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Effects and Action Mechanisms of Korean Pear (*Pyrus pyrifolia cv. Shingo*) on Alcohol Detoxification

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Korean pear (*Pyrus pyrifolia cv. Shingo*) has been used as a traditional medicine for alleviating alcohol hangover. However, scientific evidence for its effectiveness or mechanism is not clearly established. To investigate its mechanism of alcohol detoxification, both *in vitro* and *in vivo* studies were performed with an aldehyde dehydrogenase 2 (*ALDH2*) alternated animal model. The pear extract (10 mL/kg bw) was administered to *Aldh2* normal (C57BL/6) and deficient (*Aldh2* –/–) male mice. After 30 min, ethanol (1 g or 2 g/kg bw) was administered to the mice via gavage. Levels of alcohol and acetaldehyde in blood were quantified by GC/MS. First, it was observed that the pears stimulated both alcohol dehydrogenase (ADH) and ALDH activities by 2~3- and 1.3-fold in *in vitro* studies, respectively. Second, mouse PK data (AUC_{∞} and C_{max}) showed that the pear extract decreased the alcohol level in blood regardless of ALDH2 genotype. Third, the pear increased the acetaldehyde level in blood in *Aldh2* deficient mice but not in *Aldh2* normal mice. Therefore, the consistent *in vitro* and *in vivo* data suggest that Korean pears stimulate the two key alcohol-metabolizing enzymes. These stimulations could be the main mechanism of the Korean pear for alcohol detoxification. Finally, the results suggest that polymorphisms of human *ALDH2* could bring out individual variations in the effects of Korean pear on alcohol detoxification. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: pear; alcohol; ADH; ALDH; gene knockout mice; detoxification.

INTRODUCTION

Environmental diseases can be preventable through the regulation of environmental toxicants or lifestyle improvement. In particular, chemopreventive approaches with food have been recognized as an effective individual effort to protect against environmental diseases. In addition, advances of pharmacogenetics or pharmacogenomics lead chemopreventive approaches for personalized protection from toxicants.

Alcohol drinking often causes alcohol hangover symptoms, such as headache, fatigue, diarrhea, dizziness, muscle pain, cerebral vascular diseases, accidents violence and increased risk for cancer mortality. Serial alcohol hangover may be induced from alcohol-induced electrolyte imbalance, hypoglycemia, dehydration or gastrointestinal disturbances (Swift and Davidson, 1998). To alleviate these symptoms, various agents, such as teas, seeds and vegetables, for the prevention and/or treatment for alcohol hangover are traditionally used and proposed (Table 1). These studies investigated mechanisms of the candidates, such as antioxidative effects for alcohol-induced oxidative stress, inhibition of alcohol absorption with chemical binding and stimulation of alcohol metabolism or elimination (Table 1). However, there is no compelling evidence reported suggesting that any conventional or complementary intervention is effective for preventing or treating alcohol hangover from all randomized controlled trials (Pittler *et al*., 2005). Thus, ideal agents for alcohol hangover are still in demand and should demonstrate alcohol detoxification with strong scientific evidence.

Korean pear (*Pyrus pyrifolia cv. Shingo*) has been used as a traditional medicine for alcohol hangover in Korea. It is large (approximately 700 g/each) and round, and contains high contents of water, compared with Western pears. The composition of the major components of Korean pear, i.e. water, fiber, potassium and calcium, is different from that of Western pear (Table 2, RDA; USDA; Zhang *et al*., 2003). Regarding functional components, Korean pear retains approximately 5 and 0.5 μmol/g of dry weight of total phenols and flavonoids, respectively (Hong, 2005). The flavonoids include catechin, rutin, quercetin and kaempferol. Moreover, the peel of Korean pears contained 7- and 10-fold higher levels of total phenols (35 μmol/g) and flavonoids (9.5 μmol/g) than those in the flesh, respectively. The protective effects of the pears against alcohol hangover in a human trial were reported (Yang and Park, 2010). However, protective mechanisms of the pears have not been established completely on alcohol hangover or intoxification.

