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Original Article

Berberine's Therapeutic Prospects in Parkinson's Disease: A Spotlight on Cholesterol Regulation for Cognitive Improvement

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ABSTRACT

Background: Cholesterol synthesized in astrocytes of the cerebrum plays a pivotal role in regulating hippocampal neurogenesis and cognitive function. Dysregulation of cholesterol metabolism has emerged as a key contributor to the pathogenesis of Parkinson's disease. Elevated cholesterol levels in the brain are associated with increased oxidative stress and subsequent neurodegeneration of hippocampal pyramidal neurons, culminating in cognitive impairment. Berberine, an isoquinoline alkaloid has the potential to modulate cholesterol synthesis through HMG-CoA inhibition. **Aim:** This study aims to elucidate the therapeutic potential of berberine in mitigating cognitive impairment in Parkinson's disease by conferring protection to hippocampal pyramidal neurons through regulating cholesterol homeostasis. **Materials and Methods:** Parkinson's disease was induced in male Sprague Dawley rats through the administration of rotenone (intraperitoneal, 2.5 mg/kg) for 42 days, followed by treatment with the berberine (oral administration, 10 mg/kg and 40 mg/kg) for 21 days. The efficacy of berberine was assessed through evaluations encompassing cognitive function, motor coordination, locomotor activity, biochemical analyses, and histopathological examinations. **Results:** Our findings revealed that berberine, administered intraperitoneally at a dose of 40 mg/kg, effectively ameliorated the symptoms associated with Parkinson's disease. This amelioration was concomitant with reduced cholesterol levels within the brain and an elevation in dopamine levels when compared to the disease-induced control group. The hippocampus of the berberine-treated group showed preserved pyramidal neurons and a decrease in macrophage and microglial infiltration, which were strongly correlated with the reported improvement in cognitive performance. **Conclusion:** Our study underscores the potential therapeutic utility of berberine in mitigating cognitive impairment in Parkinson's disease. The findings presented here provide valuable insight into the mechanisms underlying the beneficial effects of berberine in Parkinson's disease and suggest its promise as a therapeutic agent in managing cognitive deficits associated with this neurodegenerative disorder through regulating cholesterol homeostasis.

Keywords: Parkinson's Disease, Cognitive impairment, Dopamine, Cholesterol, Alpha-synuclein, Berberine.

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INTRODUCTION

Parkinson's Disease (PD) stands as the most prevalent neurodegenerative disease, characterized by a deficiency in dopamine levels and motor impairments. Within the spectrum of PD symptoms, dementia is a widely acknowledged manifestation. Dementia is noted in 10% to 30% of individuals afflicted with PD, with an annual incidence rate ranging from 4.2% to 9.5%.[1] Factors like age, environment, genetics, immunity of the individual, and sex also play a prominent role in the development of PD. Past decade's epidemiological studies conducted on the prevalence of PD among sex differences reveal that; PD has a high impact on men i.e., two times more in rate of prevalence when compared to women.[2] Previous investigations have reported certain distinctive features in PD patients, including hippocampal atrophy, the presence of Lewy bodies, and the occurrence of visual hallucinations.[3]

Among various mechanisms, dysregulation of cholesterol metabolism has emerged as a key contributor to the pathogenesis of PD. Cholesterol synthesis takes place within astrocytes situated in the cerebrum, with these cells' cholesterol actively participating in myelin synthesis by oligodendrocytes and the regulation of synaptic function.[4] Cholesterol

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molecules associate with Apolipoprotein E (APOE) to generate APOE-Cholesterol (APOE-CH) particles. These particles are subsequently released into the extracellular milieu facilitated by ATP-Binding Cassette (ABC) transporters. Following their release, these complexes undergo endocytosis by neurons through Low-Density Lipoprotein Receptor (LDLR) and low-density Lipoprotein Receptor-Related Protein 1 (LRP1) receptors, leading to the separation of APOE from cholesterol.[5] The deposition of cholesterol within neuronal structures exerts deleterious effects, with disturbances in its metabolic processes yielding cytotoxic oxysterols. Dysregulation of cholesterol homeostasis detrimentally affects hippocampal neurogenesis and culminates in the neurodegeneration of hippocampal pyramidal neurons, ultimately giving rise to cognitive deficits[6] (Figure 1). Consequently, an exploration into the impact of cholesterol on Parkinson's disease assumes significance, as it may unveil potential associations between aberrations in cholesterol metabolism and the etiology of the disease.[7] Alpha-synuclein (α-Syn), a 140-residue lipid-binding protein, is abundantly expressed in the brain and primarily localizes within synaptic vesicles, mitochondria, and the endoplasmic reticulum. The actions of α-Syn are intricately governed by the soluble N-ethylmaleimide-Sensitive factor Attachment protein Receptor (SNARE) complex and cholesterol content within lipid rafts. *In vitro* studies have demonstrated that cholesterol modulation influences α-Syn expression and its subsequent aggregation results in the formation of α-Syn oligomers. These oligomers engage with membranes possessing a neutral charge, leading to the adoption of a 'tilted peptide' configuration.[8] This interaction can be influenced by a variety of factors, including fatty acids, phospholipids, and gangliosides, among others.

