RESEARCH ARTICLE

Preclinical Estimation of Effect of Piperine on Anti-Parkinsons Activity of Berberine Estimated by Behavior Modification Scale

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ABSTRACT

Objective: Parkinson's disease (PD) leads to involuntary and uncontrolled muscle reactions. Berberine (BBR) is a quaternary ammonium compound of herbal origin. As it prevents dopaminergic neuronal loss and brain damage, especially related hippocampus, it can be explored in the treatment of PD. This study aimed to assess how BBR affected the behavior of rats with a PD model.

Method: A 2 µg/mL solution of 6- hydroxydopamine-Hbr (6-OHDA) prepared with ascorbic acid 0.2 mg/mL added to put off auto-oxidation. It was kept on ice until it was injected. Rats were grouped into six groups of six rats, each at random. Animals in group 1 were given double-distilled water. (*i. e.*); group 2, received 6-OHDA, group–3, received BBR (50 mg/kg, oral), group 4 received BBR (50 mg/kg) and 1% piperine (PIP); group 5 received BBR (50 mg/kg) and 2% PIP and group 6 received BBR (50 mg/kg) and 3% PIP for 14 days.

Result: BBR therapy has been shown to protect rats from numerous behavioral and metabolic changes caused by 6-Hydroxydopamine and to improve Parkinson's symptoms. The results show a significant improvement in the behaviour of rats with Parkinsonism caused by 6-OHDA when treated with BBR and PIP. The results indicate that PIP's co-administration improves BBR's therapeutic activity in treating PD markedly. The incorporation of 2% PIP shows the best results, as there is not much difference between the 2 and 3% doses, though the activity increases significantly when compared with that of 1% PIP.

Conclusion: According to reports, BBR has a strong anti-effect against Parkinson's, but due to its low bioavailability, it is challenging to use it clinically. The presence study suggests that adding a bio enhancer like PIP may improve the bioavailability of BBR and thus improve its efficacy. The results show that co-administration of piprine greatly enhances the effect of BBR in treating Parkinson's.

Keywords: Behavioral study, Berberine, Drug schedule, Neuroprotective, Parkinson's disease, Piperine (PIP).

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INTRODUCTION

Parkinson's Disease (PD)

Parkinsonism is a chronic, slowly increasing neurological illness causes symptoms which contribute to minimize the quality of life associated with one's health (QOL).[1] Reduced movements, rigidity and tremor are the characteristics of PD.[2] Essay on the Shaking Palsy was the term. Dopamine production via the nigrostriatal pathway is most impaired in PD, resulting in a dopamine shortage, particularly in the corpus striatum and basal ganglia of the brain.[3]

The development and course of neurological disorders are influenced by a variety of metabolic mechanisms. The concepts of oxidative stress and antioxidants may function in the etiology of Parkinsonism, both directly as well as indirectly.[4]

Pill rolling tremors, akinesia, rigidity, kinesia, instable posture, arm swinging in rhythm with legs is disturbed, oculogyric crisis, nervous depression, involuntary tremors.

Signs and Symptoms

The various symptoms are recorded *i.e.,* (i) Motor symptom (a) Cardinal symptoms (b) Other motor symptoms

- Cardinal symptoms

Four symptoms are considered cardinal in PD:

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Tremor

Rest tremor frequency in PD is typically is 3–6 Hz which is low to moderate-range with amplitude ranging from less than 1 to 10 cm broad. The so-called pill-rolling, abduction-adduction tremor is the most characteristic tremor in this disorder. Tremor occurs in tongue, jaw, lower limbs.[5]

Rigidity

Flaccid locomotion of the afflicted section (limbs or neck) during examination reveals increased muscular tone, comprising both flexor and extensor muscle groups.[5]

Bradykinesia

Improper motions of body parts, slowness of movements with a consistently reduced speed are also described as a cardinal feature.[5]

Postural and Gait Impairment

Neuropsychiatric issues can arise as a result of PD. Speech, cognition, mood, behavior, and thought disorders are included. The elderly is more likely to develop Parkinsonism, with the widely held reasons happening beyond the age of 50. Independent of depression or dementia, cognitive deficits occur at both the early and late phases of the disease. Working memory, reaction inhibition, and behavioral flexibility are all affected by these deficits, which primarily affect the prefrontal brain and dopamine-dependent executive processes.[4]

The deficient in postural reflexes, leads to falls in Parkinson's patients. They tend to assume a stooped posture. PD is characterized by a sluggish stride with a thin base and shuffling of small steps, as the posture and gait should be observed in both open corridors and while moving through tiny entrances or spaces.[5]

All measurements of dopamine transmission were hindered at later phases of measurement, and cell loss of dopamine neurons was pervasive. Animal displayed symptom that was analogous to those seen in people with severe Parkinsonism.[6]

Berberine (BBR)

BBR has pharmacological and medicinal chemical applications. BBR, in fact, is an important natural alkaloid for the development of novel, selective, and effective medications through the modification, replacement, and condensation of functional groups in crucial places for the synthesis of diverse bioactive derivatives.

