Effect of BR-16A (Mentat®), a polyherbal formulation on drug-induced catalepsy in mice

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Parkinson’s disease (PD) is a neurodegenerative disease characterized by the selective loss of dopamine (DA) neurons of the substantia nigra pars compacta (SNc). The events, which trigger and/or mediate the loss of nigral DA neurons, however, remain unclear. Neuroleptic-induced catalepsy has long been used as an animal model for screening drugs for Parkinsonism. Administration of haloperidol (1 mg/kg, ip) or reserpine (2 mg/kg, ip) significantly induced catalepsy in mice. BR-16A (50 and 100 mg/kg, po), a polyherbal formulation or ashwagandha (50 and 100 mg/kg, po), significantly reversed the haloperidol or reserpine-induced catalepsy. The results indicate that BR-16A or ashwagandha has protective effect against haloperidol or reserpine-induced catalepsy and provide hope that BR-16A could be used in preventing the drug-induced extrapyramidal side effects and may offer a new therapeutic approach to the treatment of Parkinson's disease.

Keywords: Ashwagandha, BR-16A, Catalepsy, Haloperidol, Reserpine

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under standard light/dark cycle with food and water provided ad libitum. Animals were acclimatized to laboratory condition before test. Each animal was used once. The experiments were performed between 0900-1600 hrs. The experimental protocols were approved by the Institutional Ethics Committee and were conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals.

Drugs, dosages and treatment schedule—Following drugs were used in the study at the dosages mentioned: haloperidol (1 mg/kg, ip, Searle, India), reserpine (2 mg/kg, ip, Loba Chemical, India), BR-16A (50 and 100 mg/kg, po, Himalayan Drug Company, Bangalore), and Ashwagandha root extract (50 and 100 mg/kg, po, Himalayan Drug Company, Bangalore). Reserpine was dissolved in few drops of acetic acid and volume was made up with distilled water. BR-16A or ashwagandha was suspended in 0.5% of sodium carboxy-methyl-cellulose. Haloperidol was dissolved in distilled water. All drugs were administered in a constant volume of 1 ml/100 g body weight of mouse. Drugs were administered 30 min before haloperidol or reserpine administrations to overnight-fasted animals. Overnight fasted animals were used in order to increase the drug absorption of orally administered drugs.

Behavioral assessment—A cataleptic behaviour was measured with a high bar test method. Catalepsy score was measured for 4 hr at one-hour intervals after haloperidol or same cataleptic score after 4 hr in reserpine administration, by gently placing both the forepaw of the mouse over a metal bar (diameter 2-5 mm suspended 6 cm above the tabletop). The intensity of catalepsy was assessed by counting the time in seconds until the mouse brought both forepaws down to the tabletop, with a maximum cutoff time of 3 min. Finally, scores at different time points (0, 60, 120, 180 and 240 min after haloperidol injection) were added and expressed as cumulative catalepsy score for comparison purpose. Similarly, catalepsy score was measured 4 hr after reserpine administration in reserpine model. In all the experiments the scorer was blind to the treatment given to the mice.

Statistical analysis—Catalepsy data were expressed as mean ± SE and analyzed by one-way analysis of variance (ANOVA) followed by Dunnett test. In all the tests, the criterion for statistical significance was P<0.05.

Results

Effect of BR-16A or Ashwagandha on haloperidol induced catalepsy—In the present study haloperidol produced a time dependent increase in cataleptic state, which was significant as compared to vehicle treated animals (Fig.1). BR-16A (50 and 100 mg/kg, po), significantly reduced severity of haloperidol-induced catalepsy at all time intervals (Fig. 2). Ashwagandha (50 and 100 mg/kg, po) significantly and dose dependently reduced cataleptic score as compared to haloperidol alone treated animals at 60, 120 and 180 min (Fig. 3). BR-16A or Ashwagandha reduced the cumulative catalepsy score as compared to haloperidol treated animal (Table 1).

Effect of BR-16A or Ashwagandha on reserpine-induced catalepsy—Reserpine (2 mg/kg, ip) produced significant catalepsy as compared to vehicle treated
BR-16A or Aswagandha dose dependently (50, 100 mg/kg, po) reduced the severity of reserpine-induced catalepsy (Table 2).

**Discussion**

Haloperidol-induced catalepsy is one of animal models to test for the extrapyrimidal side effects of antipsychotic drugs\(^\text{16}\). The haloperidol, (a non-selective D\(_2\) dopamine antagonist)-induced catalepsy is primarily due to blockade of dopamine receptors in the striatum. Serotonin is also involved in neuroleptic catalepsy\(^\text{17}\).

Protective effect of BR-16A (50 and 100 mg/kg) or Aswagandha (50 and 100 mg/kg) against haloperidol (1 mg/kg) or the vesicular monoamine transporter blocker, reserpine (2 mg/kg)-induced catalepsy suggests that these herbal drugs influence not only dopamine receptor-mediated neurotransmission but also serotonergic receptor-mediated neurotransmission. The results are also consistent with the earlier study reporting valuable effect of Aswagandha against haloperidol-induced tardive dyskinesia\(^\text{13}\).

Further, Aswagandha, which is one of the ingredients of the BR-16A formulation, also reduced the severity of both haloperidol and reserpine-induced catalepsy score. Aswagandha has been proved to be neuroprotective in stress-induced dopamine neuron degeneration\(^\text{18}\). It has been shown to be a free radical scavenger and inhibited lipid peroxidation in the central nervous system\(^\text{19}\).

The above observations indicate that anticaatleptic effect of BR-16A may be due to Ashwagandha present in the formulation. However role of other ingredient present in the BR-16A formulation cannot be ignored and required to be investigated.

**References**