Berberine, an isoquinoline alkaloid phytochemical derived from several medicinal plants such as Berberis vulgaris (barberry), Berberis aristata (tree turmeric), Berberis aquifolium (Oregon grape), or Tinospora cordifolia, possesses notable anti-inflammatory and anti-cancer properties[9] etc., Berberine has an astounding ability to cross the blood-brain barrier which can exhibit a promising neuroprotective action against neurodegenerative disorders like Parkinson's disease, Alzheimer's disease, cerebral ischemia, anxiety, etc., Recent advancements in drug-targeted delivery techniques and nanotechnology helped in the formulation of berberine in various dosage forms. Such formulated oral berberine had elevated the dopamine levels in the brain, alleviating the symptoms of Parkinson's disease.[10] Furthermore, it has been demonstrated to significantly reduce the cholesterol levels in murine models through the inhibition of 3-Hydroxy-3-Methylglutaryl coenzyme A (HMG CoA) reductase via phosphorylation mediated by the adenosine monophosphate-Activated Protein Kinase (AMPK) pathway. So, in the above-discussed context, the inhibition of HMG CoA reductase by berberine may effectively diminish cholesterol levels within the brain, thereby impeding the aggregation of α-synuclein, which in turn protects the pyramidal neurons.[11]

So, the study aims to elucidate the therapeutic potential of berberine in mitigating cognitive impairment in Parkinson's disease by conferring protection to hippocampal pyramidal neurons through regulating cholesterol homeostasis.

MATERIALS AND METHODS

Chemicals

The Rotenone was purchased from Sigma-Aldrich Solution. The Berberine tablets were obtained from Barbotine, Akumentis Healthcare Limited. The Levodopa-Carbidopa tablets (Syndopa) which contained 200 mg levodopa and 50 mg carbidopa obtained from JSS Hospital Pharmacy, Mysore.

Animal model and Experimental design

Sprague Dawley male rats 6 to 8 weeks and body weight 150-250 g were acquired with an IAEC approval No: JSSAHER/CPT/IAEC/081/2021. Male rats were selected for this study based on the epidemiological factors as the incidence of PD is more predominant in males than females. Animals were divided into six groups and kept in polypropylene cages with an aerated environment retaining temperature at 23±3°C and humidity levels at 40-70%. The rooms followed the 12 hr L and 12 hr D cycle and minimal sound (<80 decibels). Animals were fed with quality rodent feed and pure water. Animals were allowed to familiarize themselves with the new environment for 7 days before the commencement of the experiment. All the animal investigational procedures were approved and supervised by IAEC- JSSCPM (Table 1).

Table 1: Grouping of the animals. The animals were divided into six groups *n*=6.

Groups	No. of animals	Treatment, Dose, Duration and Route
Control	6	Vehicle (sunflower oil).
Disease induced	6	Rotenone (2.5 mg/kg X 42 days i.p).
Standard	6	Rotenone (2.5 mg/kg X 42 days i.p)+levodopa (10 mg/kg i.p X 21 days).
Low dose	6	Rotenone (2.5 mg/kg X 42 days i.p)+Berberine (10 mg/kg, p.o) (21 days of study).
High dose	6	Rotenone (2.5 mg/kg X 42 days i.p)+Berberine (40 mg/kg, p.o) (21 days of study).
Combination	6	Rotenone (2.5 mg/kg X 42 days i.p)+Berberine (40 mg/kg X 21 days, p.o)+levodopa (10 mg/kg i.p X 21 days).