BBR and Memory

BBR has a variety of pharmacological properties. It's an acetylcholinesterase inhibitor comparable to galantamine, a medicine used to treat Alzheimer's disease, and it could be used as a low-molecular-weight neurotrophic agent to treat neurodegenerative diseases like Alzheimer's disease by potentiating NGF-induced differentiation in brain cells.

Furthermore, it has been observed that during cerebral ischemia, excessive NMDA-receptor activation and up-regulation can cause mitochondrial dysfunction and dramatically elevated ROS,[7] suggesting that BBR can reduce ROS levels by suppressing NMDA-receptor. BBR's neuroprotective benefits may be due to its ability to reduce ROS generation.[8]

The anti-amnesic BBR result after 14 days is due to the increase in cholinergic neuronal activity in the both central and peripheral nervous systems.[8] SCOP-induced amnesia is lessened by long-term treatment of BER.[9]

MATERIALS AND METHODS

Grouping and Randomization

Animals are then grouped in to 6 groups of 6 animals each, using random selection:

Group-1, (vehicle) established double distilled water (i.p.);
Group-2, established 6-OHDA
Group-3, established BBR (50 mg/kg, oral)
Group-4, established BBR and piperine (PIP)
Group -5, 6 established BBR (50 mg/kg, oral) with PIP (1, 2 and 3%) for 14 days. 6-OHDA

Induction of Parkinsonism by 6-OHDA

A 2 µg/mL solution of 6- hydroxydopamine-Hbr or 6- OHDA was prepared by using ascorbic acid 0.2 mg/mL. Group 2 animal with 6-OHDA induces PD. For group 4 to 6 inject 6-OHDA one hour before the administration of drug BBR.

Treatments Schedule

A 2 µg/mL solution of 6- hydroxydopamine-Hbr (6-OHDA) prepared with ascorbic acid 0.2 mg/mL added to put off auto-oxidation in ice bath. Male Albino rats with an average weight 250 g was randomLy grouped into six groups of six rats, each. Group 1 was given double-distilled water. (i. p.); Group 2 to 6 received 6-OHDA. Group two was an untreated group. Groups 3 were only given BBR 50 mg/kg BBR on day one. Groups 4 to 6 were administered BBR 50 mg/kg with PIP 1%, 50 mg/kg with PIP 2%, and 50 mg/kg with 3%, respectively orally after one hour of 6-OHDA administration for 14 days. On day 14, the experiment will be terminated, and the following behavioral and biochemical parameters will be measured:

Behavioral

- Escape latency in Morris Water Maze
- Locomotor activity
- Novel object recognition memory
- Passive avoidance test
- Elevated plus maze test.

Statistical Analysis

A one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test, was used to analyze the data. The threshold for statistically significant was set at $p < 0.05$ in all cases.

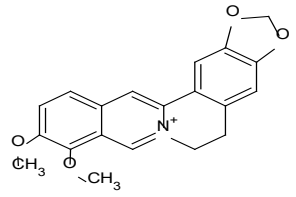

Figure 1: Chemical structure.

RESULTS

All the graph values represent the mean SEM of experimental results. α represents that p<0.001 against standard group whereas * represent p<0.001 against control group

BBR's Influence on 6-OHDA-induced Changes in Many Behavioral Parameters BBR's Effect on Spatial Navigational Task in 6-hydroxydopamine-treated Rat

Previous research shows that briefly the number of 6-hydroxydopamine-supplied animals gradually declined in comparison to the treated group during the training period, although escaping latency significantly increased [[F (5, 30) =232.1, p 0.0001] on the 15th day (p 0.05). BBR (50 mg/kg) improved memory performance compared to 6-hydroxydopamine-treated rats on the 15th day (p 0.05) but some activity shows less effect in this research addition of PIP 1, 2 and 3% with BBR. PIP 2 and 3% and BBR 50 mg/kg improved memory performance compared to 6-hydroxydopamine-treated rats on the 15th day (p 0.05).

