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Pharmacological screening to assess the antidepressant activity of *Benincasa hispida* (Thunb.) Cogn, seeds extract in Swiss albino mice

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Abstract
To evaluate the *in vivo* antidepressant activity of Methanolic extract of *Benincasa hispida* Seed (BHMSC) in Swiss albino mice. Methanolic extract of *Benincasa hispida* (BHMSC) Seed leaves was prepared by a continuous method using the Soxhlet apparatus. The extract was subjected to phytochemical screening followed by acute oral toxicity studies in mice. In this study, EASL (administered at doses of 100 and 200 mg/kg body weight) was tested on different groups of mice. The Standard group received Imipramine hydrochloride (15 mg/kg body weight) orally. Additionally, Test Group 3 received a combination of 100 mg/kg EASL and 10 mg/kg Imipramine. The Control group was given Normal saline (10 ml/kg body weight). The researchers evaluated the antidepressant activity using the modified Forced Swimming Test (FST) and the Tail Suspension Test (TST). During the FST and TST, the period of immobility was observed. Immobility is considered indicative of antidepressant activity. The results demonstrated a significant dose-dependent antidepressant effect of BHMSC in Swiss albino mice across all test groups (Test groups I, II, and III). However, further investigations are necessary to identify the active constituents of BHMSC and understand its molecular target mechanism for potential use in humans.

Keywords: *Benincasa hispida*, antidepressant activity, forced swimming test, tail suspension test

Introduction
Depression, a serious neurological disorder, manifests with disturbances in sleep, appetite, cognition, and energy [1]. It can be a potentially life-threatening condition that affects millions of people globally, spanning all age groups from childhood to later life. The burden it places on society is substantial.
The hallmark symptoms of depression form a triad:
Low or depressed mood
Anhedonia (reduced ability to experience natural rewards)
Low energy or fatigue [2].
Major Depression (MD), formerly known as unipolar depression, follows a clinical course characterized by one or more major depressive episodes. These episodes occur without a history of manic, mixed, or hypomanic episodes. Common features include feelings of guilt, insomnia or hypersomnia, and suicidal ideation or acts [3]. The lifetime prevalence of depression in the general population worldwide ranges from 10% to 20%, with a female-to-male ratio of approximately 5:2. While most patients recover from depressive episodes, a significant proportion become chronic. After 5 or 10 years of potential follow-up, about 12% and 7% of patients, respectively, remain depressed [4].
Mood disorders rank as the second primary cause of disability-adjusted life years globally and are the leading cause of years lived with disability across all age groups. Treatment options include drugs, but each has a success rate of approximately 60%. Additionally, most therapies require several weeks of treatment before improvements in signs and symptoms become evident. Antidepressants, while effective, can also lead to various side effects [5].
Benincasa hispida, also known as winter melon, ash gourd, ash guard, winter gourd, white pumpkin, and wax gourd, belongs to the family Cucurbitaceae. This common vegetable crop is notably popular in Asian countries for both biological and medicinal purposes [6, 7].

Every part of the plant is utilized medicinally. The plant grows annually and has crawling, branched tendrils that can climb with support or sprawl along the ground. Its stems are thick, hairy, conspicuously grooved, and lined with sharp bristles. The leaves are spherical and kidney-shaped, with a rough surface. The plant produces beautiful golden-yellow flowers, and its fruits contain various white-colored embedded seeds [7-9]. Medicinally, this plant has been used to address various complaints, including gastrointestinal problems, respiratory diseases, heart diseases, diabetes mellitus, and urinary diseases [9]. Historically, the fruits of *Benincasa hispida* have been used for various purposes, including as a laxative, diuretic, tonic, aphrodisiac, cardiotonic and for addressing urinary calculi, blood diseases, insanity, epilepsy, schizophrenia, and other psychological disorders [9-13]. Additionally, they were employed to treat jaundice, dyspepsia, fever, and menstrual disorders. The plant contains a rich array of phytochemicals, such as alkaloids, flavonoids, tannins, glycosides, phenolic compounds, amino acids, steroids, triterpenoids, and saponins. Notably, polyphenols exhibit potent antioxidant activity, which can help mitigate the side effects of conditions like neurodegenerative diseases, cardiovascular issues, cancer, liver disease, and infectious diseases. Furthermore, tannins play a significant role by inhibiting pancreatic lipase activity and fat absorption from the intestine. The methanolic extract of the fruit has been reported to possess several properties, including being antiulcer, anti-inflammatory, antihistaminic, antidepressant and a bronchodilator. It also exhibits analgesic and diuretic effects. In addition to the aforementioned phytochemicals, the plant contains disaccharides like glucose, sucrose, and maltose.

