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ANTI-PARKINSON'S ACTIVITY OF SORAFENIB IN 6-OHDA INDUCED RAT MODEL

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ABSTRACT: Objective: Studies have shown that sorafenib an anti-cancer agent has a neuroprotective effect. This study evaluated the neuroprotective activity of sorafenib in 6-OHDA induced rat model of Parkinson's disease. **Methods:** 6-OHDA was injected into the forebrain bundle through the stereotaxic apparatus to induce fast and severe degeneration in dopaminergic neurons of substantianigra. The animals were divided into four groups. Group I- vehicle control, Group II- 6-OHDA induced, Group III- 6- OHDA + Levodopa (6 mg/kg), Group IV- 6-OHDA + sorafenib (10 mg/kg s.c). Treatment was given for 21 days after induction of 6-OHDA. The animals were subjected to behavioral parameters such as apomorphine-induced rotations, grip strength, catatonia and biochemical parameters such as total protein estimation, reduced glutathione, lipid peroxidase, calcium concentration in the brain. **Results:** Sorafenib significantly decreased the apomorphine-induced rotations as well as catatonia and significantly increased ($p<0.001$) the grip strength when compared to 6-OHDA. In biochemical estimation total protein and glutathione is increased ($p<0.001$). Both lipid peroxidase and calcium level have been decreased significantly ($p<0.001$) when compared to 6. OHDA. **Conclusion:** In the present study, antiparkinson's effect of an LRRK2 inhibitor, sorafenib was evaluated in the 6-OHDA lesioned rat model. Behavioral and biochemical parameters were carried out. The parameters revealed that the LRRK2 inhibitor, sorafenib has shown significant antiparkinson's activity. The estimated parameters altered the normal behavior of the animal and the drug treatment protected the diseased brain of rat.

INTRODUCTION: Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by loss of dopaminergic neurons in the substantianigra and it affects movement, muscle control, balance and numerous other functions [1, 2]. The disease was named after a neurologist James Parkinson who first detailed the disorder and its symptoms during the 19th century. The clinical syndrome consists of four cardinal features: bradykinesia, muscular rigidity, resting tremor and impairment of postural balance [3].

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PD is the second most common neurodegenerative disease after Alzheimer's disease, affecting approximately 1% to 2% of the population older than age 60. PD can occur at any age and for both sexes but mainly a condition of middle-aged or aged people. More than 10 million people have PD across the world [4, 5].

PD is the loss of cells in the substantianigra of the brain, which is responsible for the production of dopamine. This results in the loss of balance between excitatory and inhibitory effects on the brain and makes the nerve cells in this region to be out of control [6]. The increase in the overall excitatory drive in basal ganglia further disrupts the voluntary motor control. This leaves the individual unable to direct or control movement. This leads to the initial symptoms of PD. As the disease progresses, other areas of the brain and nervous

system degenerate, as well as causing a more profound movement disorder [7, 8]. 6-hydroxydopamine (6-OHDA) uses the same catecholamine transport system as do dopamine, leading to specific damage *via* oxidative stress to dopaminergic neurons [9]. Many shreds of evidence suggest that LRRK2 is a crucial factor for understanding the etiology of PD. LRRK2 is a large, widely expressed, multi-domain and multifunctional protein, whose mutations are a major cause of inherited PD [10].

Researches in animal model suggest that the overexpression of LRRK2 in drosophila leads to age-dependent dopamine responsive reduction in locomotor activity and loss of dopamine neurons. Also in a similar manner, overexpression of LRRK2 results in degeneration of dopamine neurons in *C. elegans* [11]. There is a wide pathological spectrum associated with LRRK2 mutations and the same mutations can cause quite diverse neuropathology. Most of the reported cases show pathological characteristics of the presence of lewy bodies, lewy nutritis, and substantianigra neuronal loss. Thus mutations or overexpression in LRRK2 remains as one of the most common pathogenesis for PD [12].

Sorafenib is a kinase inhibitor drug which inhibits several tyrosine-protein kinases such as VEGPR, PDGFR, and Raf family kinase and is also an LRRK2 inhibitor. It is approved for the treatment of primary kidney cancer, advanced primary liver cancer, and radioactive iodine resistant advanced thyroid carcinoma [13]. In this study, sorafenib being an LRRK2 inhibitor is evaluated for its antiparkinson's effect by inhibiting the overexpression or mutation of LRRK2 gene, thus preventing dopamine oxidation and aggregation of unwanted proteins, which can lead to neurodegeneration [14, 15].

