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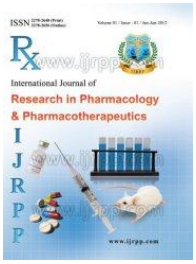

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MK‑801‑induced psychosis diminishing impact of *TecomaStans* in mice

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ABSTRACT

The goal of this study was to investigate the effect of Tecomastansethanolic extract (EETS) on the psychosis induced by MK-801 in mice. MK-801-treated mice were administered for 14 days using EETS (1 and 2 g / kg, p.o.) Specific behavioral parameters and neurochemical measures such as dopamine (DA), 5-hydroxytryptamine (5-HT), norepinephrine (NE), gamma-aminobutyric acid (GABA), glutamate, and glycine were assessed as well as indicators of oxidative stress such as nitrite rates.

Psychosis-induced mice showed a significant increase in immobility time in forced swimming test, locomotive operation, and decrease in durability in rota-rod testing, escape latency time in Cook's pole test while EETS treatment showed a significant improvement in the above-mentioned behavioral parameters in psychosis induced by MK-801. In addition, psychosis caused by MK-801 in mice showed a substantial increase in DA, 5-HT and NA levels and a decrease in brain GABA, glutamate, and glycine levels. In comparison, EETS therapy at both doses greatly altered the parameters of neurochemistry. Additionally, EETS treated mice showed a substantial reduction in EETS acetylcholinesterase, D-amino acid oxidase enzyme activity, and the levels of nitrite elevated by MK-801 administration. Via neuromodulation and reduced oxidative stress, EETS therapy once for 14 days (1 and 2 g / kg) substantially improved behavioral symptoms in experimentally induced psychosis.

Keywords: Psychosis, Acetylcholinesterase, GABA, MK‑801, EETS.

INTRODUCTION

Globally, the psychological condition, schizophrenia, impacts about 1 per cent of the total population. This is the society's seventh most costly medical disease.[1] Different environmental and developmental factors endorse it as a polygenetic condition.[2] It is an extremely complex condition

caused by positive, negative, and uncoordinated symptoms [3]. Such symptoms are presumed to occur due to deficiencies in dopaminergic, [4] glutamatergic, [5] and serotonergic pathways, [6] and a correlation between certain hyperdopaminergic pathway [7] explains the cause of this disorder. Most of the antipsychotic medications cause many nasty side effects, such as extrapyramidal syndrome, obesity, hyperglycemia, and hyperlipidemia. Therefore, these synthetic molecule disadvantages forced us to work in the line of natural remedies that are readily available in daily life and are able to decrease the disorder-related symptoms with minimal to no side effects. Until now, there has been no study on cranberry's antipsychotic ability. The proposed research work was therefore intended to study the effects of cranberry in Swiss Albino female mice on MK-801-induced psychosis.

Tecomastans leaves contain the tecomin alkaloids and tecostamine is a potent hypoglycaemic agent when administered intravenously. Anthranilic acid is responsible for the Diabetic Action. The origins of diuretics and vermifuge are strong. Tecoma is not a poisonous herb, because it is used as a treatment for diabetes in Latin America and for feeding cattle and goats in Mexico, respectively. The preliminary phytochemical screening of ethanolic l extract by *Tecomastans* showed the presence of flavaniods, phenols, alkaloids, tannins, steroids, triterpenes, anthraqunones, and saponinsetc [8,9].

MATERIALS AND METHODS

Collection and extraction of plant

In the month of May 2019 the Tecomastans flowers were collected from Tamil Nadu in Rasipuram [Namakkal District]. A specimen of plant herbarium had been stored in the section Pharmacognosy. From the descriptions available in the literature, Dr. G.V.S.Murthy, Joint Director of the Indian Botanical Survey, Southern Circle, TNAU Campus, Coimbatore identified the herb. The floral petals were dried in the shade between 10–12 days. The flower petals were pulverized to a coars 40-mesh powder after complete drying in a mechanical grinder. The powdered material was subjected to sohxlet extraction during 18 h at 50–55 ° C with ethanol. Afterwards, the extract was concentrated under vacuum and dry air [10].

Drugs and chemicals

Procured MK-801 from Sigma Aldrich (USA). Throughout the analysis, analytical grade reagents and chemicals were used, and purchased from different locations. Saline has been used to dissolve MK-801 to get 0.35 mg / ml of stock solution. Drug solutions were formulated by suspending the product in distilled water every day. *Tecomastans* ethanol extract (EETS) has been prepared in stock solutions of 1 and 2 g / kg, respectively.