Plant Profile [9]

Scientific Classification

Kingdom: Plantae
Order: Cucurbitales
Family: Cucurbitaceae
Tribe: *Benincaseae*
Subtribe: Benincasinae
Genus: *Benincasa*
Species: B. hispida
Scientific name: *Benincasa hispida* (Thub.) Cogn.
Vernacular name:
Sanskrit: Kushmanda, Brihatphala, Pushpaphala, Pitapushpa, etc.
Hindi: Petha, Pethakaddu.
English: Ash gourd (Chinese) Winter melon, Fuzzy melon, Green pumpkin, Wax gourd, White gourd, furry Melon.

Global distribution

It is likely native to Japan, Java, and Malaysia, and is cultivated extensively in India and other warm countries. In the plains of India, Burma, and Ceylon, it is grown for its fruits, while in hilly regions, cultivation occurs up to an elevation of 4, 000 feet. Seeds are sown in the plains during February-March and in the hills from March to May."

Propagation and Cultivation

In the plains, crops can be grown during late winter using playhouse technology. Seedlings are typically planted between December and January. The optimal temperature range for growth is 73°F to 82°F, with moderate rainfall, avoiding hot and humid tropical conditions. It takes approximately five months for the plants to mature. If large fruits are desired, they can be cultivated on flat ground; otherwise, they are allowed to climb on fences [14].

Materials and Methods

The experiment was carried out after obtaining due clearance from the Institutional Animal Ethics Committee of Sri Vijay Vidyalaya College of Pharmacy, Dharmapuri, Tamil Nadu.

Animals

This study utilized Swiss albino mice weighing 22-25g. Groups of them were kept in polypropylene cages with a 12-hour light/dark cycle and controlled humidity and temperature (25±2% and 55±2%, respectively). They were given water *ad libitum* and the usual rodent food. The studies were conducted in a noise-free environment from 9:00 to 15:00.

Plant materials and preparation of drug solution

Benincasa hispida seeds were collected from Bannari Hill (Dimbam), Coimbatore district, Tamilnadu state, and it was authenticated by ABS Medicinal Garden, Salem, Tamil Nadu. The first procedure involved defatting a 100-gram sample of dry powder with petroleum ether to remove lipid components. After the sample was defatted, it was extracted five times with 500 ml of methanol using a Soxhlet apparatus to ensure that all the bioactive chemicals were fully recovered. The Methanolic Extract of Bioactive Components from Herbal substance was then isolated by separating and condensing the methanolic extract using a vacuum evaporator. This process's total yield, or the percentage of the finished product relative to the beginning mass of dry powder, was calculated to be 20% w/w. For the duration of the experiment, the extract was kept in a glass bottle and kept in a refrigerated environment to maintain its efficacy and composition [14].

The phytochemical screening of the methanol extract of *Benincasa hispida* Methanolic seed extract (BHMSE) was screened for the presence of various phytoconstituents like proteins, tryptophan, sterols, volatile oils, glycosides, phenolic compounds and carbohydrates, flavonoids, and alkaloids carried out.

Forced swim test

All the groups of animals were subjected to forced swim test after administering the respective drug solutions. On day 0, in training session, mice were forced to swim individually in a vertical Plexiglas cylinder (Height: 40 cm; diameter: 18 cm) containing fresh water up to 15 cm maintained at 25°C for 15 minutes and the animals were observed for 6 minutes. In this test, after a brief spell of vigorous activity, animals show a posture of immobility which was characterized by floating motionless in the water making only those movements necessary to keep the head above the water. This immobility reflects the state of depression. Each mouse was subjected to this procedure 24h prior and 1h after administration of respective drugs for 5 minutes in the test session, and the duration of immobility during last 4 minutes was recorded. Actual test recordings were done on 1st, 7th and 14th day of treatment. After recording of mobility, immobility time, each mouse was removed, wiped with dry cloth and allowed to dry before being returned to their home cages.

