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Research Article

NEURORESTORATIVE ROLE OF *HYPERICUM HOOKERIANUM* ETHANOLIC EXTRACT ON BRAIN TOTAL ANTIOXIDANT STATUS AND LIPID PEROXIDATION IN HALOPERIDOL INDUCED SCHIZOPHRENIA IN SWISS ALBINO MICE

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ABSTRACT
Schizophrenia is the result of altered cellular homeostasis by oxidative damage in brain which in turn involves in various forms of neurotoxicity including neuronal death. The ethanolic extract of aerial parts *Hypericum hookerianum* plant has long been used in traditional medicine and in folk treatment for various neurological ailments. The neuroprotective and neurorestorative effect of *Hypericum hookerianum* was attributed to its antioxidant activity. In the present study the antioxidant potential of *Hypericum hookerianum* was evaluated in haloperidol induced schizophrenic rat brains. Swiss albino mice of either sex weighing 21-30 g were treated with haloperidol and also treated with *Hypericum hookerianum.* Oxidative stress was assessed by measuring the extent of lipid peroxidation, total protein content and also totals antioxidant activity in mice brain. Haloperidol stress caused an alteration in oxidative stress markers with a significance increase in brain lipid peroxidation and decrease in total protein content and total antioxidant activities in brain homogenate of treated mice. *Hypericum hookerianum* has significantly minimized the oxidative stress effects by significant decrease in lipid peroxidation level and also an increase in reduced protein level as well as total antioxidant activities. Results of the present study indicated that *Hypericum hookerianum* has antioxidant potential against haloperidol -induced oxidative damage in mice brain.
Keywords: Schizophrenia, Haloperidol, Total Antioxidant Capacity (TAC), Lipid Peroxidation, *Hypericum hookerianum* (Hh)

INTRODUCTION

Schizophrenia is a serious hereditary disorder of the brain resulting from abnormalities that arise early in life and disrupt normal development of the brain Schizophrenia has 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 very difficult rehabilitation measures[1]. 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[2]. 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[3]. There is abundant evidence that free radicals is involved in membrane pathology in the central nervous system and may play a role in neuropsychiatric disorders include schizophrenia[4]. The chemical nature of schizophrenic brain is still not completely understood. The brain and nervous system are particularly prone to free radical damage, since the membrane lipids are very rich in polyunsaturated fatty acids and certain areas of human brain are very rich in iron, which plays an essential role in generating free radical species[5]. Free radicals adversely modify biologically active molecules and whole cells and are implicated in a variety of neurodegenerative diseases including schizophrenia and ageing[6,7]. The ability of a tissue or fluid to buffer the effects of reactive oxygen species is called total antioxidant capacity. Blood and brain contains many antioxidant molecules that prevent and/or inhibit harmful free radical reactions[8]. Since anti oxidative effects of antioxidant components are additive, the measurement of total antioxidant capacity reflects the anti oxidative status of brain or plasma. We evaluated the total anti oxidative status of brain by FRAP assay as proposed by (Benzie and Strain, 1996, 1999)[9,10]. Total antioxidant capacity parameter summarizes overall activity of non-enzymic antioxidants and antioxidant enzymes. It provides information about antioxidant types and their concentration without exact qualitative differentiation. Free radicals, primarily the reactive oxygen species, (ROS), super oxide and hydroxyl radicals, which are highly reactive, having an unpaired electron in an atomic or molecular orbit, are generated under physiological conditions during aerobic metabolism. As free radicals are potentially toxic, they are usually inactivated or scavenged by antioxidants before they can inflict damage to lipids, proteins or nucleic acids. Alteration in the oxidant–antioxidant profile is known to occur in Schizophrenia[11,12]. The brain makes up about 2 % of body mass but consumes 20 % of metabolic oxygen. The vast majority of energy is used by the neurons[13]. Due to the lack of glutathione-producing capacity by neurons, the brain has a limited capacity to detoxify ROS. Therefore, neurons are the first cells to be affected by the increase in ROS and shortage of antioxidants and as a result, are most susceptible to oxidative stress. Lipid peroxidation is a chain reaction between polyunsaturated fatty acids and ROS. It produces lipid peroxides and hydrocarbon polymers that are both highly toxic to the cell[14]. Malonyldialdehyde (MDA) is an end product of per oxidation of polyunsaturated fatty acids and related esters, and is, therefore, used as a marker of lipid peroxidation[15]. Recent reports of Herken *et al*., 2001; Akyol *et al*., 2004; Hui-chun *et al*., 2006)[3,4,16] also indicate increased levels of other lipid peroxidation markers in psychiatric disorders, thus confirming an increased oxidative

