Original Article

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Effect of the Aqueous Extract of Mentha Arvensis on Haloperidol Induced Catalepsy in Albino Mice

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ABSTRACT

Neuroleptic drugs (D2 blockers) which are used for the treatment of psychotic disorders, especially for schizophrenia, are known to produce extra-pyramidal side effects (EPS). Catalepsy was induced by these drugs in animals and these animals have been used as models to study the extra-pyramidal side effects which are associated with anti-psychotic agents in human beings. In the present study, we found out the protective effect of the aqueous extract of *Mentha arvensis* (MA) on haloperidol (2.0 mg/kg po administration) induced catalepsy in mice, by employing the standard bar test and the assessment of the locomotor activity. The mice were allocated to six groups, with each group containing seven animals. The effects of the test drug MA (500 and 1000mg/kg doses) and the standard drug, trihexyphenidyl (0.1mg/kg) were assessed after their repeated dose administration in mice for fourteen days, 30 minutes prior to the administration of haloperidol. The mice were sacrificed on the fourteenth day and the TBARS, glutathione, SOD and the catalase activities in their brain tissues were estimated by using the Ohkawa et al., Sedlak and Lindsay, Clairbone, Marklund and Marklund respectively. A significant ($P<0.001$) reduction in the cataleptic scores was observed in the test drug treated groups as compared to the toxic control, with a maximum reduction in the group with a drug dose of 1000 mg/kg. Similarly, our study suggested that MA had significantly reduced othe xidative stress and the cataleptic score which was induced by haloperidol. Hence, it could be used to prevent the drug- induced extra-pyramidal side effects.

Key Words: Catalepsy; Anti-oxidant; Parkinson's disease; Haloperidol; *Mentha arvensis*

INTRODUCTION

Worldwide, researchers have come to know that catalepsy does not appear of its own accord; instead, that it often manifests as a one in a constellation of the symptoms which are caused by psychotic disorders. Nowadays, the usage of typical anti-psychotic drugs has been limited because of the side effects and the toxicity which are produced by them [1]. Haloperidol is a widely and commonly prescribed typical anti-psychotic drug which is used for the treatment of schizophrenia and other effective disorders [2,3]. Receptor binding studies have shown that haloperidol was equivalent to fluphenazine and that it was about twice as active as chlorpromazine, as an inhibitor of the binding of dopamine to the dopamine receptor. It has a high affinity for the dopamine D2 receptors and it acts by blocking them [1]. But, haloperidol causes movement disorders such as the narcoleptics malignant syndrome, dystonias and tardive dyskinaesias [1]. Oxidative stress, which is a culprit in many human diseases, has been implicated in haloperidol toxicity [4]. Extra pyramidal symptoms (EPSs), including pseudoparkinsonism, occur as distressing side effects in 20-75% of the patients who are administered typical anti-psychotics [5]. The blockade on the dopamine receptor which is caused by haloperidol increases the dopamine turnover in humans and rats [6].

It has been proposed that haloperidol induced oxidative stress arises from the generation of free radical catecholamine metabolism by monoamine oxidases (MAOs) [7]. The acute [8] and chronic [9] administration of haloperidol in mice resulted in the generation of significant oxidative stress in their brain regions, as was evidenced by loss of the nonprotein thiol anti-oxidant glutathione (GSH) and by the increase of the lipid peroxidation product, malonaldehyde. The brain system is highly susceptible to oxidative damage [10] as it is enriched with the more easily peroxidable fatty acids and as it is not particularly enriched with the anti-oxidant defenses. Newer approaches which are used to treat the oxidative damage in the brain like *Mentha arvensis,* have anti-oxidant potential [11].

Since haloperidol induced catalepsy has an underlying pathology of increased oxidative stress, the present study was designed to evaluate the effect of *Mentha arvensis* on haloperidol induced catalepsy. Trihexyphenidyl HCl was used as a standard drug [12].