Experimental animals

The typical Swiss Albino mice weighing 25-30 g used from home laboratory. The animals were kept under standardized environmental conditions in animal room, Pharmacology Department, Excel College of Pharmacy, Komarapalayam (22-28oC, 60-70 percent ratio, 12 hr dark / light cycle); The animals were given regular mouse chows (SaiDurga Feeds and Foods, Bangalore, India), and water ad lib. Five days before conduct research, the mice were adjusted to the laboratory environment. The behavioral experiments were carried out in a noise-proof, quiet laboratory between 9.00 and 18.00 h.

Treatment schedule

After acclimatization all mice were randomly divided into five groups (n = 6 in each group). Group I: Normal Regulation (10 ml / kg saline, i.p.). Group II: Effective (MK-801, 0.3 mg / kg, i.p.) control [11] Group III: clozapine [12] + MK-801 (0.3 mg / kg, i.p.). Group IV: EETS [13] + MK-801 (0.3 mg / kg, i.p.). Group V: EETS (2 g / kg, per capita) + MK-801 (0.3 mg / kg, per capita). Over two weeks, all of the above medications were given daily to different classes. Positive parameters, i.e. locomotive operation, were evaluated using a photoactometer [14], negative parameters were evaluated using forced swimming test [15] and rota-rod devices[16], and executive functions were evaluated using Cooke's pole device [17] on the 1st, 7th, 14th and 15th days of drug treatment.

Estimation of tissue nitrite content

Nitrite assessments were carried out colorimetrically using Griess reagent and brain

homogeneous supernatant free of protein.[18] Brain homogeneous protein-free supernatant and Griess reagent (sulfanilamide 1 percent w / v, naphthylethylenediaminedihydrochloride 0.1 percent w / v, and orthophosphoric acid 2.5 percent v / v) were combined in equal amounts and held at room temperature for 1 Absorbance calculation was performed at 540 nm, and then compared to sodium nitrite normal absorbance.

Estimation of brain acetylcholinesterase activity

Ellman's test measured the activity of in vivo acetylcholinesterase (AChE) in the brain with minor modifications. [19] Animals were sacrificed and entire brains were dissected in ice-cold 0.1 M phosphate-buffered saline (pH 8.0). Tissue homogenization was performed using a homogenizer in ice-cold 0.1 M phosphate buffered saline (pH 8.0) and centrifuged at 1000 g for 10 min at 4 ° C. In AChE assay the supernatant was collected and used as a source of enzyme. Ellman's buffered reagent (160 µL) and Acetylthiocholine (30 µL) iodide solution were reacted for 10 min. at room temperature. Immediately after applying 60 µL supernatant to the process mixtures, absorbance was recorded at 412 nm using Bioradmicroplate Reader 680XR. Positive control group tests for inhibitory activity in AChE were contrasted with other groups.

Estimation of D‑amino acid oxidase activity

D-amino acid oxidase (DAO) activity according to the stated method was calculated colorimetrically. [20] homogenized Brain tissue in a pyrophosphate buffer of 7 mM (pH 8.3) Homogenate centrifugations were performed at 550 g for 5 min, followed by supernatant estimation. The reaction mixture consisted of 0.3 ml of 0.133 M pyrophosphate buffer (pH 8.3) with catalase 700 IU / ml, 0.3 ml of 0.1 M D-alanine, 0.2 ml of 0.1 mMflavin adenine dinucleotide, and 0.1 ml of 70 per cent (v / v) methanol. The experiment was induced by inserting 0.1 ml of supernatant solution based on sample behavior into the reaction mixture at 37 ° C up to 60 min. Thereafter, extinction of the response was aided by the totaling 1 ml of 10% v/v trichloroacetic acid (TCA). TCA included to the reaction mixture previous to the origination of enzyme reaction was marked as blank. Upon centrifugation, the supernatant was collected for 20 min at 700 / g. For 0.5 ml of the supernatant, 0.5 ml of 5 N KOH and 0.5 ml of 0.5 per cent were found in 0.5 N HCl 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole. The solution was held at ambient temperature for 15 min and then with vigorous shaking added 0.5 of 0.75 percent w / v KIO4 in 0.2 N KOH to it. They measured absorbance at 550 nm. The activity of the DAO was determined using the formula given: activity (mol / min) = 2,584 A / t. Where, A = sample differential absorbance at 550 nm, and t = reaction period (min).