Tail suspension test

All the groups of animals were subjected to this test by suspending them on a string held by a metal stand, by an adhesive tape placed 1 cm from the tip of the tail and the string was 58 cm above the table top. The duration of mobility immobility of the mice was recorded for a period of last 4 minutes during a period of 5 minutes observation. Mice were considered immobile when they hang passively and completely motionless. During the experiment, each animal under test was both acoustically and visually isolated from other animals. Mice were considered immobile when they hang passively and completely motionless. Readings were taken on 1st, 7th and 14th day of treatment.

Anti-depressant drugs employed in the study

Selective Serotonin (5-HT) Reuptake Inhibitors (SSRIs), Fluoxetine hydrochloride (20mg) (FXH20) and Traditional tricyclic antidepressants (TCAs), Imipramine hydrochloride (15mg), (IMH15).

Statistical analysis: 2-way ANOVA followed by Duncan's t-test, were used to compare differences among groups. Data are presented as mean ± SEM, where $p<0.05$ was considered as significant. The Graph Pad prism software (v.10.1.2) was used for the data analysis [15-16].

Results

Table 1: Result of chemical group tests of the methanolic extract of *Benincasa hispida*

Extract	Carbohydrates	Tannins	Flavonoid	Saponin	Phenols	Steroids	Alkaloids	Glycosides
Benincasa hispida	++	++	++	+	+++	++	+++	+++

ME- Methanolic extract; (+): Present; (-): Absent; (+++); Reaction intensity is high; (++): Reaction intensity is medium; (+): Reaction intensity is normal; phytochemical screening tests for the detection of various active constituents. The extract showed the presence of alkaloids, tannins, steroids, phenolic and flavonoids, carbohydrates, and glycosides in crude extract of *Benincasa hispida* seeds as depicted in Table 1

General animal behavioural profile

The results obtained from the different experiments are shown in Table 2. The methanolic extract of BHMSE at different dose 50, 100, 200mg/kg has affected spontaneous activity, sound, and touch responses at doses above 50mg/kg and produced moderate or slight response relating to awareness and alertness. The methanolic extract caused a significant depression of these responses when comparable to standard drugs FXH20, IMH15 [17]

Table 2: Effect of BHMSE 1, 2, 3 and FXH20, IMH15 on general behavioural profile

Behavior pattern	BHMSE: 1, 2, 3 (mg/kg)			FXH20	IMH15	0.9% NaCl (10ml/ kg)
	50	100	200			
Spontaneous activity	+	+++	+++	++++	++++	-
Alertness	+	++	++	+++	++	-
Awareness	++	+++	++	++	++	-
Sound response	++	++	+	+++	++	-
Touch response	++	+++	++	++++	++++	-
Pain response	++	+++	+++	++++	++++	-

N=2: Ip-Intraperitonial-No effect; + slight Response; ++ moderate Response; +++ strong Response; ++++ very strong Response.

The antidepressant activity was evaluated 60 min after the drug administration on days 1, 7 and 14 by employing tail suspension test (TST) and Forced swimming test (FST)

Effects of the methanolic extract of *Benincasa hispida* on the duration of immobility time in the Mouse Tail suspension test (TST)

Effects of oral administration of the Methanolic extract of *Benincasa hispida*, FXH20 (Fluoxetine HCL) and IMH15 (Imipramine HCL) on the duration of immobility in the mouse tail suspension test were shown in Table.3. In anti-depression behavioural TST models, *BHSE* at doses of 100 mg/kg significantly decreased the immobility period of the mice when compared to the control group. FXH20 and IMH15 at a dose of 20, 15 mg/kg respectively also decreased the immobility period when compared to the control group. As BHMSC exhibited a highly significant ($p<0.001$) effect compared to the control group on day 14.