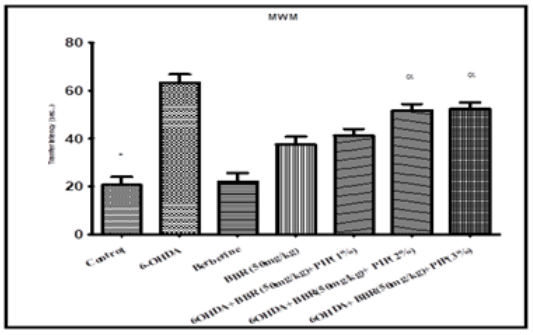

Figure 2: Effect on transfer delay (Morri's water maze).

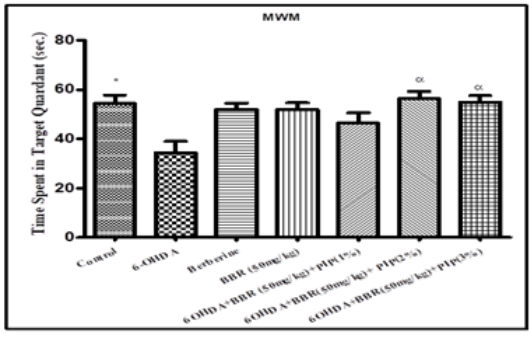

Figure 3: Effect on time spent in target quadrant (Morri's water maze).

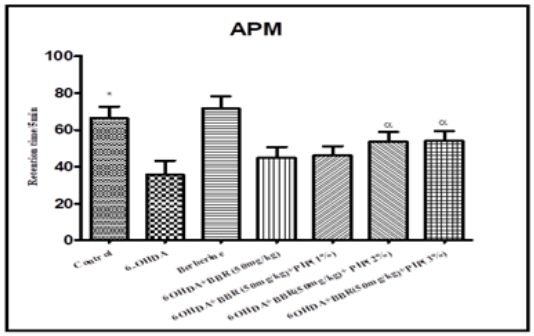

Figure 4: Effect on locomotor activity (Actophotometer).

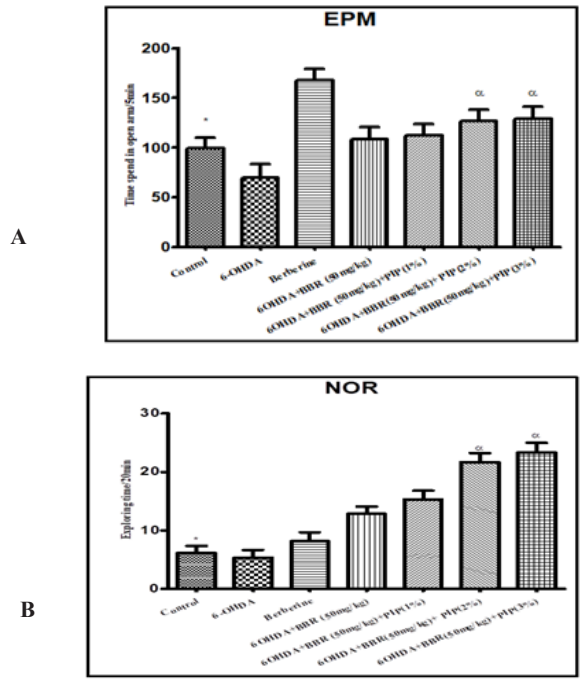

Figure 5: Effect on Exploring time in the object recognition test. (A) 30 min (B) 24 hours.

The number of 6-hydroxydopamine-supplied animals gradually declined in comparison to the treated group during the training period, although escaping latency significantly increased [F (5, 30) = 232.1, p 0.0001] on the 15th day (p 0.05). BBR 50 mg/kg PIP 2 and 3% oral improved memory performance compared to 6-hydroxydopamine-treated rats on the 15th day (p 0.05), whereas rats treated with 6-hydroxydopamine did not exhibit any difference in memory function at a lower dose of BBR (50 mg/kg PIP 1%) (Figures 2 and 3).

BBR's Effect on Locomotors Activity

When compared to the vehicle-controlled institution, 6-OHDA treatment resulted in a substantial decrease in locomotor attention (p 0.05). Similarly, BBR with PIP therapy (50/1, 50/2, and 50/3%, mg/kg, oral.) [F (5, 30) =163.7, p 0.0001] significantly increased locomotor relaxation in 6-OHDA-injected rats (Figure 4). However, when compared to 6-OHDA-treated rats, a lesser dose of BBR with PIP 50/1% mg/kg, oral had no effect on locomotor interest. BBR with PIP (50/3%, mg/kg, oral) demonstrated no significant effect when compared to vehicle-treated rats (Figure 4).

