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Effect of Ethanolic Extract of Black Tea on Haloperidol-Induced Catalepsy in Mice

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ABSTRACT

Neuroleptic drugs (D_2 blockers) used in the treatment of psychotic disorders especially in schizophrenia are known to produce extrapyramidal side effects (EPS). Catalepsy was induced by these drugs in animals and these have been used as models for the extrapyramidal side effects associated with antipsychotic agents in human beings. In the present study, we have find out the antioxidant effect of the ethanolic extract of black tea in catalepsy on haloperidol (2.0mg/kg p.o administration) induced catalepsy in mice by employing the standard bar test and locomotor activity. Mice were allocated to seven groups, each group containing seven animals the standard drugs trihexphenidyl HCl (0.1mg/kg) were assessed after repeated dose administration for twelve days, 30 minutes prior to the haloperidol. Mice were sacrificed on the twelve days and TBARS (Thiobarbituric Acid Reactive Substances), GLUTATHION (GSH), SOD (Superoxide dismutases) and CATALASE (CAT) activity in the brain tissue was estimated by using standard procedure. A maximum reduction in the cataleptic scores was observed in test drug treated groups at 8 mg/kg dose and which was significant ($P<0.001$). Maximum reduction in TBARS ($P<0.001$) was also observed in the dose 4 mg/kg and 8 mg/kg group. Our study suggests that black tea has significantly reduced oxidative stress and the cataleptic score and increase locomotor activity induced by haloperidol. It could be used to prevent drug-induced extrapyramidal side effects.

Key words: Catalepsy; Antioxidant; Parkinson's disease; Haloperidol; Black tea

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INTRODUCTION

Haloperidol is an antipsychotic drug, which is used in the treatment of schizophrenia and other affective disorders. It blocks the dopaminergic action in the nigro-strial pathway leading to high frequency of extrapyramidal motor side effects [1]. In animal models, haloperidol induces a behavioral state known as catalepsy in which the animals are unable to correct externally imposed postures [2]. The use of haloperidol has been associated with an increased level of oxidative stress in the brain [3]. This evidence suggests a possible role for antioxidants in the treatment of haloperidol-induced catalepsy. Oxidative stress, a cause in many human diseases has been implicated in haloperidol toxicity and extrapyramidal symptom (EPS) [4, 5]. The blockade of dopamine receptor by haloperidol increases dopamine turn over 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]. Acute and chronic administration of haloperidol to mice resulted in the generation of significant oxidative stress in brain regions as evidenced by loss of the nonprotein thiol antioxidant glutathione (GSH) and increase in the lipid peroxidation product malonaldehyde [8,9]. Brain system is highly susceptible to oxidative damage [10]. Hong et al. suggested that the minimizing effect of black tea extract on the eicosanoid accumulation and oxidative damage in addition to the reduction of neuronal cell death could eventually result in protective effect on ischemia/reperfusion-induced brain injury and behaviour deficit [11]. So, new approaches to treat the oxidative damage in brain by administration of black tea as antioxidant [12].

Tea is one of the most widely consumed beverages in the world today, second only to water, well ahead of coffee, beer, wine and carbonated soft drinks [13,14]. The tea plant, Camellia sinensis, is a member of the Theaceae family, and black, oolong, and green tea are produced from its leaf and buds. Tea consumption began about 5000 years ago in southwest China. Western cultures favour black tea, which is prepared through the oxidation, curing process of maceration and exposure to atmospheric oxygen [15]. Several epidemiological studies and clinical trials showed that tea might reduce the risk of many chronic diseases, including cardiovascular disease, reduce the risk of stroke and coronary heart disease [16, 17]. Of the total amount consumed in the World, 78% is black, 20% green and 2% oolong tea [15].

BT production involves enzymatic transformation (by POD) of 75% of catechins contained in tea leaves into multimeric polyphenols – theaflavin (TF; dimeric) and thearubigin (TR; polymeric) which imparts distinctive color and taste to BT. During these processes, the catechins are converted to theaflavins and thearubigins [18]. The most common flavonoids in BT are the flavan-3-ols which are mainly epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG). The TFs are dimmers – theaflavin (TF_1), theaflavin 3-gallate (TF_2A), theaflavin 3'-gallate (TF_2B), and theaflavin 3, 3'-gallate (TF_3) [19].

