

# Antioxidant and antiparkinsonian activity of *Passiflora incarnata* leaves

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**Abstract** Herbal remedies for human brain disorders are much preferred over synthetic drugs because of various side effects of synthetic drugs ranging from sleep disorders to withdrawal syndromes. *Passiflora incarnata* Linn (Passifloraceae) has been widely used in traditional medicine in West India, Mexico, the Netherlands, and South America. It has been used as an anxiolytic and sedative-hypnotic since ancient times. The main constituents of leaves of *P. incarnata* are flavonoid and indole alkaloids based on  $\beta$ -carboline ring system viz., harman, harmine, harmalol and harmaline. Harmine and harmaline alkaloids are reported to be effective antiparkinsonian compounds. The objective of present investigation was to evaluate antiparkinsonian activity and antioxidant activity of butanol extract of *P. incarnata* leaves (BEPI). Antiparkinsonian activity of BEPI was studied using haloperidol induced catalepsy and tacrine induced jaw movements. The antioxidant activity of BEPI was studied using DPPH scavenging assay and  $H_2O_2$  scavenging assay. The results of present study has shown that butanol extract of *P. incarnata* leaves (BEPI) ( $150\text{ mg kg}^{-1}$  and  $300\text{ mg kg}^{-1}$ , i.p.) significantly ( $p \leq 0.001$ ) reduced the duration of haloperidol induced catalepsy as well as tacrine induced jaw movements. BEPI has also shown significant antioxidant effect. The result obtained in current study indicates that BEPI possesses antiparkinsonian as well as antioxidant activity which may be useful in symptomatic relief of PD and to prevent progression of PD.

**Keywords** Antioxidant activity · Antiparkinsonian activity · DPPH scavenging activity · Haloperidol · Tacrine

## Introduction

Parkinson's disease (PD) is a slowly progressive neurodegenerative disease. In PD, there is a loss of dopaminergic neurons projecting from substantia nigra pars compacta (SNPC) to neostriatum leading to the imbalance between dopamine and acetylcholine. The mainstay of PD treatment has been the use of drugs which facilitate the presynaptic release of dopamine and anticholinergic drugs (Sharma and Sharma 2007). Neuroprotective therapies hold promise for slowing progression of the disease because they can protect the cells that produce dopamine. Oxidative stress plays an important role in the pathogenesis of PD (Sudha et al. 2003). Neurons of substantia nigra (SN) may be particularly vulnerable to oxidant stress, because the oxidative metabolism of dopamine has the potential to generate cytotoxic free radicals. Dopamine can be oxidized by either monoamine oxidase or undergo autooxidation to generate hydrogen peroxide ( $H_2O_2$ ).  $H_2O_2$  can damage the neuron directly or indirectly through the formation of hydroxyl radicals in presence of ferrous ions. Neuromelanin present within the SN neurons has the potential to promote site-specific accumulation and reduction of iron thereby potentiating iron-induced lipid peroxidation and consequent cell death.  $H_2O_2$  is normally detoxified by reduced glutathione (GSH) in the reaction catalyzed by GP, thus an increased rate of dopamine turnover or a deficiency of GSH could lead to oxidative stress. Thus, it appears that free radicals may be one of the important agents responsible for destruction of SN neurons, thereby leading to PD (Youdim et al. 1993; Youdim and Riederer 1997). Antioxidants have been studied for their effectiveness in reducing these deleterious effects and neuronal death in many in vitro and in vivo

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studies. An increasing number of studies demonstrated the efficacy of polyphenolic antioxidants from fruits and vegetables to reduce or to block neuronal death occurring in the pathophysiology of these disorders (De Rijk et al. 1997; Charles 2006). Several agents already in therapeutic use might exert some of their effects by antioxidant action, including selegiline (deprenyl), apomorphine and nitecapone (Halliwell 2001).

*Passiflora incarnata* Linn (Passifloraceae) has been widely used in traditional medicine in West India, Mexico, the Netherlands and South America. It has been used as an anxiolytic and sedative-hypnotic since ancient time. Aerial parts of *P. incarnata* have been used as sedative, anxiolytic, antispasmodic, analgesic, anticonvulsant, and wormicidal and also in whooping cough, bronchitis, asthma, and other tough coughs. *P. incarnata* is also known to possess antitussive, analgesic, anticonvulsant, antiasthmatic, aphrodisiac and anti-inflammatory activity (Dhawan et al. 2004).

