Pharmaceutical Biology
2007, Vol. 45, No. 4, pp. 267–273

informa
healthcare

Memory-Enhancing Activity of *Thespesia populnea* in Rats

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Abstract

Thespesia populnea Soland ex. Correa (Malvaceae) is a large tree found in the tropical regions and coastal forests of India. Various parts of *Thespesia populnea* are found to possess useful medicinal properties such as antifertility, antibacterial, anti-inflammatory, antioxidant, purgative, and hepatoprotective activities. The current study was undertaken to investigate the effects of *Thespesia populnea* bark on memory in rats. Elevated plus-maze and Hebb-Williams maze served as the exteroceptive behavioral models for testing memory. Diazepam-, scopolamine-, and ageing-induced amnesia served as the interoceptive behavioral models. The ethanol extract of *Thespesia populnea* (TPE) was administered orally in three doses (100, 200, and 400 mg/kg) for 7 successive days to different groups of young and aged rats. TPE (200 and 400 mg/kg, p.o.) resulted in significant improvement in memory of young and aged rats. TPE also reversed the amnesia induced by scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.). Cholesterol-lowering, anticholinesterase, anti-inflammatory, and antioxidant properties of *Thespesia populnea* may favorably contribute to its memory-enhancement effect. Therefore, *Thespesia populnea* bark appears to be a promising candidate for improving memory, and it would be worthwhile to explore the potential of this plant in the management of Alzheimer patients.

Keywords: Amnesia, elevated plus-maze, Hebb-Williams maze, memory, *Thespesia populnea.*

Introduction

Dementia is a syndrome of gradual onset and continuing decline of higher cognitive functioning. It is a common disorder in older persons and becomes more prevalent in each decade of life (Dhingra et al., 2005). Approximately 10% of adults 65 years and older and 50% of adults older than 90 years have dementia (Adelman & Daly, 2005). The most common cause of dementia is Alzheimer disease, which is a progressive neurodegenerative disorder associated with loss of neurons in distinct brain areas (Dhingra et al., 2004). The central cholinergic pathways play a prominent role in memory processes (Nabeshima, 1993). Centrally acting antimuscarinic drugs (e.g., scopolamine) impair memory in animals (Higashida & Ogawa, 1987) and human beings (Sitaram et al., 1978). Currently, the allopathic system of medicine principally relies on nootropic agents such as piracetam, aniracetam, fosracetam, nefiracetam, and so forth, and anticholinesterases such as donepezil, metrifonate, rivastigmine, and so forth (Ringman & Cummings, 1999; Sramek et al., 2000; Mashkovskii & Glushkov, 2001; Potkin et al., 2001; Balaraman & Shingala, 2002; Sugimoto et al., 2002; Gauthier et al., 2003). Because the allopathic system of medicine is yet to provide a radical cure for Alzheimer disease, it is worthwhile to look for new directions to minimize the memory loss of patients with neuropsychiatric disorders. The utility of traditional medicines may be explored for treating patients with dementia.

Thespesia populnea Soland ex. Correa (Malvaceae) is a large tree found in tropical regions and coastal forests of India. Gossypol was found to be the major component of *Thespesia populnea* (Akhila & Rani, 1993) producing anti-inflammatory (Benhaim et al., 1994) and antifertility effects in rats (Murthy et al., 1981; Ghosh & Bhattacharya, 2004) as well as in human beings (Qian & Wang, 1984). Four naturally occurring quinines, viz. thespone, mansonone-D, mansonone-H, and thespesone, have also been extracted from heartwood of *Thespesia populnea* (Johnson et al., 1999). In the indigenous system

Accepted: November 17, 2006.

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DOI: 10.1080/13880200701214631

of medicine, the paste of the fruits, leaves, and roots of *Thespesia populnea* is applied externally for various skin diseases. The leaves are applied locally for their anti-inflammatory effects in swollen joints (Anonymous, 1995). The fruits of the plant are used in Ayurveda for the control of diabetes (Sathyanarayana et al., 2004). The barks and flowers possess astringent, hepatoprotective, and antioxidant activity in rats (Shirwaikar et al., 1995; Ilavarasan et al., 2003a, 2003b). Immunohistochemical studies revealed the existence of chronic inflammation in certain regions of the brain in Alzheimer disease patients. Because inflammation can be damaging to the host tissue, anti-inflammatory and antioxidant drugs might be beneficial in controlling the progression of Alzheimer disease (McGeer & McGeer, 1999). In light of the above, the current study was undertaken to investigate the effects of *Thespesia populnea* bark on cognitive functions in rats.

