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RESEARCH ARTICLE

# Reversal of haloperidol-induced orofacial dyskinesia by *Murraya koenigii* leaves in experimental animals

Rupali Patil, Yogesh Hiray, Sandesh Shinde, and Padmaja Langade

Department of Pharmacology, MGV's Pharmacy College, Panchavati, Nashik 422003, India

## Abstract

**Context:** Orofacial dyskinesia (OD) is a late complication of prolonged neuroleptic treatment characterized by involuntary movements of the oral region. Chronic treatment with neuroleptics leads to development of vacuous chewing movements (VCMs). VCMs in rats are widely accepted as an animal model of OD.

**Objective:** To study the effect of *Murraya koenigii* L. (Rutaceae) leaves on haloperidol-induced OD.

**Materials and methods:** Effect of alcohol extract of *M. koenigii* leaves (EEMK) and its alkaloid fraction (AMK) on body weight, locomotor activity, behavioral parameters, such as VCMs, tongue protrusions (TPs), orofacial bursts (OBs), and biochemical parameters such as antioxidant defense enzymes levels [superoxide dismutase (SOD) and catalase (CAT)], glutathione (GSH) levels, and lipid peroxidation (LPO) in the forebrain region was studied in haloperidol-treated rats.

**Results:** Rats chronically treated with haloperidol (1 mg/kg, i.p., 21 days) significantly decreased locomotion and developed VCMs, OBs, and TPs. Biochemical analysis reveals that chronic haloperidol-treated rats also showed decreased levels of SOD and CAT. Chronic haloperidol treatment significantly induced LPO and decreased the forebrain GSH levels in the rats. Co-administration of EEMK (100 and 300 mg/kg, p.o.) and AMK (30 and 100 mg/kg, p.o.) along with haloperidol significantly reversed the effect on locomotion. EEMK and AMK significantly reversed the haloperidol-induced decrease in forebrain SOD and CAT levels in rats and significantly reduced the LPO and restored the decreased GSH levels by chronic haloperidol treatment.

**Conclusion:** The study concludes that *M. koenigii* could be screened as a potential drug for the prevention or treatment of neuroleptic-induced OD.

**Keywords:** Carbazole alkaloids, antioxidant, orofacial dyskinesia, vacuous chewing movements

## Introduction

Haloperidol is a widely used neuroleptic drug for the treatment of acute and chronic psychosis. The use of typical antipsychotics such as haloperidol is limited by their tendency to produce a range of extrapyramidal movement disorders such as Parkinson's disease, akathisia, dystonia, and tardive dyskinesia (TD). TD occurs in 20–40% of the patient population undergoing chronic neuroleptic therapy. TD is characterized by repetitive involuntary movements, usually involving the mouth, face, and tongue, and sometimes limb and trunk musculature (Egan et al., 1997; Casey, 2000; Kulkarni & Naidu, 2001). TD may persist for months or years after drug withdrawal and, in some

patients, it is irreversible. Because of its severity, high incidence, and potential irreversibility, TD is considered as a major clinical and ethical issue in psychiatry.

Oxidative stress and products of lipid peroxidation (LPO) are implicated in the etiopathology of TD (Cadet et al., 1986; Coyle & Puttfarcken, 1993; Andreassen & Jorgensen, 2000). Chronic treatment with neuroleptics is reported to increase free radical production and oxidative stress (Balijepalli et al., 2001). Haloperidol increases oxidative stress in brain tissue (Sagara, 1998).

Elkashef and Wyatt (1999) reported that rats with vacuous chewing movements (VCMs) had significantly higher

thiobarbituric acid reactive substances (TBARS) in the striatum, suggesting increased LPO and free radical production in these animals. The chronic use of neuroleptics is also reported to cause decreases in the activity of antioxidant defense enzymes superoxide dismutase (SOD) and catalase (CAT; Cadet et al., 1987). Free radicals are thought to play a role in aging process, and age is one of the risk factors for the development of TD. A positive correlation exists between increasing age and the development of TD, further supporting the role of free radicals in the pathogenesis of TD (Richardson et al., 1986). Vitamin E, an antioxidant and free radical scavenger, has been reported to be effective in the treatment of TD (Elkashef & Wyatt, 1999; Gupta et al., 1999; Soares & Mcgrath, 2002), suggesting the potential role of free radicals in the pathogenesis of TD.

