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Evaluation of anti cataleptic principles of medicinal plant extracts against parkinson‘s disease

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Abstract: *Betula pendula*is a well-known plant which is being used in Indian traditional system which has been reported to have a number of uses. But the role of ethanolic extract of this leaves in the treatment of some CNS associated disorders has not been evaluated. Hence this dissertation is emphasized to explore the effect of ethanolic extract of this leaves on haloperidol induced catalepsy in rats. In the present study the effect of EEBP on extra pyramidal symptoms such as rigidity, motor co-ordination and depression, key parameters found in Parkinson's disease was studied. In haloperidol induced catalepsy EEBP at the dose of 400 mg/kg exhibited significant anticataleptic activity. EEBP showed comparable anticataleptic actions with that of standard drug L-DOPA+ carbidopa. EEBP at a dose of 400 mg/kg significantly, increase the exploratory behaviour like head dipping and line crossing in haloperidol administered rats. The standard drugs L-DOPA+carbidopa significantly increased the exploratory behaviour in haloperidol administered rats. From the observations of above studies it could be envisaged, that the protective effect of EEBP against symptoms of Parkinson's disease (catalepsy) is due to regulation in neurotransmitters i.e. dopamine, serotonin, glutamate and antioxidant enzyme systems which are playing an important role in protection of catalepsy. Further studies have to be conducted on the various extracts and isolated principles of the plant for their effects on other CNS disorders.

INTRODUCTION

Betula pendula is one of Britain's most common native trees and is also widespread across Europe. It was one of the first trees to regenerate itself in this country after the Ice Age. It is a medium sized, deciduous tree, growing up to 25m in height. Its branches and stems arch gracefully giving it an elegant appearance, hence the name Lady of the Woods.[4,5] Early in spring, catkins will appear closely followed by bright green foliage[5]. The leaves are small and triangular, wide at the base and with double toothed margins. In Autumn they turn a beautiful golden yellow.[5] The attractive white bark adds to the beauty of this tree and also gives it winter interest. As it ages, the bark develops dark cracks and crevices at the base

Chemical constituent of *betula pendula*

These are the chemical constituents present in betula pendula leaf extract. They are Betulin, Betulinic acid Platyphylloside, Papyriferic acid, Procyanidin[5], Proanthocyanidin.

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Medical Uses of betula pendula

Birch leaves flushing therapy for bacterial and inflammatory diseases of urinary tract and renal gravel as well as assisting with rheumatic complaints

Traditional uses of betula pendula

Birch leaves were classified as a traditional herbal medicine based on many years of experience, birch leaves[5] can be used to increase the amount of urine and thus used for flushing the urinary tract in light urinary problems. They are traditionally used to help the excretory function of the kidneys or to improve the condition of rheumatic complaints.

Literature survey

Central Nervous System associated diseases are appearing as a major threat in the future because of increasing mental stress, work load and strain which are essential in developing world. Unknowingly this throws in to a state where there is more chance of CNS disorders. Atmospheric pollutants, toxins also causing neurodegenerative diseases like Parkinson's disease and Alzheimer's disease**.** Herbal drugs are having diversified uses are always an alternative option to the synthetic drugs which are well known for their adverse effects. Since the existing antiparkinson's drugs encounter many side effects and need for prolonged treatment including questionable efficacy in the treatment, may cause Parkinson's related movement problems like hallucinations and orthostatic hypotension.[1,2] These reasons force the area of research to find new and improved treatments which will encounter the adverse effects and drawbacks of the existing treatments.

Long term treatment with haloperidol, a classical neuroleptic drug widely used for the treatment of schizophrenia and affective disorders can lead to Parkinson's like symptoms. It blocks dopamine receptors, and concomitant increase in turnover of this amine may contribute haloperidol[3] toxicity due to generation of free radicals and increased lipid peroxidation. Dementia has been associated with drug-induced parkinsonism and has been suggested to support the role of underlying brain damage.