The main constituents of leaves of *P. incarnata* are flavonoid (0.25 %) such as vitexin, isovitexin, orientin, isoorientin, apigenin and kampferol. Besides flavonoid, various indole alkaloids based on  $\beta$ -carboline ring system viz., harman, harmine, harmalol and harmaline are reported to be present in *P. incarnata*. In addition, various other phytoconstituents reported to be present in *P. incarnata* include: carbohydrates, essential oil, amino acids and a cyanogenic glycoside gyanocardin (Soulimani et al. 1997). Harmine and harmaline alkaloids are reported to be effective anti-Parkinson compounds (Jean and Richard 2004). Hence, the aim of present investigation was to study antiparkinsonian activity of *P. incarnata* leaves.

## Materials and methods

### Plant material

The fresh leaves of *P. incarnata* were collected in the month of June, July and August from local nursery in Pune region India. The plant was identified and authenticated by Dr. Dinesh Shirodkar, Botanical Survey of India, Pune, India. (Voucher Specimen No: PASSIN 3).

### Preparation of extracts

Shade dried leaves (1,000 g) were powdered and macerated with ethanol for 48 h. The extract was evaporated to dryness. The leaf extract was suspended in water and fractioned successively with hexane, chloroform, ethyl acetate and n-butanol (BEPI). The percentage yields of extracts were 11.7 % w/w, 1.1 % w/w, 0.9 % w/w and 22.5 % w/w, respectively.

### Chemicals

Ethanol, hexane, chloroform, ethyl acetate and n-butanol (S.D. Fine Chem. Limited, Mumbai, Maharashtra, India) of highest quality were used.

### Drugs

Haloperidol (RPG Life Sciences Ltd, Mumbai), L-DOPA (Alembic Limited, Vadodara), tacrine (Sigma-Aldrich, Mumbai)

### Dose selection

An acute toxicity study by European Medicines Agency, 2008 (Anonymous 2008) reported LD<sub>50</sub> of *P. incarnata* as 3,140 mg kg<sup>-1</sup>, i.p. in mice and 3,510 mg kg<sup>-1</sup>, i.p. in rats. Considering these LD<sub>50</sub> values, 1/10th (300 mg kg<sup>-1</sup>, i.p.) and 1/20th (150 mg kg<sup>-1</sup>, i.p.) dose of LD<sub>50</sub> was used in the present study.

### Standardization of extract for Chrysin by RP-HPLC-UV method

Acid hydrolysis of the BEPI was done according to the method reported in the literature (Ali et al. 2004). 30 mg of BEPI were hydrolyzed with 2N HCl in methanol (30 ml) at 80 °C for 2 h. The liberated aglycone was extracted several times with ethyl acetate and examined by HPLC. The acidic mother liquor was neutralized with Na<sub>2</sub>CO<sub>3</sub>, filtered, and evaporated to dryness for examination of the sugar moiety. The ethyl acetate fraction was dried and this fraction was used for the Chrysin estimation.

The HPLC analysis was carried out using Waters HPLC system (Cyber Lab HPLC, LC-100) consisting of 515 binary pumps, 2487 dual wavelength UV detector, and Rheodyne manual injector with 20 micro liter loop. The chromatographic separation was achieved on reversed-phase analytical column (Variance C18 250×4.6 mm, Microsoft MV 100–5). The mobile phase consisted of acetonitrile. Mobile phase was filtered through a 0.45- $\mu$ m membrane. The flow rate was set to 0.5 ml/min and was detected at 269 nm for determination of chrysin. The injection volume was 20  $\mu$ l, and the peaks were identified by comparison with the retention times of authentic chrysin.

### Animals

Swiss albino mice (25–30 g) and Wistar rats (120–150 g) of either sex was used. Animals were housed under standard conditions of temperature (24±2 °C) and relative humidity (30–70 %) with a 12:12 h light: dark cycle. The animals were fed with standard pellet diet and water ad libitum. The institutional animal ethical committee approved all the

**Table 1** Chrysin content of extract BEPI and BEPIF

Extract	Retention time	Area	Chrysin ( $\mu\text{g}$ )	Chrysin content of extract (mg/gm)
Chrysin	3.11	64310.9	100	–
BEPI	3.08	40899.6	63	10.63

experimental protocols. Experiments were carried out as per CPCSEA guidelines.