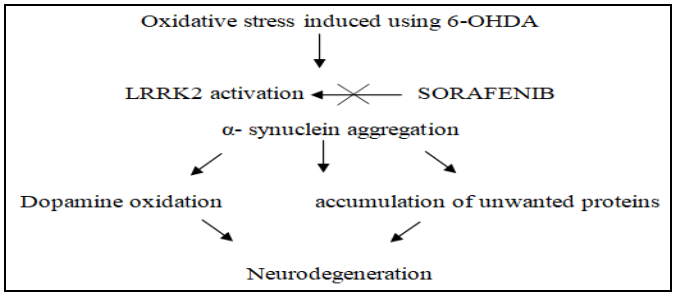

FIG. 1: NEURODEGENERATIVE PATHWAY SORAFENIB

MATERIALS AND METHODS:

Chemicals: The chemicals which were used for the present study were procured from Sigma and Himedia. All other chemicals and reagents used were of analytical grade.

Animals and Experimental Groups: Healthy, male Wistar rats (180-220g) were obtained from Central animal house facility from JSS College of Pharmacy, Ootacamund, Tamil Nadu. The animal was kept in a well-ventilated room and the animals had exposed to 12 h day and night cycle. The animals were housed in large spacious, hygienic polypropylene cages during the course of the experiment period. The animals were fed with water and rat feed *ad libitum*. All the experiments were performed after obtaining prior approval from CPCSEA and IAEC. The animals were housed in suitable environmental conditions. Approval no.: JSSCP/ IAEC/ M.PHARM/PH.COLOGY/05/2016-17). Animals were divided into four groups of six animals each. Group I- vehicle control, Group II- 6-OHDA induced, Group III- 6- OHDA + Levodopa (6 mg/kg), Group IV- 6-OHDA + sorafenib (10 mg/kg s.c). Treatment was given for 21 days after induction of 6-OHDA.

Surgical Procedure: Animal were anesthetized with ketamine (100mg/kg i.p), xylazine (15 mg/kg i.m) and then placed in a stereotaxic apparatus. The scalp was retracted and unilateral holes were drilled in the skull above the injection site. The needle of a 10 µl Hamilton syringe was lowered to the appropriate coordinate [tooth bar: ± 0.0m m; anterior/posterior: -4.8 mm; medial/lateral:- 2.2 mm; ventral/dorsal:- 7.2 mm] were determined from bregma. Injection of 6-OHDA hydrobromide in 4 µl 0.9% saline with 0.02 µg/ml ascorbic acid) was then made over 5 min and the needle was left in place for a further 5 min. 6-OHDA lesions were made in an identical manner except for that vehicle alone was injected. The scalp was then sutured closed by keeping a gel followed by application of neomycin ointment for the proper healing of the wound. All efforts were made to minimize animal pain and suffering [14, 15, 16].

Behavioral Evaluation:

Apomorphine Induced Rotation: Apomorphine induced rotational test was carried out in the three weeks after the lesion. Animals were habituated 5

min before the injection of apomorphine (0.5 mg/kg, s.c). Contralateral rotations were measured. The animal showing at least 7 turns/min in both the tests was included in this study. The animal was observed for 10 min period for counting circling behavior. Contralateral rotations of different groups were compared to control group [17].

Grip Strength: Rotarod apparatus is used to assess the muscle grip strength by testing the ability of rats to remain on the revolving rod. The apparatus has a horizontal rough metal rod of 3 cm diameter attached to a motor with variable speed. The 70 cm long rod was divided into 4 sections. Each rat was given 5 trials at 20 rpm before actual readings were taken. The 'fall of time' was measured and it is compared in treatment group [18].

Catatonia: The major clinical symptom of Parkinson's disease includes difficulty to move and change the posture and tremors. So by this parameter, we could observe the severity of catatonia as followed:

Stage I- Rats moves normally when placed on the table = (score-0). Stage II- Rats moves only when touched/ pushed = (score-0.5). Stage III- Rats placed on the table with front paws set at least on a 3 cm high block fails to correct the posture on 10 sec = (score -0.5 for each paw total=1). Stage IV- Rats fails to remove when front paws are placed alternately on 9 cm block = (score-1 for each paw total-2). Thus for a single rat maximum possible score would be 3.5 revealing total catatonia [19].