Table 3: Effect of BHMSE: 1, 2, 3 and FXH20, IMH15 on the duration of the immobility period in the Tail suspension tests (TST)

Animal Group code	Drug	Dose (mg/kg)	Number of Swiss albino mice	Duration of immobility (s)		
				Day 1	Day 7	Day 14
Group-I	Control	10 ml	10	192±6.48	196±6.13	198±6.28
Group-II	FXH20 (Fluoxetine HCL)	20	10	138.75±7.46*	111.87±7.52**	102.87±7.82***
Group-III	IMH15 (Imipramine HCL)	15	10	148.8±5.91*	136.1±4.56*	114.4±2.61**
Group-IV	BHMSE:1	50	10	187±7.52	169±5.01	157±6.12*
Group-V	BHMSE:2	100	10	168.2±3.17**	129.85±2.02**	108.1±1.29***
Group-VI	BHMSE:3	200	10	181±4.52*	163±3.08*	151±1.21*

Each value represents the Mean ± S.E.M. of 10 animals. Separate groups of animals were employed for recording immobility periods in TST; Data were analyzed by 2-way ANOVA followed by Duncan's t-test. *, P>0.05; **, P>0.01; ***, P>0.001 when compared with control groups.

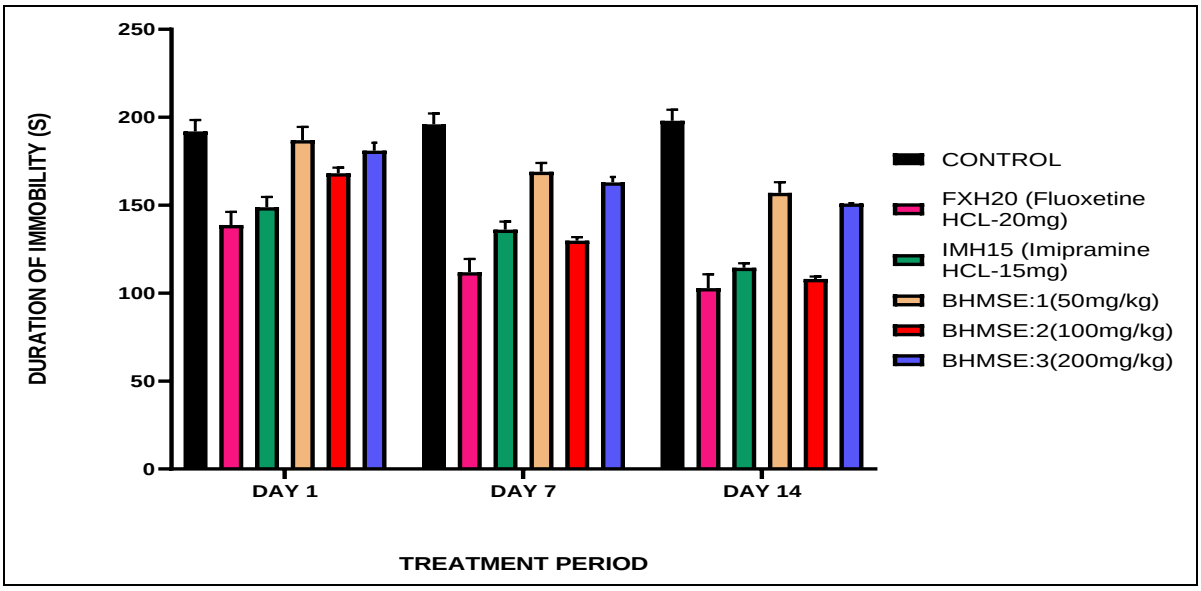

Fig 1: Effect of BHMSE: 1, 2, 3 and FXH20, IMH15 on the duration of the immobility period in the Tail suspension tests (TST)

Forced swim test (FST)

In anti-depression behavioural of FST models, *BHSE* at doses of 100 mg/kg significantly decreased the immobility period of the mice when compared to the control group. FXH20 and IMH15 at a dose of 20, 15 mg/kg respectively also decreased the immobility period when compared to the control group. As BHMSC exhibited a highly significant (p<0.01) effect compared to the control group on day 14.