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Table 1. Previous chemoprevention studies for alcohol intoxification

Mechanism	Materials	Methods	References
Stimulation of antioxidant enzymes	Barley, ginseng, green tea, asparagus, beta-carotene, Evodiae fructus extracts, Fenugreek seeds	Animal experiment (mice or rats)	Giriwono *et al.*, 2010; Li *et al.*, 2010; Wojciech *et al.*, 2010; Kim *et al.*, 2009; Lin *et al.*, 2009; Cho *et al.*, 2005; Thirunavukkarasu *et al.*, 2003
Reduced systemic absorption of alcohol	Combined aqueous extracts of *Gingko biloba*, *Mentha arvensis* var. *piperascens*, *Citrus unshiu*, and *Pueraria lobata* var. *chinensis*	Animal PK study (rats)	Shin *et al.*, 2005
Stimulation of ADH and ALDH	Asparagus, Evodiae fructus extracts, glycerate	*In vitro* (HepG2 cells); Animal experiments (rats)	Kim *et al.*, 2009; Cho *et al.*, 2005; Eriksson *et al.*, 2007
Acceleration of alcohol elimination	Fructose	Human trial	Uzuegbu and Onyesom, 2009
Reduction of C-reactive protein (inflammation)	*Opuntia ficus indica*	Human trial	Wiese *et al.*, 2004
Chemical binding to acetaldehyde	Cysteine	Human trial	Salaspuro *et al.*, 2002

Table 2. Comparison of major components between Korean pears and western pears

Amount per 100 g of pear	Korean pears	Western pears
Water (g)	88.4	83.7
Carbohydrate (g)	10.9	15.4
Total dietary fiber (g)	1.8	3.1
Total sugar (g)	11.7	9.8
Fructose (g)	6.0	6.23
Protein (g)	0.3	0.5
Fat (g)	0.1	0.2
Minerals		
Potassium (mg)	171.0	119
Calcium (mg)	2	9
Vitamins		
Vitamin C (mg)	4.0	4.2

Based on RDA site and Zhang *et al*. (2003) for Korean pears and USDA site for Western pear, Bartlett (*Pyrus communis*).

Genetic variations in alcohol metabolic enzymes may affect individual susceptibility to alcohol toxicity. Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are known as the key enzymes for alcohol metabolism and as enzymes with genetic polymorphisms (Eng *et al.*, 2007). Many East Asians experience severe hangover symptoms, which may, in part, result from their high susceptibility to alcohol due to genetic variations in *ADH* and *ALDH*. Therefore, numerous commercial products have been developed in the Asian markets for the treatment of alcohol hangover. However, most products for alcohol hangover have been developed without scientific evidence on the mechanisms of alcohol detoxification.

Aldh2 targeted animals, i.e. *Aldh2* knockout (*Aldh2* −/−) mice, have been developed for extrapolation to humans (Isse *et al.*, 2002). The *Aldh2* −/− mice have a stop codon in the inserted phosphoglycerate kinase promoter gene after exon 3. A deficiency in mRNA, protein and mitochondrial oxidation activity of ALDH2 was detected (Kitagawa *et al.*, 2000). Therefore, this mouse model is useful for investigation of *ALDH2* deficient diseases and the development of alcohol hangover treatment.

This study focused on the two key enzymes for alcohol detoxification, ADH and ALDH, and investigated the effects and mechanisms of Korean pear on alcohol metabolism with *in vitro* and *in vivo* pharmacokinetic approaches.

MATERIALS AND METHODS

Sample preparation. Korean pears were obtained from the Seoul Horticultural Cooperative (Seoul, S. Korea). The pears (≈700 g/pear) were rinsed with distilled water, allowed to air dry and cut into eight pieces of equal mass (each piece, ≈ 85–90 g). Pear extracts from the pear pieces were prepared using an expeller type juicer (NJE-2005SY, NUC, Daegu, S. Korea). The pear extracts were filtered with Whatman filter paper No. 2 (Maidstone, England) and vacuum packed in 110 mL polyethylene bags. The samples were kept at −20 °C until the experiments.