Polyphenols found in tea have a greater antioxidant activity than do either vitamins C or E and are believed to be suitable for protection against reactive oxygen species (ROS) and their

associated pathologies [20]. Green tea polyphenols (GTPs) and especially the gallic acid moiety are known to scavenge O-2, HO. and ROO. [21]. It was reported that GTPs can scavenge ROS in all cellular compartments, in a variety of cells and in different body compartments before they have time to cause damage [22]. Yokozawa et al. [23] reported that green tea polyphenol was administered to rats at a daily dose of 50 or 100 mg/kg body weight for 30 days with a 2% w/w arginine diet. In rats given tea polyphenol the SOD and catalase activities, which were suppressed by excessive arginine administration, were increased dose-dependently, implying the biological defense system was augmented because of free radical scavenging activity. Young rats when drunken green tea for five weeks, GSH content of serum increased slightly, whereas the index of the total antioxidant status increased significantly and lipid peroxidation products, particularly malondialdehyde (MDA) was significantly diminished [24]. In the central nervous tissue, the activity of SOD and glutathione peroxidase (GSHpx) decreased, while the activity of glutathione reductase and catalase increased after drinking green tea for five weeks by young rats. Moreover, the level of LOOH, 4-HNE and MDA significantly decreased [11, 24]. Therapeutic uses of BT are Cardio protective, Antiulcer Antidiabetic Antimutagenic Anticlastogenic Antiproliferative, Anticancer, Anti-inflammatory and Antipathogenic [25-27].

Since haloperidol induced catalepsy has underlying pathology of increased oxidative stress. Present study was designed to evaluate the effect of ethanol extract of black tea on haloperidol induced catalepsy by using Trihexyphenidyl HCl as standard drug [28].

MATERIALS AND METHODS

Anti cataleptic study:

Plant material: The plant materials were collected locally from Delhi, India. The plants were authenticated by Dr. M.P. Sharma, professor, Department of Botany, Faculty of Science, Hamdard University, New Delhi.

Preparation of Extract: The sample was air dried and extracted with ethanol by refluxing for 12 hour. The extract was evaporated to dryness under reduced pressure and controlled temperature. The ethanol extracts yielded brownish solids and stored in desiccators till further used.

Animal: Studies were conducted in Eight-week-old Swiss albino mice (weighing 20–30 g) and obtained from the central animal house Jamia Hamdard, New Delhi, was 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 laboratory conditions before testing. Each animal was used once. Experiments were performed between 10.00 and 16.00hrs. The studies was approved by Institutional ethical committee 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: Trihexyphenidyl HCl (Wyeth Limited, Goa) and haloperidol (RPG Life Science Ltd. Ankleshwar) were suspended/ dissolved in 1% carboxymethyl cellulose solution. The group was received normal saline (10ml/kg) served as control, Trihexyphenidyl HCl (0.1mg/kg), black tea (4 mg/kg and 8 mg/kg) and haloperidol (2 mg/kg) were given orally to the test animals [29, 30].

Experimental design

Haloperidol Induced Catalepsy (HIC): Catalepsy was induced with haloperidol (2.0 mg/kg orally) and was assessed at by means of a standard bar test and locomotor activity in every fourth, eight and twelve day of drugs treatment [31, 32]. Catalepsy was assessed in terms of the time for which the mouse maintained an imposed position with both front limbs extended and resting on a 4 cm high wooden bar (1.0cm diameter). The end point of catalepsy was considered to occur when both front paws were removed from the bar or if the animal moved its head in an exploratory manner. A cut-off time of 300 second was applied. All observations were made between 10.00 and 16.00 hrs in a quiet room at 23-25º C.

Scoring method: If the animal maintained the imposed posture for at least 20 seconds, it was considered cataleptic and time was recorded in second. The animals were tested in every 4th, 8th and on the 12th day of drugs treatment and only the greater duration of immobility were considered.

In this study, black tea was administered once daily, 30 min prior to the haloperidol administration for twelve days. Catalepsy was determined 30 min after haloperidol administration on the 4th, 8th and on the 12th day of treatment. The animals were then sacrificed by cervical dislocation and the TBARS, GSH, CAT and SOD activity of the whole brain tissue was estimated [33-36].

Assessment of locomotor activity

Photoactometer test: This test measures exploration and voluntary locomotion within an enclosed area. Objective value for spontaneous motor activity was obtained with a photoactometer (Techno electronics, Lucknow, India). Mice were placed individually in a 30x30 cm black metal chamber with a screen floor and a light-tight lid. Six beans of red light will be 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 damp towel before each use. Mice were placed in the chamber one hour after oral administration of the drug. They were allowed to acclimate for 2 min, and then light beam breaks would be counted for the next 10 min [32].

Statistical analysis

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For each group, mean± SEM was calculated and the data was analyzed by one way ANOVA, followed by Dunnett's Multiple Comparison test by using SPSS-10. P values <0.05 was considered to be statistically significant.

RESULTS

The effects of oral administration of ethanol extract of black tea on haloperidol induce catalepsy in mice are analyzed. Oral administration of the standard drug and all doses of the test drugs are given 30 min before the haloperidol dose for the twelve days continuously as shown in Table 1.