*Murraya koenigii* L. (Rutaceae) is a rich source of carbazole alkaloids having antioxidant activity (Zheng & Wang, 2001). Hence, in this study, we explored the potential of *M. koenigii* through the use of behavioral and biochemical models of orofacial dyskinesia (OD) in rats. In the present study, we investigated the effect of alcoholic extract of *M. koenigii* leaves (EEMK) and its alkaloid fraction (AMK) on haloperidol-induced OD. The effect of EEMK and AMK on locomotor activity and biochemical parameters such as protective antioxidant enzyme levels (SOD and CAT), glutathione (GSH) levels, and LPO in the forebrain region was also studied in haloperidol-treated rats.

## Methods

### Animals

Male albino Wistar rats ( $150 \pm 20$  g) were obtained from Bharat Serum and Vaccines Ltd., Thane. Animals were housed in five groups at ambient temperature of  $25 \pm 1^\circ\text{C}$ . Animals had free access to water and food. They were deprived of food but not water 4 h before the experiment. The experiments were carried out between 9.00 and 14.00 h. All the experimental procedures and protocols used in this study were approved by the Institutional Animal Ethics Committee of M.G.V.'s Pharmacy College, Nashik. Ethical guidelines were strictly followed during all the experiments.

### Plant material

Leaves of *M. koenigii* were obtained from Aushadhi Bhavan, Ayurved Seva Sangh, Nashik in August, 2010, and identified by Dr. P.G. Diwakar, Jt. Director, Botanical Survey of India, Pune, where a voucher specimen (MUKKID 1) has been retained.

Leaves of *M. koenigii* were dried, powdered, and defatted with the petroleum ether ( $60\text{--}80^\circ\text{C}$ ) using Soxhlet's extractor. The petroleum ether was removed and marc was air dried. Thereafter marc was successively extracted with ethanol. The extract was concentrated and evaporated to dryness. The yield of crude alcohol extract of *M. koenigii* (EEMK) was found to be 5.6% w/w. EEMK was further subjected to the isolation of alkaloids as described earlier (Cordell, 1981). Yield of AMK was found to be 49.37% w/w.

## Drugs and treatment schedule

Haloperidol (1 mg/kg, i.p.; Serenace, Searle India, India) was diluted with distilled water and administered intraperitoneally once daily in the morning (1100 h). EEMK (100 and 300 mg/kg), AMK (30 and 100 mg/kg), and vitamin E (10 mg/kg) were administered orally once per day (1000 h) for a period of 21 days in a constant volume of 0.5 mL/100 g body weight of rat. Behavioral assessments were done 24 h after the last dose of haloperidol. Drug doses were selected on the basis of previous studies conducted in our laboratory. Group I received vehicle. Group II received haloperidol (1 mg/kg) alone. Group III received EEMK (100 mg/kg) + haloperidol (1 mg/kg). Group IV received EEMK (300 mg/kg) + haloperidol (1 mg/kg). Group V received AMK (30 mg/kg) + haloperidol (1 mg/kg). Group VI received AMK (100 mg/kg) + haloperidol (1 mg/kg). Group VII received vitamin E (10 mg/kg) + haloperidol (1 mg/kg).

## Assessment of OD

### Behavioral parameters

Rats were placed individually in a small ( $22 \times 22 \times 22$  cm) Plexiglas cage immediately after administration of haloperidol. The number of VCM, along with number of orofacial burst (OB) and tongue protrusion (TP) was scored for the period of 1 h (Salamone et al., 1986).

### Locomotor activity

To analyze changes in spontaneous locomotor activity caused by treatment with haloperidol and/or EEMK or AMK, the animals were placed individually in the center of an open-field arena divided into 16 equal squares, as previously described (Vogel & Vogel, 2002). The number of line crossings was measured over 5 min and taken as an indicator of locomotor activity.