Analyses of ADH and ALDH activities. The effects of the pears on ADH activity were analysed as described by Itoh *et al*. with minor modifications (1997). First, the linearity of the ADH activity was obtained *in vitro* and the optimal condition for the analysis of ADH activity established. The reaction mixture consisted of 0.06 M of glycine-HCl buffer (pH 10), 0.2U of ADH (A7011, Sigma-Aldrich Co, St Louis, MI) in 0.1% of bovine serum albumin (BSA) (Promega, Madison, WI), 0.5% of Triton X-100, 4 mM of NAD^+ and 10–80 μL of the pear extracts in a final volume of 1 mL. After preincubation at 25 °C for 3 min without ethanol, the mixture was incubated with the addition of 12.5 mM of ethanol. The incubation was carried out at 25 °C for 5 min. The reduction of NAD^+ into NADH was measured at 340 nm with a UV/VIS spectrophotometer (Ultrospec 2000, Pharmacia, Cambridge, England).

The effects of the pear extracts on ALDH activity were evaluated by the method of Itoh *et al.* (1997). The reaction mixture consisted of 0.05 M of sodium-potassium phosphate buffer (pH 7.4), 0.9 U of ALDH (A6338,

Sigma) in 0.1% of BSA, 0.05 M of pyrazole, 0.5% of Triton X-100, 3 mM of $MgCl_2$, 6 mM of NAD^+ and 20–80 μL of the pear extracts in a final volume of 1 mL. After pre-incubation at 25 °C for 3 min, the reaction was initiated by adding 50 mM of acetaldehyde. The incubations were carried out at 25 °C for 5 min and the bio-produced NADH was measured.

To rule out potential yeast- or bacterial-induced artifacts, the measurements of NAD^+ reduction were corrected by subtracting values of the baseline responses, which were observed in the absence of ethanol.

Animals. The *Aldh2*^{tm1kaw}/*Aldh2*^{tm1kaw} (*Aldh2* −/−) mice were maintained from the C57BL/6 strain. They were backcrossed with C57BL/6 for more than ten generations (Isse *et al*., 2002). Ten to twelve week-old male *Aldh2* +/+ and *Aldh2* −/− mice were housed in plastic cages in an air-conditioned room (23–25 °C) under a 12 h light/dark cycle. Prior to the treatment, the animals were fasted overnight without wood chip bedding, but were allowed free access to the water in cages. The animals were treated according to the guidelines of the Ethics Committee of Animal Care and Experimentation, University of Occupational and Environmental Health, Japan.

Animal treatments. Due to different analytical detection limits of ethanol and acetaldehyde in GC/MS, the mice were treated with two different alcohol concentrations.

For ethanol analysis, *Aldh2* +/+ and *Aldh2* −/− mice ($n = 16$, 22.86 ± 0.83 g; $n = 24$, 23.45 ± 3.15 g, respectively) were fasted overnight and divided into two groups: controls and pear-treated. Initially, the pear extracts (10 mL/kg bw, ≈ a pear for a person, i.e. 700 g/60 kg bw) or an equivalent volume of water was administered to the treatment group or the controls, respectively. After 30 min, 1 g of ethanol/kg bw (≈ average volume of alcohol intake of S. Korean adults) was administered to mice via gavage. Six to eight mice were in the treated group. All experiments were performed in duplicate.

For analyses of acetaldehyde, 2 g of ethanol/kg bw was administered to *Aldh2* +/+ ($n = 8$, 20.97 ± 2.43 g) and *Aldh2* −/− mice ($n = 16$, 20.58 ± 0.78 g) via gavage after with or without pear treatment. The mice were anesthetized with ketamine (100 mg/kg bw) and xylazine (20 mg/kg bw) by intraperitoneal injection.

GS/MS analyses of ethanol and acetaldehyde. For serum ethanol measurement, 3 μL of the blood was collected from the tail vein using an ice-cold syringe and transferred into 1.7 mL of ice-cold 0.6 N perchloric acid (PCA) solution. The PCA solution containing the blood samples was centrifuged ($4000 \times \mathbf{g}$) at 4 °C for 10 min. Half ml of the supernatant were collected in 10 mL of gas-tight vials with caps. Quantification of ethanol and acetaldehyde by GC/MS were performed according to the method described by Isse *et al*. (2005): the samples were placed in a heating block at 65 °C for 10 min. The headspace gas was transferred via a headspace sampler (Hewlett-Packard 7694, Wilmington, DE) to a GC (Hewlett-Packard 6890, Wilmington, DE) connected to a MS (JOEL JMS-BU20, Tokyo, Japan). Ethanol and other components were separated on a 60 m × 0.25 mm inner diameter Aquatic capillary column (GL Sciences, Tokyo, Japan) with a 1.0 μm film thickness. The injection port temperature was 200 °C. The column oven temperature was programmed to increase from 40 to 50 °C at a rate of 2 °C/min and from 50 °C to 170 °C at a rate of 40 °C/min. For ethanol measurement, the flow rate of the carrier gas (helium) was 1.0 mL/min (split ratio 5:1) and electron impact ionization was performed at 70 eV.