stress in schizophrenia. Though there is accumulating evidence of altered antioxidant capacity in schizophrenia, studies of antioxidant systems in schizophrenia has produced the usual medley of conflicting results. *Hypericum hookerianum* (Hooker's St. Johns wort) is a small wide fully hardy perennial evergreen shrub with yellow flowers *Hypericum hookerianum* belongs to the family of Hyperiaceae is a well-known plant among the 20 different species of *Hypericum* found in India[17]. It is mainly present in Asia – tropical areas, Bangladesh, Bhutan. In India *Hypericum hookerianum* mainly in the areas of Arunachal Pradesh, Karnataka, Manipur, Meghalaya, Sikkim, Tamil Nadu mainly in Nilgris, India. Antibacterial spectrum of *Hypericum hookerianum* has been reported. The anxiolytic potential of ethanolic extract of *Hypericum hookerianum* in stress induced swiss albino mice was evaluated[18]. The physicochemical parameters, preliminary phytochemicals analysis and elemental analysis of plant *Hypericum hookerianum* aerial parts was also already evaluated[19]. Literature is stating that *Hypericum* species is having wide clinical and medicinal applications, but so far there is no detailed evaluation about this plant. *Hypericum hookerianum* is having neuroprotective and anti oxidative potential and is being used in folk medicine by ethnic community to treat mental illnesses. 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 the total antioxidant capacity, lipid peroxidation and total protein content in Haloperidol induced Schizophrenia 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 and Collection Unit, (Central Council for Research in Homoeopathy), and Department of AYUSH. The collected plant was subjected to shade drying 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 get a coarse powder. A weighed quantity of powder (950 g) was sieved and subjected to hot solvent extraction at the temperature range of 40-80^{0}C, 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 under reduced pressure. The percentage % yield of extracts was calculated.

Drugs and chemicals

All the drugs and bio chemicals used in this experiment were purchased from Sigma Chemical Company Inc., St Louis, Mo, USA. The chemicals were of analytical grade.

Experimental animal studies

Colony in bred strains Swiss albino mice of either sex weighing 21-30 g were used for pharmacological studies. The animals were kept under standard conditions (day/night rhythm) 8.00 am - 8.00 pm, 22 ± $^{\circ}$ C room temperature, in poly propylene cages. The animals were purchased from KMCH College of Pharmacy Coimbatore, India were fed on pelleted standard diet (KMCH Pharmacy, Coimbatore, India) 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. It is randomly distributed into 5 different groups with 5 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
- **Induced group treated with Haloperidol**
  Treatment with Haloperidol (2.5mg/kg .i p.). Make a stock solution containing 0.3 mg/ml of the drug and inject 1 ml/100 g body weight of mouse[20]
- **Plant extract treated group I**
  The plant extract was weighed as per the dosage 200 mg/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 (2 mg/kg, i.p.); prepare a stock solution containing 0.4 mg/ml of drug and inject 0.5 ml/100 g body weight of animal[21,22]

Dissection and Homogenization

Chronic haloperidol treated animals on day 22nd after behavioral quantification was sacrificed by decapitation. The brains were removed and put on ice. A 10 % (w/v) tissue homogenate was prepared in 0.1 M phosphate buffer (pH 7.4). The post nuclear fractions for biochemical assays were obtained by centrifugation of the homogenate at 12,000 × g for 60 minutes at 4°C. The sub cortical region of brain comprised all of the forebrain which included the hippocampus, thalamus, hypothalamus and other sub thalamic structures for the estimation of Total antioxidant Capacity, lipid peroxidation and tissue total protein.