Evaluation of Muscle coordination (Rotarod test)

The rats were previously trained in the rotating cylinder before the test day at 25 rpm speed twice daily. On the experiment day, the speed was maintained at 25 rpm during the test session. The rats were placed on the rod lane and the timer was started. Once the rat fell off the rod, the latency time to the fall was recorded. Each rat was tested for three trials at a five-minute interval with a maximum trial length of 300 s per trial. The average latency time for each rat was calculated.[12]

Evaluation of Locomotory Activity (Actophotometer)

The locomotor activity of the rats was recorded by using an actophotometer. The actophotometer was provided with a photocell connected to the digital counter. The animals were placed inside the photocell and the digital counter was started. The locomotory activity of all animals was recorded and the count was kept track for 5 min.[13]

Evaluation of Cognitive Function (Novel Object Recognition Test)

The test was conducted with two objects: a familiar object and a novel object both objects should contain the same height and volume but are different in appearance. During the period of habituation, the animals were allowed to explore the empty arena for 5 min and placed back in their respective cages. On the training day, the animals were placed in an arena but with two familiar objects kept on either side of the apparatus. On the third day, the animals were allowed to explore the arena in the presence of a familiar object and a novel object. Rodents usually had an exploring nature. The amount of time taken by the animal to explore the novel object was recorded. If the total exploration time of any animal is <10 s, then such animals were not considered for the test. Sitting/ climbing on the object wasn't measured as exploration. This test is used for assessing the impaired cognitive agility of rodents.[14]

Evaluation of Biochemical Estimation

Total cholesterol

The amount of cholesterol present in the sample is estimated by the colorimetric method. The cholesterol in the sample is converted into a colored complex and then its absorbance is measured at a wavelength of 505 nm. Based on the cholesterol levels, the color intensity varies.[15]

Triglycerides

The amount of triglyceride present in the sample is estimated by the colorimetric method. The triglyceride in the sample is converted into a colored complex and then its absorbance is measured at a wavelength of 505 nm. Based on the cholesterol levels, the color intensity varies.[16]

HDL

The amount of HDL present in the sample is estimated by the colorimetric method. The HDL in the sample is converted into a colored complex and then its absorbance is measured at a wavelength of 600nm. The intensity of the color formed is directly proportional to the amount of HDL present in the sample. The cholesterol esters are broken down into cholesterol and fatty acids. The cholesterol is oxidized and converted into Cholestenone and H_2O_2. H_2O_2 is added with 4 amino acids to produce color.[17]

Dopamine

The brain samples were homogenated with the help of HPLC-grade ice-cold methanol. After that, the samples were kept in a cooling centrifuge at 4°C and 20000 rpm for 15 min. Collected the supernatant, and stored it at -80°C until performing the HPLC.[18]

Histopathological studies

All animal brain samples were collected and stored in a 10% formalin solution and neuronal count was performed by Nissl staining.

Statistical analysis

All the raw data obtained was analysed using Graph pad Prism 8.0. The data was subjected to two-way ANOVA followed by Tukey's Multiple Comparison test. Values of $p<0.05$ were considered statistically significant.

RESULTS

Evaluation of the effect of berberine in rotenone-induced Parkinson's disease model by muscle coordination (Rotarod test)

The administration of rotenone to male Sprague Dawley rats caused a fall in motor functions. The animals started to lose motor coordination and grip strength after the first week of administration of rotenone. The motor function of the animals was assessed using the rotarod test, and the motor function was found to decline compared to the control group.

The berberine administration shows a significant increase in motor function in the rotenone-induced Parkinson's model. The animals treated with a high dose of berberine showed a significant increase (9.4±1.16) in motor function, but the combination group treated with both berberine and levodopa (11.2±2.86) showed more effect than the high dose (Figure 2a).

Evaluation of the effect of berberine in rotenone-induced Parkinson's disease model by Locomotory activity (Actophotometer)

In the present study, the animals are subjected to an actophotometer to evaluate the effect of locomotion. The results

show that locomotion of the disease-induced group (220±5.3) was significantly reduced when compared to the control group (451±3.63). Upon berberine treatment, the animals showed an increase in locomotor activity for low dose (264±5.6), high dose (289±2.8), and combination dose (273±2.46). Compared to the low, high, and combination doses, the high dose (289±2.8) (p<0.001) shows a significant increase in locomotor activity (Figure 2b).