Mentha arvensis belongs to the family, Lamiaceae, which is popularly known as pudina, which is a common household remedy that has found its use in the Indian indigenous system of medicine against several ailments as an anaesthetic, anti-phlogistic, anti-depressant, anti-microbal [13], antiseptic, anti-spasmodic, carminative, digestive, expectorant, nervine, stomachic, tonic and anti-fertility drug [14]. It has beta-galactosidase activity [15] and it protects against radiation-induced lethality [16]. It contains menthol (66%), (-)-menthyl acetate (15%) and (-)-menthone (8%) and it also has some phenolic content.

MATERIALS AND METHODS

Animal

Eight week old Swiss albino mice (weighing 20–30 g) which were obtained from the central animal house, Jamia Hamdard, New Delhi, India, were used in the study. The animals were housed under standard 12hr: 12hr light/dark cycles and were provided with food and water *ad libitum*. The animals were acclimatized to the laboratory conditions before testing them. Each animal was

used once. The experiments were performed between 10.00 and 16.00hrs.The studies was approved by the institutionl ethical committee of Jamia Hamdard and the study was conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals.

Drugs and Dosage

Mentha arvensis was the test drug which was used. It was collected locally and it was identified by a botanist, Dr. M.P. Sharma, Professor, Department of Botany, Faculty of Science, Hamdard University, New Delhi-62. The *Mentha arvensis* was extracted with double distilled water. The extract which was thus obtained was vacuum evaporated in order to make it into powder form for it to be redissolved in double distilled water. It was stored in air tight containers which were protected from light. Trihexyphenidyl HCl (Wyeth Limited, Goa) and haloperidol (RPG Life Science Ltd. Ankleshwar) were suspended/ dissolved in 1% carboxy methyl cellulose solution. The treatments which were received by each group (each group consisted of seven animals, n=7) are shown in [Table/Fig-1]. The group which received normal saline (10ml/kg) served as the control group. The normal saline, trihexphenidyl Hcl (0.1mg/kg), MA (500 and 1000 mg/kg) [17], and haloperidol (2 mg/kg) were given orally.

Experimental Design

Haloperidol Induced Catalepsy (HIC): Catalepsy was induced with haloperidol (2.0 mg/kg p.o.) and it was assessed at by means of a standard bar test and by the assessment of the locomotor activity on every fourth, eighth and fourteenth day of the drug treatment, as shown in [Table/Fig-2] [18, 19]. The catalepsy was assessed in terms of the time for which the mouse maintained an imposed position with both the front limbs extended and resting on a 4 cm high wooden bar (1.0cm diameter). The end point of the catalepsy was considered to occur when both the front paws were removed from the bar or if the animal moved its head in an exploratory manner. A cut-off time of 300 seconds was applied. Between the determinations, the animals were returned to their individual home cages. All the observations were made between 10.00 and 16.00 hrs in a quiet room at 23-25° C.

Group (n=7)	Drug Treatment	Dose (mg/kg), Route of administration (p.o.) (for 14 days)
I	Normal saline	10 ml / kg
II	HAL	2 mg / kg
III	THP+HAL	0.1 mg / kg+2 mg/kg
IV	MA_1+HAL	500 mg /kg+2 mg/ kg
V	MA_2+HAL	1 gm / kg+2 mg / kg
VI	MA_2 per se	1 gm / kg

[Table/Fig-1]: Treatment schedule
HAL=Haloperidol, THP=Trihexyphenidyl HCl, MA =*Mentha arvensis* extract
n=number of animals used in each group. (7 mice /group)
No of groups=6
Treatment duration=14 days

Scoring Method

If the animal maintained the imposed posture for at least 20 seconds, it was considered to be cataleptic and the time was recorded in seconds. The animals were tested on every fourth, eighth and fourteenth day of the drug treatment and only the greater duration of the immobility was considered.