Biochemical Evaluation:

Estimation of Total Protein: Extraction of protein from sample-Extraction was carried out with buffer. 500 mg of the brain sample was weighed and homogenized with 5-10 ml of the buffer. Then homogenized was centrifuged and the supernatant was collected. Different dilutions of BSA are prepared (0.05 to 1 mg/ml). From these different dilutions, 0.2 ml was taken in tubes and 2 ml of an alkaline solution of copper sulfate reagent (analytical reagent). These solutions were incubated at room temperature for 10 min. Then 0.1 ml of reagent Folin-Ciocalteau was added to each tube mixed well and incubated for 30 min. The blue color was developed. Absorbance was measured by colorimeter at 660 nm [20, 21].

Estimation of Reduced Glutathione (GSH): GSH is a non-protein compound containing sulphydryl group in its structure. DTNB (5, 5' dithiobis – 2-nitro benzoic acid) is a disulfide chromagen that is reduced by sulphydryl compounds to a yellow-colored compound. The absorbance of the reduced chromagen is measured at 412 nm. The GSH content was calculated as µmol DTNB conjugate formed/mg protein using a molar extinction coefficient of 13.6×10^3 M/cm[22].

Estimation of Lipid Peroxidation: The lipid peroxidation level of the brain was measured as malondialdehyde, which reacts with thiobarbituric acid as thiobarbituric acid reactive substance (TBARS) to produce a red-colored complex that has a peak absorbance (A) at 535 nm. A mixture of trichloroacetic acid, thiobarbituric acid, and HCl was added to 1 ml of homogenate, and the mixture was heated for 45 min in a boiling water bath. After cooling and centrifugation at 500 rpm for 20 min, the absorbance was measured at 535nm. The level of TBARS was calculated by C (M) = absorbance/ 1.65×10^5. [23]

Estimation of the Rat Brain Calcium Level: Calcium level in the brain was a carrier at the end of the study. Brain samples were collected & weighed and dried at 115 °C for 20 h and reweighed. Dry samples were ashed gradual heating up to 550 °C for 24 h. The ash was dissolved in nitric acid to ensure the optimum concentration of analyses for atomic absorption. The concentration of calcium level was determined by atomic absorption spectroscopy [24, 25].

Statistical Analysis: Statistical analysis was performed using Graph pad prism version 6.0 software. All the values were expressed as mean ± standard error mean (SEM). Statistical significance of difference was calculated using ANOVA followed by Bonferroni multiple comparison tests.

RESULTS:

Evaluation of Behavioral Parameters:

Estimation of Apomorphine Induced Rotations: The results given in **Fig. 2** showed that the untreated 6-OHDA group showed an average 10 of contralateral rotations in 10 min, as related to the control group which showed almost no behavioral, alteration after the apomorphine administration.

The treatment group showed a decrease in (0) rotation.

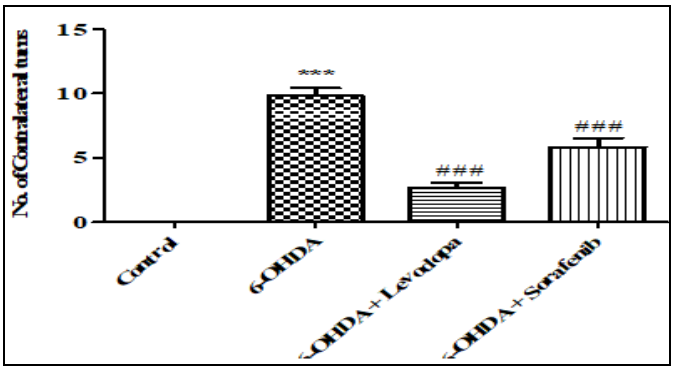

FIG. 2: ESTIMATION OF APOMORPHINE INDUCED ROTATIONS. Values are mean ± SEM; n=6 in each group. ***p<0.001 when compared with the vehicle control group; ### p<0.001 when compared with 6-OHDA control; One-way ANOVA followed by Bonferroni multiple comparison test.