Materials and Methods

Plant material

The fresh bark of *Thespesia populnea* was collected during the month of June 2004 from Erode situated in the state of Tamil Nadu (India). The plant material was taxonomically identified and authenticated by the Head, Raw Materials, Herbarium and Museum Division, National Institute of Science Communication and Information Resources (NISCAIR; New Delhi India). A voucher specimen (NISCAIR/RHM/535/10) has been deposited at the herbarium of NISCAIR, and a sample of the specimen is also preserved at the Pharmacology Division of the Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology (Hisar, India) for ready reference.

Preparation of the extract

The freshly collected bark was dried under shade, sliced into small pieces, pulverized using a mechanical grinder, passed through 40-mesh sieve, and preserved in an air-tight container for further use. The powdered bark (2.25 kg) was extracted with 95% ethanol using a Soxhlet extractor, at room temperature. After exhaustive extraction, the ethanol extract was filtered and concentrated by distillation process. A brownish-black colored residue was obtained (yield 17.8% w/w), which was kept in a desiccator. This ethanol extract of *Thespesia populnea* bark (TPE) was used in further experiments.

Animals

All the experiments were carried out using male Wistar rats procured from the disease-free small animal house of CCS Haryana Agricultural University, Hisar (Haryana), India. Young (3–4 months old) rats weighing around 150 g and aged (12–15 months old) rats weighing around 250 g were used in the current study. The animals had free access to food and water, and they were housed in a natural (12-h each) light-dark cycle. Food given to animals consisted of wheat flour kneaded with water and mixed with a small amount of refined vegetable oil. The animals were acclimatized for at least 5 days to the laboratory conditions before behavioral experiments. Experiments were carried out between 0900 h and 1800 h. The experimental protocol was approved by the institutional animal ethics committee, and the care of laboratory animals was taken as per the guidance of CPCSEA, Ministry of Forests and Environment, Government of India (registration number 0436).

Drugs

The drugs used in this study were obtained from following drug houses: scopolamine hydrobromide (Sigma-Aldrich, St. Louis, MO, USA), diazepam injection (Calmpose, Ranbaxy, India), and piracetam (UCB India Ltd., India).

Vehicle

Plant extract (TPE) was suspended in 2% (w/v) gum acacia and administered orally to rats. Scopolamine hydrobromide, diazepam, and piracetam were dissolved separately in normal saline and injected i.p. Volume of oral administration and i.p. injection was 1 mL/1000 g of rat.

Drug treatment

In the current investigation, the rats were divided into 40 different groups for employing various interoceptive and exteroceptive memory models. Each group comprised a minimum of six animals. TPE (100, 200, and 400 mg/kg) was administered orally for 7 successive days to young and aged rats. Ninety-minutes after the administration of the last dose (on the seventh day), rats were exposed to the training session using elevated plus-maze and Hebb-Williams maze. Retention (memory) was recorded after 24 h (on the eighth day). Amnesia was induced in separate groups (interoceptive models) of young rats by scopolamine (0.4 mg/kg, i.p.) or diazepam (1 mg/kg, i.p.) 90 min after the last dose of extract (100, 200, and 400 mg/kg, p.o.) administration on the seventh day. The animals were exposed to the training session (on the seventh day) 45 min after scopolamine or diazepam injection. The retention (memory) was measured after 24 h (on the eighth day). Piracetam (400 mg/kg, i.p.) was used as an established nootropic agent and was injected for 7 days to positive control groups. All control group animals received vehicle (0.5% w/v CMC) for 7 consecutive days.

