Asian Journal of Biomedical and Pharmaceutical Sciences
ISSN : 2249 - 622X

RESEARCH ARTICLE

Received on: 12/05/2014
Accepted on: 25/06/2014
Published on: 16/07/2014

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QR Code for Mobile users

Conflict of Interest: None Declared !

DOI: 10.15272/ajbps.v4i33.502

Protective effect of *Hypericum hookerianum* in reversing haloperidol induced schizophrenia-like behaviors in Swiss albino mice

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Abstract

A major mental disorder that affects young people, schizophrenia (Greek "split mind") is characterized by a variety of symptoms including but not limited to , loss of contact with reality, bizarre behaviour, disorganized thinking, speech, decreased emotional expressiveness ,loss of contact with reality and society and long-lasting, not completely successful treatment. Anti-psychotics are the drugs used to treat schizophrenia. Typical anti-psychotics like haloperidol produce serious side effects leading to patient noncompliance and loss of quality of life. These side effects are due to pro-oxidant property of haloperidol which causes oxidative stress induced neuronal damage. Herbs have been shown to have neuroprotective potential especially those belonging to Hypericum species - *Hypericum hookerianum* has proven neuroprotective potential and is being used in folk medicine by ethnic communities to treat mental illnesses. However scientific validation of the healing properties of this plant has so far been lacking. It is in view of this,the current study was undertaken to investigate the protective effect of *Hypericum hookerianum* in reversing haloperidol induced schizophrenia-like behaviors in Swiss albino mice. Haloperidol was administered to mice (2.5mg/kg i.p -0.4ml from the prepared stock solution) for a period of 21 days. All the behavioral assessment was carried out 24 h after the last dose of haloperidol. The behavioral assessments were observed on 2nd, 7th, 14th and 22nd day of treatment with Haloperidol. Ethanolic extract of *Hypericum hookerianum* (EEHH) at a dose of 200mg/kg and 400 mg/kg treated groups were compared with Haloperidol treated group. Results of pre pulse inhibition, locomotor activity, plus maze performance and stair case tests have showed that the *Hypericum hookerianum* shows a lot of potential in the treatment of diminishing catatonic schizophrenia related behaviours. The major phytocostituents like flavanoids, polyphenols, saponins etc., present in the plant is believed to have the neuroprotective effect.

Keywords: Schizophrenia, Haloperidol, *Hypericum hookerianum*, behavioral study, animal models

Cite this article as:
Uma Devi Pongiya,Badarunnisa Mohammed Kandanath, Yalaga Rama Rao, Mohammed RafiqKhan. Protective effect *of Hypericum hookerianum* in reversing haloperidol induced schizophrenia-like behaviors in Swiss albino mice. Asian Journal of Biomedical and Pharmaceutical Sciences; 04 (32); 2014. 14-23.

INTRODUCTION:

Schizophrenia belongs to a debilitating group of brain disorders characterized by symptoms such as hallucinations, delusions, disorganized communication, poor planning, reduced motivation, and less sociability [1]. Even though the incidence of the disorder is relatively low (median value 15.2 per 100,000 persons per year), the condition is one of the major contributors to the global burden of disease [2]. The substantial burden of disease is a reflection of two features of schizophrenia: (a) the disorder usually has its onset in early adulthood, and (b) despite optimal treatment, approximately two-thirds of affected individuals have persisting or fluctuating symptoms [3]. The symptoms of schizophrenia fall into three broad categories: Positive, negative and cognitive symptoms [4]. Signs and symptoms that occur continuously and progressively may indicate schizophrenia. The etiology of this psychiatric disorder still remains elusive.

Schizophrenia is a multifactor disorder of mind with a constant prevalence of 1-2% in the population. It causes not only significant physical morbidity and social incompatibility to the patients, but also invites major economic hardship for its lengthy diagnostic procedure, devastating course, frequent treatment failures and difficult rehabilitation measures [5] Such a debilitating picture of schizophrenia has made it an enticing research topic in psychiatry. The specific cause of schizophrenia is still unknown, but research has shown that the brains of people with schizophrenia are different from the brains of people without the illness [6]. Like many other medical illnesses such as cancer or diabetes, schizophrenia seems to be caused by a combination of problems including various social, psychological, developmental, environmental, anatomic, genetic, biochemical and other factors [7].