Neurochemical estimation

Brain was weighted, and an electric homogenizer used 10 percent w / v 0.17 M perchloric acid for 30 s for homogenization. Centrifugation at 1000 rpm was performed and the supernatant was subsequently isolated and tested for neurotransmitters, or held at −70 ° C until assayed. RP-HPLC coupled with electrochemical detector (Waters Company, Milford, USA) was used to estimate specific neurotransmitter concentrations. Estimates were directed by a few technical changes.

Used Sunfire® C18 column, used methanol (15% v/v) as mobilephase in an solution containing (pH 4.2) 32 mM citric acid, disodium hydrogen orthophosphate 12.5 mM, octyl sodium sulfate 0.5 mM, EDTA 0.5 mM, and KCl 2 mM was utilized for separation and the flow rate employed was 1.2 ml/min at 3000 psi operating pressure. The operating potential on electrochemical detector was kept at 0.61 V. The specifications were prepared by spiking fixed standard quantity (dopamine [DA], norepinephrine [NE], 5-hydroxytryptamine [5-HT], gamma-aminobutyric acid [GABA], glycine, and glutamate) into 1 ml of pooled supernatant. Estimated levels of endogenous neurotransmitters, like 5-HT, NE, glycine, DA, GABA and glutamate in brain homogenate aliquots [21, 22].

Statistical analysis

All the data is shown as mean ± standard mean error. The findings were measured using GraphPad Prism 5.0 (GraphPad Software, Inc., La Jolla, CA 92037 USA), a computer-based fitting system. Analysis of statistical difference between the mean of

the different groups was evaluated using a one-way variance analysis followed by Dunnet's P < 0.05 post-hoc check.

RESULTS

EETS effect on time of immobility in forced swim test

On day 1 the length of immobility in positive control mice was not substantially different from that of normal control mice. MK-801 resulted in a significant (P<0.001) increase in the length of the immobility from day 7 to day 15 relative to standard monitoring. However, the treatment with clozapine and ACE (1 and 2 g / kg) showed a small decrease in immobility period (P < 0.001) from day 7 to day 15 compared with positive control animals [Table 1].

Table 1: EETS effect on immobility duration in forced swim test

Groups	Duration of immobility (s)			
	Day 1	Day 7	Day 14	Day 15
I	1.31±0.12	1.48±0.32	1.80±0.02	1.31±0.45
II	1.49±0.23	3.17±0.17###	3.48±0.14###	4.64±0.64###
III	1.38±0.57	1.67±0.48***	1.64±0.34***	1.20±0.27***
IV	1.67±0.32	1.65±0.35***	1.02±0.21***	1.46±0.39***
V	1.49±0.25	1.64±0.18***	1.02±0.28***	1.69±0.27***

Data represent mean±SEM (*n*=6). Values are statistically evaluated using ANOVA analysis followed by Dunnett's*post hoc* test. ###*P*<0.001 as compared to normal control; ****P*<0.001 as compared to positive control. SEM=Standard error of the mean, ANOVA=Analysis of variance.

EETS effect on rota rod test

The time of permanence in positive control mice on day 1 was not substantially different (P < 0.001) from normal control. There was a small (P < 0.001) decrease in longevity in positive control mice relative to normal control mice on day 14 and 15, but no substantial improvement was observed on day 7. In comparison, EETS therapy (1 and 2 g / kg) showed a marked improvement in permanence time (P < 0.001) on days 14 and 15 as opposed to positive control mice [Table 2].

Table 2: EETS effect on rota rod test

Groups	Time of permanency (s)			
	Day 1	Day 7	Day 14	Day 15
I	151.67±14.39	119.17±15.24	180.33±6.89	197.17±19.06
II	150.00±4.88	99.83±6.33###	66.83±7.70###	60.50±11.65###
III	152.00±9.41	131.00±21.20***	167.16±12.06***	179.83±22.65***
IV	151.00±7.64	122.50±9.93***	122.33±19.05***	177.67±13.4***
V	153.00±5.43	117.00±18.35***	135.33±15.21***	171.83±14.20***

Data represent mean±SEM (*n*=6). Values are statistically evaluated using ANOVA analysis followed by Dunnett's*post hoc* test. ###*P*<0.001 as compared to normal control; ****P*<0.001 as compared to positive control. SEM=Standard error of the mean, ANOVA=Analysis of variance

Effect of EETS on escape latency test

There was a substantial decrease (P < 0.001) in the length of positive test mice's escape latency from day 7 to day 15 as opposed to standard control animals. In addition, EETS (1 and 2 g / kg)-treated mice showed a significant (P < 0.001) improvement

in the length of the escape latency from day 7 to day 15 compared with positive control animals [Table 3].