A wide variety of pathological conditions including cancer, rheumatoid arthritis, Alzheimer's disease, diabetes mellitus, ischemia, atherosclerosis and Parkinson's disease[4] appear to have etiological relation to the reactive oxygen species (ROS) induced and free radical mediated oxidation of biomolecules, which take place in conditions with inadequate antioxidant defence stress. Prevention of the initial cellular damage caused by these species has been the subject of intense investigation and resulted in the discovery of several naturally occuring or synthetic substances, which have been accredited as potent antioxidants.

Since *Betula pendula* was widely used in Ayurvedic preparations for some urinary infections and having antioxidant property, an attempt has been made to evaluate the role of *Betula pendula* in the treatment Parkinson's disease which if proven to be satisfactory will be beneficial in the prevention of this disease in future.

Experimental protocol was designed with the following objectives:

1) To evaluate the activity of ethanolic extract of *Betula pendula* alone in the haloperidol induced catalepsy.

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2) To compare the anticataleptic activity of L-DOPA+Carbidopa combination in haloperidol induced catalepsy.

The following studies were performed on the leaves of *Betula pendula*).

- ❖ Preparation of ethanolic extract of *Betula pendula* leaves.
- ❖ Preliminary phytochemical screening of ethanolic extract.
- ❖ Acute oral toxicity study.
- ❖ *Invivo* pharmacological evaluation.
- Anticataleptic activity using block method.
- Exploratory behavior in hole board apparatus.

3. TOXICOLOGICAL EVALUATIONS

ACUTE ORAL TOXICITY STUDY

The procedure was followed by using OECD 423 (Acute Toxic Class Method). The acute toxic class method is a step wise procedure with three animals of a single sex per step. Depending on the mortality or moribund status of the animals and the average two to three steps may be necessary to allow judgment on the acute toxicity of the test substance. This procedure results in the use number of animals while allowing for acceptable data based scientific conclusion. The method used to defined doses (5, 50, 500, 2000 mg/kg body weight) the results allow a substance to be ranked and classified according to the Globally Harmonized System (GHS) for the classification of chemicals which cause acute toxicity (OECD, 2002).

EXPERIMENTAL PROCEDURE

Female wistar rats weighing 150-250 gm were used for the study. The starting dose level of EEGS was 2000 mg/kg body weight p.o as most of the crude extracts possess LD 50 value more than 200 mg/kg p.o. Dose volume was administered 0.2ml per 100gm body weight to overnight fasted rats with were *ad libidum*. Food was withheld for a further 3-4 hours after administration of EEGS and observed for signs for toxicity. The body weight of the rats before and after administration were noted that changes in skin and fur, eyes, mucous membranes, respiratory, circulatory, autonomic and central nervous system and motor activity and behavior pattern were observed and also sign of tremors, convulsions, salivation, diarrhea, lethargy, sleep and coma were noted. The onset of toxicity and signs of toxicity also noted.