Assement of Locomotor Activity

Photoactometer test: This test measures the exploration and the voluntary locomotion within an enclosed area. The objective value for the spontaneous motor activity was obtained by using a photoactometer (Techno electronics, Lucknow, India). The mice were placed individually in a 30×30 cm black metal chamber with a screen floor and a light-tight lid. Six beams of red light were focused 2 cm above the floor in to photocells on the opposite side. Each beam interruption was registered as an event on the external counter. The floor of the chamber was wiped clean with a damp

Group	Drug treatment	Catalepsy score on 4th day	Catalepsy score on 8th day	Catalepsy score on 14th day
I	Normal saline	1.42±0.05*	1.42±.05*	1.42±0.05*
II	HAL	220.71±11.15	231.42±11.21	237.14±8.29
III	THP+HAL	26.42±1.28*	27.85±1.01*	30.14±2.44*
IV	MA_1+HAL	88.14±3.73*	90.14±2.98*	95.14±5.2.18*
V	MA_2+HAL	68.85±5.44*	68.42±5.67*	75.00±5.35*
VI	MA_2 per se	1.33±.05	1.33±.05	1.34±0..05

[Table/Fig-2]: Effect of haloperidol, trihexyphenidyl HCl, and *Mentha arvensis* extract on catalepsy score on 4th, 8th and 14th day of drugs treatment
Results are expressed as mean ± SEM. The results were analyzed by Analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison test. n=7; * =P <0.001; # =p<0.001; ** =p<.01; ##=p<.01; ***=p<0.05; ### =p<0.05; * Vs. group II.

Group	Drug treatment	Locomotor activity on 4th day	Locomotor activity on 8th day	Locomotor activity on 14th day
I	Normal saline	400±10.24*	398.1±9.72*	388.85±12.05*
II	HAL	135.33±4.26	125.33±2.40	107.83±7.48
III	THP+HAL	347.57±9.99**	338.57±9.11*	331.57±11.30**
IV	MA_1+HAL	258.57±10.10*	245.71±8.69*	235.71±8.69*
V	MA_2+HAL	305.42±7.58*	297.42±9.45*	288.57±9.61*
VII	MA_2 per se	391.42±8.57	383.57±10.73	376.85±12.33

[Table/Fig-3]: Effect of haloperidol, trihexyphenidyl HCl and *Mentha arvensis* extract on locomotor activity on 4th, 8th and 14th day of drugs treatment
Results are expressed as mean ± SEM. The results were analyzed by Analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison test. n=7; * =P <0.001; # =p<0.001; ** =p<.01; ##=p<.01; ***=p<0.05; ### =p<0.05; * Vs. group II.

towel before each use. The mice were placed in the chamber one hour after the oral administration of the drug. They were allowed to acclimate for 2 min, and then the light beam breaks were counted for the next 10 min [19].

In this study, MA was administered once daily, 30 min prior to the haloperidol administration, for fourteen days. Catalepsy was determined 30 min after the haloperidol administration on the fourth, eighth and on the fourteen day of the drug treatment. The animals were then sacrificed by cervical dislocation and the TBARS, glutathione, catalase and SOD [20-23] activities of their whole brain tissue were estimated by using the Ohkawa et al [20], Sedlak and Lindsay, Clairbone, Marklund and Marklund respectively.

Assay of TBARS

Lipid peroxidation is a free radical mediated event. The primary products of such a damage are a complex mixture of peroxides which then breakdown to produce carbonyl compounds. The malondialdehyde (MDA) is one such carbonyl compound, which forms a characteristic chromogenic adduct with two molecules of TBA. The colourimetric reaction of TBA with MDA, a secondary product of lipid peroxidation, has been widely accepted for measuring lipid peroxidation. The total protein which was present in the homogenate was estimated by following the method which was described by Lowry et al [24]. The units of the TBARS activity which were determined, were expressed in terms of nmoles MDA/mg protein [20].

Assay of Glutathione

This spectrophotometric procedure was based on the method of Ellman i.e. DTNB [5, 5'-dithiobis-(2-nitrobenzoic acid)] is reduced by –SH groups to form one mole of 2-nitro-5- mercaptobenzoic acid per mole of –SH, as described by Sedlak and Lindsay. The units of the GSH activity which were determined were expressed in terms of nmoles µg/mg protein [21].

Assay of SOD

The assay of SOD was carried out, based on the ability of the enzyme to inhibit the auto-oxidation of pyrogallol, as described by Marklund and Marklund. The total protein which was present in the homogenate was estimated by following the method which was described by Lowry et al [24] . The units of the SOD activity which were determined were expressed in terms of milligrams of the total protein [22].