Elevated plus-maze

Elevated plus-maze served as the exteroceptive behavioral model to evaluate memory in rats. The procedure,

technique, and end point for testing memory was followed as per the parameters described by the investigators working in the area of psychopharmacology (Itoh et al., 1990; Reddy & Kulkarni, 1998; Parle et al., 2005). The elevated plus-maze apparatus for rats consisted of a central platform (10 cm × 10 cm) connected to two open arms (50 cm × 10 cm) and two covered (enclosed) arms (50 cm × 40 cm × 10 cm), and the maze was elevated to a height of 50 cm from the floor (Parle & Singh, 2004). On the first day (i.e., seventh day of drug treatment), each rat was placed at the end of an open arm, facing away from the central platform. Transfer latency (TL) was defined as the time (in seconds) taken by the animal to move from the open arm into any one of the covered arms with all its four legs. TL was recorded on the first day (training session) for each animal. The rat was allowed to explore the maze for another 2 min and then returned to its home cage. Retention of this learned-task (memory) was examined 24 h after the first day trial (i.e., eighth day, 24 h after last dose). Significant reduction in TL value of retention indicated improvement in memory.

Hebb-Williams maze

Hebb-Williams maze is an incentive-based exteroceptive behavioral model useful for measuring spatial working memory of rats (Parle & Singh, 2004). It mainly consists of three components: animal chamber (or start box), which is attached to the middle chamber (or exploratory area), and a reward chamber at the other end of the maze in which the reward (food) is kept. All three components are provided with guillotine removable doors. On the first day (i.e., seventh day of drug treatment), the rat was placed in the animal chamber or start box and the door was opened to facilitate the entry of the animal into the next chamber. The door of the start box was closed immediately after the animal moved into the next chamber to prevent back-entry. Time taken by the animal to reach the reward chamber from the start box was recorded on the first day (training session) for each animal. Each animal was allowed to explore the maze for 3 min with all the doors opened before returning to its home cage. Retention of this learned task (memory) was examined 24 h after the first day trial (i.e., eighth day, 24 h after last dose) (Parle et al., 2005).

Statistical analysis

All the results were expressed as mean ± standard error (SEM). Data was analyzed using one-way ANOVA followed by Dunnett's *t*-test and Student's unpaired *t*-test. p values <0.05 were considered as statistically significant.

Results

Effect on transfer latency (using elevated plus-maze)

Whereas TL of the second day reflected retention of information or memory. TPE (100 mg/kg) administered for 7 days orally did not have any significant effect on TL of the eighth day in the elevated plus-maze test. The young and aged animals treated orally with 200 and 400 mg/kg showed remarkable reduction ($p < 0.001$) in TL of the eighth day, indicating significant improvement in memory (Fig. 1). Scopolamine hydrobromide (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) injected before training significantly increased ($p < 0.001$) TL on the eighth day indicating impairment in memory (Fig. 2). The TPE at higher dose levels (200 and 400 mg/kg, p.o., for 7 successive days) successfully reversed memory deficits induced by scopolamine and diazepam. Piracetam (used as the positive control) at a dose of 400 mg/kg, i.p., also improved memory in both young and aged rats and reversed the amnesia induced by scopolamine and diazepam as expected.

Effect on time taken to reach reward chamber (using Hebb-Williams maze)

Time taken to reach the reward chamber (TRC) on the eighth day (24 h after last dose) reflected the memory of animals. Significant reduction in TRC value indicated improvement in memory. TPE (100 mg/kg, p.o.) did not show any significant effect on TRC compared with the control group of young rats. Ageing process remarkably ($p < 0.001$) increased TRC of aged rats (Fig. 3). TPE (100 mg/kg, p.o.) did not have any effect on ageing-induced amnesia as indicated by non-significant changes in TRC values. On the other hand, the higher doses of 200 and 400 mg/kg TPE administered orally in young ($p < 0.01$) and aged ($p < 0.001$) rats for 7 days markedly reduced TRC compared with the respective control groups (Fig. 3). Scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) significantly increased ($p < 0.001$) TRC compared with the control group of young rats, indicating impairment of memory (amnesia). TPE administered for 7 days reversed the amnesia induced by both scopolamine and diazepam (Fig. 4). The groups of rats that were treated with piracetam (400 mg/kg, i.p.) for 7 successive days showed improvement ($p < 0.001$) in memory of young as well as aged rats. Piracetam also reversed amnesia induced by scopolamine and diazepam.