Despite advances in neurotransmitter identification and the development of drugs targeting these transmitters, total remission of the disease is not always achieved. Potential etiologies other than neurotransmitter dysfunction merit consideration. Social withdrawal, sloppiness of dress and hygiene, and loss of motivation and judgment are all common in schizophrenia [8]. Impairment in social cognition is associated with schizophrenia. Haloperidol is a widely prescribed typical antipsychotic for treatment of schizophrenia and other effective disorders [9]. But, the use of typical antipsychotics such as haloperidol is limited by its tendency to produce a range of Extra Pyramidal symptoms (EPS) associated with consumption of Dopamine antagonists. These effects result directly or indirectly from D2 receptor blockade and constitute one of the main disadvantages for therapeutic use of typical neuroleptics like haloperidol. Haloperidol is metabolized by an oxidase and generates large quantities of oxyradicals and a potent toxic pyridinium like metabolite which contribute to oxyradical injury in schizophrenic patients. Therefore commonly used neuroleptics have pro-oxidant property. Some of the typical neuroleptics have been found to increase the oxidative stress mediated neuronal damage in animals. This neuronal damage by pro-oxidant action of neuroleptics has led to suggest that Tardive Dyskinesia (TD) is a result of neuroleptic-induced oxidative injury. The antipsychotic response of neuroleptics may depend on its pro-oxidant property and the level of pre-existing oxidative stress in patient. Oxidative stress can also trigger apoptosis [10]. Since the synthetic drugs used for schizophrenia has more side effects especially neurological, herbal therapy is promising option. Therefore this study was undertaken to investigate the potential application of *Hypericum hookeranium* for treatment of psychotic disorders but without the side effects associated with the use of synthetic drugs.

Hypericum hookerianum (Hooker's St. Johns wort) is a small, wide and hardy perennial evergreen shrub with yellow flowers *Hypericum hookerianum. Hyperiaceae* is a well-known plant among the 20 different species of *Hypericum* found in India [11]. It is mainly prevalent in Asia – tropical areas, Bangladesh, Bhutan. In India *Hypericum hookerianum* mainly in the areas of Arunachal Pradesh, Karnataka, Manipur, Meghalaya, Sikkim, Tamilnadu mainly in Nilgris. Antibacterial spectrum of *Hypericum hookerianum* has been reported [12]. The anxiolytic potential of ethanolic extract of *Hypericum hookerianum* in stress induced swiss albino mice was evaluated [13] . *Hypericum hookerianum* stem parts possess potent antitumor activity against DLA induced tumor in mice [14]. The wound healing potential of *Hypericum hookerianum* leaf and stem extracts has been evaluated [15] [16]. The physicochemical parameters, preliminary phytochemicals analysis and elemental analysis of plant *Hypericum hookerianum* aerial parts was already evaluated [17].

Studies done in the past have suggested that Hypericum species has potential wide clinical and medicinal applications, but so far there is no detailed evaluation about this plant. *Hypericum hookerianum* possesses neuroprotective potential and is being used in folk medicine by ethnic communities to treat mental illnesses [13]. But there is no detailed scientific validation about this plant. It is in view of this that the current study was undertaken to investigate the

protective effect of *Hypericum hookerianum* in reversing haloperidol induced schizophrenia-related behaviors in Swiss albino mice.

MATERIALS AND METHODS

Collection and authentication of the Plant material:

The plant material in this study was collected from the Nilgris, Western Ghats of India. The plant was authenticated by Dr. S. Rajan, Field Botanist, Survey of Medicinal Plants & Collection Unit, (Central Council for Research in Homoeopathy), and Department of AYUSH. The collected plant was subjected to shade drying at room temperature for about 5 weeks. The dried plant material was crushed to powder mechanically and sieved and stored in air tight container for further analysis.

Preparation of the Extract:

The shade dried aerial parts of *Hypericum hookerianum* was pulverized to a coarse powder. A weighed quantity of powder (950g) was sieved and subjected to hot solvent extraction at the temperature range of 40-80ºC, extracted with pet ether, chloroform and ethanol successively by soxhlation method, water by maceration method at room temperature and concentrated over water bath and evaporated at 50 degree C under reduced pressure and then lyophilized. The percentage yield of extracts was calculated.