### Body weight change

Haloperidol is known to increase body weight (Fell et al., 2004). Effect of EEMK and AMK on body weight of rats after treatment with haloperidol was observed.

### Dissection and homogenization

The animals were sacrificed by decapitation immediately after behavioral assessments. The brain was removed; forebrain was dissected out and was rinsed with isotonic saline and weighed. A 10% (w/v) tissue homogenate was prepared in 0.1 M phosphate buffer (pH = 7.4), the post-nuclear fraction for CAT assay was obtained by the centrifugation of homogenate at 1000g for 20 min at  $4^\circ\text{C}$ , and for other enzyme assays, the postnuclear fraction was obtained by centrifugation at 12,000g for 60 min at  $4^\circ\text{C}$ .

### Superoxide dismutase

The assay of SOD was based on the ability of SOD to inhibit spontaneous oxidation of adrenaline to adrenochrome (Misra & Fridovich, 1972; Saggu et al., 1989). To 0.05 mL supernatant, 2.0 mL of carbonate buffer and 0.5 mL of EDTA were added. The reaction was initiated by the addition of 0.5 mL of epinephrine, and the auto-

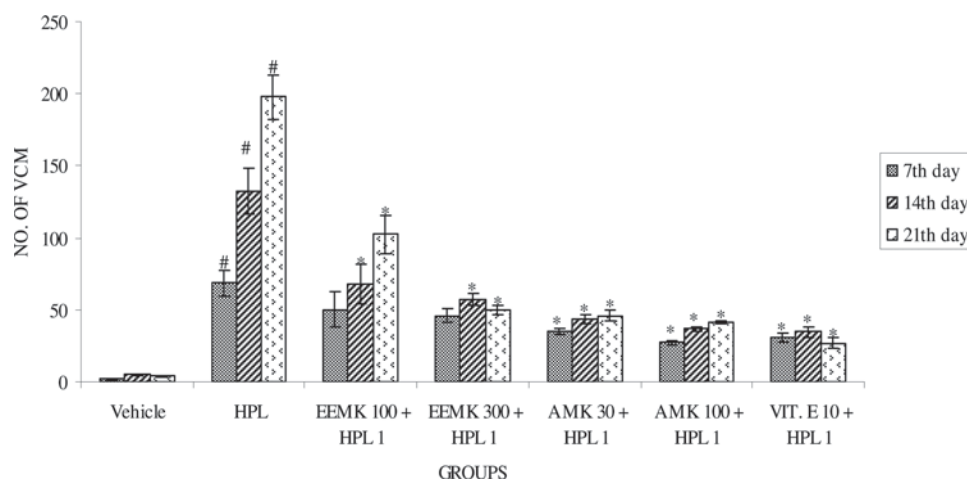


Figure 1. Effect of *Murraya koenigii* on haloperidol-induced VCMs in rats.  $n=5$ . The observations are mean  $\pm$  SEM. \* $p<0.05$  compared with vehicle-treated group. \* $p<0.05$  compared with haloperidol-treated group. One-way ANOVA followed by Dunnett's test. HPL: Haloperidol, EEMK: alcohol extract of *Murraya koenigii* leaves, AMK: alkaloids isolated from EEMK.

oxidation of adrenaline ( $3 \times 10^{-4}$  M) to adrenochrome at pH 10.2 was measured by following change in OD at 480 nm. The change in OD every minute was measured at 480 nm against reagent blank. The results were expressed as units of SOD activity (mg/protein). One unit of SOD activity induced ~50% inhibition of adrenaline. The results were expressed as nmol SOD U/mg wet tissue.

#### Catalase

The CAT activity assay was based on the ability of CAT to induce the disappearance of hydrogen peroxide (Beers & Sizer, 1952). The reaction mixture consisted of 2 mL phosphate buffer (pH=7.0), 0.95 mL of hydrogen peroxide (0.019 M), and 0.05 mL supernatant in final volume of 3 mL. Absorbance was recorded at 240 nm every 10 s for 1 min. One unit of CAT was defined as the amount of enzyme required to decompose 1  $\mu$ mol of peroxide per min, at 25°C and pH=7.0. The results were expressed as units of CAT activity (mg protein). Units of activity were determined from the standard graph of  $H_2O_2$ . The results were expressed as CAT U/mg wet tissue.