Table 4: Effect of BHMSE 1, 2, 3 and FXH20, IMH15 on the duration of the immobility period in the Forced swim test (FST)

Animal group code	Drug	Dose (mg/kg)	Number of Swiss albino mice	Duration of immobility (s)		
				Day 1	Day 7	Day 14
Group-I	Control	10 ml	10	189±6.12	194±6.18	191±6.57
Group-II	FXH20 (Fluoxetine HCL)	20	10	124.55±6.16*	121.47±5.56*	92.6±5.24***
Group-III	IMH15 (Imipramine HCL)	15	10	136.88±6.51*	136.1 ±5.56*	102.6±2.01**
Group-IV	BHMSE:1	50	10	172±4.59	155±3.23	167.7±2.72
Group-V	BHMSE:2	100	10	168.2±3.17*	122.85±2.89**	100.2±1.09***
Group-VI	BHMSE:3	200	10	177±4.21*	168±3.88*	155.3±2.22

Each value represents the Mean ± S.E.M. of 10 animals; Separate groups of animals were employed for recording immobility periods in FST; Data were analyzed by 2-way ANOVA followed by Duncan's t-test *, P>0.05; **, P>0.01; ***, P >0.001 when compared with control groups.

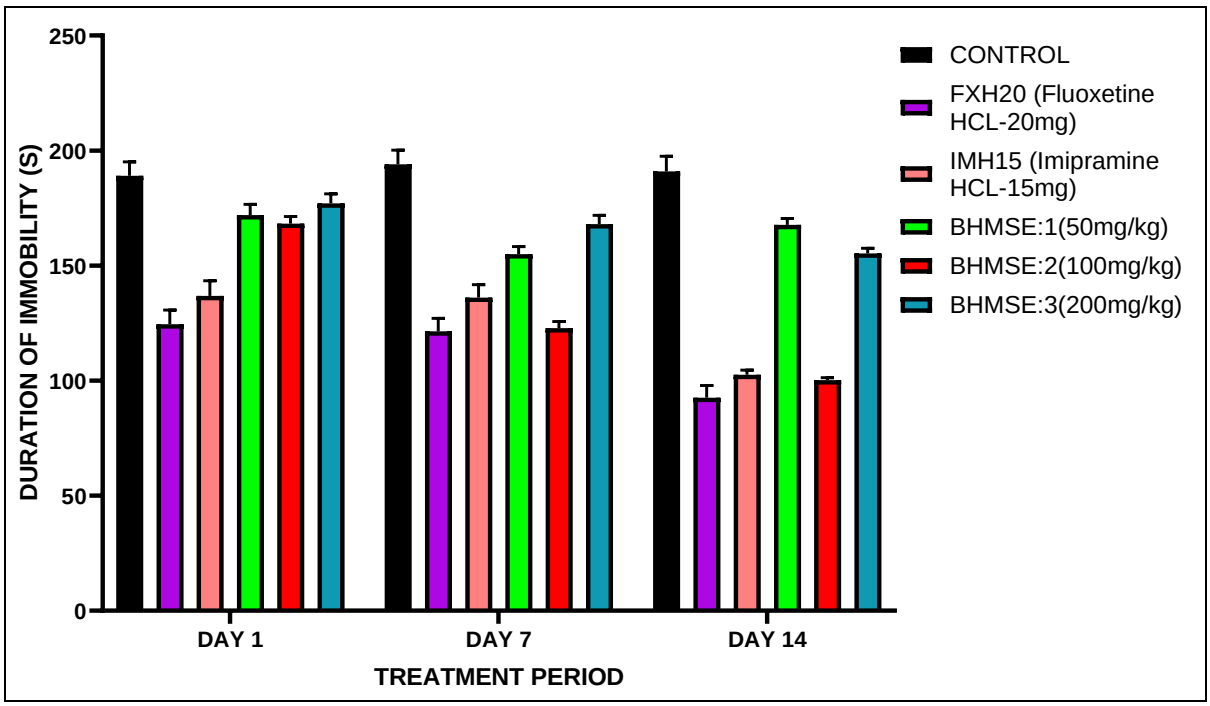

Fig 4: Effect of BHMSE 1, 2, 3 and FXH20, IMH15 on the duration of the immobility period in the Forced swim test (FST)

Discussion

In recent years, neurological disorders are becoming more common. As a result, finding natural compounds with neuropharmacological benefits will require. In this work, I employed pharmacological techniques to assess the antidepressant efficacy of a *Benincasa hispida* Methanolic seed extract BHMSE: 1, 2, 3 in the different concentration of 50, 100, 200 mg/kg respectively. The results were compared with the standard antidepressants FXH20 (Fluoxetine HCL) and IMH15 (Imipramine HCL).

On preliminary phytochemical analysis of BHMSE showed the presence of proteins, tryptophan, sterols, volatile oils, glycosides, phenolic compounds, carbohydrates, flavonoids, and alkaloids, shown in the Table 1.