Experimental Animal Studies:

Colony in bred strains Swiss albino mice of either sex weighing 21-30g of same age were used for pharmacological studies. The animals were kept under standard conditions (day/night rhythm) 8am-8pm, 22±2ºC room temperature, in poly propylene cages. The animals were purchased from KMCH College of Pharmacy, Coimbatore, were fed on pelleted standard diet (KMCH Pharmacy, Coimbatore) and water *ad libitum.* The animals were housed for one week in poly propylene cages prior to the experiments to acclimatize to laboratory conditions. All experiments were carried out between 9.00 and 12.00 hours. The animals were randomly distributed into 5 different groups with 5 (3 males and 2 females) animals in each group under identical conditions throughout the experiments. All the experimental protocols were approved by Institutional Animals Ethics Committee (IAEC) as per provisions of Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), New Delhi, India

Drug Administration in Animal Groups (For 21 days):

Control Group: Treatment with 0.5 ml of distilled water (oral administration)

Induced group treated with Haloperidol:

Treatment with Haloperidol (2.5mg/kg, i.p.). A stock solution was prepared containing 0.3mg/ml of the drug and injected 1ml/100g body weight of mouse [18].

Plant extract treated group I:

The plant extract was weighed as per the dosage 200mg/kg in 1 ml, administered orally.

Plant extract treated group II:

The plant extract was weighed as per the dosage 400 mg/kg in 1 ml, administered orally.

Standard group treated with drug Scopolamine:

Treatment with Scopolamine (2mg/kg, i.p.); A stock solution was prepared containing 0.4 mg/ml of drug and injected 0.5 ml/100 g body weight of animal [19].

Acute toxicity studies was performed for the extracts to ascertain safe dose by acute oral toxic class method of Organization of Economic Co-operation and development as per the 423 guidelines (OCED). Based on acute toxicity studies, the plant extract doses 200 mg and 400 mg had been chosen[20] .

Behavioural Assessment in Animal Model (Swiss Albino Mice):

Haloperidol was purchased from Sigma (Aldrich, USA). Haloperidol was administered to mice (2.5 mg/kg i.p - 0.4 ml from the prepared stock solution) for a period of 21 days. All the behavioural assessment was carried out 24 h after the last dose of haloperidol. The behavioural assessments were observed on 2nd, 7th, 14th and 22nd day of treatment with Haloperidol. Ethanolic extract of *Hypericum hookerianum* (EEHH) at a dose of 200 mg/kg and 400 mg/kg treated groups were compared with Haloperidol treated group. The analysis of following tests were conducted.

Assessment of schizophrenia-related behaviour:

Deficits in pre - pulse inhibition are common in schizophrenic patients and may measure attentional dysfunctions that contribute to auditory hallucinations. Pre-pulse inhibition is a sensorimotor gating reflex, similarly quantitated in mice, rats, and humans. When the startle stimulus is immediately preceded by a milder stimulus, delivered immediately before the startle stimulus, the mouse will flinch less to the startle stimulus. Pre-pulse tone of 80 dB are randomly presented at 30, 45, and then for 60 secs. Whole body flinch amplitude showing compulsive behaviors observed is recorded (Number of lickings and sniffings). To evaluate a separate sensory modality, a puff of air is used as the prepulse, before the acoustic or tactile startle stimulus [21,22]

Behavioral assessment by locomotor activity:

The locomotor activity was monitored using an actophotometer (INCO AMBALA, India). Before subjecting the animal to cognitive task, they were individually placed in the actophotometer and the total activity count was registered for 10 min. The locomotor activity was expressed in terms of total photo beam interruption counts per 10 min per animal. Increase in count was regarded as central nervous system stimulant activity while decrease in count was regarded as depressant activity.

Transfer latency on elevated plus maze:

Cognitive behaviour was assessed by using the elevated plus-maze learning task, which measures spatial long-term memory. Transfer latency (TL), the time in which the animal moves from the open arm to the enclosed arm was utilized as an index of learning and memory process. The elevated plus-maze consisted of two open arms (50x10 cm) and two closed arms (50x10 x40cm) with an open roof. The maze was elevated to a height of 50 cm from the floor. The animals were placed individually at the end of either of the open arms and the transfer latency was noted on the first day. If the animal did not enter an enclosed arm within 90 seconds, it was gently pushed in to the enclosed arms and the TL was assigned as 90 seconds. To become acquainted with the maze, the animals were allowed to explore the plus-maze for 20 seconds after reaching the closed arm and then returned to its home cage. Retention was examined 24h after the first day trial. In the present study the transfer latency was quantified on days 2, 7, 14 and 22 on haloperidol treated animals [23]].

Stair Case test:

The test was carried out essentially as described by Simiand et al (1984) [23] and consisted of placing the experimental animal on an enclosed stair case made of grey plastic. Each step was 2.5cm in height, 7.5cm in length and 11cm in width. The apparatus was 45cm in length with one end 12cm and other end 25cm in height. The number of steps climbed and rearing made in 3 min period were observed. The step climbing count was increased every time the animal moved from one step to another in ascending direction. The apparatus was briefly wiped with a wet paper towel and dried between animals. Animals were moved to the testing room prior to the testing commenced [24].