#### Reduced glutathione

Reduced GSH (S-glutamyl cysteinyl glycine) plays an important role in the protection of cells against damage from endogenous and exogenous free radicals and oxidants. Reduced GSH was determined by the method of Ellman (1959). To the homogenate, 10% TCA was added, centrifuged, and treated with 1.0 mL of Ellman reagent [19.8 mg of 5,5'-dithiobisnitro benzoic acid in 100 mL of 1.0% sodium citrate and 3 mL of phosphate buffer (pH=8.0)]. The color developed was measured at 412 nm. The results were expressed as nmol GSH/mg wet tissue.

#### Lipid peroxidation

LPO as evidenced by the formation of TBARS was measured by the method of Niehaus and Samuelson (1968). In brief, 0.1 mL of homogenate (Tris-HCl buffer, pH 7.5) was treated with 2 mL of (1:1:1 ratio) TBA-TCA-HCl reagent

(thiobarbituric acid 0.37%, 0.25 N HCl, and 15% TCA) and placed in water bath for 15 min, cooled, and centrifuged at room temperature for 10 min at 1000 rpm. The absorbance of clear supernatant was measured against reference blank at 535 nm. The results were expressed as LPO nmol/mg wet tissue.

#### Statistical analysis

The mean  $\pm$  SEM values were calculated for each group. One-way ANOVA followed by Dunnett's multiple comparison tests were used for statistical analysis. Values of  $p<0.05$  were considered statistically significant.

## Results

### Behavioral effects of chronic haloperidol or *M. koenigii* treatment in rats

Haloperidol (1 mg/kg) treatment significantly increased the frequency of VCMs, OBs, and TPs in rats compared with vehicle-treated controls. EEMK (100 and 300 mg/kg) and AMK (30 and 100 mg/kg) significantly attenuated haloperidol-induced VCM (Figure 1), OB (Figure 2), or TP (Figure 3).

### Effect of *M. koenigii* on locomotor activity

Haloperidol treatment decreases the number of squares traversed by rats. Co-administration of EEMK (100 and 300 mg/kg) and AMK (30 and 100 mg/kg) significantly increased the number of squares traversed compared with haloperidol-treated group (Figure 4). Haloperidol treatment exhibited significant increase in the number of grooming in rats. Treatment with EEMK (100 and 300 mg/kg) and AMK (30 and 100 mg/kg) significantly reduced the number of grooming (Figure 5).

### Effect of *M. koenigii* on body weight

Haloperidol treatment exhibited significant increase in body weight compared with vehicle-treated animals. Treatment with EEMK (100 and 300 mg/kg) in