Estimation of Grip Strength: Rotarod result showed the motor co-ordination in rodents which is given in **Fig. 3**. Control group stayed almost all-time in the experiment (120s).

On the other hand, the treatment groups showed a significant increase in the fall of time when compared to the 6-OHDA group (p<0.001).

Estimation of Catatonia Activity: The result given in **Fig. 4** showed that the 6-OHDA group showed a significant increase in catatonia score when compared to the control group (p<0.001).

In comparison with the 6-OHDA group with the treatment, groups showed a significant decrease in catatonia score.

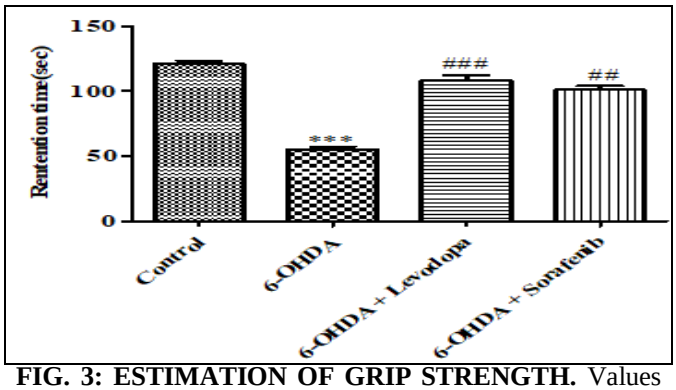

FIG. 3: ESTIMATION OF GRIP STRENGTH. Values are mean ± SEM; n=6 in each group. ***p<0.001 when compared with vehicle control group; ### p<0.001, ## p<0.01, when compared with 6-OHDA control; One-way ANOVA followed by Bonferroni multiple comparisons test.

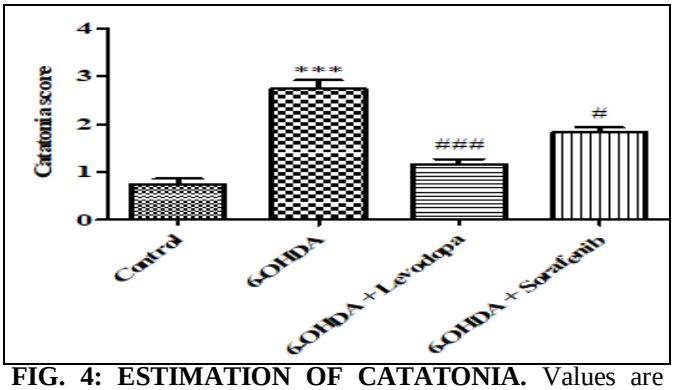

FIG. 4: ESTIMATION OF CATATONIA. Values are mean ± SEM; n=6 in each group. ***p<0.001 when compared with vehicle control group; ### p<0.001, # p<0.05 when compared with 6-OHDA control; One-way ANOVA followed by Bonferroni multiple comparisons test.

Evaluation of Biochemical Parameters:

Estimation of Total Protein: The results of the study are given in **Fig. 5**. Significant reduction in the concentration of protein was observed in the 6-OHDA lesioned group compared to vehicle control (p<0.001). When compared with the 6-OHDA group, the concentration of protein was significantly increased for L-DOPA and sorafenib treated group.

Estimation of Reduced Glutathione: Antioxidant activity was measured by the estimation of reduced glutathione. The result given in **Fig. 6** showed that while comparing with the control group, the 6 - OHDA administered group showed a decrease in glutathione level (p<0.001). Reduced glutathione was significantly increased in the treatment groups when compared to the 6- OHDA group.

Estimation of Lipid Peroxidase: The results of the study are given in **Fig. 7**. A significant increment in the MDA level was observed in the 6-OHDA lesioned group compared to vehicle control (p<0.001).

When compared with the 6-OHDA group, MDA level was significantly decreased for L-DOPA and sorafenib treated group.

Estimation of Calcium Concentration in Rat Brain: The results of the study are given in **Fig. 8**. Significant increase in the calcium level was observed in the 6-OHDA lesioned group compared to vehicle control (p<0.001). When compared with the 6-OHDA group, calcium level was significantly decreased for L-DOPA and sorafenib treated group.