Assessment of Learning and Memory using Hebb's William Maze (Rectangular Maze):

The maze consisted of completely enclosed rectangular box with an entry and reward chamber appended at opposite ends. The box was partitioned with wooden slats into blind passages leaving just twisting corridor leading from the entry to the reward chamber. All the mice were familiarized with Hebb's William Maze for a period of 10 min prior to the test. This is known as training session. The mice of all 5 groups including the control and standard drug treated (Haloperidol) were prepared for the analysis. The mouse was placed in the entry chamber and the timer was activated as soon as the mouse leaves the entry chamber. The time taken for the mouse to reach the reward chamber was taken as the transfer latency. From each group at least four readings were taken, the average is taken as learning score (transfer latency) for that animal. Lower scores of assessment indicate efficient learning while higher score indicate poor learning in animals. During learning assessment, the animals were exposed to food and water only after 1 hour of maze exposure [25, 26].

RESULTS AND DISCUSSIONS

Assessment of Schizophrenia related behavior:

Selected parameters:

The following parameters were followed,

Assessment of pre-pulse inhibition:

a. Number of sniffings
b. Number of lickings

The effect of EEHH on the HAL induced compulsive behaviours in mice (Table 1). The rate of pre-pulse inhibition was observed significantly ($p<0.05$) in groups treated with EEHH at a dose of 400 mg/kg equitant to that of the standard drug scopolamine. The dose of EEHH at 200 mg/kg shown less pre-pulse inhibition compared to the EEHH at the dose of 400 mg/kg. Auditory stimulus given at different time length enhanced the compulsive behaviour in induced animals observed with increase in number of sniffing can be related as the effect of auditory hallucination.

Parameter	Control	Standard	200mg treated	400mg treated	Induced
Auditory stimulus- 30 sec	5	7	8	6.5	9
2nd Day Auditory stimulus- 45 sec	3.5	6	7	6	10
Auditory stimulus- 60 sec	4	3	6	4	11
Mean	4.17	5.33	7.00	5.50	10.00
Std.Error	0.441	1.20	0.577	0.764	0.577
Value	4.17±0.441	5.33±1.20	7.00±0.577	5.50±0.764	10.00±0.577

Table 1. Assessment of pre pulse inhibition (Number of sniffings).

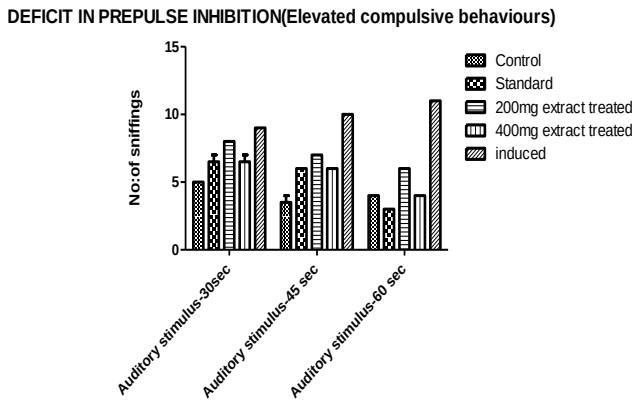


Figure 1. Effect of EEHH on HAL and startle stimulus induced auditory hallucination showing deficit in pre-pulse inhibition with increased number of sniffing. EEHH at the dose of 400mg/kg significantly ($p<0.05$) shown pre-pulse inhibition similar to that of scopolamine treated group. Values expressed as mean± SEM, n=5 compared with HAL treated group (ANOVA followed by Dunnett's test).

Assessment of pre-pulse inhibition (Number of lickings):

The effect of EEHH on the HAL induced compulsive behaviours in mice. The rate of pre-pulse inhibition was observed significantly ($p<0.05$) in groups treated with EEHH at a dose of 400 mg/kg equitant to that of the standard drug scopolamine. The dose of EEHH at 200 mg/kg shown less pre-pulse inhibition compared to the EEHH at the dose of 400 mg/kg. Auditory stimulus given at different time length enhanced the compulsive behaviour in induced animals observed with increase in number of lickings can be related as the effect of auditory hallucination (Table 2).