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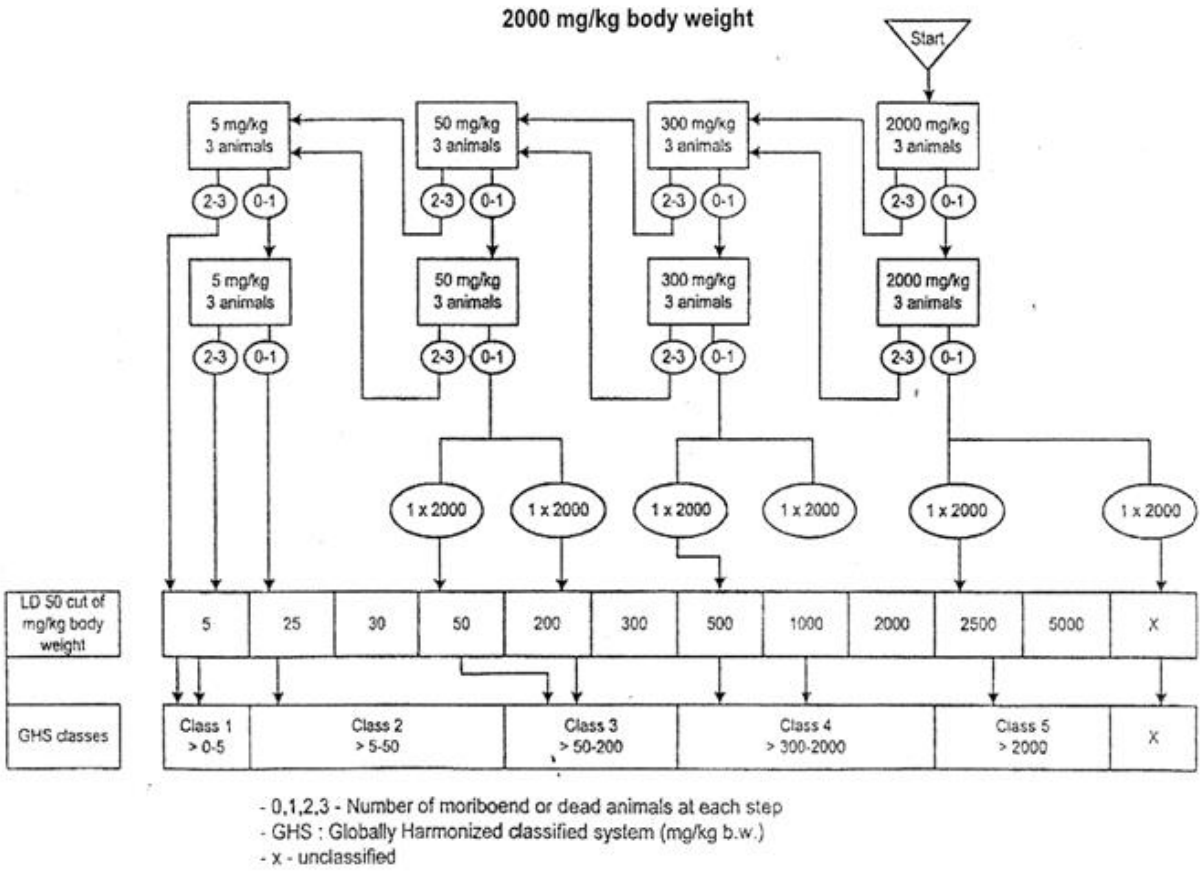

Fig. 1: Flow chart for acute toxic class method (OECD guidelines 423)

4. PHARMACOLOGICAL STUDIES

4.1 Catalepsy induced by chronic haloperidol administration in experimental rats.[30,31,32,.]

Haloperidol (1.0 mg/kg, ip) was administered daily to the rats for a period of 20 days to induce catalepsy. Plant extract and standard drugs were administered orally 30 min before to the haloperidol treatment. The animals were divided in to five groups, each containing 6 animals.

GROUP I : The animals received 1% tween 20 (5 ml/kg, po) and served as control.

GROUP II : The animals received haloperidol (1.0 mg/kg, ip) and served as negative control.

GROUP III: The animals received haloperidol (1.0 mg/kg, ip) and treated with L-DOPA+Carbidopa (100+25 mg/kg, po) suspended in 1% tween 20. This group served as standard.

GROUP IV : The animals received haloperidol (1.0 mg/kg, ip) and treated with EEBP (200 mg/kg, po) suspended in 1% tween 20.

GROUP V: The animals received haloperidol (1.0 mg/kg, ip) and treated with EEBP (400 mg/kg, po) suspended in 1% tween 20.

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Invivo pharmacological studies were carried out on last day of the experiment, and then the animals were sacrificed for biochemical parameters.

***In vivo* pharmacological studies:**

4.2 Effect of the EEBP and standard drugs L-DOPA+Carbidopa on haloperidol induced catalepsy in rats (Block method 0-3.5 scale).[28,29]

The effect of test drug and standard drugs on haloperidol induced catalepsy was studied by the following method.