Assay of Catalase

In the UV range, H_2O_2 shows a continuous increase in the absorption with decreasing wavelength. The decomposition of H_2O_2 can be followed directly by the decrease in the absorbance at 240 nm. The difference in absorbance (ΔA) per unit time is a measure of the catalase activity. The units of the CAT activity which were determined were expressed in terms of nmolH_2O_2/mg protein [23].

STATISTICAL ANALYSIS

For each group, the mean± SEM was calculated and the data was analyzed by using one way ANOVA, followed by the Tukey-Kramer multiple comparison test. P values of <0.05 were considered to be statistically significant.

RESULTS

In the present study, the administration of the standard drugs and all the doses of the test drug, 30 min prior to the administration of the haloperidol dose on the fourteenth day, showed significantly (P<0.001) lower cataleptic scores than in the toxic control group in a dose and time dependent manner.

TBARS Activity

The TBARS levels were found to be significantly increased (p<.001) in the brain tissue of the haloperidol (2 mg/kg p.o.) treated animals, as shown in [Table/Fig-4].

GLUTATHIONE Activity

There was a significant increase (p<.05) in the levels of GSH in the *Mentha arvensis* pretreated mice as compared to the haloperidol 2 mg/kg p.o treated mice.

SOD Activity

In the mice who were pretreated with *Mentha arvensis,* the levels of SOD were significantly reduced (p<.001) as compared to those in the haloperidol 2 mg/kg p.o. treated mice [Table/Fig-4] shows the effect of the significant and dose dependent recovery on the haloperidol induced elevation of the SOD levels in animals.

CATALASE Activity

There was a significant increase (p<.001) in the levels of catalase in the *Metha arvensis* pretreated mice as compared to the haloperidol 2 mg/kg p.o. treated mice, as shown in [Table/Fig-4]

DISCUSSION

The treatment with haloperidol often because distressing side effect involving the extra-pyramidal tract these adverse reactions comprise of variety of movement disorders, including drug induced Parkinsonism [25]. This occurs in 20-40% of the patient population. The chronic use of haloperidol sometimes leads to irreversiable extra pyramidal disturbances such as tardive dyskinaesia. Similar disorders are reproducible in normal monkeys who are treated for many months with haloperidol and so, these symptoms are not

Group	TBARS (nmoles MDA/mg protein)	GSH (µg/mg protein)	SOD (Units/mg protein)	CAT (nmolH_2O_2/mg protein)
I	3.27±0.08*	3.87±0.14*	2.41±0.17*	39.28±1.47*
II	8.88±0.13*	2.17±0.18	7.07±0.14	20.7±1.59
III	4.01±0.15*	3.52±.04*	2.51±0.14*	32.42±1.32***
IV	6.14±0.26*	2.38±0.18*	3.98±0.11*	27.42±1.44*
V	5.94±0.20*	2.94±0.24**	3.92±0.11*	28.8±1.38*
VI	3.45±0.21	3.80±0.14	2.31±0.13	38±1.06

[Table/Fig-4]: Effect of haloperidol, trihexyphenidyl HCl, and *Mentha arvensis* extract on oxidative stress markers.
Results are expressed as mean ± SEM. The results were analyzed by Analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison test.
n=7; * =P <0.001; # =p<0.001; ** =p<.01; ##=p<.01; ***=p<0.05; ### =p<0.05; * Vs. group II.

merely an interaction between the psychotic state and the drug effects are largely due to the drug alone.

Since haloperidol induced catalepsy had an underlying pathology of increased oxidative stress and as *Mentha arvensis* was high anti oxidants, in the present study, the effect of *Mentha arvensis* was evaluated in haloperidol induced cataleptic mice.