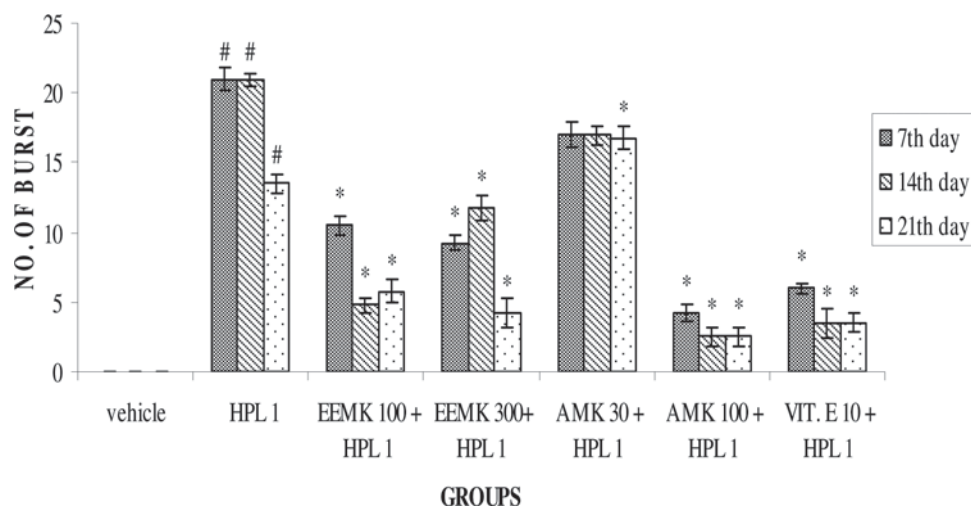


Figure 2. Effect of *Murraya koenigii* on haloperidol-induced OB in rats.  $n=5$ . The observations are mean  $\pm$  SEM. <sup>#</sup> $p < 0.05$  compared with vehicle-treated group. <sup>\*</sup> $p < 0.05$  compared with haloperidol-treated group. One-way ANOVA followed by Dunnett's test. HPL: Haloperidol, EEMK: alcohol extract of *Murraya koenigii* leaves, AMK: alkaloids isolated from EEMK.

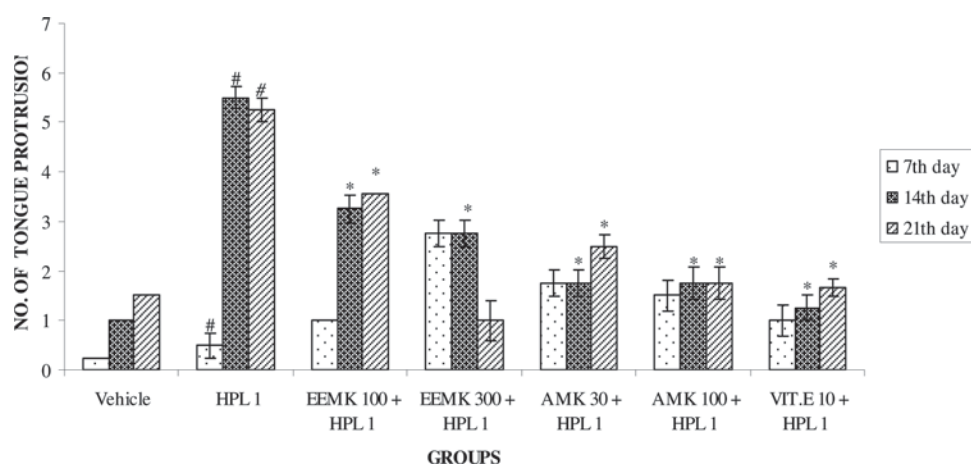


Figure 3. Effect of *Murraya koenigii* on haloperidol-induced TP in rats.  $n=5$ . The observations are mean  $\pm$  SEM. <sup>#</sup> $p < 0.05$  compared with vehicle-treated group. <sup>\*</sup> $p < 0.05$  compared with haloperidol-treated group. One-way ANOVA followed by Dunnett's test. HPL: Haloperidol, EEMK: alcohol extract of *Murraya koenigii* leaves, AMK: alkaloids isolated from EEMK.