#### Anti-Parkinsonian activity

##### A] Haloperidol induced catalepsy:

Adult male Swiss albino mice (25–30 g) were divided into four groups ( $n=6$ ). Mice were pretreated with vehicle, BEPI (150 and 300 mg  $\text{kg}^{-1}$ , i.p), and L-DOPA (30 mg  $\text{kg}^{-1}$ , i.p.) 30 min before haloperidol (1 mg  $\text{kg}^{-1}$ , i.p.). The duration of catalepsy was measured at 0, 30, 60, 90, 120, and 150 min after haloperidol administration using bar test. Both the forepaws of the animals were placed on a wooden bar elevated three cm above the ground and duration of catalepsy was measured. A cut-off time was 300 s (Nair and Arjuman 2007).

##### B] Tacrine induced jaw movements:

Rats divided into four groups and treated with vehicle, BEPI (150 and 300 mg  $\text{kg}^{-1}$ , i.p), and L-DOPA. After 20 min, tacrine (2.5 mg  $\text{kg}^{-1}$ , i.p.) was administered and the number of tremulous jaw movements and orofacial bursts were measured for 60 min. Tremulous jaw movements were defined as vertical deflections of the lower jaw not directed at a particular stimulus (Kasture et al. 2009).

#### Antioxidant activity

##### 1] DPPH (1, 1-diphenyl-2-picrylhydrazyl) assay

The free radical scavenging activity of the extract was measured in terms of hydrogen donating or radical

scavenging ability using the stable free radical DPPH. 0.1 mM solution of DPPH in methanol was prepared and 1.0 ml of this solution was added to 3.0 ml of extract solution in water at various concentrations (2–1,000  $\mu\text{g ml}^{-1}$ ). The mixture was incubated for 45 min at room temperature and the absorbance was measured at 517 nm against the corresponding blank solution. Ascorbic acid was used as reference. Percentage inhibition of DPPH free radical was calculated based on the control reading, (which contained DPPH and distilled water without any extract) using the following equation:

$$\text{DPPH Scavenged (\%)} = [(A_c - A_t) / A_c] \times 100$$

Where  $A_c$  and  $A_t$  are the absorbance of the control and extract or standard respectively (Jiin-Tzong et al. 2001).

##### 2] $\text{H}_2\text{O}_2$ Scavenging Activity

The  $\text{H}_2\text{O}_2$  scavenging activity of the extract was determined according to the method of Ruch et al. A solution of  $\text{H}_2\text{O}_2$  (40 mM) was prepared in phosphate buffer (pH 7.4). 3.4 ml (16–1,000  $\mu\text{g ml}^{-1}$ ) extract in phosphate buffer were added to solution  $\text{H}_2\text{O}_2$  (0.6 ml, 40 Mm). Absorbance was determined at 230 nm after 10 min against a blank solution containing phosphate buffer without hydrogen peroxide. The percentage of  $\text{H}_2\text{O}_2$  scavenging of extract and ascorbic acid (standard compound) was calculated as:

$$\% \text{ Scavenged } \text{H}_2\text{O}_2 = [(A_c - A_t) / A_c] \times 100$$

Where  $A_c$  and  $A_t$  are the absorbance of the control and extract or standard respectively (Ranju et al. 2011).

#### Results

In RP-HPLC-UV method authentic sample of chrysin showed retention at 3.11 min. n- butanol extract of *P. incarnata* leaves (BEPI) showed similar retention time as that of authentic chrysin. The result of HPLC analysis of BEPI have shown varied amount of chrysin. The results of HPLC analysis are given in Table 1.

**Table 2** Effect of BEPI on haloperidol-induced catalepsy in mice

Treatment (mg $\text{kg}^{-1}$ , ip)	Duration of catalepsy (seconds) (Mean $\pm$ SEM)					
	0 min	30 min	60 min	90 min	120 min	150 min
Vehicle (0.1 ml)	2.5 $\pm$ 0.645	75 $\pm$ 21.285	201.25 $\pm$ 16.2	297.5 $\pm$ 2.5	300 $\pm$ 0	300 $\pm$ 0
L-DOPA (30)	1.25 $\pm$ 0.25	80 $\pm$ 15.67	103.5 $\pm$ 12.2*	183.75 $\pm$ 16.25*	149.75 $\pm$ 19.95*	144.25 $\pm$ 52.5*
BEPI (150)	1.25 $\pm$ 0.25	64.5 $\pm$ 11.85	85.25 $\pm$ 32.2*	183.5 $\pm$ 42*	161.75 $\pm$ 21.85*	147 $\pm$ 18.15*
BEPI (300)	1.5 $\pm$ 0.28	58.25 $\pm$ 4.33	65 $\pm$ 12.4*	161 $\pm$ 29.2*	152.75 $\pm$ 13.15*	142 $\pm$ 13.3*