Parameter	Control	Standard	200mg treated	400mg treated	Induced
Auditory stimulus- 30 sec	4	7	8	7	9
2nd Day Auditory stimulus- 45 sec	4	5	7	5	10
Auditory stimulus- 60 sec	4	4	5	4	11
Mean	3.67	5.33	7.33	5.33	10.00
Std.Error	0.333	0.882	0.333	0.882	0.577
Value	3.67±0.333	5.33±0.882	7.33±0.333	5.33±0.882	10.00±0.577

Table 2. Assessment of pre pulse inhibition (Number of lickings).

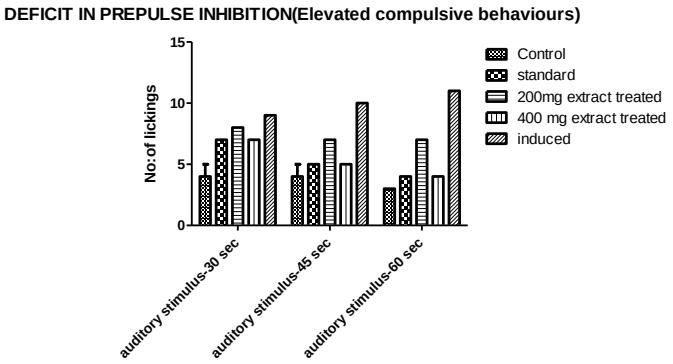


Figure 2. Effect of EEHH on HAL and startle stimulus induced auditory hallucination showing deficit in pre-pulse inhibition with increased number of lickings. EEHH at the dose of 400mg/kg significantly ($p<0.05$) shown prepulse inhibition similar to that of scopolamine treated group. Values expressed as mean± SEM, n=5 compared with HAL treated group (ANOVA followed by Dunnett's test).

Effect of Chronic EEHH Treatment on HAL induced alteration in locomotor activity:

Assessment of locomotor activity (in 5 minute):

The effect of EEHH on the HAL induced alteration in locomotor activity (Table 3). HAL significantly decreased the locomotor activity ($p<0.05$) when compared to the control group. EEHH significantly reversed the HAL induced decrease in locomotor activity as compared to the HAL group at the doses of 200 mg/kg and 400 mg/kg ($p<0.05$) as shown in the figure 3. Before treatment the animals from each group showed proper locomotor activity which was reduced by the treatment of haloperidol and recovered when treated with the plant extract.

Parameter	Control	Standard	200mg treated	400mg treated	Induced
Before treatment	278	278	277	278	276
2nd Day	278	291	280	291	265
7th Day	276	292	282	292	265
14th Day	277	293	283	293	263
22nd Day	278	294	284	294	263
Mean	277	289	281	289	266
Std.Error	0.400	2.87	1.24	2.94	2.44
Value	277±0.400	289±2.87	281±1.24	289±2.94	266±2.44

Table 3. Assessment of locomotor activity (in 5 minute).

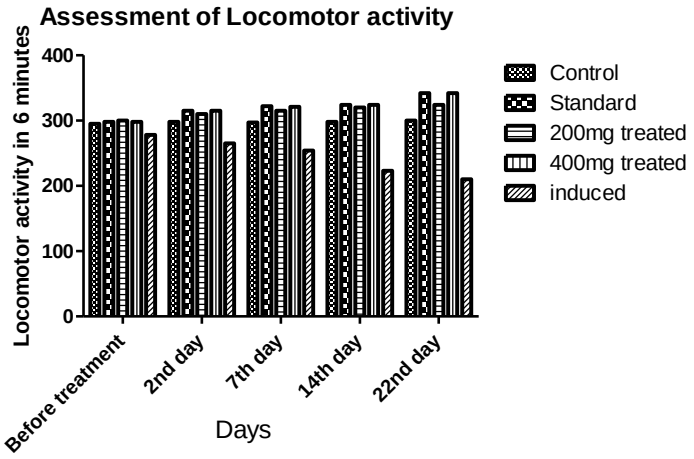


Figure 3. Effect of chronic administration of EEHH on HAL induced alteration in locomotor activity in mice. Values are expressed as mean± SEM, n=5; p<0.05 compared with HAL induced group (ANOVA followed by Dunnett's test).