Severity of catalepsy was measured every 30 min, thereafter up to a total duration of 3 hours. Catalepsy of an individual rat was measured in a stepwise manner by a scoring method as described below. The method assessed the ability of an animal respond to an externally imposed posture.[25,26]

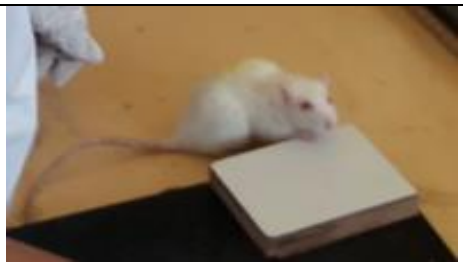
STAGE I: The rat was taken out of the home cage and placed on a table. Rat moves freely no score was given.

STAGE II : If the rat failed to move when touched gently on the back or pushed, score of 0.5 assigned.

STAGE III: The front paws of the rat were placed alternately on a 3 cm high block. If the rat failed to correct the posture within 15 sec, a score of 0.5 for each paw was added to the score of Step I.

STAGE IV: The front paws of the rat were placed alternately on a 3 cm high block. If the rat failed to correct the posture within 15 sec, a score of 1 for each paw was added to the scores of Step I, Step II. Thus for an animal, the highest score was 3.5 (cut-off score) and that reflects in total catalepsy.

STAGE 1



STAGE 2

STAGE 3

STAGE 3

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Fig-2: Cataleptic stages in rats

4.3 Effect of the EEBP and standard drugs L-DOPA+Carbidopa on exploratory behaviour (Head dipping)[7,9,10]

The effect on exploratory behavior (head dipping) was measured for 10 min at every 30 min upto 3 hours using hole board.

The hole board made of plywood has the size (60 cm X 60 cm, 3 mm thick). The mat finished of the upper surface avoids reflections which might alter the behaviour of the animal. The board embodies 9 uniformly distributed holes each of 5 cm in diameter. Each rat was acclimatized for 10 min and number of holes explored through head plunging acts during the total observation time period were noted. Care has to taken to avoid multiple events (two or more head plunging in quicker session). A fresh exploration was considered when the animal neatly plunged its head once and did something else in between like grooming, taking a short walk etc. before plunging its head for the next time. One animal at a time was tested for each activity.

Fig. 3. Exploratory behavior (head dipping) was measured using hole board

4.4 Effect of the EEBP and standard drugs L-DOPA+Carbidopa on exploratory behaviour (Line crossing)[30,31]

The effect on exploratory behavior (line crossing) was measured for 10 min at every 30 min upto 3 hours using hole board.

The hole board made of plywood has the size (60 cm X 60 cm, 3 mm thick). The mat finished of the upper surface avoids reflections which might alter the behaviour of the animal[21,22,23]. The board embodies 9 uniformly distributed lines. Each rat was acclimatized for 10 min and the

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number of line crossing acts, during the total observation period was counted. Care has to taken to avoid multiple events.

5. RESULTS

PLANT AUTHENTIFICATION:

The leaves of betula pendula are collected and it is identified by identified and authentificated by Dr.K.Madhava Chetty ,plant taxonomist, Assistant professor, Department of botany ,sri venkateswara university, Tirupathi, Andhra Pradesh, India.

COLLECTION AND PREPARATION OF PLANT EXTRACT

The fresh leaves were collected and dried then finally grinded,this powder was mixed with ethanol and water in the ratio of 50:50.then the extractions were performed with constant stirring at 4 ± 1^0C for 24 h, in the dark the extract solutions of betula pendula were recovered by filtration using whatman filter paper[24,25], 0.45µm. the supernant was measured and excess of ethanol was removed under vaccum using a rotary evaporator and frozen at at 80^0c for 24h.all extracts were dried in a freeze dryer ubder vaccumat-60^0c for three days to remove moisture[11,12,14].

PRELIMINARY PHYTOCHEMICAL SCREENING

The percentage yield and consistency of various extracts of leaves of *Betula pendula* were presented in the table 1. The ethanol extract gives the high percentage of yield and it was found to be 14.50%w/w.