$n=6$ , \* $P<0.001$  compared to vehicle treated group (ANOVA followed by Dunnett's test)

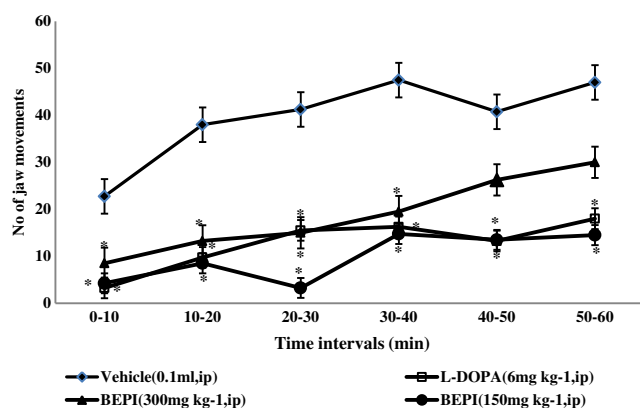
Antiparkinsonian activity was studied using haloperidol induced catalepsy and tacrine induced jaw movements. In the present study, haloperidol ( $1 \text{ mg kg}^{-1}$  i.p.) produced significant catalepsy at 30 min after haloperidol administration. However, maximum catalepsy was produced after 120 min in vehicle treated animals. The pretreatment with BEPI ( $150 \text{ mg kg}^{-1}$  and  $300 \text{ mg kg}^{-1}$ , i.p.) showed a significant ( $P < 0.001$ ) reduction in the haloperidol induced catalepsy after 60 min onwards. Table 2 represents effect of BEPI on haloperidol induced catalepsy.

In the present study, tacrine ( $2.5 \text{ mg kg}^{-1}$ , i.p.) produced maximum numbers of tremulous jaw movements during 30–40 min interval. Pretreatment with BEPI (150 and  $300 \text{ mg kg}^{-1}$ , i.p.) significantly reduced the tacrine induced jaw movements as well as number of bursts induced by tacrine. Figures 1, 2 and 3 represent effect of BEPI on tacrine induced tremulous jaw movements.

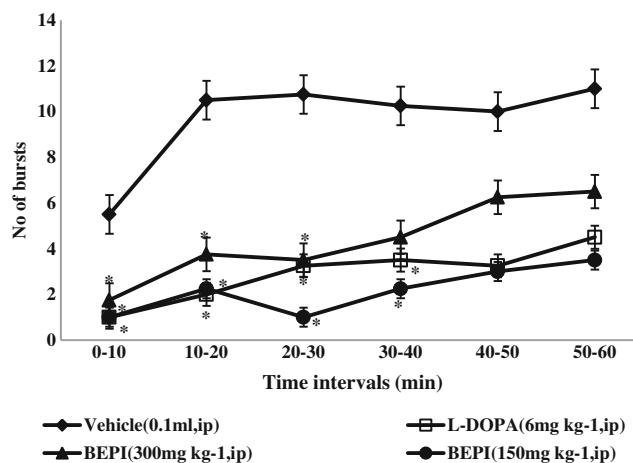
The antioxidant activity of BEPI was studied using DPPH (1, 1-diphenyl-2-picrylhydrazyl) scavenging assay and  $\text{H}_2\text{O}_2$  scavenging assay and  $\text{IC}_{50}$  value of BEPI was found to be 37.59 and  $31.92 \text{ } \mu\text{g/ml}$  respectively (Table 3). Thus, BEPI was found to have significant antioxidant effect which is comparable to standard ascorbic acid. The results are demonstrated in Figs. 4 and 5.

## Discussion

The present study evaluated the effects of n-butanol extract of *P. incarnata* leaves (BEPI) in experimentally induced animal model of PD. Neuroleptic-induced catalepsy in rodents was used as an animal model for screening drugs for Parkinsonism. It is a robust behavioural method for studying nigrostriatal function and its modulation by various neurotransmitters. Evidence indicates that drugs which potentiate or inhibit neuroleptic induced catalepsy in rodents might aggravate or reduce the extra pyramidal side effects, respectively.