The extracts were tested for the general behavioural patterns like spontaneous activity, sound, and touch responses at doses above 50mg/kg and produced moderate or slight response relating to awareness and alertness. The methanolic extract caused a significant antidepression responses when comparable to standard drugs FXH20, IMH15, the results were shown in the Table 2.

The main objective of these tests is to show the duration of immobility response, that reflects the common depressive condition of learned helplessness or despair.

Two behavioural despair tests that predicted the clinical success of various antidepressant drugs were the tail suspension test and Forced swim test (TST and FST) as described by Porsolt *et al*., 1977b [18]*:* Butterweck *et al*., 1998 [19]. These tests were used to evaluate BHMSE's potential as an antidepressant effect.

On the results of TST screening studied the Methanolic seed extract BHMSE: 1, 2, 3 on the immobility behaviors in mice. The extract at oral doses from 50 to 200 mg/kg for 14 days treatment showed significantly decreased the duration of immobility. Shown in the Table.3. It was noted that the animals treated at different doses of BHMSE: 1, 2, 3 (50, 100, 200 mg/kg) the concentration of dose increases the immobility duration was decreased on 14-day treatment and when compared with the antidepressant drugs the immobility pattern of BHMSE: 2 (100mg/kg) showed significant antidepressant effect. Shown in the Figure.5.

FST screening studied the Methanolic seed extract BHMSE: 1, 2, 3 on the immobility behaviors in mice. The extract at oral doses from 50, 100, 200 mg/kg for 14 days treatment, significantly decreased the duration of immobility. Shown in the Table.4. It was noted that the animals treated at different doses of BHMSE: 1, 2, 3 (50, 100, 200 mg/kg) the concentration of dose increases the immobility duration was decreased on 14-day treatment for FST and when compared with the antidepressant drugs the immobility duration of BHMSE: 2 (100mg/kg) showed significant antidepressant effect. Shown in the Figure 6.

Hence, changes in locomotor activity induced on by chemicals that stimulate the central nervous system could be responsible for changes in immobility the above result from the study showed that it may be raising norepinephrine, dopamine, and serotonin levels while lowering GABA levels, the extract would have an antidepressant effect. Antidepressant drugs have been developed to enhance the amounts of these monoamines [20-21].

Monoamine imbalances in brain regions (primarily the frontal cortex, striatum, hippocampal regions, and hypothalamus) that control behavioural activities like emotion, motivation, learning, and memory are hypothesized to be the cause of depression. The pathophysiology of depression is also influenced by dysfunctions of the serotonergic neurotransmission system, namely those that result in decreased brain levels of serotonin (5-HT) and 5-HIAA, the main metabolite of 5-HT [22-23].

Hence the *Benincasa hispida* Methanolic seed extract contains such bioactive compounds such as flavonoids and some other bioactive compounds which may be responsible for the antidepressant activity may be through the Serotogenic pathway /Monoaminergic pathway (MAO).

Further studies are required to establish if these compounds from BHMSE extracts in-depth investigations needed to find the exact mechanism of antidepressant action in animal models.

Conclusion

The main purpose of the current study was to evaluate the antidepressant effect of a particular BHMSE extract by employing the Tail Suspension Test (TST) and Forced Swim Test (FST) with the conventional medication selective serotonin (5-HT) reuptake inhibitor FXH20 (Fluoxetine HCL-20mg) and Traditional tricyclic antidepressantIMH15 (Imipramine HCL-15mg).

In conclusion, BHMSE exhibited strong antidepressant effects in Swiss albino mice without causing any motor incoordination. While the exact process behind the reported antidepressant effect is still unclear, the results of the experiments point to a potentially direct or indirect stimulation of the central serotonergic transmission/ Monoaminergic (MAOs) systems from the Swiss albino mice study. Therefore, when compared to currently available drugs, BHMSE may prove to be a potentially beneficial natural psychopharmacological agent with fewer side effects for treating behavioural depression and a variety of anxiety-related disorders and as well as neuroprotective agent.

Further studies required to deeper understanding of the mechanism of action, research using receptor binding assays, interaction analysis, and Neurotransmitter assays are required.

Conflict of interest statement

We declare that we have no conflict of interest.

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