Effect of Chronic EEHH treatment on elevated plus maze performance:

Assessment of transfer latency in elevated plus maze (3 minutes):

The effect of EEHH on HAL induced mice (Table 4). The transfer latency measured on days 2, 7, 14 and 22 of the vehicle treated mice were drastically shorter than on the first day, indicating the ability of rats to recall the learned aspect in a lesser period of time. Before inducing the mice shown increase in transfer latency compared to that of EEHH treated at the dose 200 mg/kg and 400 mg/kg. However the Transfer latency of HAL induced group was found statistically significant ($p<0.05$) in comparison with vehicle treated animals, EEHH treated at the dose of 200 mg/kg and 400 mg/kg, and standard drug treated group whose transfer latency was decreased significantly equitant as that of the 400 mg/kg treated group indicating the similar kind of action on memory enhancement.

Parameter	Control	Standard	200mg treated	400mg treated	Induced
Before treatment	50	53	53	51	54
2nd Day	51	50	52	49	58
7th Day	53	47	49	47	60
14th Day	49	45	47	44	62
22nd Day	48	44	45	42	65
Mean	50.2	47.8	49.2	46.6	59.8
Std. Error	0.860	1.66	1.50	1.63	1.85
Value	50.2±0.860	47.8±1.66	49.2±1.50	46.6±1.63	59.8±1.85

Table 4. Assessment of transfer latency in elevated plus maze (3 minutes).

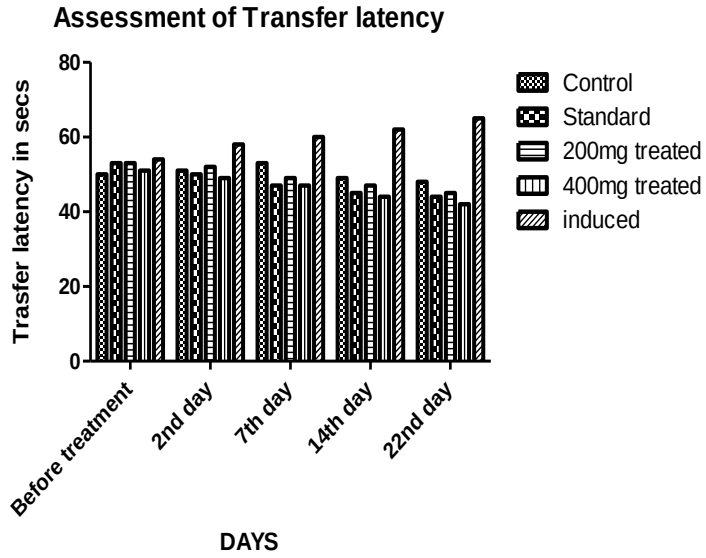


Figure 4. Effect of chronic administration of EEHH on HAL induced memory dysfunction in mice. Values expressed as mean± SEM, n=5; p<0.05
compared with HAL induced group. Before treatment a slight elevation in transfer latency noticed as compared to that of 200mg/kg, 400mg/kg dose of EEHH and Scopolamine treated groups.(ANOVA followed by Dunnett's test).

Effect of Chronic Treatment of EEHH on stair case performance of HAL induced mice:

Parameters chosen:

The following parameters were followed

a. Number of climbings
b. Number of rearings

Stair case test-Number of climbings in 3 minutes:

The effect of EEHH in HAL induced symptoms of anxiety was assessed (Table 5). Significant decrease in number climbings was observed on the days 2, 7, 14 and 22 of treatment with HAL. EEHH 200mg/kg and 400 mg/kg doses showed significant ($p<0.05$) increase in the number of climbings compared to that of HAL treated group (Figure 5). Standard drug Scopolamine treated group have shown significant increase in number of climbings when compared to the HAL treated group as which it indicates that the activity of the standard drug is similar to that of 400 mg/kg dosage of the plant extract.

Parameter	Control	Standard	200mg treated	400mg treated	Induced
Before treatment	16	18	16	28	16
2nd Day	17	21	12	22	12
7th Day	18	23	13	23	10
14th Day	19	25	13	25	7
22nd Day	19	27	14	27	5
Mean	17.8	22.8	13.6	23	10
Std.Error	0.583	1.56	0.678	1.52	1.92
Value	17.8±0.583	22.8±1.56	13.6±0.678	23.0±1.52	10±1.92

Table 5. Stair case test-Number of climbings in 3 minutes.