Discussion

Memory refers to the storage, retention, and recall of information including past experiences, knowledge, and thoughts (Parle et al., 2004). Drugs that enhance acquisition and recall of associative memory represent

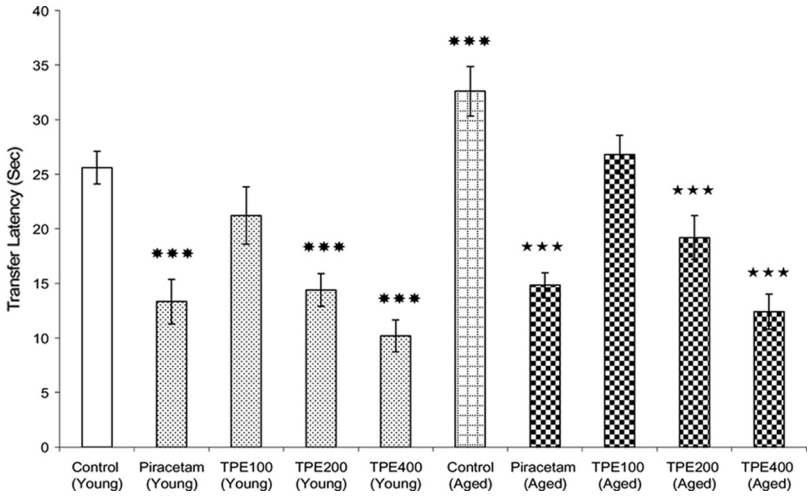

Figure 1. Effect of various concentrations of *Thespesia populnea* bark extract (TPE 100, 200, and 400 mg/kg) administered orally for 7 successive days on transfer latency of young (3–4 months) and aged (12–15 months) rats using elevated plus-maze. Piracetam (400 mg/kg, i.p.) was used as a standard drug. Values are in mean ± SEM (n = 6). One-way ANOVA followed by Dunnett's *t*-test and Student's unpaired *t*-test. ✱✱✱ denotes $p < 0.001$ compared with control group of young rats. ★★★ denotes $p < 0.001$ compared with control group of aged rats.

important goals in the therapy of cognitive disorders. In the current study, *Thespesia populnea* extract administered orally for 7 days improved the memory of rats as reflected by diminished TL and TRC values compared with those of control animals. Furthermore, pretreatment with TPE for 7 days protected the animals from memory deficits induced by intraperitoneal injection of scopolamine or diazepam, in addition to ageing-induced amnesia (a natural process). Piracetam, the established nootropic agent, was used as a standard drug.

The main histologic features of Alzheimer disease include extracellular protein deposits, termed β-amyloid (Aβ) plaques, Aβ deposits in blood vessels, and intraneuronal neurofibrillary tangles (Sayre et al., 1997; Sparks et al., 2000). Abnormal accumulation of cholesterol increases Aβ in cellular and most animal models of Alzheimer disease, and drugs that inhibit cholesterol synthesis lower Aβ in these models (Mori et al., 2001; Puglielli et al., 2003). Our previous finding indicated that the animals treated with TPE showed significant reduction in cholesterol levels in young and aged mice compared with control group (Vasudevan & Parle, 2007). Therefore, it seems likely that *Thespesia populnea* may prove to be a useful anti-Alzheimer agent, in view of its memory-enhancing property observed in the current study.