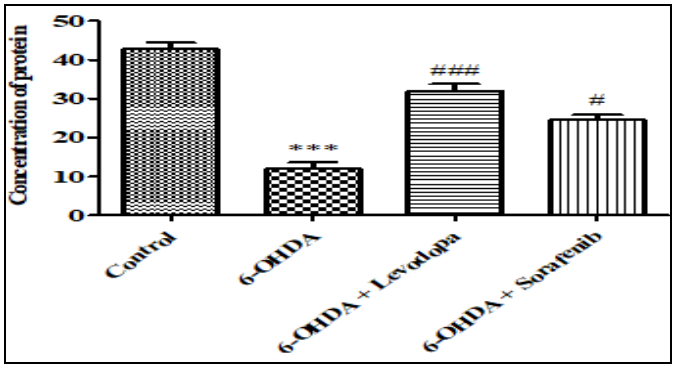

FIG. 5: ESTIMATION OF TOTAL PROTEIN. Values are mean ± SEM; n=6 in each group. Values are mean ± SEM; n=6 in each group. ***p<0.001 when compared with vehicle control group; ### p<0.001 when compared with 6-OHDA control; One-way ANOVA followed by Bonferroni multiple comparisons test.

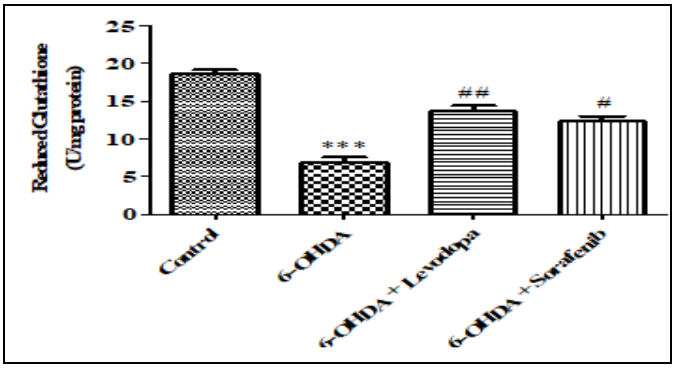

FIG. 6: ESTIMATION OF REDUCED GLUTATHIONE. Values are mean ± SEM; n=6 in each group. ***p<0.001 when compared with vehicle control group; ## p<0.01, # p<0.05 when compared with 6-OHDA control; One-way ANOVA followed by Bonferroni multiple comparisons test.

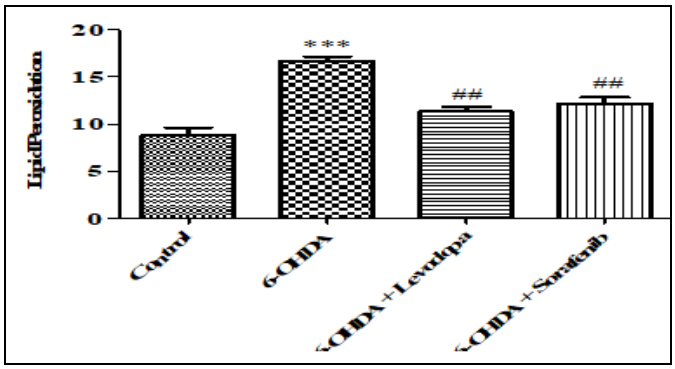

FIG. 7: ESTIMATION OF LIPID PEROXIDASE. Values are mean ± SEM; n=6 in each group. ***p<0.001 when compared with vehicle control group; ## p<0.01, p<0.01 when compared with 6-OHDA control; One-way ANOVA followed by Bonferroni multiple comparisons test.