Table 1: Administration of drugs pattern for 12days

Group (n=7)	Drug Treatment	Dose (mg/kg) for 12 days)
I	Control	10 ml / kg
II	HAL(toxic control)	2 mg / kg
III	BTE (D_2) per se	8 mg/kg
IV	THP +HAL	0.1 mg / kg +2 mg/kg
V	BTE (D_1) +HAL	4 mg / kg + 2 mg / kg
VI	BTE (D_2) +HAL	8 mg /kg + 2 mg / kg
VII	THP+BTE (D_2)+HAL	0.1 mg / kg + 8 mg / kg + 2 mg / kg

HAL=Haloperidol, THP=Trihexyphenidyl HCl, BTE=Black tea extract, D_1 and D_2 = different dose

The effects of oral administration of ethanol extract of black tea on haloperidol induce catalepsy activity in mice are analyzed (Table-2).Black tea pre-treatment in the doses of 4 mg/kg (D1) and 8 mg/kg (D2) significantly reduced ($p<0.001$) the duration of catalepsy produced by 2 mg/kg haloperidol treatment. Results shows significant and dose dependent recovery on haloperidol induced catalepsy of animal due to black tea D1 and D2 pre-treatment.

Table 2: Effect of haloperidol, Trihexyphenidyl HCl, Black tea extract on catalepsy score

Group	Drug treatment	Mean catalepsy score ± SEM , n= 7		
		4^{th} day	8^{th} day	12^{th} day
I	Control	1.42±0.05*	1.42±.05*	1.42±0.05*
II	HAL(toxic control)	220.71±11.15	231.42±11.21	237.14±8.29
III	BTE (D_2) per se	1.34±.06	1.34±.06	1.34±0.06
IV	THP +HAL	26.42±1.28*	27.85±1.01	30.14±2.44*
V	BTE (D_1) +HAL	73.57±3.56*	73.42±3.25*	76.4±2.42*
VI	BTE (D_2) +HAL	60.14±2.55*	61.57±2.56*	64.28±3.15*
VII	THP+BTE(D_2) +HAL	20.14±1.10*	22.0±1.17*	22.85±0.96*

* Vs. group II: * $p < 0.001$, ** $p < 0.01$, *** $p < 0.05$

Black tea pretreatment in the doses of 4 mg/kg (D1) and 8 mg/kg (D2) significantly increased ($p<0.001$) the locomotor activity which was impaired by 2 mg/kg p.o. haloperidol

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treatment, represented in Table-3. A significant and dose dependent recovery on locomotor impairment was found in black tea D1 and D2 groups.

Table 3: Effect of haloperidol, trihexyphenidyl HCl, black tea extract alone and in combination on locomotor activity on 4th, 8th and 12th day of drugs treatment

Group	Drug treatment	Mean locomotor activity ±SEM, n=7		
		4th day	8th day	12th day
I	Control	400±10.24*	398.1±9.72*	388.85±12.05*
II	HAL(toxic control)	135.33±4.26	125.33±2.40	107.83±7.48
III	BTE (D_2) per se	398.57±10.10	391.42±12.03	382.14±13.08
IV	THP +HAL	347.57±9.99**	338.57±9.11*	331.57±11.30**
V	BTE (D_1) +HAL	206.20±8.27*	201.42±5.96*	191.42±8.07*
VI	BTE (D_2) +HAL	262.85±12.28*	254.28±10.65*	247.28±11.29*
VII	THP+BTE(D_2) +HAL	358.57±7.99*	241.57±6.62	333.14±5.88*

* Vs. group II: * p < 0.001, ** p < 0.01, *** p < 0.05

The level of biochemical parameters TBARS, Glutathione, SOD and CAT were analyzed and tabulated in Tabel-4. TBARS levels were found to be significantly increased (p<.001) in brain tissue of haloperidol (2 mg/kg.) in all drug treated animals. There was a significant increase (p<.001) in the levels of GSH in pre-treated mice as compared to haloperidol 2 mg/kg treated mice. In the mice pretreated with black tea as well as p.o. (D2) the level of SOD were significantly reduced (p<.001) as compared to haloperidol 2 mg/kg p.o. Results showed significant and dose dependent recovery on haloperidol induced elevation of SOD level in animal. There was a significant increase (p<.001) in the levels of catalase in black tea pretreated mice as compared to haloperidol 2 mg/kg treated mice.

Table 4: Effect of haloperidol, trihexyphenidyl HCl, black tea extract alone and in combination on oxidative stress markers.