Evaluation of the effect of berberine in rotenone-induced Parkinson's disease model by Cognitive function (Novel Object Recognition Test)

In the present study, the disease-induced group shows a significant decrease (p<0.01) in exploration time when compared to the control group. On administration of berberine, the exploration time increased significantly (p<0.001). A high dose of berberine (40 mg/kg), (9.2±0.48) shows increased exploration time when compared with the diseased-induced group (Figure 2c).

Evaluation of the effect of berberine in rotenone-induced Parkinson's disease model by biochemical estimation

Total cholesterol

The data obtained on the effect of treatment with various doses of berberine on total cholesterol is shown in Figure 3a. The data reveal that induction with rotenone significantly increases the total cholesterol level to 35.3±1.36. Treatment with various doses of berberine shows a significant decrease in total cholesterol level (low dose -24.06±1.49, high dose -28.8±0.93, combination -25.5±0.79) respectively. Moreover, the highest dose of berberine 28.8±0.93 shows an approximately equal value to that of the standard treated group 30.8±1.36.

Triglycerides

The data obtained on the effect of treatment with various doses of berberine on triglycerides is shown in Figure 3b. The data

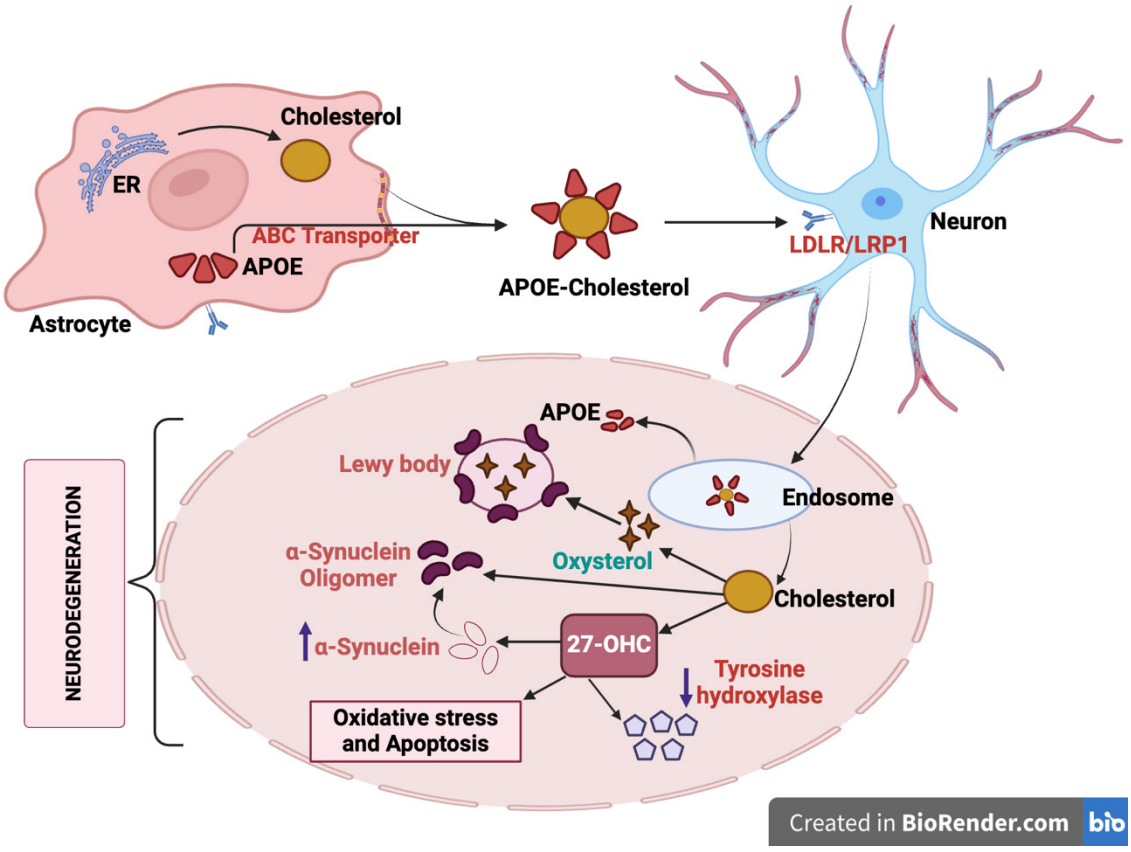


Figure 1: Cholesterol metabolism in Parkinson's disease (PD).

reveal that induction with rotenone significantly increases the triglyceride level to 100±1.05. Treatment with various doses of berberine shows a significant decrease in total cholesterol level (low dose -62.9±3.13, high dose -69.39±1.69, combination -73.3±2.23) respectively. Moreover, the highest dose of berberine 69.39±1.69 shows an approximately equal value to that of the standard treated group 70.8±1.36.