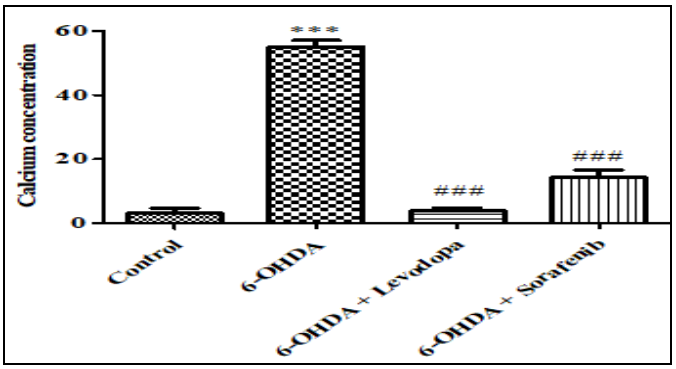

FIG. 8: ESTIMATION OF CALCIUM CONCENTRATION IN RAT BRAIN. Values are mean ± SEM; n=6 in each group. ***p<0.001 when compared with vehicle control group; ### p<0.001, ### p<0.001 when compared with 6-OHDA control; One-way ANOVA followed by Bonferroni multiple comparisons test.

DISCUSSION: Anti-parkinson agent partially relieve the symptoms of this disease, but they are not able to block dopaminergic neurodegeneration thus the disease continues to progress. Currently, there is a great demand for new therapies that prevent neuronal death. New therapeutic strategy for PD must identify compounds that are neuroprotective and able to cross the BBB to produce the desired effects without causing adverse side effects. The sorafenib in 6-OHDA induces PD was analyzed in 14 days treatment with these LRRK2 inhibitors led to positive results with its preclinical antiparkinson's efficacy.

Sorafenib is widely used in cancer treatment clinically. As an anti-cancer drug, it is considered its effect on LRRK2 results with its antiparkinson's effect. In this study, apomorphine-induced circling behavior was carried out. Apomorphine is a mixed (D1 & D2) dopamine receptor agonist that does not share transport or metabolic pathways with levodopa and presumably acts by direct stimulation of the dopamine receptor. Circling controversial to the lesion site following the administration of dopamine agonist results from stimulation of dopamine receptor. The 6-OHDA induced rats showed a greater level of circling behavior and other treatment groups including levodopa and sorafenib treated rats might be replenishing dopamine or might have dopaminergic neurons in substantianigra. Further, it could presumably suggest the confirmation of nigral lesion in all the treatment groups. It was observed that sorafenib decreased the number of contralateral rotation of lesioned rats, suggestive of its neuroprotective effect.

Rotarod experiments demonstrated the impairment in the motor function and coordination in Parkinson's rats. 6-OHDA group showed less retention time on the rotating rod when compared to the control group suggesting impairment in their ability to integrate sensory input with appropriate motor commands to balance their posture. Lack of

motor coordination and maintenance of normal limb posture has been reported in PD condition. The treatment with sorafenib in rats increased the retention time when compared to 6-OHDA induced rats. This evaluation revealed the efficacy of sorafenib in increasing muscle tone and thus could correlate with possible action on CNS. It was found that sorafenib caused a pronounced increased in dopamine levels in substantianigra region of 6-OHDA lesioned rats and it could be a result of protection of dopaminergic neurons by sorafenib.

Levodopa treatment hiked the dopamine levels and it is easily demonstrated by its high concentration after the treatment. The beneficial roles of the test drug in retaining dopamine levels demonstrated the protection of nigral neurons. In this study, the total protein concentration reduced significantly in 6-OHDA induced group, whereas the test drug could increase the total protein concentration in 6-OHDA lesioned rats. This result suggests the possible neuroprotective effect of the test drug.

In this study, different *in-vivo* anti-oxidant levels were estimated and determined whether the drug treatment could elevate or suppress the natural antioxidant enzymes intracellular in substanianigra region. With respect to this study, the findings showed that the sorafenib treatment could maintain the normal range of natural antioxidant enzymes in brain tissue. This has given us knowledge of the possible role of antioxidant enzyme in protecting the mitochondrial activities and reduces in-vivo oxidative stress in neurons.

CONCLUSION: In the present study, antiparkinson's effect of an LRRK2 inhibitor, sorafenib is evaluated in the 6-OHDA lesioned rat model. Parameters such as apomorphine-induced rotation, grip strength, catatonia, total protein, glutathione level, lipid peroxidation, calcium concentration in the brain were carried out. The above parameters revealed that the LRRK2 inhibitor, sorafenib has shown significant antiparkinson's activity in 6-OHDA lesioned rat models. The estimated parameters altered the normal behavior of the animal and the drug treatment protected the diseased brain of rat.

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CONFLICT OF INTEREST: There is no conflict of interest.

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