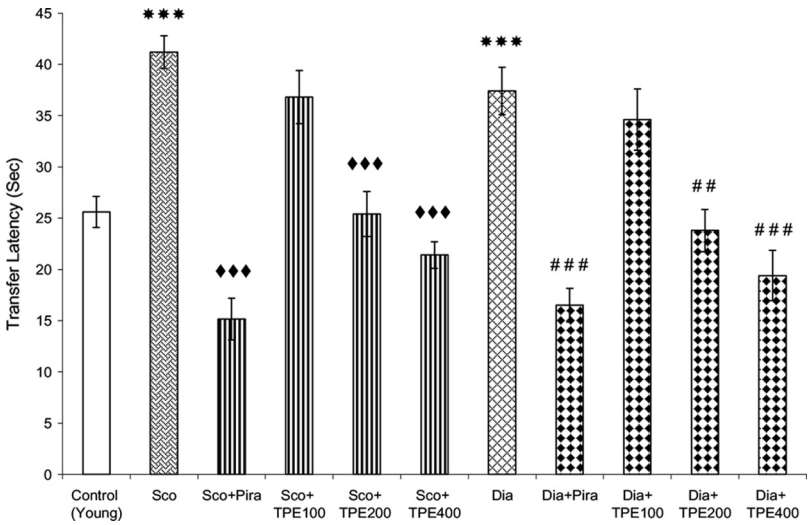

Figure 2. Reversal of scopolamine (0.4 mg/kg, i.p.) or diazepam (1 mg/kg, i.p.) induced amnesia by *Thespesia populnea* bark extract (TPE 100, 200, and 400 mg/kg, p.o.) in young rats using elevated plus-maze. Piracetam (Pira) 400 mg/kg, i.p., was used as a standard drug. Values are in mean ± SEM (n = 6). One-way ANOVA followed by Dunnett's *t*-test and Student's unpaired *t*-test. ✱✱✱ denotes $p < 0.001$ compared with control group of young rats. ♦♦♦ denotes $p < 0.001$ compared with scopolamine (Sco) alone. ## denotes $p < 0.01$ compared with diazepam (Dia) alone. ### denotes $p < 0.001$ compared with diazepam (Dia) alone.

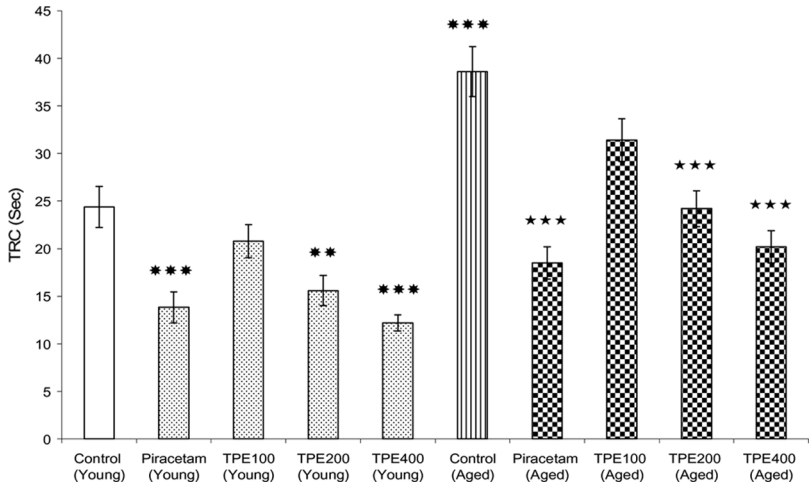

Figure 3. Effect of various concentrations of *Thespesia populnea* bark extract (TPE 100, 200, and 400 mg/kg) administered orally for 7 successive days on TRC of young (3–4 months) and aged (12–15 months) rats using Hebb-Williams maze. Piracetam (400 mg/kg, i.p.) was used as a standard drug. Values are in mean ± SEM (n = 6). One-way ANOVA followed by Dunnett's *t*-test and Student's unpaired *t*-test. ✶✶ denotes $p < 0.01$ compared with control group of young rats. ✶✶✶ denotes $p < 0.001$ compared with control group of young rats. ★★★ denotes $p < 0.001$ compared with control group of aged rats.

It has been observed that elderly patients suffering from Alzheimer disease showed reduction in symptoms of Alzheimer disease upon chronic use of anti-inflammatory drugs (Rao et al., 2002; Stephan et al., 2003). Epidemiologic studies have almost confirmed that nonsteroidal anti-inflammatory drugs reduce the incidence of Alzheimer disease (Breitner, 1996). *Thespesia populnea* has been shown to produce anti-inflammatory action in rodents and human neutrophils (Benhaim et al., 1994; Anonymous, 1995). This anti-inflammatory effect of *Thespesia populnea* would certainly help Alzheimer patients by taking care of the inflammatory component of Alzheimer disease.