Table 1: Percentage yield and Consistency of *Betula pendula* extracts

Parameter	Ethanol Extract
Percentage of yield (w/w)	14.50
Consistency	Sticky

The results of phytochemical studies of various extracts of leaves of *Betula pendula*were presented in the table 2. The various extracts revealed the presence of phytoconstituents such as steroids, triterpenoids, flavonoids glycosides, tannins, fixed oils, gums and mucilages.

Table 2: Phytochemical studies of *Betula pendula* extract

Tests	Ethanol
Alkaloids	-
Carbohydrates	-
Steroids	+
Triterpenoids	+
Flavonoids	+

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Glycosides	+
Gums & mucilage	+

– / + = Absence / Presence

From the results of the phytochemical screening of extracts of *Betula pendula*, it is concluded that the medicinal value of this plant may be attributed due to the presence of various phytoconstituents viz., alkaloids, carbohydrates, triterpenoids, flavonoids, tannins, gums and mucilages. The ethanol extract gives high percentage yield. Hence, we have evaluated the ethanol extract of the leaves of *Betula pendula* for screening the various pharmacological potential.

ACUTE ORAL TOXICITY STUDY

Table 3: Acute Toxicity class method OECD guidelines 423

S.No	Groups	Dose/kg b.w	Weight of animals		Signs of Toxicity	Onset of Toxicity	Duration of Study
			Before Test	After Test			
1	EEBP	2000 mg	170 g	185 g	No signs of Toxicity	Nil	14 days
2	EEBP	2000 mg	182 g	194 g	No signs of Toxicity	Nil	14 days
3	EEBP	2000 mg	200g	200 g	No signs of Toxicity	Nil	14 days

The body weight of the rats before and after administration were noted that there is no changes in skin and fur, eyes, mucous membranes, respiratory, circulatory, autonomic and central nervous system and motor activity and behavior pattern were observed and also no sign of tremors, convulsions, salivation, diarrhea, lethargy, sleep and coma were noted. The onset of toxicity and signs of toxicity also not there. In further study there was no toxicity/ death were observed at these levels, same dose levels as per OECD guidelines 423 (acute toxic class method).

IN VIVO PHARMACOLOGICAL ACTIVITY

Effect of EEBP on Haloperidol Induced Catalepsy (0-3.5 SCALE)

The cataleptic scores are depicted in **Table 4**. There was a significant difference ($P<0.01$) between control group (I) and negative control group (II) in catalepsy. The EEBP treated groups

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shows significant anticataleptic action. EEBP at dose level of 400 mg/kg particularly, shows anticataleptic action comparable to standard drug group (III) treatment. There was a significant difference (P<0.01) between negative control group (II) and EEBP treated groups (IV, V) in catalepsy.

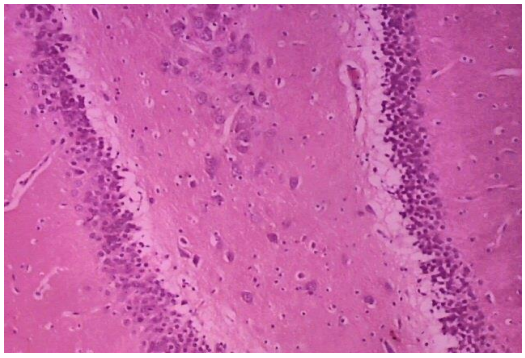
EEBP at dose level of 400 mg/kg, showed good anticataleptic action at 30, 150, 180 min after haloperidol challenge.

Effect of EEBP on Exploratory Behavior

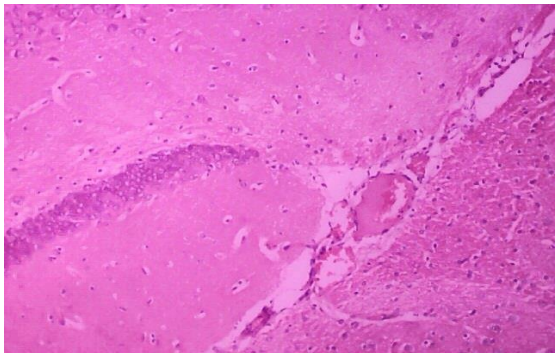
The exploratory behaviour was expressed by head dippings and line crossings. Head dippings are shown in **Table 5,** and line crossings are shown in **Table 6**. Negative control group (II) indicated decrease in exploratory behaviour i.e. head dippings and line crossings when compared with control group. The results presented by the EEBP treated groups show significant (P<0.01 and P<0.05) increase in head dippings and line crossings when compared with negative control group at 90, 120, 150, 180 min after haloperidol challenge.