BBR's Effects on Novel Object Recognition Memory

The item reputation test exploration times for the 2 retention lengths are shown in Figures 4 and 5. (30 minutes and 24 hours, respectively). The fast-term 30 minute maintenance C program language period [F (5, 30) =112.6, p0.0001] and the 24 hour maintenance trial [F (5, 30) =139.9, p0.0001] both showed a significant effect of Parkinson introduction and BBR administration. According to a post hoc investigation, 6-OHDA-triggered PD rats explored less to the radical item in both retention trials than non-Parkinson rats (p 0.05).

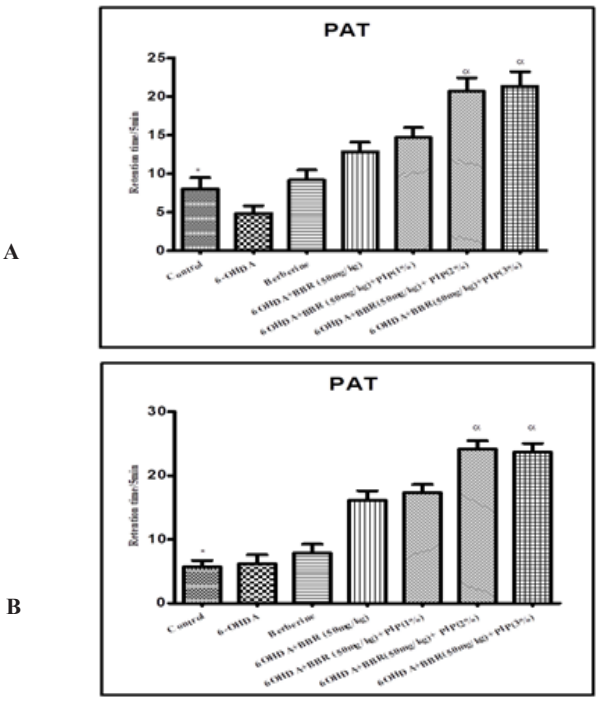

Figure 6: Effect on Exploring time in the passive avoidance test. (A) 30 minute (B) 24 hours.

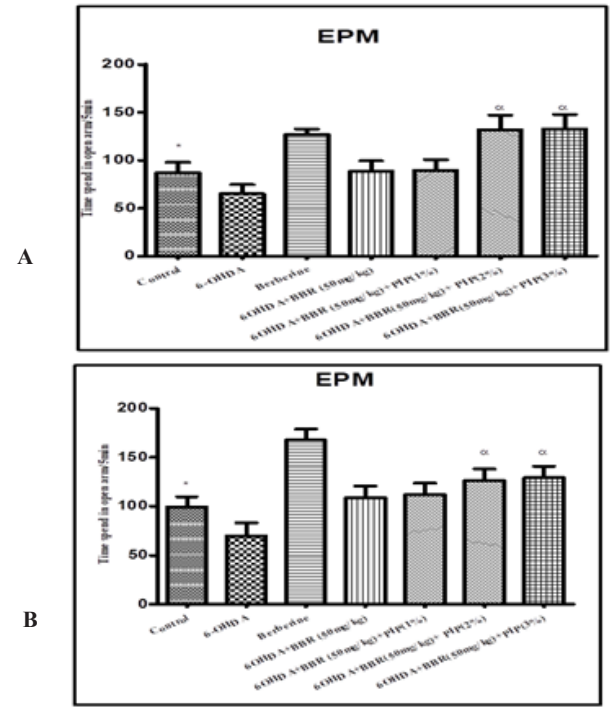

Figure 7: Effect on Exploring time in the elevated plus maze test. (A) 30 minute (B) 24 hour.

Similarly, BBR-treated PD rats examined more unique gad ads in each retention session than the car-treated group (p0.05).

Effect of BBR on Passive Avoidance Test

The research ratios for the passive avoidance check are shown in Figures 7 for the two maintenance periods (30 minutes and 24 hours, respectively A one-way ANOVA showed that the Parkinson introduction and BBR treatment had a significant impact on the fast-term, 30 minute retention language in addition to the 24 hour retention trial (F (5, 30) =139.9, p0.0001). When compared to non-disease Parkinson's rats, 6-OHDA precipitated PD rats explored significantly fewer areas during each retention session ($p<0.05$). Furthermore, in each retention session, BBR with PIP-treated PD rats explored more to passive avoidance than automobile-treated organization rat ($p < 0.05$).