For acetaldehyde analysis, 300 μL of the blood was collected from a right atrium and transferred into 1.7 mL of 0.6 N ice-cold PCA solution. The flow rate of the carrier gas was 1.0 mL/min (split ratio 10:1), and electron impact ionization was performed at 300 eV. Each injection was analysed with a selected ion monitoring method: at *m*/*z* 45 and 46 for ethanol; at *m*/*z* 43 and 29 for acetaldehyde.

Statistical analyses. Pharmacokinetic (PK) parameters, i.e. AUC_∞, T_{max} and C_{max}, were calculated with the Bioavailability Analysis Program (BA Calc 2002, Seoul National University, Seoul, S. Korea). Data were expressed as the mean with standard deviation (STD) and $p < 0.05$ was considered statistically significant.

After verifying a normal distribution, the Student's *t*- or Wilcoxon-test was used to compare ADH and ALDH activities, area under the curve (AUC_∞) of blood ethanol and acetaldehyde levels between the control and the pear-treated groups. Regression analyses were used to estimate correlations between the pear treatment and ADH or ALDH responses on alcohol treatment. Changes in blood alcohol during the experiment period were compared between the control and the pear groups using repeated ANOVA. All statistical analyses were performed using the SPSS statistical software 11.5.0 (SPSS Inc., Chicago, USA).

RESULTS

Effects of Korean pear on ADH and ALDH activity

In vitro studies were performed to evaluate the impact of Korean pear on the two key enzymes of alcohol metabolism, i.e. ADH and ALDH. The pear treatment increased ADH (R^2, 0.57; $p < 0.01$ by regression analysis: Fig. 1) and ALDH (R^2, 0.45; $p < 0.05$: Fig.1) activities.

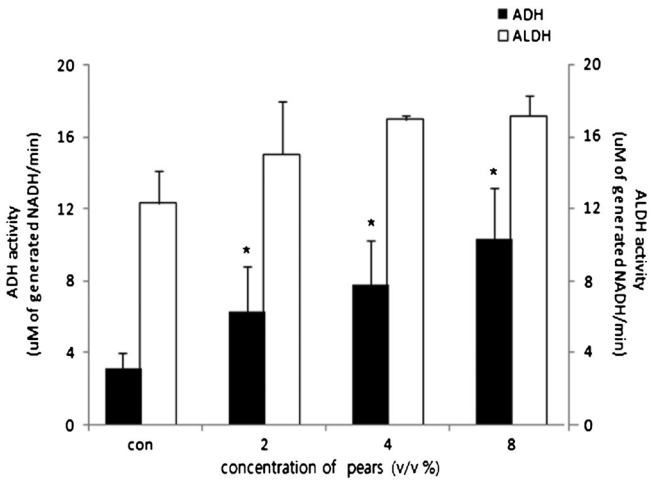

Figure 1. Effects of the pear treatment on ADH and ALDH activities in ($n = 5$ for each concentration): ADH and ALDH activities were adjusted for baselines, i.e. the condition without ethanol: con., controls. *Significant difference of ADH activities was observed between control vs treated groups ($p < 0.05$).

While ALDH activities were increased approximately 30% compared with the control group, ADH activities were induced 2–3 fold in a dose dependent manner.