HDL

The data obtained on the effect of treatment with various doses of berberine on HDL is shown in Figure 3c. The data reveal that induction with rotenone significantly increases the HDL level to 87.2±2.36. Treatment with various doses of berberine shows a significant decrease in HDL level (low dose-68.5±4.24, high dose-48.04±3.54, combination-61.28±3.55) respectively. Moreover, the highest dose of berberine, 48.04±3.54 shows an approximately equal value to that of the standard treated group 50.04±1.36.

The results were expressed in mean±standard error of the mean, no. of. animals=5; i.e. analysed by subjecting raw data to two-way ANOVA followed by Tukey's Multiple Comparison test.

Dopamine

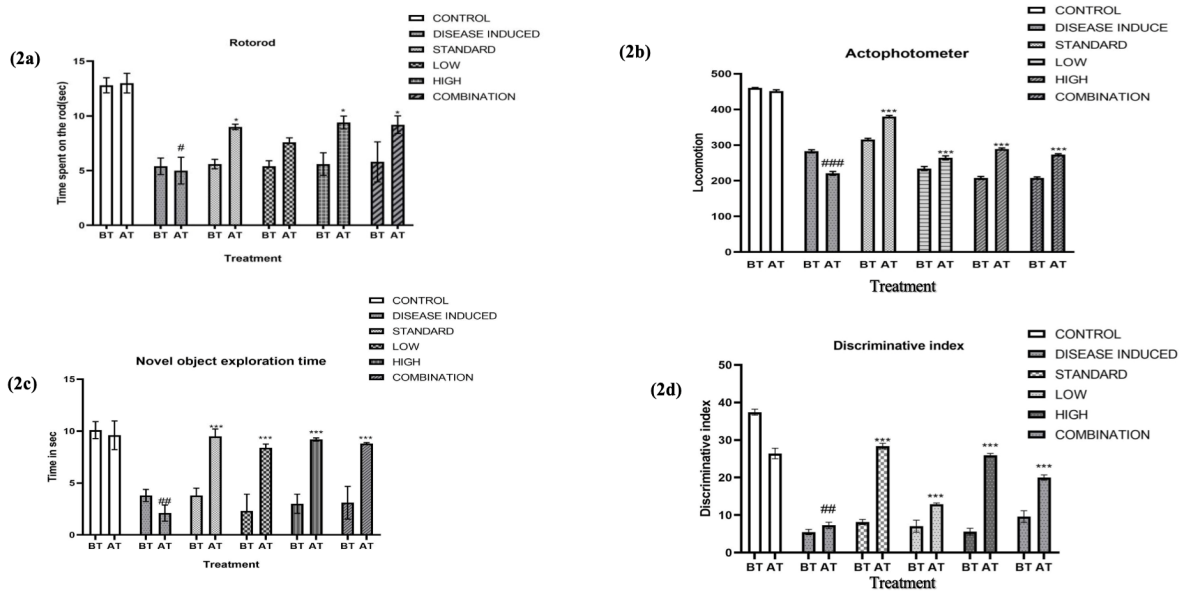
The data obtained on the effect of treatment with various doses of berberine on dopamine is shown in Figure 4. The data reveal that induction with rotenone significantly decreased dopamine levels. Treatment with various doses of berberine shows a significant increase in the dopamine level (low dose-0.89 mg/mL, high dose-0.989 mg/mL, combination dose-0.97 mg/mL) respectively (Table 2). Moreover, the highest dose of berberine shows approximately equal value to that of the standard treated group 1.00 mg/mL.

Table 2: Evaluation of the effect of berberine on Dopamine in rotenone-induced Parkinson's model.