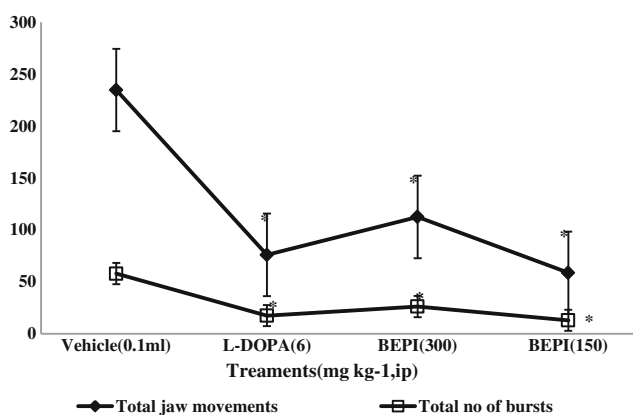
**Fig. 1** Effect of n- butanol extract of *P. incarnata* leaves (BEPI) on number of tacrine induced jaw movements;  $n=6$   $*P < 0.001$  compared to vehicle treated group (ANOVA followed by Dunnett's test)



**Fig. 2** Effect of n- butanol extract of *P. incarnata* leaves (BEPI) on number of tacrine induced bursts;  $n=6$   $*P < 0.001$  compared to vehicle treated group (ANOVA followed by Dunnett's test)

Drugs useful in the treatment of Parkinsonism inhibit haloperidol induced catalepsy (Nair and Arjuman 2007). Haloperidol blocks dopamine  $\text{D}_2$  receptors and produces a state of catalepsy in animals by reducing dopaminergic transmission in basal ganglion. Anticholinergic drugs are most effective in counteracting the catalepsy induced by haloperidol in experimental animals (Klemm 1985). In current study, pre-treatment with BEPI ( $150 \text{ mg kg}^{-1}$  and  $300 \text{ mg kg}^{-1}$ , i. p.) significantly reduced the haloperidol induced catalepsy which is indicative of its antiparkinsonian potential.

The acetylcholinesterase inhibitor, tacrine, induces a characteristic motor effect in rats known as tremulous jaw movements or vacuous jaw movements which shares some characteristics with human Parkinsonian tremors (Michael et al. 1997). Tacrine induced tremulous jaw movements in rat have been used as a model for screening antiparkinsonian activity (Salamone et al. 1998). DeBoer et al. reported that cholinergic stimulation induces Parkinsonian symptoms, and evidence indicates that dopamine antagonism or depletions can enhance



**Fig. 3** Effect of n- butanol extract of *P. incarnata* leaves (BEPI) on total number of jaw movements and bursts induced by tacrine;  $n=6$   $*P < 0.001$  compared to vehicle treated group (ANOVA followed by Dunnett's test)

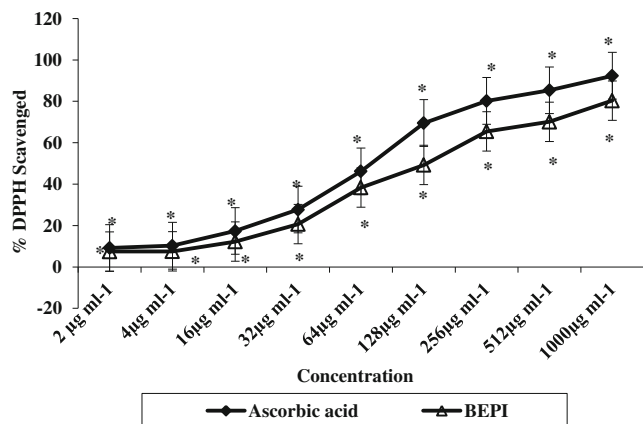
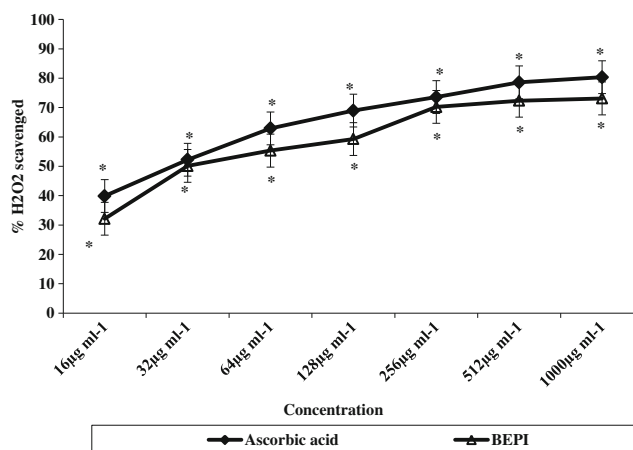
**Table 3** IC<sub>50</sub> value of BEPI