Effects of Korean pear on the level of blood alcohol

The pear treatment reduced the level of blood ethanol in both *aldh+/+* and *aldh−/−* mouse groups. These reductions were more evident in the *Aldh2* −/− mice (Table 3). The AUC_{∞} and C_{max} of blood alcohol were decreased significantly in the pear-treated group, particularly in the *Aldh2*−/− mice (controls vs pears, 16.26 ± 1.90 mM vs 11.2 ± 2.43 mM: $p < 0.05$). However, there was no difference in the T_{max} between the pear treatment and the control groups, regardless of *Aldh2* genotype. As T_{max} reflects the time that the rates of absorption and elimination are equal, the decrease of AUC_{∞} and C_{max} by the pear treatment appears to be contributed by a combination of absorption, elimination and metabolism of alcohol. The pear treatment showed different patterns of elimination of blood alcohol between the *Aldh2* −/− and *Aldh2* +/+ mice ($p = 0.03$ and $p = 0.12$, respectively).

Impacts of ALDH genotype in alcohol metabolism

Approximately 2-fold higher alcohol and 7-fold higher acetaldehyde levels in blood were observed in *Aldh2*−/− animals compared with those in *Aldh2*+/+ animals ($p < 0.01$: Table 3, 4). It reflects that excessive accumulation of acetaldehyde in *Aldh2*−/− mice was caused by the delay in alcohol metabolism compared with *Aldh2*+/+ mice. These results are consistent with Isse *et al.* (2005). Thus, an 'interaction between genetic factors and foods' was observed. Individual differences in the response to pear treatment for detoxification of alcohol is expected to be due to genetic variations of *ALDH2*.

DISCUSSION

The study demonstrated that the pear treatment stimulated ADH or ALDH activities in *in vitro* studies. In addition, the *in vivo* study showed a decrease in alcohol level in blood after the pear treatment. This implies that the pear treatment activated alcohol metabolism, inhibited alcohol absorption and/or the acceleration of alcohol/aldehyde elimination due to metabolic stimulation.

The peak level of blood acetaldehyde after alcohol treatment is known to be between 0.5 and 1 h from the previous report (Isse *et al.*, 2005). The present analysis of peak level showed that the pear treatment induced different trends in acetaldehyde levels between different ALDH2 genotypes (Table 4); the pear treatment significantly increased acetaldehyde levels in the *Aldh2* −/− mice, but not in the *Aldh2* +/+ mice. Thus, the *Aldh2* −/− mice showed the pear-stimulation of ADH from the pear-induced acetaldehyde in the *ALDH2*-blocked condition. In addition, we expect the pear-involvement of both of ADH and ALDH activity among *Aldh2* normal mice.

Table 3. Alcohol levels in blood with/without pear treatment

Mouse (*n*)	Treatment	Ethanol levels (mM)						
		0 h	0.25 h	0.5 h	1 h	2 h	3 h	AUC_{∞} (mM × h)
Aldh2 +/+ (16)	Control	N.D.	70.29 ± 13.36	78.07 ± 33.77	72.06 ± 57.05	23.54 ± 39.46	3.20 ± 5.94	6902.72 ± 6144.32
	Pear	N.D.	68.98 ± 19.66	72.05 ± 50.36	54.13 ± 54.21[a]	22.68 ± 32.85	1.79 ± 3.34	5974.04 ± 5411.35
Aldh2 −/− (24)	Control	N.D.	122.47 ± 33.37	162.59 ± 19.04	117.70 ± 39.26	57.46 ± 21.20	38.36 ± 18.03	14922.04 ± 3876.30
	Pear	N.D.	94.12 ± 17.62	111.97 ± 24.26[a]	75.28 ± 27.68	52.19 ± 29.63	32.28 ± 15.36	11279.72 ± 3203.15[a]

All values represent mean ± STD.
N.D.: non detectable.
[a] $p < 0.05$: significant decrease, compared with the controls.

Table 4. Interaction between *ALDH2* genotypes and the pear treatment on peak acetaldehyde levels (μM)

Mice (*n*)	Control (12)	Pear treatment (12)	*p* value
Total (24)	49.86 ± 33.37	70.12 ± 48.27	0.16
Aldh2 +/+ (8)	10.64 ± 2.37	9.53 ± 2.56	0.55
Aldh2 −/− (16)	63.88 ± 25.84	100.42 ± 22.61	0.01[a]

[a]Significantly different from controls.