Effect of EEBP on Histopathological Changes of Brain

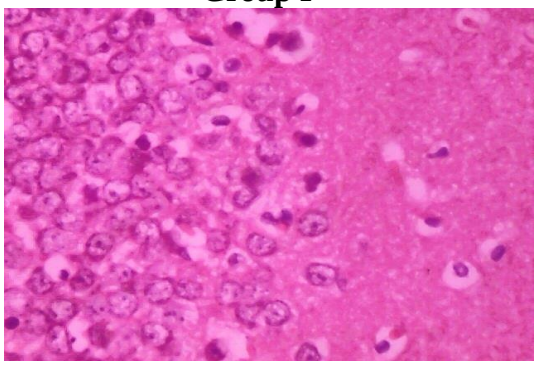
Histopathological examination of brain sections of normal control group showed normal cellular architecture cells (Fig. 1). Disarrangement of normal brain cells with necrosis, degeneration of brain cells were observed in haloperidol treated rats. The brain sections of the groups-III, IV and V rats treated with standard, EEBP at the dose of 200 and 400mg/kg, p.o, showed a sign of protection as it was evident by the absence of necrosis in a dose dependent manner[14,15,16].



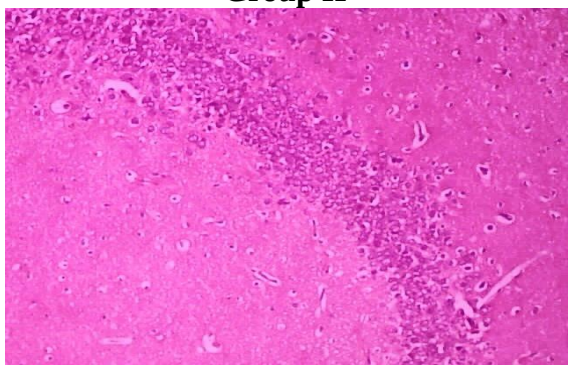
Group I



Group II



Group III



Group IV

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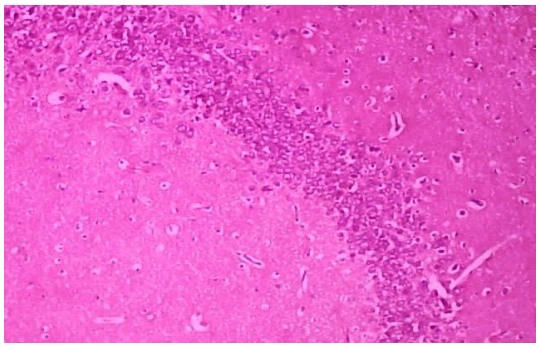

Group V

Figure 4. Histopathological Studies on Brain

Table 4: Effect of EEBP on catalepsy (0-3.5 scale)

Group	Catalepsy					
	30 min	**60 min**	**90 min**	**120 min**	**150 min**	**180 min**
I	0.00	0.00	0.00	0.00	0.00	0.00
II	2.8±0.13 ^{a**}	3.0±0.18 ^{a**}	3.4±0.00 ^{a**}	3.4±0.00 ^{a**}	3.4±0.00 ^{a**}	3.4±0.00 ^{a**}
III	0.76±0.10 ^{b**}	1.14±0.10 ^{b**}	1.34±0.10 ^{b**}	1.03±0.08 ^{b**}	1.01±0.08 ^{b**}	0.70±0.12 ^{b**}
IV	1.8±0.13 ^{b*}	2.5±0.12 ^{bns}	2.5±0.12 ^{b**}	2.08±0.15 ^{b**}	2.16±0.17 ^{b**}	2.17±0.10 ^{b**}
V	1.30±0.10 ^{b**}	1.64±0.16 ^{b**}	1.64±0.10 ^{b**}	1.65±0.21 ^{b**}	1.57±0.17 ^{b**}	1.57±0.10 ^{b**}

The values are expressed as mean ± SEM of 6 animals.
Comparisons were made between : a-Group I with Group II
b-Group II with Group III, IV, V
Statistical significance test for comparison was done by ANOVA , followed by Dunnett's 't' test.
**P<0.01, *P<0.05, ns- Non significant.