Group	Mean ±S EM (n=7) level of reactive components		Mean ±S EM (n=7) activity of enzymes	
	TBARS (nmoles MDA/mg protein)	GSH(µg/mg protein)	SOD(Units/mg protein)	CAT(nmol H_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	3.38±0.17	3.81±0.14	2.38±0.17	39±1.15
IV	4.01±0.15 *	3.52±.04*	2.51±0.14*	32.42±1.32***
V	5.11±0.18 *	2.5±0.13*	3.97±.09*	27.85±1.26*
VI	4.95±0.32 *	3.05±0.18*	3.14±0.23*	29.0±1.55*
VII	3.65±0.30 *	3.55±0.04*	2.78±0.18*	33.40±0.922*

* Vs. group II: * p < 0.001, ** p < 0.01, *** p < 0.05

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DISCUSSION

Typical neuroleptic agents like chlorpromazine, haloperidol and reserpine induce a cataleptic state in rodents and these are being used as models to test the extrapyramidal side effects involved with it. Neuroleptic induced catalepsy has been linked to a blockade of postsynaptic striatal dopamine D1 and D2 receptors [37]. Despite this evidence, several other neurotransmitters such as acetylcholine, serotonin, angiotensin, adenosine, or opioids have also been implicated. In addition to implications of various neurotransmitters in catalepsy, many preclinical and clinical studies have proposed reactive oxygen species in haloperidol induced toxicity. Evidence indicates that drugs which potentiate or attenuate neuroleptic catalepsy in rodents might aggravate or reduce the extrapyramidal signs respectively, in human beings. In the present study, BT was found to effectively reduce the HIC and it is comparable to that produced by the standard drugs, trihexyphenidyl HCl.

BT has been found to significantly decrease the SOD and TBARS levels and increase the level of GSH and CAT in mice brain; this suggested that it shows significant antioxidant properties in rat brain. The super oxide dismutase enzyme (SOD) is a major factor in oxygen toxicity and the SOD enzyme constitutes an essential defence against it. In the presence of a free radical quenching agent, the induction of the antioxidant enzyme is minimised. It is well established that the administration of haloperidol leads to an increase in the oxidative stress in the brain tissue. The increase in SOD observed in the present study supports the above concept. This study reveals that the BT treated groups significantly reduce ($P<0.001$) both oxidative stress and the catalepsy score induced by haloperidol.

Treatment with haloperidol often because distressing side effect involving the extrapyramidal tract, these adverse reactions comprise of variety of movement disorders, including drug induced Parkinsonism [38]. Which occurs in 20-40% of patient population? The chronic use of haloperidol sometimes leads to irreversible extra pyramidal disturbances such as tardive dyskinesia. Similar disorders are reproducible in normal monkeys treated for many months with haloperidol, so that these symptom are not merely an interaction between psychotic state and the drug effect are largely due to drug alone. Since haloperidol induced catalepsy has underlying pathology of increased oxidative stress and black tea is high in anti oxidant constituent. Therefore the present study effect of black tea was evaluated on haloperidol induced catalepsy.

In the present study, twelve days haloperidol treated animals showed severe cataleptic response, decreased level of glutathione and catalase and increased the level of lipid peroxidation products and super oxide dismutase as compared control animals. This result is in agreement with the previous studies of haloperidol on extra pyramidal symptom and markers of oxidative stress (GSH, SOD, CAT and TBARS). Thus, suggesting the possible induction of free radical generation by haloperidol treatment that is corroborating our study with haloperidol induced oxidative stress. However, the exact mechanisms by which haloperidol increases free radical production are not clear. A group of workers reported that MAO is associated with

production of hydrogen peroxide, which is readily converted to hydroxyl radical and thus initiate a destructive lipid peroxidation cascade mechanism. Haloperidol are reported to suppress the activity of certain detoxifying enzymes, leaving cell unprotected especially if the basal enzyme activity is low or free radical scavenging mechanism are less effective. Haloperidol (HP) is converted to potentially toxic (HHP^+) metabolites that may play a role in extrapyramidal side effect observed in patients treated with haloperidol [39].

Another possible mechanism could be effect of neuroleptics on mitochondrial respiration. Metabolites of haloperidol inhibit complex-I of electron transport chain [40]. The capability of antipsychotic drugs to clinically induce extrapyramidal syndrome seems to correlate well with their inhibitory effect on complex- I inhibition. Whatever be the mechanism of unbalanced production of reactive oxygen species (ROS) and oxidative stress by haloperidol, black tea were found to be effective in decreasing the oxidative stress in haloperidol treated animals.

Black tea having anti oxidative properties reduced the duration of catalepsy and increase locomotor activity and decreased the elevated level of lipid peroxidation in haloperidol treated animals, elevated the cellular defense mechanism such as glutathione, further suggesting the role of free radicals in the pathophysiology of haloperidol induced extrapyramidal syndrome.

The antioxidant activity of black tea could be possibly due to the direct scavenging of the superoxide radicals by the polyphenols or the flavonoids known to be present in these drugs. From the present study, it can be concluded that the black tea may prove to be beneficial adjuvant in the treatment of drug-induced extrapyramidal side effects and related disorders. The above results give strong evidence for further evaluation of use of black tea in combination therapy along with typical antipsychotic agents

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