Group	Concentration of Dopamine (mg/mL)
Control	0.990
Disease induced	0.708
Standard	1.00
Low dose	0.89
High dose	0.989
Combination	0.97

Histopathology

The histopathological data obtained on the effect of treatment with various doses of berberine on rotenone-induced Parkinson's disease is shown in Figure 5. The data revealed that the control and standard groups had normal nerve cells in the hippocampal region of the brain. Induction of rotenone showed the presence of macrophages, microglia, and degenerated pyramidal neurons in the diseased group. Treatment with various doses of berberine shows a significant decrease in the presence of macrophages and microglia in low dose; high-dose groups and the combination showed results similar to that of control and standard.



denotes p<0.01 when compared to control,
****,*** denotes p<0.01 and p<0.001 when compared to disease group**

Figure 2: Effect of Berberine 2a - on motor coordination (Rotorod test). 2b – on Locomotory Activity (Actophotometer). 2c –on Cognitive function (NORT). 2d –on Discriminative index.

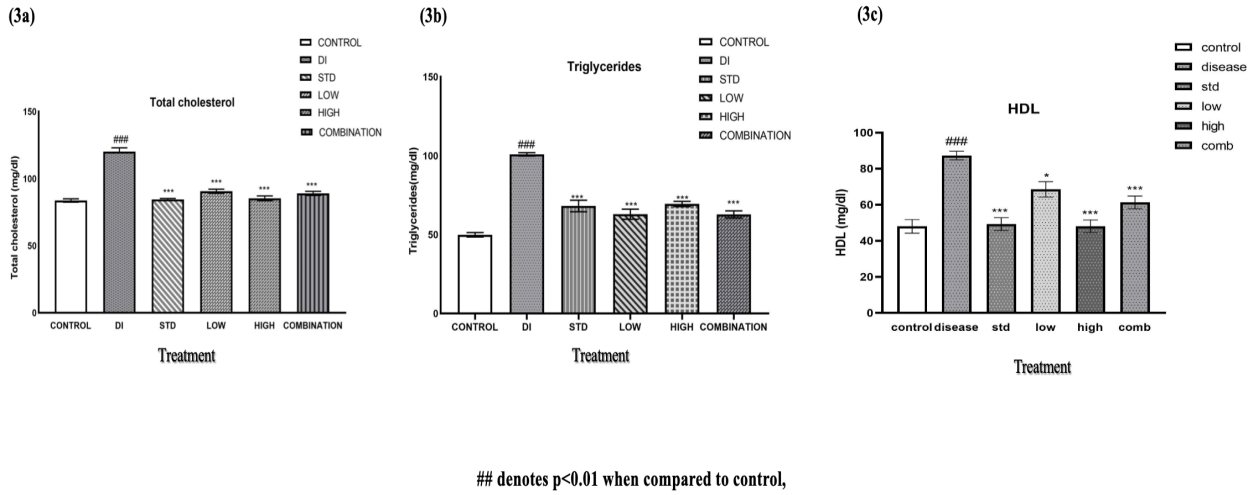


Figure 3: Effect of Berberine 3a: on total cholesterol. 3b: on triglycerides. 3c: on HDL.