In the present study, the animals who were treated for fourteen days with haloperidol showed severe cataleptic responses. Further, the animals (haloperidol treated) showed decreased levels of glutathione and catalase and increased levels of lipid peroxidation products and super oxide dismutase as compared to the vehicle toxic control animals. This result was in agreement with that of previous studies which were done on the effects of haloperidol on the extra pyramidal symptoms and the markers of oxidative stress (GSH, SOD, CAT and TBARS), thus suggesting the possible induction of free radical generation by haloperidol treatment. The results of our study were consistent with previous reports of the studies which were done on haloperidol induced oxidative stress [26]. But the exact mechanisms by which haloperidol increased free radical production were not clear. The enzymatic degradation by MAOs was associated with the production of hydrogen peroxide, which was readily converted to the hydroxyl radical in the presence of iron. Thus, it could initiate a destructive lipid peroxidation cascade, but an increased dopamine (DA) turnover, leading to hydrogen peroxide production which might not be exclusively involved in the degeneration of oxidative stress. The auto-oxidation of DA which resulted in the production of superoxide radicals might have contributed to the unbalanced production of the free radicals. However, other mechanisms may also be involved. Haloperidol was reported to suppress the activity of certain detoxifying enzymes, thus leaving the cell unprotected, especially if the basal enzyme activity was low or if the free radical scavenging mechanisms were less effective. Haloperidol (HP) is converted to potentially toxic (HHP^{+}) metabolites which may play a role in the extrapyrimidal side effects which are observed in the patients who are treated with haloperidol [27]. Another possible mechanism could be the effect of neuroleptics on the mitochondrial respiration. The metabolites of haloperidol inhibit complex-I of the electron transport chain [28]. The capability of the anti-psychotic drugs to clinically induce the extra-pyramidal syndrome seems to correlate well with their inhibitory effect on the complex- I inhibition. Whatever could have been be the mechanism of the unbalanced production of the reactive oxygen species (ROS) and the oxidative stress by haloperidol, *Mentha arvensis* was found to be effective in decreasing the oxidative stress in the haloperidol treated animals.

The anti-oxidative properties of *Mentha arvensis* reduced the duration of the catalepsy, decreased the elevated levels of lipid peroxidation in the haloperidol treated animals and elevated the cellular defense mechanisms such as glutathione, further suggesting the role of free radicals in the pathophysiology of the haloperidol induced extra-pyramidal syndrome.

The anti-oxidant activity of pudina could be possibly due to the direct scavenging of the superoxide radicals by the polyphenols or the flavanoids which are known to be present in these drugs. The combination of black tea and *Mentha arvensis* was found to be more effective than black tea or *Mentha arvensis* alone. From the present study, it can be concluded that *Mentha arvensis* may prove to be a beneficial adjuvant in the treatment of drug-induced extra-pyramidal side effects and related disorders. The above results have given strong evidence for the further evaluation of the use of *Mentha arvensis* in combination therapy along with typical anti-psychotic agents like haloperidol.

REFERENCES

[1] Goldstein SR, Matsummoto RR, Thompson TL, Patrick RL, Bowen WD, Walker JM. Motor effect of two sigma ligands which was mediated by nigrostraital dopamine neurons. *Synapse* 1998; 4:254-58.

[2] Seeman P, Corbett R, Nam D, Van Tol HH. Dopamine and serotonin receptors: Amino acid sequences, and their clinical roles in neuroleptic Parkinsonism. *Jpn J Pharmacol* 1996; 71: 187-204.

[3] Kulkarni SK, Naidu PS. Tardive dyskinesia: An update. *Drugs of Today* 2001; 37:97-119.

[4] Cadet JL, Lohr JB, Jested V. Free radical and tardive dyskinesia. *Trends Neurosci* 1986; 9:107-08.

[5] Eranti VS, Gangadhar BN, Jankiramaiah N. Haloperidol induced extra-pyramidal reaction: lack of the preventive effect of vitamin E. *Psychopharmacology* 1998; 140:418-20.

[6] Mackay AVP, Iversen LL, Rosser M, Spokes E, Brid E, Arregui A, et al. Increased brain dopamine receptor in schizopherenia. *Arch Gen Psychiatry* 1982; 39:991-97.

[7] Mahdik SP, Mukherjee S. Free radical pathology and anti-oxidant defense in schizopherenia: a review. *Schizophr Res* 1996; 19:1-17.