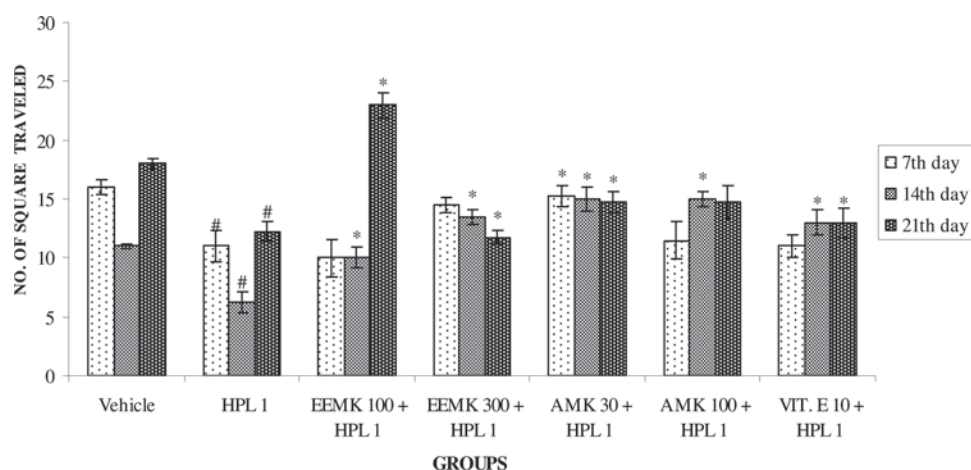


Figure 4. Effect of *Murraya koenigii* on number of squares traveled in haloperidol-treated rats.  $n=5$ . The observations are mean  $\pm$  SEM. <sup>#</sup> $p < 0.05$  compared with vehicle-treated group. <sup>\*</sup> $p < 0.05$  compared with haloperidol-treated group. One-way ANOVA followed by Dunnett's test. HPL: Haloperidol, EEMK: alcohol extract of *Murraya koenigii* leaves, AMK: alkaloids isolated from EEMK.



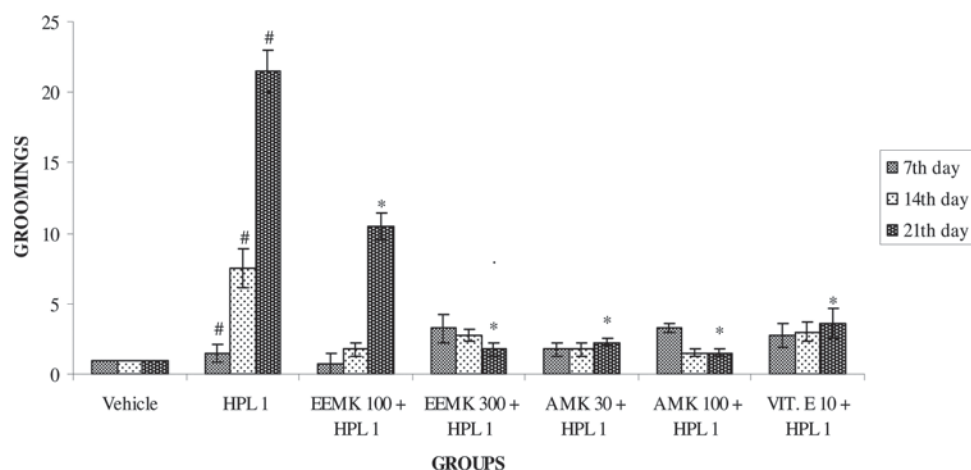


Figure 5. Effect of *Murraya koenigii* on grooming in haloperidol-treated rats.  $n=5$ . The observations are mean  $\pm$  SEM.  $^{\#}p<0.05$  compared with vehicle-treated group.  $^{*}p<0.05$  compared with haloperidol-treated group. One-way ANOVA followed by Dunnett's test. HPL: Haloperidol, EEMK: alcohol extract of *Murraya koenigii* leaves, AMK: alkaloids isolated from EEMK.

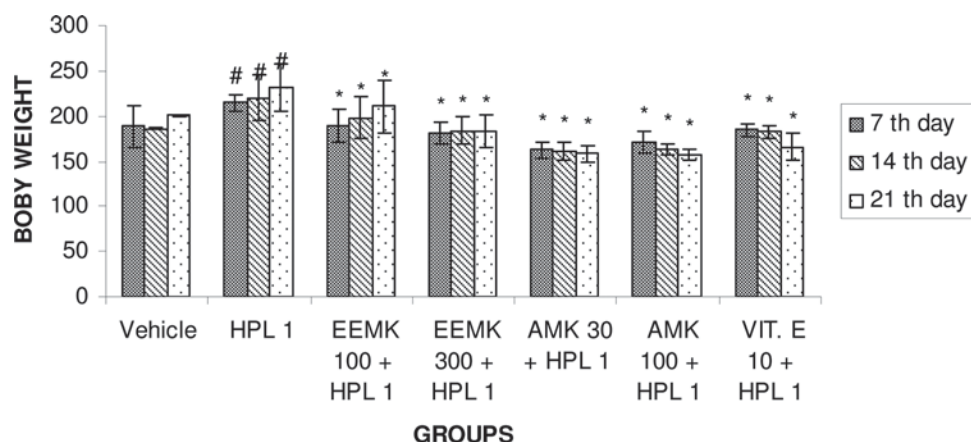


Figure 6. Effect of *Murraya koenigii* on body weight in haloperidol-treated rats.  $n=5$ . The observations are mean  $\pm$  SEM.  $^{\#}p<0.05$  compared with vehicle-treated group.  $^{*}p<0.05$  compared with haloperidol-treated group. One-way ANOVA followed by Dunnett's test. HPL: Haloperidol, EEMK: alcohol extract of *Murraya koenigii* leaves, AMK: alkaloids isolated from EEMK.

haloperidol-treated animals significantly restored the body weight compared with the haloperidol-treated group (Figure 6).