Measurement of Total Antioxidant capacity [TAC]

The whole brain was removed and rinsed with ice-cold 0.1 M phosphate buffer (pH 7.4) 10 times (w/v). The homogenate was immediately centrifuged at 10,000'g for 15 minutes and aliquots of supernatant was separated and used for antioxidant studies. The TAC of the brain was measured using a novel, automated, spectrophotometric measurement method developed by Benzie and Strain[9,10] and modified by Erel[23]. In this method, hydroxyl radical, which is the most potent biological radical, is produced. In the assay, ferrous ion solution, which is present in Reagent 1, is mixed with hydrogen peroxide, which is present in Reagent 2. The sequential produced radicals, such as brown-colored dianisidine radical cation, produced by the hydroxyl radical, are also potent radicals; in this assay, the anti oxidative effect of the sample against the potent free radicals` reactions, which is initiated by the produced hydroxyl radical, is measured. The assay results are expressed as mmol Trolox equivalent L^{-}[19,10,24]. The precision of this assay is excellent. Accurate measurements of TAC can be obtained in as little as

10 min, making this assay eminently suitable for the clinical biochemistry laboratory[25].

Measurement of Lipid Peroxidation

Lipid peroxidation in brain was estimated colorimetrically by measuring thiobarbituric acid reactive substances (TBARS). Tissue homogenate 0.1 ml was treated with 2 ml of TBA-TCA-HCL reagent (0.37 % TBA,0.25 M HCL, and 15 % TCA,1:1:1 ratio), placed for 15 minutes in a water bath and then cooled and centrifuged at 3500 rpm for 10 minutes at room temperature, the absorbance of clear supernatant was measured at 535 nm against a reference blank. Values were expressed as μM of MDA released/mg protein[26].

Estimation of Total Protein

Protein estimation was done according to Lowry *et al* (1951). The protein content of brain tissue was estimated using bovine serum albumin as standard[27].

RESULTS AND DISCUSSION

Effect of Chronic EEHH on Total Protein Levels in Chronic HAL Treated Mice

Estimation of total protein

HAL treated groups indicated a significant ($p < 0.05$) decrease in total protein content (Figure 1) when compared to the vehicle treated groups, significantly increased which was by the EEHH which was significantly increased by the EEHH treated groups at doses 200 mg/kg and 400 mg/kg; in which the later dose observed to improve the protein content in the brain of HAL induced animals more effectively than the standard drug scopolamine. Significant increase in brain protein level compared with the HAL treated group.

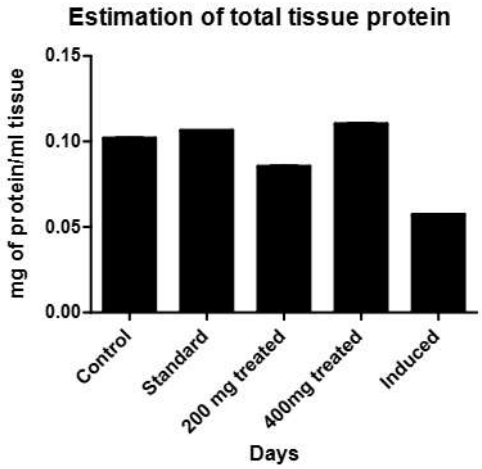

Figure 1: Effect of Chronic administration of EEHH on HAL mediated brain total protein level

Values expressed as mean ± SEM, n = 5; $p < 0.05$ compared with HAL treated group (ANOVA followed by Dunnett's test)

From the study it is clear that *Hypericum hookeranium* have wide range of potential against catatonic schizophrenia. 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.

Effect of Chronic EEHH on the Brain MDA Level in Chronic HAL treated mice

Chronic HAL treatment to mice on alternate days for 5 days induced lipid peroxidation as indicated by a significant ($p < 0.05$) rise in brain MDA levels compared with the vehicle treated mice. Chronic administration of EEHH (200 mg/kg and 400 mg/kg) to HAL treated animals significantly reversed the extent of lipid peroxidation compared with HAL only treated mice (Figure 2)