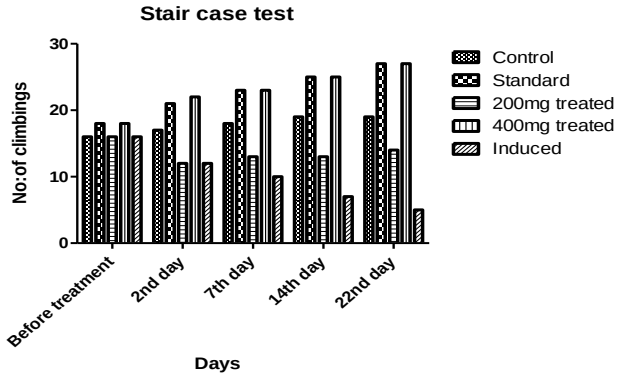


Figure 5. Effect of chronic administration of EEHH on HAL induced symptoms of anxiety in mice. Before treatment, the mice showed proper rate of climbings. The values were expressed as mean± SEM, n=5; p<0.05 compared with the HAL treated groups (ANOVA followed by Dunnett's test).

Stair case test-Number of rearings in 3 minutes:

The effect of EEHH in HAL induced symptoms of Anxiety was assessed (Table 6). Significant decrease in number of rearing was observed on the days 2, 7, 14 and 22 of treatment with HAL. EEHH 200 mg/kg and 400 mg/kg in doses shown significant (p<0.05) increase in the number of climbings compared to that of HAL treated group (Figure 6). Standard drug Scopolamine treated group have shown significant increase in number of rearings when compared to the HAL treated group as which it indicates the activity of the standard drug is similar to that of 400 mg/kg dosage of the plant extract.

Parameter	Control	Standard	200mg treated	400mg treated	Induced
Before treatment	8	8	9	9	12
2nd Day	7	15	17	15	24
7th Day	6	13	16	13	26
14th Day	8	12	15	14	27
22nd Day	8	11	14	11	28
Mean	7.40	11.8	14.2	12.4	23.4
Std. Error	0.400	1.16	1.39	1.08	2.93
Value	7.40±0.400	11.8±1.16	14.2±1.39	12.4±1.08	23.4±2.93

Table 6. Stair case test-Number of rearings in 3 minutes.

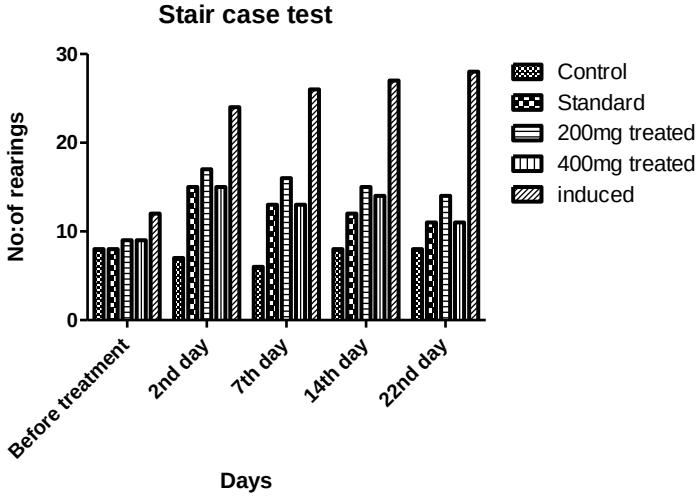


Figure 6. Effect of chronic administration of EEHH on HAL induced symptoms of anxiety in mice showing increased number of rearings. Before treatment the mice showed proper rate of rearings. The values were expressed as mean± SEM, n=5; p<0.05 compared with the HAL treated groups (ANOVA followed by Dunnett's test).

Effect of chronic EEHH treatment on rectangular maze performance on HAL treated mice:

Assessment of transfer latency in rectangular maze (in 5 minutes):

The transfer latency measured on days 2, 7, 14 and 22 (Table 7). Transfer latency before treatment was also observed in the animals of all groups to be having more latency to reach the reward chamber from the entry chamber than that of the EEHH treated animals in the dosage of 200 mg/kg and 400 mg/kg and the standard drug scopolamine treated group but less to that of HAL treated group. However, the transfer latency of HAL induced mice were found statistically significant ($p<0.05$) in comparison with HAL induced group on respective day of observation, indicating the poor retention ability of HAL treated mice. Chronic treatment with EEHH (200 mg/kg and 400 mg/kg) significantly and dose dependently shortened the Transfer latency of HAL treated mice.

Parameter	Control	Standard	200mg treated	400mg treated	Induced
Before treatment	210	212	211	213	212
2nd Day	212	199	209	199	223
7th Day	212	198	208	199	223
14th Day	212	198	208	199	224
22nd Day	213	197	207	198	225
Mean	212	201	209	202	221
Std. Error	0.490	2.82	0.678	2.86	2.38
Value	212±0.490	201±2.82	209±0.678	202±2.86	221±2.38

Table 7. Assessment of transfer latency in rectangular maze (in 5 minutes).