### Biochemical changes after chronic haloperidol or *M. koenigii* treatment in rats

#### Effect of *M. koenigii* on SOD

Haloperidol-treated rats showed decreased levels of antioxidant enzyme, SOD, in forebrain homogenates. Administration of EEMK (100 and 300 mg/kg) and AMK (30 and 100 mg/kg) significantly reversed the haloperidol-induced decrease in forebrain SOD levels compared with haloperidol-treated rats (Table 1).

#### Effect of *M. koenigii* on CAT

Haloperidol-treated rats showed decreased levels of antioxidant enzymes CAT in forebrain homogenates. Administration of EEMK (100 and 300 mg/kg) and AMK (30 and 100 mg/kg) significantly reversed the haloperidol-induced decrease in forebrain CAT levels compared with haloperidol-treated rats (Table 1).

#### Effect of *M. koenigii* on LPO

Haloperidol treatment for 21 days induced LPO as indicated by significant raise in forebrain MDA levels compared with control rats. Administration of EEMK (100 and 300 mg/kg) and AMK (30 and 100 mg/kg) along with haloperidol significantly reversed the extent of LPO compared with haloperidol-treated rats (Table 1).

#### Effect of *M. koenigii* on GSH

Administration of haloperidol significantly decreased the forebrain GSH levels. Administration of EEMK (100 and 300 mg/kg) and AMK (30 and 100 mg/kg) significantly reversed the haloperidol-induced decrease in the forebrain GSH level compared with haloperidol-treated rats (Table 1).

## Discussion

In the present study, chronic haloperidol-treated animals showed increased frequencies of VCMs and TPs compared with vehicle-treated control animals. Chronic

Table 1. Effect of *Murraya koenigii* on biochemical parameters in haloperidol-treated rats.

Treatment	SOD (U/mg of wet tissue)	CAT (U/g of wet tissue)	GSH (nmol/mg of wet tissue)	LPO ( $\mu$ mol/mg of wet tissue)
Vehicle	0.1655 $\pm$ 0.03	0.3158 $\pm$ 0.01	8.682 $\pm$ 0.68	3.26 $\pm$ 0.23
HPL 1	0.1573 $\pm$ 0.02#	0.2478 $\pm$ 0.02#	5.901 $\pm$ 0.28#	7.95 $\pm$ 0.76#
EEMK 100 + HPL 1	0.220 $\pm$ 0.01*	0.2817 $\pm$ 0.02	8.613 $\pm$ 0.10*	5.84 $\pm$ 1.45
EEMK 300 + HPL 1	0.258 $\pm$ 0.01*	0.5748 $\pm$ 0.07*	11.54 $\pm$ 1.05*	3.53 $\pm$ 0.87*
AMK 30 + HPL 1	0.223 $\pm$ 0.02*	0.4725 $\pm$ 0.02*	10.59 $\pm$ 0.16*	3.27 $\pm$ 1.22*
AMK 100 + HPL 1	0.2395 $\pm$ 0.006*	0.653 $\pm$ 0.02*	11.76 $\pm$ 0.30*	2.97 $\pm$ 0.94*
Vitamin E 10 + HPL 1	0.2948 $\pm$ 0.01*	0.7547 $\pm$ 0.05*	12.84 $\pm$ 0.16*	2.63 $\pm$ 0.47*

$n=5$ . The observations are mean  $\pm$  SEM.

#  $p<0.05$  compared with vehicle-treated group.

\*  $p<0.05$  compared with haloperidol-treated group. One-way ANOVA followed by Dunnett's test.

treatment with EEMK and AMK significantly reversed the induced VCMs and TPs.