Table 5: Effect of EEBP on exploratory behaviour-head dipping

Group	Head dipping					
	30 min	**60 min**	**90 min**	**120 min**	**150 min**	**180 min**
I	7.25±0.420	7.87±0.21	8.12±0.65	7.30±0.21	6.42±0.42	6.23±0.39
II	0.4±0.22 ^{a**}	0.73±0.31 ^{a**}	0.15±0.17 ^{a**}	0.4±0.22 ^{a**}	0.31±0.21 ^{a**}	0.5±0.22 ^{a**}
III	4.27±0.31 ^{b**}	6.80±0.31 ^{b**}	8.17±0.54 ^{b**}	8.73±0.31 ^{b**}	8.73±0.42 ^{b**}	7.23±0.21 ^{b**}
IV	0.4±0.22 ^{bns}	1.23±0.21 ^{bns}	2.4±0.22 ^{b**}	3.15±0.31 ^{b**}	3.15±0.17 ^{b**}	2.77±0.31 ^{b*}
V	0.76±0.17 ^{bns}	3.2±0.26 ^{b**}	4.15±0.31 ^{b**}	5.31±0.33 ^{b**}	4.40±0.22 ^{b**}	4.15±0.48 ^{b**}

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The values are expressed as mean ± SEM of 6 animals.
Comparisons were made between : a-Group I with Group II
b-Group II with Group III, IV, V
Statistical significance test for comparison was done by ANOVA , followed by Dunnett's 't' test.
**P<0.01, *P<0.05, ns- Non significant.

Table6: Effect of EEBP on exploratory behaviour-Line crossing

Group	Line crossing					
	30 min	**60 min**	**90 min**	**120 min**	**150 min**	**180 min**
I	78.35±3.67	74.17±3.52	81.66±4.17	79.72±1.84	87.24±3.42	76.54±3.19 a**
II	7.34±0.54 a**	3.36±0.28 a**	2.22±0.56 a**	2.25±0.40 a**	3.0±0.76 b**	3.53±1.07 b**
III	35.21±2.78 b**	57.17±3.27 b**	71.0±4.46 b**	76.32±4.75 b**	81.5±4.49 b**	81.17±5.28 b**
IV	10.28±0.33 bns	21.12±1.48 b*	24.83±1.7 b**	36.78±1.2 b**	40.5±2.68 b**	34.6±2.06 b**
V	12.57±0.42 bns	28.29±3.22 b**	43.0±2.06 b**	57.0±3.6 b**	64.0±2.49 b**	57.0±2.47 b**

The values are expressed as mean ± SEM of 6 animals.
Comparisons were made between : a-Group I with Group II
b-Group II with Group III, IV, V
Statistical significance test for comparison was done by ANOVA, followed by Dunnett's 't' test.
**P<0.01, *P<0.05, ns- Non significant.

DISCUSSION

The present study revealed the anticataleptic effects of ethanolic extract of *Betula pendul a*in haloperidol model of catalepsy in rats. Neuroleptic like haloperidol induced catalepsy in rats is used to evaluate the drugs for their antiparkinsonism effects. In this study the EEBP was screened for its effect in haloperidol induced catalepsy in rats.
EEBP at dose of 400 mg/kg exhibited a pharmacological effect similar to that of standard drug (L-DOPA+ carbidopa). Haloperidol a neuroleptic, upon long term administration causes oxidative stress, resulting from alterations of mitochondrial electron transport chain, has been responsible for its neurotoxicity.

