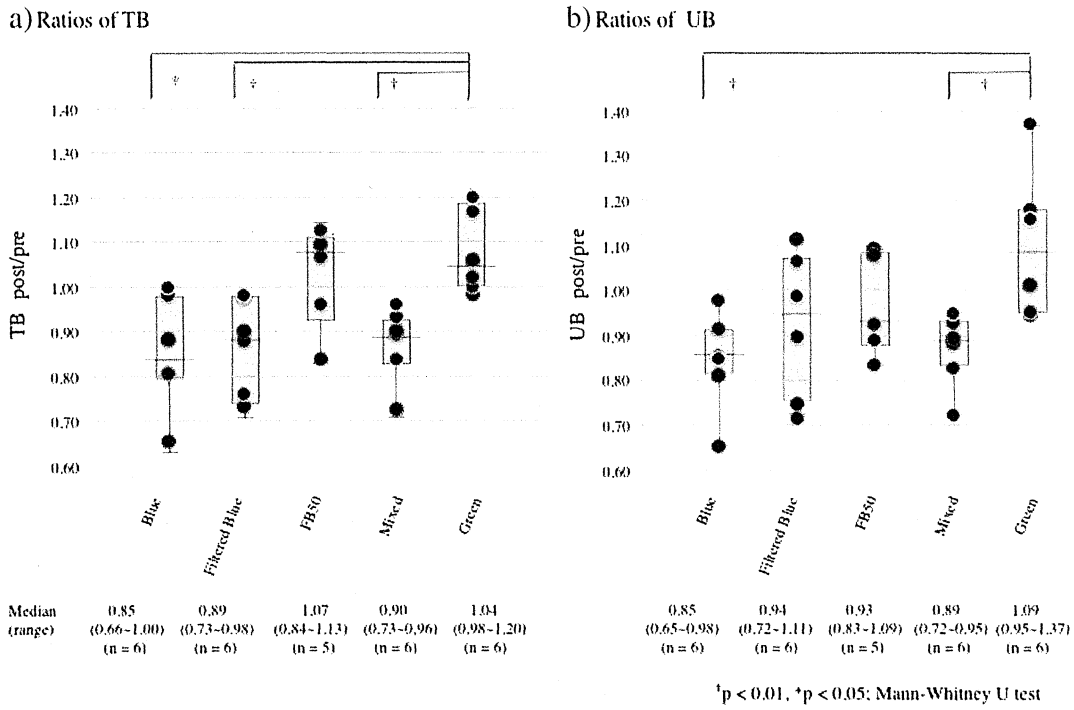


Fig. 2. Effects of phototherapy on total (TB) and unbound (UB) bilirubin. Blue; No.10 and No.11 (5–7 weeks-old), filtered blue; No.3 and No.6 (5 weeks-old), No.2 and No.5 (6 weeks-old), No.1 and No.4 (7 weeks-old), FB50; No.8 and No.9 (5 weeks-old), No.7 (6 weeks-old), No.7 and No.8 (7 weeks-old), mixed; No.2 and No.5 (5 weeks-old), No.1 and No.4 (6 weeks-old), No.3 and No.6 (7 weeks-old), and green; No.1 and No.4 (5 weeks-old), No.3 and No.6 (6 weeks-old), No.2 and No.5 (7 weeks-old). a) Illumination with blue, filtered blue, and mixed light-emitting diodes (LED) significantly reduced TB compared with green LED, $^{*}p < 0.05$; $^{\dagger}p < 0.01$ (Mann–Whitney *U* test). b) Blue and mixed LED phototherapy significantly reduced UB and TB ratio compared with green LED phototherapy.

of blue light alone, without raising total intensity, and that simultaneous phototherapy at two wavelengths might reduce oxidative stress. We also reconfirmed that although phototherapy with blue light has therapeutic value, irradiation with light at the near-ultraviolet end of the spectrum should be excluded.

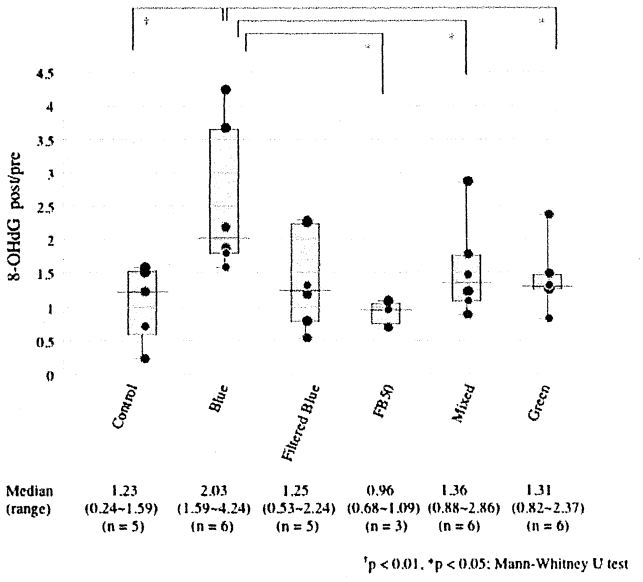


Fig. 3. Ratios of urinary 8-OHdG before and after phototherapy. Control; No.7 and No.12 (5 weeks-old), No.8 and No.12 (6 weeks-old), No.12 (7 weeks-old), Blue; No.10 and No.11 (5 ~ 7 weeks-old), filtered blue; No.3 and No.6 (5 weeks-old), No.2 and No.5 (6 weeks-old), No.1 and No.4 (7 weeks-old), FB50; No.8 (5 weeks-old), No.7 (6 weeks-old), No.7 (7 weeks-old), mixed; No.2 and No.5 (5 weeks-old), No.1 and No.4 (6 weeks-old), No.3 and No.6 (7 weeks-old), and green; No.1 and No.4 (5 weeks-old), No.3 and No.6 (6 weeks-old), No.2 and No.5 (7 weeks-old). Ratios were higher after phototherapy with blue LED, than with all other types of light except for filtered blue LED, $^{*}p < 0.05$; $^{\dagger}p < 0.01$ (Mann–Whitney *U* test). 8-OHdG, urinary 8-hydroxy-2′-deoxyguanosine.

Far more premature neonates are treated by phototherapy today than during the 1980s when it was initially applied. Tyson and colleagues have recently reported that aggressive phototherapy increases mortality while decreasing profound impairment among the smallest and sickest newborns [20]. In addition, excessive phototherapy should be avoided because bilirubin itself has anti-oxidant effects. Bilirubin is known to be an anti-oxidant; assessment of this characteristic and possible effects on 8-OHdG were beyond the scope of this study. Our study strongly suggests that additional assessment of different wavelengths for phototherapy in human neonates may prove beneficial.

Conflict of interest statement

None of the authors has financial and personal relationships with other individuals or organizations that could inappropriately influence this work, or potential conflicts of interest including employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other sources of funding.

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