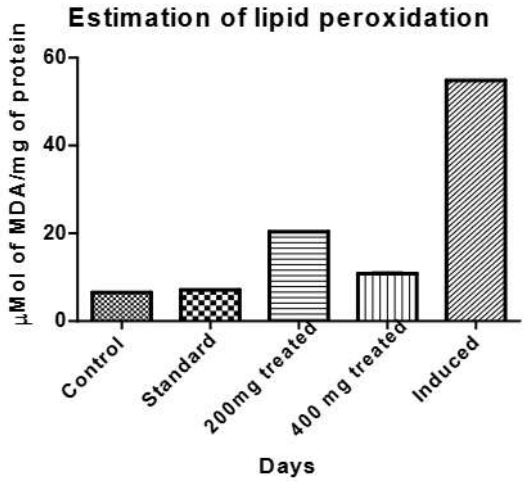

Figure 2: Effect of chronic administration of EEHH on HAL mediated brain Malonyl dialdehyde (MDA) level
Values expressed as mean ± SEM, n = 6; $p < 0.05$ compared with HAL treated groups. (ANOVA followed by Dunnett's test)

Ethanolic extract of plant has shown to possess anti lipid peroxidation effect which is due to the removal of super oxide and hydroxyl radicals. Reports have indicated that excess production of free radicals (Oxidation stress) is associated with Tardive Dyskinesia in schizophrenics[28]. Oxidative stress is a shift towards oxidation in oxidation reduction reaction, which leads to cellular damage and is indicated by oxidized product of lipids and proteins. The effect can be related to reduction in specific antioxidant mechanisms[29]. Umadevi P, 2001 studied on *Occumum sanctum*[30] and Ali *et al*; 2000 studied on *Rhazye stricta*[31] ascertain that the herbal preparation that have anti-depressant potential also possess antioxidant effect. Sagara using rat primary cortical neurons and mouse hippocampal cell line HT-22 showed that Haloperidol caused a sequence of cellular alteration that lead to cell death and production of reactive oxygen species[32]. Neuronal loss in striatum of animals chronically treated with neuroleptics has been reported[33]. Haloperidol induced catatonic schizophrenia, TD and oxidative stress can be prevented by using herbal formula which is rich of dietary supplements like anti oxidants and essential fatty acids. Neuroleptics act by blocking dopamine receptors[34] and increase catecholamine turnover, which leads to excessive free radical generation. Increased metabolism of catecholamines produces large amount of free radicals which are cytotoxic[35]. Chronic HAL treatment increased lipid peroxidation and also nucleic acid peroxidation[36]. Current findings increased lipid peroxidation in HAL treated group support the involvement of oxidative stress in schizophrenia

Estimation of total antioxidant capacity

Experimental Animal Groups	TAC/ mmol Trolox equivalent L^{-1}
Control	3.621 ± 0.071
Standard	3.176 ± 0.0925
200 mg treated	2.319 ± 0.0608
400 mg treated	2.703 ± 0.0854
Induced	1.824 ± 0.0392

There is a large amount of convincing data demonstrating that Reactive Oxygen Species (ROS) are involved in initiation and development of many different forms of schizophrenia. TAC of plasma was significantly lower in haloperidol induced mice with schizophrenia than in control groups. Current results indicates that the oxidative/ anti oxidative balance shifted towards oxidative status, namely increased oxidative stress was present in groups treated with haloperidol induced schizophrenic mice compared with healthy control groups. It was indicated that ROS and other oxidants could be also formed in the normal physiological process[37]. Increased ROS, in turn, enhance LPO products, thus, lead to tissue injury[38]. H_2O_2 and other derivatives of peroxides increase in some conditions, diffuse into plasma. Here, antioxidant components of plasma overwhelm them and they are simultaneously consumed[39,40].

CONCLUSION

The brain exhibits numerous morphological and functional alterations during schizophrenia. Oxidative stress, a factor implicated in the pathogenesis of schizophrenia complications may towards some of these alterations. Treatment of haloperidol induced schizophrenic mice with *Hypericum hookerianum* ethanolic extract significantly decreased the lipid peroxidation and significantly increased the total antioxidant status. Since the study of induction of the antioxidant enzymes is considered to be a reliable marker for evaluating the antioxidant efficacy of the medicinal plant, these findings are suggestions of possible antioxidant role played by *Hypericum hookerianum* ethanolic extract in addition to its anti depressive effect. Until now we have not found univocal molecular basis of schizophrenia which might be due to free radicals. Further studies comprise of isolation of active principle in the plant extract responsible for this reversion is looked-for.

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