[8] Shivakumar BR, Ravindranath V. Oxidative stress and induced by administration of the Neuroleptics drug haloperidol attenuated by higher doses of haloperidol. *Brain Research* 1992; 595:256-62.

[9] Shivakumar BR, Ravindranath V .Oxidative stress and thiol modification which was induced by chronic haloperidol administration. *J Pharmacol Exp Ther* 1993;265:1137-41.

[10] Floyd RA, Carney JM. Free radical damage to protein and DNA: A mechanism which is involved and the relevant observation in brain undergoing oxidative stress. *Ann Neurol* 1992; 32:S22-27.

[11] Dorman HJ, Koşar M, Kahlos K, HolmY, Hiltunen R. The anti-oxidant properties and the composition of the aqueous extracts from Mentha species, hybrids varieties, and cultivars. J *Agric Food Chem* 2003; 51(16):4563-99.

[12] Yamada H, Momose T, Okada M, Kuroiwa Y. Anti-cholinergic drugs: response of Parkinsonism not responsive to levodopa. *J Neurol Neurosurg Psychiatry* 2002; 72(1):111-13.

[13] Coutinho HD, Costa JG, Lima EO, Falcao-Silva VS, Siqueira-Junior JP. The potentiating effect of Mentha arvensis and chlorpromazine on the resistance to aminoglycosides of Methicillin –Resistant Staphylococcus aureus. *In Vivo* 2009; 23(2):287-89.

[14] Sharma N, Jocob D. The anti-fertility investigation and the toxicological screening of the petroleum ether extract of the leaves of Mentha arvensis L. in male albino mice. *Ethnopharmacol*. 2001; 75(1):5-12.

[15] Chowdhury BR, Chakraborty R, Raychaudhuri U. Study on the beta-galactosidase enzymatic activity of herbal yogurt. *Int J Food Sci Nutr* 2008; 59(2):116-22.

[16] Jagetia GC. The radioprotective potential of plants and herbs against the effects of ionizing radiation. *J Clin Biochem Nutr* 2007;40(2):74-81.

[17] Jagetia GC, Baliga MS. Influence of the leaf extract of Mentha arvensis Linn. (Mint) on the survival of mice who were exposed to different doses of gamma radiation. *Strahlentherapie and Onkologie* 2002; 178:91-98.

[18] Sanjay N Mandhane, Rahul T. Adenosinergic modulation of drug induced catalepsy in mice. *Psychopharmacology* 1999; 144:398-404.

[19] Lennert H, Hoyer S. The intra-cerebroventicular administration of streptozocin causes long term diminution in the learning and memory abilities and in the cerebral energy metabolism in adult rats. *Behav Neurosci* 1998; 112:1199-208.

[20] Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by the thiobarbituric acid reaction. *Anal Biochem* 1979; 95:359-64.

[21] Sedlak J, Lindsay RH. Estimation of the total protein (bound) and the nonprotein sulfhydryl groups in tissues by using Ellman's reagent. Anal. *Biochem* 1968; 25:192-205.

[22] Clairbone A. Assay of Catalase. In: Greenwald RA, ed. Hand book of method of oxygen free radical research; Boca Raton,Fla; CRC press;1985;283-84.

[23] Marklund S, Marklund G. Involvement of the super oxide anion radical in the auto oxidation of pyrogallol and a convenient assay for super oxide dismutase. *Eur J Biochem* 1974; 47:469-74.

[24] Peterson GL. A review on the folin phenol protein quantification method of Lowry, Rosenbrough, Farr and Randall. *Anal Biochem* 1979; 100:201-20.

[25] Marsedan CD, Jenner P. The pathophysiology of the extra-pyramidal side effects of neuroleptic drugs. *Pshchol Med* 1980; 10:55-72.
[26] Sagara Y. Induction of reactive oxygen species in neurons by haloperidol. *J Neurochem* 1998; 71:1002-12.
[27] Garrod JW, Fang J. The metabolism of haloperidol. *Xenobiotica* 1993; 23:495-508.
[28] Burkhardt C, Kelly JP, Lim YH, Filley CM, Prker WDJ. Neuroleptic medication inhibits complex–I of the electron transport chain. *Ann Neurol* 1993; 33:512-17.

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