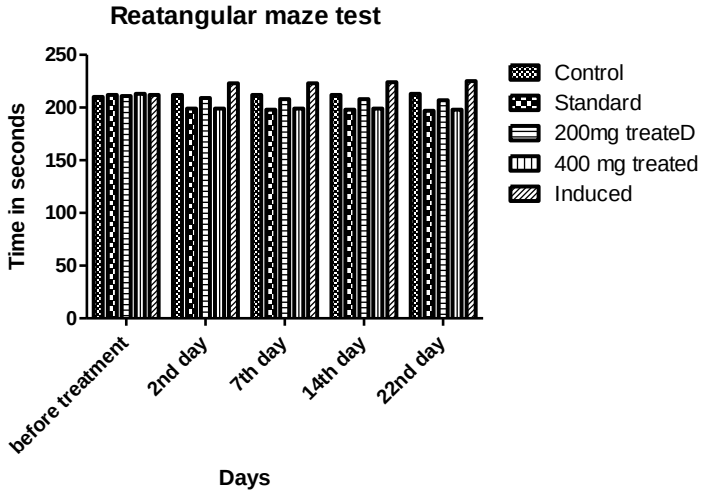


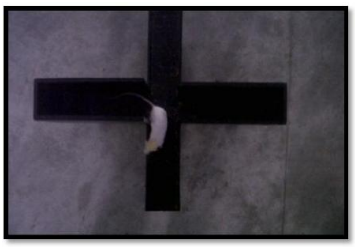
Figure 7. Effect of chronic administration of EEHH on HAL induced memory impairment and cognitive disorder in mice. Values expressed as mean± SEM, n=5; $p<0.05$ compared with HAL induced groups (ANOVA followed by Dunnett's test).

We also observed an increment in the levels of antioxidant enzymes; Lipid peroxidation was accelerated in EEHH treated animals and significant improvement was also seen in transfer latency of mice in elevated plus maze, rectangular maze and improvement in locomotor ability was also observed. Assessment of antidepressant activity was conducted using the tail suspension test; in which antidepressant like activity is found in mice treated with EEHH had a much lower immobility time in the current study similar to that of study done by Cryan et al (2003) [25]. It is known that catatonic schizophrenia affects every aspects of the human functioning. Thinking feeling and behaviour affects by disorder assessed through the transfer latency in the animals treated with EEHH at dose 400mg/kg. The sense disturbances in mice behavior assessed by locomotor activity assessment showed elevated motor activity in EEHH treated animals equivalent to the activity of standard drug scopolamine individuals with catatonic schizophrenia often show extreme immobility. The immobility of HAL treated group of animal was improved by the EEHH, whereas previous studies by Masugi et al (1999) [27] failed to demonstrate any effect of detection of mGluR7in basal locomotion. Intra peritoneal administration of flavanoid apigenin at doses of 12.5 and 25 mg/kg significantly decreased the duration of immobility in mice; but this behavioural effect was blocked by D_2 antagonist Haloperidol [28].

Assessment of schizophrenia related beaviour


Number of sniffings **Number of leakings**


Behavioural assessment by locomotor activity




Assessment of transfer latency using EPM


Assessment of motor efficiencies:
Number of climbings **Number of rearings**


Assessment of learning memory by Hebb's maze

CONCLUSION

From the study it is clear that *Hypericum hookerianum* has wide range of potential against diminishing catatonic schizophrenia related behaviours. The major phytocostituents like flavanoids, polyphenols, saponins etc., present in the plant is believed to have the neuroprotective effect. This has shown wide significance in elevation of total protein level in brain induced with Haloperidol. It also showed a wide improvement in memory enhancement, which might be due to the increased level of neurotransmitters. The plant has shown its efficiency in diminishing the extra pyramidal side effects and behavioral impairments in HAL induced animals. The learning deficits in HAL induced animals were rectified by the treatment of EEHH which is believed to enhance the functioning of limbic system and frontal lobe of the brain structure.

ACKNOWLEDGEMENTS

The authors are grateful to The President Dr. Ketema Daddy, The Academic Vice –President Ato Awel Ahmed, The Dean of Natural Science Ato Buzayehu, Dean of Post Graduate Studies Dr. Kasahun Tare, Mr.Abdul Kadir Subhe, Head, Chemistry and The HOD of Biology Tilaye Atnaf of Madawalabu University, Ethiopia for their encouragement and support to carry out this research publication.

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