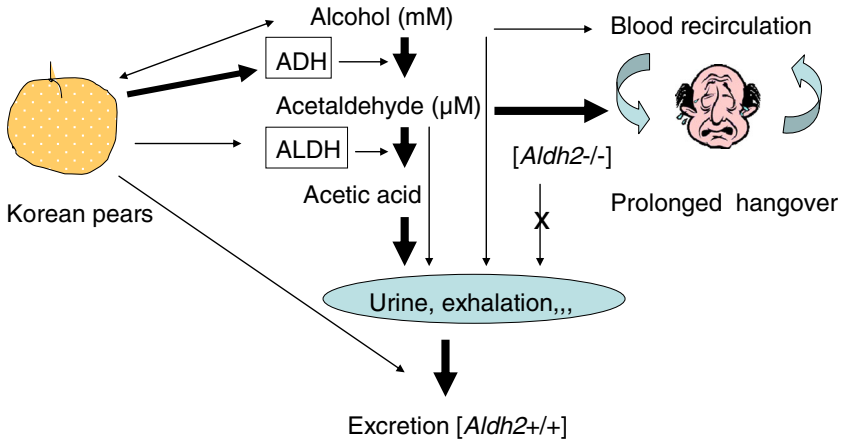

Figure 2. Schematic diagram for potential roles of pears in alcohol detoxification: Korean pear stimulated both ADH and ALDH activities. Alcohol level in blood was decreased due to the pear-stimulated ADH activities and/or elimination. Korean pear may anticipate in decrease of toxic acetaldehyde due to increased ALDH activities in ALDH2 normal individuals: →stimulation; ↔, inhibition. This figure is available in colour online at wileyonlinelibrary.com/journal/ptr.

Shin *et al*. reported that combined aqueous extracts of *Gingko biloba, Mentha arvensis* var. *piperascens, Citrus unshiu* and *Pueraria lobata* var. *chinensis* decreased alcohol levels in blood and reduced *AUC* and $C_{max.}$ They suggested these decreased alcohol levels are the result of a reduced systemic absorption rather than increased elimination (Shin *et al*., 2005). Thiol or polyphenol compounds are expected to inhibit the absorption of alcohol or acetaldehyde via chemical binding to them and lower levels of blood alcohol or acetaldehyde (Salaspuro *et al*., 2002). In addition, dietary fiber such as pectin, which is a main component of the pears, delayed gastric emptying (Sanaka *et al*., 2007) and may decrease blood ethanol (Matsuda *et al*., 2002). Thus, the PK study showed that Korean pear may inhibit alcohol absorption via its abundant fibers or polyphenols and decrease the AUC_{∞} of blood alcohol.

Acetaldehyde is a main toxic metabolite of alcohol and is closely related to alcohol hangover. Over 1000 fold higher levels of alcohol than acetaldehyde in body were estimated (Table 3–4). Thus, not only the elimination of acetaldehyde but also various elimination pathways of alcohol may be contributing factors for alcohol hangover. The potential role of Korean pears for preventing of alcohol hangover are summarized in Fig. 2, based on results from the present study. Considering the components of the pears (Table 2), it is suggested that plenty of water, potassium, fructose and fiber in Korean pear prevents alcohol-induced dehydration, electrolyte imbalance, hypoglycemia or gastrointestinal disturbances to alleviate alcohol-hangover (Table 2).

Additionally, the effects of Korean pear on ADH and ALDH activities were compared in the different parts of Korean pear and it was found that the water soluble part of the peel highly stimulates the enzymes, compared with other parts (Lee, 2009). Thus, highly concentrated components in the peel part, e.g. polyphenols including arbutin or catechin, are expected to be one of the main functional compounds for alcohol detoxification.

There is a potential limitation that should be considered when interpreting these results. Because it was not possible simultaneously to analyse levels of alcohol and acetaldehyde in the blood samples due to 1000-fold different minimum detection levels between acetaldehyde and alcohol, much larger volumes of samples for acetaldehyde analyses were needed than for alcohol analyses. Multiple samples were used to analyse alcohol, however, acetaldehyde analyses were performed at the peak level and did not provide whole PK parameters for acetaldehyde to match with the alcohol-analysed spots.

In summary, it was demonstrated that Korean pear stimulated ADH as well as ALDH activities and decreased blood alcohol. In addition, individual responses to pear treatment on alcohol exposure differ due to the ALDH2 genetic polymorphism.

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Conflict of Interest

The authors have declared that there is no conflict of interest.

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