Numerous reports indicate that an excessive production of free radicals is associated with chronic neuroleptic use and might contribute to the onset of TD and other movement disorders, such as dystonia and Parkinson's disease (Cadet et al., 1986). This effect may be related to a reduction in specific endogenous antioxidant mechanisms, such as a decrease in GSH levels (Shivakumar & Ravindranath, 1993) and low levels of antioxidant defense enzymes such as SOD and CAT (Elkashef & Wyatt, 1999).

The molecular mechanisms by which neuroleptics increase oxygen free radical production are unknown. Neuroleptics act by blocking dopamine receptors (Creese et al., 1976). Such blockade results in increased dopamine turnover, which in turn could conceivably lead to an increased production of hydrogen peroxide, resulting in oxidative stress (Cohen & Spina, 1988; Elkashef & Wyatt, 1999). Oxygen free radicals are also reported to diminish the dopamine. However, this does not seem to be the only mechanism responsible for the GSH/ATP depletion observed during haloperidol treatment (Vairetti et al., 1999). Sagara (1998) showed that haloperidol causes a sequence of cellular alterations that leads to cell death, and the production of reactive oxygen species (from the mitochondria but not from the metabolism of catecholamines) is an integral part of this cascade. Thus, the possibility of a direct interaction with specific membrane components exists. Cohen and Zubenko (1985) demonstrated that striatal cell membranes of rats chronically treated with neuroleptics exhibit abnormal physicochemical properties. It is conceivable that the changes in membrane properties may be related to free radical production. Another possibility is that neuroleptics suppress the activity of certain detoxifying enzymes, leaving cells unprotected especially if basal enzyme activity is low or the free radical scavenging mechanisms are less effective. Free radicals are highly reactive with specific cellular components and have cytotoxic properties (Ravindranath & Reed, 1990), and neuronal loss in the striatum has been reported in animals treated chronically with neuroleptics (Nielsen & Lyon, 1978).

Neuroleptics may also have a direct cytotoxic effect via the production of toxic metabolites (Gorrod & Fang,

1993; Wright et al., 1998). Galili et al. (2000) reported that the direct neurotoxic effects of haloperidol and its metabolites on mouse neuronal cultures and PC-12 cells were reversed by antioxidants. Burkhard et al. (1993) reported that, like MPP+, the metabolites of haloperidol, chlorpromazine, and thioxanthine inhibited Complex I of the electron transport chain; clozapine was also found to inhibit Complex I, but at a much higher concentrations—this might be one of the possible mechanisms for the development of TD.

In the present study, chronic haloperidol-treated animals showed low levels of detoxifying enzymes such as SOD and CAT compared with vehicle-treated control animals, suggesting a possible induction of free radical generation by chronic haloperidol treatment. Chronic haloperidol-treated animals showed decreased levels of GSH and increased levels of LPO products compared with vehicle-treated control animals. EEMK and AMK induced the production of SOD and CAT, decreased the elevated level of LPO products in haloperidol-treated animals, also elevated the cellular defense mechanisms such as GSH, and also further suggesting the role of free radical in the pathophysiology of haloperidol-induced OD and possible antioxidant action of *M. koenigii*.

The mechanism by which *M. koenigii* prevents haloperidol-induced oxidative damage and OD is unclear. *M. koenigii* has been reported to activate antioxidant defensive enzymes, including increasing levels of SOD, GSH reductase, and CAT (Sathaye et al., 2011; Yankuzo et al., 2011). Another reported mechanism of *M. koenigii* action involves free radical scavenging. *M. koenigii* is a highly effective OH<sup>-</sup> scavenger (Rao et al., 2007). Accordingly, one or several of these actions of *M. koenigii* may contribute to the suppression of haloperidol-induced oxidative injury and OD.

## Conclusion

The findings of this study strongly suggest that free radical toxicity and oxidative stress play an important role in the pathogenesis of OD, and that *M. koenigii* could be used for the prevention or treatment of neuroleptic-induced OD.

## Declaration of interest

The authors report no conflict of interest.

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