Antioxidant activity	IC <sub>50</sub> value (μg/ml)	
	Ascorbic acid	BEPI
DPPH scavenging activity	27.72	37.59
H <sub>2</sub> O <sub>2</sub> scavenging activity	30.62	31.92

the striatal acetylcholine release (DeBoer et al. 1993). It has been shown that antiparkinsonian agents like L-DOPA, apomorphine, amantadine, bromocriptine, and benzotropine effectively suppress tacrine induced tremulous jaw movements (Michael et al. 1997). In this investigation, pretreatment with BEPI (150 and 300 mg kg<sup>-1</sup>, i.p.) significantly reduced the tacrine induced jaw movements as well as number of bursts induced by tacrine which signifies that BEPI possess potential antiparkinsonian activity.

According to the oxidative stress theory, patients with PD cannot detoxify potentially lethal endogenous or environmental oxidants such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and free radicals (superoxide and nitric oxide) due to defective mitochondrial function. Thus, these potentially lethal oxidants oxidise cells and thereby cause cell injury (Kaufman and Milstein 2007). The use of haloperidol has been associated with an increased level of oxidative stress in the brain. This evidence suggests a possible role for antioxidants in the treatment of haloperidol-induced catalepsy (Rasheed et al. 2010).

Treatment of PD with the drug of choice, L-dopa, is limited only to the relief of symptoms, and long-term use may further add to the oxidative load by producing free radicals during normal metabolism and play a role in disease progression. Existing classes of drugs such as DA agonists, monoamine oxidase (MAO) inhibitors, catechol-O-methyltransferase inhibitors, and anticholinergic agents may be used in the early stages of the disease to relieve PD symptoms; none prevent the disease from progressing, and show debilitating side-

**Fig. 4** DPPH scavenging activity of butanol extract of *Passiflora incarnata* leaves (BEPI);  $n=3$  \* $P<0.001$  compared to blank (Student  $t$  test)**Fig. 5** H<sub>2</sub>O<sub>2</sub> scavenging activity of butanol extract of *Passiflora incarnata* (BEPI);  $n=3$  \* $P<0.001$  compared to blank (Student  $t$  test)

effects with prolonged use. Therefore, it is of utmost importance to develop new agents that show or halt the rate of PD progression. The key therapy to ameliorate oxidative stress seen in PD is to repair the damage caused by free radicals before it is too late and to protect DAergic cells. Therefore, antioxidants might be one of the ideal agents to prevent free radical-mediated tissue destruction and inhibit some of the early degenerative events trafficking in the central nervous system that lead to neurodegeneration in PD and its experimental models. The protective effects of various antioxidants to modulate oxidative stress in experimental animal models of PD have been clearly shown, indicating that antioxidant therapy may be an attractive therapeutic approach to PD. To overcome free radical-mediated consequences of disease processes and drug therapies, antioxidants are now being looked upon as persuasive therapeutics against neuronal loss, as they have the capability to neutralize free radicals (Koppula et al. 2012).

Thus, to study the probable mechanism of action, the antioxidant activity of BEPI was studied using DPPH (1, 1-diphenyl-2-picrylhydrazyl) scavenging assay and H<sub>2</sub>O<sub>2</sub> scavenging assay. It was found to have significant antioxidant effect which is comparable to standard ascorbic acid. Thus, it could be understood that BEPI possesses antiparkinsonian as well as antioxidant activity which may be useful in symptomatic relief of PD and to prevent progression of PD.

## Conclusion

The present investigation demonstrates that BEPI possesses significant antiparkinsonian activity as indicated by inhibition of haloperidol-induced catalepsy and reduction of the tacrine induced jaw movements. Further, it has been observed that BEPI possesses significant antioxidant activity. Thus, it may be concluded that bifunctional nature (antiparkinsonian as well as antioxidant activity) of BEPI may prove boon for



treatment of Parkinson's disease as well for preventing progressive neurodegeneration in Parkinson's disease.

**Conflicts of interest** None.

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