Dopamine depletion is considered as a cardinal feature in causing of PD in humans or animal models. The haloperidol (a non selective D_2 dopamine antagonist) induced catalepsy is primary due to blockade of dopamine receptors in striatum. The degeneration of dopaminergic neurons leads to an increase in population of dopamine receptors.

Defect in one or more naturally occurring antioxidant defenses could lead to oxidative stress has been implicated in PD because of coalition of four biochemical features of dopaminergic neurons in substantia nigra viz monoamino oxidase-B activity, autoxidation of dopamine, accumulation

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of iron and neuromelanin. A reduction in GSH might impair H_2O_2 clearance and promote $OH^{\cdot}$ formation and hence oxidative stress. In that all antioxidant defenses are interrelated (the disturbances in one might damage the balance in all). Antioxidants play an important role in prevention and control of PD. Many studies showing that parkinsonism was particularly protected by application of antioxidants. Drugs that enhance the availability of dopamine or prevent its breakdown afford protection against PD in humans or in animal models.[32,33]

Epidemiological studies have shown beneficial effects of flavonoids on neurodegeneration in particular. Flavonoids can protect the brain by their ability to modulate intracellular signals promoting cellular survival. Quercetin and its structurally related flavonoids showed a marked cytoprotective capacity in *in vitro* experimental conditions in models of predominantly apoptotic death. EEBP showing positive reaction for flavonoids in phytochemical screening. The neuroprotective action may be attributed to the presence of flavonoids in EEBP.[28,29,30]

Extensive evidence indicate that the part of PD symptomatology may be attributed to a dysfunctional noradrenaline system. Morphological changes in locus coeruleus, an eminently noradrenergic brain stem area has been reported in PD.

Several studies have reported on exacerbation of neuroleptic induced catalepsy by enhancing the serotonergic neurotransmission in CNS. Ondansetron by antagonizing the stimulatory effects of $5HT_3$ receptor activity on the release of dopamine, decrease in the levels of dopamine in the nigrostriatal and mesolimbic pathways.[30,31,32]

Antipsychotic effect of haloperidol is believed to be achieved by inhibition of dopeminergic transmission in rats has been proposed to be a direct consequence of antagonism of dopamine D_2 receptors. Neuroleptics like haloperidol exerts multiple events on dopeminergic signaling and produce DA related behavioural changes and catalepsy.

It can be hypothesized from this study that ethanolic extract of *Betula pendula*ameliorates the symptoms of haloperidol induced catalepsy in rats. The mechanism by which the amelioration takes place may be attributed to one or more pharmacological/biochemical mechanisms viz.

- EEBP may enhance the bioavailability of circulatory dopamine by up regulation of dopaminergic signaling.
- EEBP because of its antioxidant action showing neuroprotection.

SUMMARY AND CONCLUSION

*Betula pendula*is a well-known plant which is being used in Indian traditional system which has been reported to have a number of uses. But the role of ethanolic extract of this leaves in the treatment of some CNS associated disorders has not been evaluated. Hence this dissertation is emphasized to explore the effect of ethanolic extract of this leaves on haloperidol induced catalepsy in rats.

In the present study the effect of EEBP on extra pyramidal symptoms such as rigidity, motor co-ordination and depression, key parameters found in Parkinson's disease was studied.

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In haloperidol induced catalepsy EEBP at the dose of 400 mg/kg exhibited significant anticataleptic activity. EEBP showed comparable anticataleptic actions with that of standard drug L-DOPA+ carbidopa.

EEBP at a dose of 400 mg/kg significantly, increase the exploratory behaviour like head dipping and line crossing in haloperidol administered rats. The standard drugs L-DOPA+carbidopa significantly increased the exploratory behaviour in haloperidol administered rats.

From the observations of above studies it could be envisaged, that the protective effect of EEBP against symptoms of Parkinson's disease (catalepsy) is due to regulation in neurotransmitters i.e. dopamine, serotonin, glutamate and antioxidant enzyme systems which are playing an important role in protection of catalepsy. Further studies have to be conducted on the various extracts and isolated principles of the plant for their effects on other CNS disorders.

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