Effect of BBR on an Elevated Plus Maze Test

Illustrate the period spent in open arm for the two retention intervals in the expanded plus maze test (30 min and 24 hours, respectively). One-way ANOVA demonstrated a significant influence of Parkinson's induction and BBR therapy during the 30 minute retention c program language period [F (5, 30) =112.6, p0.0001] as well as the 24 hour retention trial [F (5, 30) =139.9, p0.0001]. During both retention trials, 6-OHDA-induced PD mice explored significantly less of the extended plus maze than non-rats Parkinson's (p0.05). BBR with PIP-treated PD rats investigated more innovative gad ads in both retention trials than the vehicle-treated group (p 0.05) (Figure 7).

DISCUSSION

The current study found that giving rats adequate amounts of BBR protects them from 6-Hydroxydopamine-induced neurotoxicity. We chose a BBR dose (50 mg/kg, Oral) based on a previous study conducted in our laboratory.[10] BBR has anti-parkinsonian activity, but its low bioavailability has made it difficult to use clinically. The current study aims to improve BBR bioavailability by adding bio enhancers such as PIP. The bio-enhancer protective effect of BBR on 6-hydroxydopamine-induced neurotoxicity in PD animal models has not been investigated. In a gift trial, BBR mimicked some of the behavioral changes brought on by 6-hydroxydopamine, offering the first concrete proof of its therapeutic value for PD. The current study found that giving mice adequate amounts of BBR protects them from 6-hydroxydopamine-induced neurotoxicity. We chose a BBR dose (50 mg/kg, Oral) based on a previous study conducted in our laboratory.[10] BBR has anti-parkinsonian activity, but its low bioavailability has made it difficult to use clinically. The current study aimed to see if adding bio enhancers like PIP could improve BBR bioavailability. BBR has not been studied for its bio-enhancer preventive effect on 6-hydroxydopamine-induced neurotoxicity in PD animal models. BBR mimicked some of the behavioral changes caused by 6-Hydroxydopamine in a gift trial, providing the first evidence of its beneficial effect on PD. In rats,[11,12] evidence suggests that a few single DA neurons are implanted inside the SN target, which includes the striatum, globus pallidus (GP), frontal cortex, and thalamus. The wide range of cognitive signals, from distant memory and applied difficulties to severe dementia, constantly complicates PD. 6-OHDA brings on nigrostriatal dopaminergic sores because it generates hydrogen peroxide and hydroxyl radicals. Three main mechanisms—producing

active oxygen by intracellular or extracellular oxidation, hydrogen peroxide production from MAO activity, or blocking the direct mitochondrial respiratory chain—should cause 6-OHDA to activate the catecholaminergic cell. Significant oxidative stress is produced by these occurrences, exacerbated by cytoplasmic calcium unfastening and decreased cyclic Amp uptake, both leading to cell death.[13] Other ROS pathways and nigral cell death are also caused by mitochondrial dysfunction. complex PD (nicotinamide adenine dinucleotide coenzyme Q reductase) degradation in the mitochondrial respiratory chain causes significant mitochondrial disruption. The cellular ATP synthesis charges the paper part of the oxidative phosphorylation (OXPHOS) device, and Complex I is implanted in the interior mitochondrial membrane. There was a decrease in leisure time and a consistent decrease in complex-I status in PD patients' SNpc.[14] After a joint injury brought on by systemic administration of DA receptor tablets, L-dopa, or dopamine release drugs, unilateral 6-OHDA-induced SNpc degeneration results in asymmetric and measurably altered motor behavior.[15] This allows for a smooth and consistent application of wound size and therapeutic agent potential effects.[13] I.C.V. 6-hydroxydopamine treatment causes hypoactivity in mice, similar to teen onset and PD.[16] It causes bradykinesia, muscle weakness, stress, and motor and behavioral problems. Prior research on neurobehavioral variability and motor deficits in mice after 6-OHDA administration[16-19] supported these findings. 6-hydroxydopamine treatment decreased ambulatory activity (as measured by the spectrophotometer) and caused a delay in withdrawal time to avoid idleness (as measured by avoidance testing tools), indicating motor impairment in a study of gifts. BBR daily therapy for 14 days is dose-dependent on 6-hydroxydopamine-induced hypo-locomotion and motor interaction. These findings suggest that giving mice BBR on a daily basis protects them from the behavioral changes caused by 6-hydroxydopamine. More research, however, is required to fully comprehend the process at work.

CONCLUSION

It was reported that BBR have potentent anti parkinsonism effect but due to its low bioavailability it was challenge to use it clinically the presence study aims that adding bio enhancer like PIP may improve the bioavailability of BBR and thus improve its affectivity the results indicate that co administration of PIP improves the effect of BBR many fold.

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