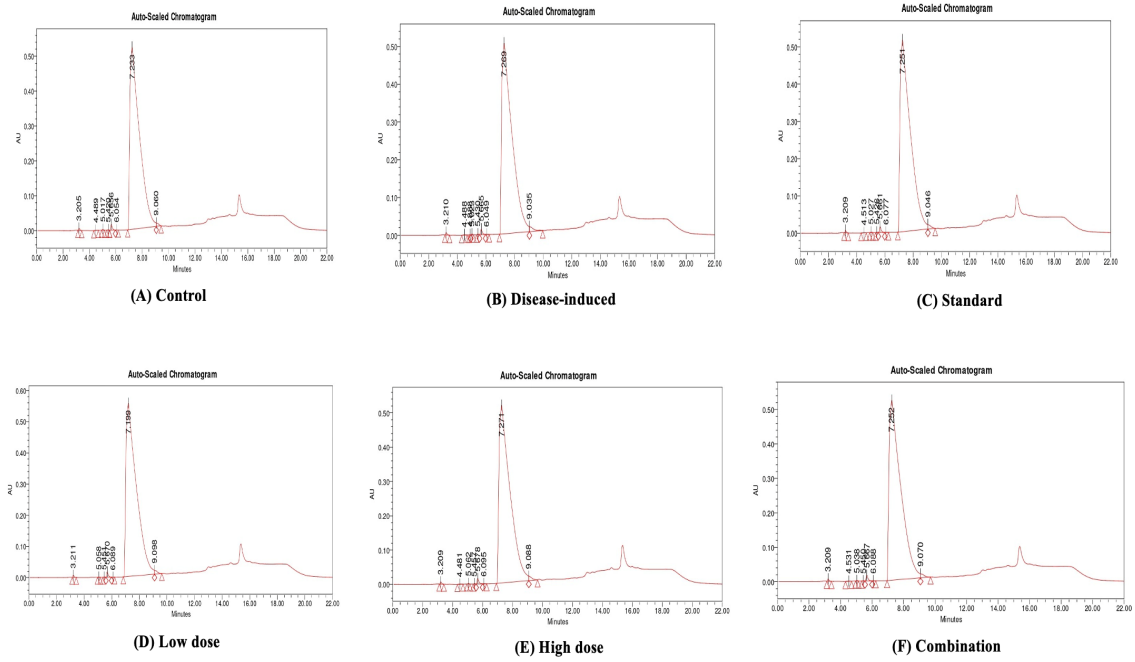
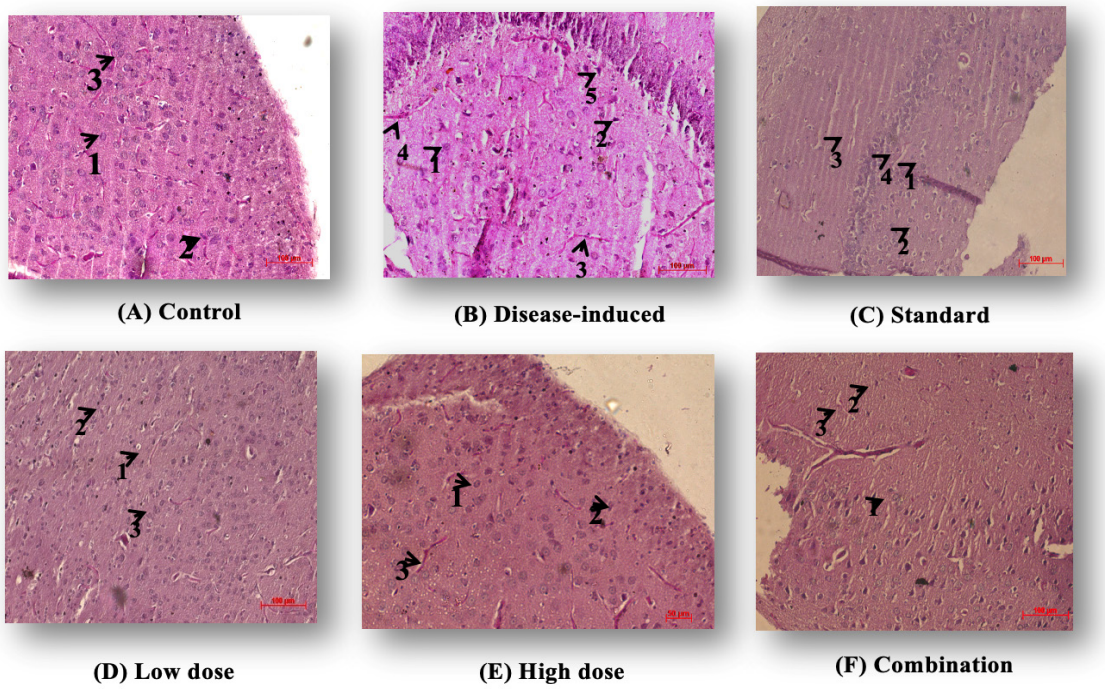


Figure 4: Effect of Berberine on Dopamine of rotenone-induced Parkinson's model.

DISCUSSION

The primary objective of this study was to assess the therapeutic potential of berberine in addressing cognitive impairment associated with PD by focusing on the protection of hippocampal pyramidal neurons through the regulation of cholesterol homeostasis. Cholesterol arises as a central signalling molecule that initiates within astrocytes and establishes a connection between the amplification of inflammation in neurons and microglia. To induce PD-like symptoms, we administered rotenone (i.p, route), which resulted in observable deficits in cognitive function, locomotor activity, muscle coordination, and cholesterol imbalance. These symptoms were evaluated through behavioural assessments. After the induction period of 42 days, treatment started with two doses of berberine (low dose–10 mg/kg, high dose–40 mg/kg) and a combination dose (berberine 40 mg/kg with levodopa). Previous studies have established that berberine, an isoquinoline alkaloid, possesses a multifaceted role in neurodegenerative processes, owing to its antioxidant and anti-apoptotic properties. Additionally, it serves as an inhibitor



In the above fig., the numbers represents the below data:
1 – Nerve cell; 2 – Glial cell; 3 – Blood vessel; 4 – Infiltration with the presence of macrophages and microglial cells ; 5 – Degeneration of pyramidal neurons

Figure 5: Effect of Berberine on the hippocampal region of the rat's brain.

of cholesterol synthesis through its effect on the HMG-CoA enzyme.