Oxygen free-radicals are implicated in the process of age-related decline in cognitive performance and may be responsible for the development of Alzheimer disease in elderly persons (Sinclair et al., 1998; Bickford et al., 2000; Berr, 2002; Butterfield & Lauderback, 2002; Floyd & Hensley, 2002; Perry et al., 2002; Rogers et al., 2003). *Thespesia populnea* has been reported to possess antioxidant property as well (Ilavarasan et al., 2003a). The neuroprotective effect of TPE may be attributed to its

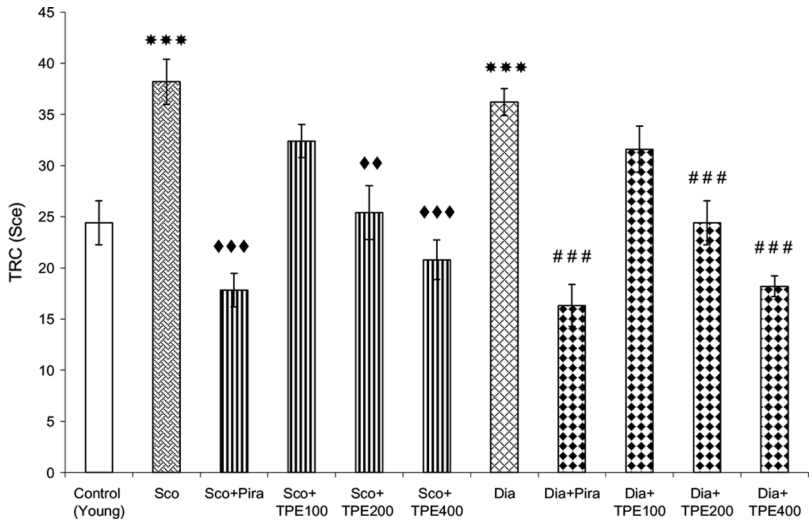

Figure 4. Reversal of scopolamine (0.4 mg/kg, i.p.) or diazepam (1 mg/kg, i.p.) induced amnesia by *Thespesia populnea* bark extract (TPE 100, 200, and 400 mg/kg, p.o.) in young rats using Hebb-Williams maze. Piracetam (Pira) 400 mg/kg, i.p., was used as a standard drug. Values are in mean ± SEM (n = 6). One-way ANOVA followed by Dunnett's *t*-test and student's unpaired *t*-test. ✶✶✶ denotes $p < 0.001$ compared with control group of young rats. ◆◆ denotes $p < 0.01$ compared with scopolamine (Sco) alone. ◆◆◆ denotes $p < 0.001$ compared with scopolamine (Sco) alone. ### denotes $p < 0.001$ compared with diazepam (Dia) alone.

antioxidant property by virtue of which susceptible brain cells get exposed to less oxidative stress resulting in reduced brain damage and improved neuronal function.

Acetylcholine is considered as the most important neurotransmitter involved in the regulation of cognitive functions. There is extensive evidence linking the central cholinergic system to memory (Olney, 1990; Peng et al., 1997; Ghelardini et al., 1998; Parle et al., 2004). Cognitive dysfunction has been shown to be associated with impaired cholinergic function and the facilitation of central cholinergic activity with improved memory (Bhattacharya et al., 1993). Selective loss of cholinergic neurons and decrease in cholinacetyltransferase activity was reported to be a characteristic feature of senile dementia of the Alzheimer type (Agnolli et al., 1983). The results of our previous study indicated that TPE showed elevation of acetylcholine level by significant reduction of cholinesterase activity in brain of young and aged mice (Vasudevan & Parle, 2007).

TPE may prove to be a useful medicine on account of its multifarious beneficial effects such as memory-improving property, cholesterol-lowering, anticholinesterase, and anti-inflammatory activities. Therefore, *Thespesia populnea* bark appears to be a promising candidate for improving memory, and it would be worthwhile to explore the potential of this plant in the management of Alzheimer patients.

Acknowledgments

The authors are deeply grateful to the Indian Council of Medical Research (ICMR), New Delhi, Government of India for the financial support of this study in the form of SRF. We are similarly grateful to Dr. R.P. Bajpai, Honorable Vice Chancellor of Guru Jambheshwar University of Science and Technology, Hisar, for his constant encouragement and inspiration. The authors thank Dr. D.N. Mishra, chairman, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, for providing facilities to carry out this project. We are grateful to Dr. P.K. Kapoor, scientist in charge, Disease-Free Animal House, CCS Haryana Agricultural University, Hisar, for continuous supply of animals.

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