In this study, we found compelling evidence that berberine significantly improved cognitive functions in diseased animal subjects. The results obtained from behavioural assessments, including the rotarod test, Novel Object Recognition Test (NORT), discriminative index, and locomotor activity analysis; collectively demonstrate a significant improvement in the berberine-treated group compared to the rotenone-induced group. These improvements in motor coordination, memory recognition, and locomotion indicate the potential neuroprotective and cognitive-enhancing effects of berberine. Furthermore, we conducted biochemical analyses to investigate the impact of berberine treatment on relevant metabolic parameters. Notably, the PD-induced group exhibited elevated levels of total cholesterol, triglycerides, and High-Density Lipoprotein (HDL). However, treatment with berberine led to a significant reduction in these parameters. This suggests that berberine may exert its cognitive benefits, at least in part, through its ability to modulate lipid metabolism and mitigate dysregulation in cholesterol levels. As every drug has its adverse effects at a particular range, LD_{50} of berberine also varies on the route of administration. Toxicity studies were done on berberine at various doses and found that it has an impact on spleen weight, blood cell count, etc., Investigations reveal that 5 mg/kg of berberine can influence the proliferation of lymphocytes and delayed-type hypersensitivity reactions; 10 mg/kg can influence decreased blood cell count; 100 mg/kg has evoked vomiting (6-8 hr) and caused death in in vivo screening models.[19] This study was done using low and high doses of berberine i.e., 10 mg/kg and 40 mg/kg which may cause the above-mentioned adverse effects upon long-term administration at negligible ranges. These effects can be normalized by the co-administration of supplements along with berberine, which may contribute to effective neuroprotective activity.

In summary, this study provides compelling evidence that berberine holds promise as a therapeutic agent for ameliorating cognitive impairment in PD. Its neuroprotective properties, coupled with its influence on cholesterol metabolism, underscore its potential for preserving hippocampal pyramidal neurons and improving cognitive function in the context of this neurodegenerative disease. These findings contribute to our understanding of the multifaceted mechanisms by which berberine may offer therapeutic benefits for Parkinson's disease.

CONCLUSION

Administration of rotenone in the i.p route induced Parkinson's along with upregulation of cholesterol in disease group animals. Administration of berberine (low, high, and combination doses) significantly reduced Parkinson's symptoms. Berberine

also reduces total cholesterol, triglycerides, and HDL levels. The cognitive function improvement can be correlated with the protection of hippocampal pyramidal neurons in the berberine-treated group. Hence, the present study shows that the administration of berberine produces an anti-Parkinson's effect through cholesterol regulation, which protects the pyramidal neurons, resulting in cognitive improvement.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The experimental design was accepted by the Institutional Animal Ethics Committee (IAEC) to carry out the research and the IAEC approval No is JSSAHER/CPT/ IAEC/081/2021. The care of rats was taken as per IAEC and CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) guidelines.

ABBREVIATIONS

PD: Parkinson's disease; **HMG-CoA:** 3-hydroxy-3-methylglutaryl coenzyme A; **α-Syn:** Alpha-synuclein; **APOE:** Apolipoprotein E; **APOE-CH:** APOE Cholesterol; **LDLR:** Low-density lipoprotein receptor; **AMPK:** Adenosine monophosphate-activated protein kinase; **ER:** Endoplasmic reticulum; **27-OHC:** 27- hydroxy cholesterol.

SUMMARY

This study aims to evaluate the therapeutic potential of berberine in cognitive impairment associated with PD by focusing on the protection of hippocampal pyramidal neurons through the regulation of cholesterol homeostasis. The study showed that rotenone administration results in PD-like symptoms like impairment in cognitive function, locomotor activity, muscle coordination, and cholesterol imbalance. Treatment with berberine significantly improved cognitive functions. Berberine treatment also led to a reduction in elevated levels of total cholesterol, triglycerides, and high-density lipoprotein. These findings suggest that berberine is a potent therapeutic agent for ameliorating cognitive impairment in PD by protecting hippocampal pyramidal neurons through modulating lipid metabolism.

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