Table 3: Effect of EETS on escape latency test

Groups	Duration of escape latency (s)			
	Day 1	Day 7	Day 14	Day 15
I	89.07±2.67	88.07±5.09	8945±3.52	89.63±1.76
II	89.40±1.60	19.23±1.22###	15.57±0.83###	12.40±0.01###
III	89.73±0.89	68.73±0.68***	72.51±1.36***	73.07±0.71***
IV	86.23±3.02	63.23±0.72***	66.07±0.79***	66.07±1.37***
V	86.73±2.06	65.07±0.61***	69.49±0.72***	69.73±0.31***

Data represent mean±SEM (*n*=6). Values are statistically evaluated using ANOVA analysis followed by Dunnett's*post hoc* test. ###*P*<0.001 as compared to normal control; ****P*<0.001 as compared to positive control. SEM=Standard error of the mean, ANOVA=Analysis of variance

Effect of EETS locomotor activity

There was a substantial increase (P < 0.001) in positive control mice locomotive activity from day 7 to day 15 as opposed to normal control animals. EETS (1 and 2 g / kg)-treated mice induced a substantial decrease (P < 0.001) in locomotive activity on days 14 and 15 relative to positive control animals [Table 4].

Table 4: Effect of EETS locomotor activity

Groups	Cut off count (s)			
	Day 1	Day 7	Day 14	Day 15
I	94.07±3.45	104.50±2.41	90.00±3.121	105.17 ± 7.27
II	104.57±3.54	131.00±3.21###	159.83±4.52###	194.63±6.81###
III	104.07±3.26	123.31±2.14***	121.83±3.30***	117.07±3.40***
IV	108.07±2.61	132.05±1.84***	127.50±1.35***	120.57±2.91***
V	117.40±5.24	130.37±4.42***	115.17±5.57***	121.47±2.75***

Data represent mean±SEM (*n*=6). Values are statistically evaluated using ANOVA analysis followed by Dunnett's*post hoc* test. ###*P*<0.001 as compared to normal control; ****P*<0.001 as compared to positive control. SEM=Standard error of the mean, ANOVA=Analysis of variance

Effect of EETS on nitrite levels and D‑amino acid oxidase activity

There was a significant (*P* < 0.001) elevation of brain nitrite levels and DAO activity in positive control animals in comparison to the normal control group. The treatment with EETS (1 and 2 g/kg) showed a significant (*P* < 0.001) reduction in brain nitrite levels and the DAO activity when compared with positive control animals [Table 5].

Effect of EETS on inhibition of acetylcholine esterase levels in the brain

The % fold change to normal control in positive control group (42%) was significantly (*P* < 0.001) reduced in comparison to the normal control animals (100%). The treatment with EETS (1 and 2 g/kg) showed a significant (*P* < 0.001) increase in % fold change (67.39% and 90.32%, respectively) as compared to the positive control group [Table 5].

Table 5: Effect of EETS on inhibition of acetylcholine esterase levels in the brain

Groups	Parameters		
	Nitrite content (µg/g of tissue protein)	DAO activity (µmol/min)	AChE inhibition (% fold change to control)
I	0.257	0.065	1.684 (100)
II	0.429###	0.133###	0.921### (54.69)
III	0.258***	0.063***	1.486*** (88.24)
IV	0.257***	0.062***	1.135*** (67.39)
V	0.264***	0.064***	1.521*** (90.32)

Data represent mean±SEM (*n*=6). Values are statistically evaluated using ANOVA analysis followed by Dunnett's*post hoc* test. ###*P*<0.001 as compared to normal control; ****P*<0.001 as compared to positive control. SEM=Standard error of the mean, ANOVA=Analysis of variance

Effect of EETS on NE levels in mice brain

Positive control animals showed large brain and epinephrine (NA) increases (P < 0.001) relative to normal control mice. Nevertheless, a small (P < 0.001) decrease in brain NA levels was seen when treated with clozapine relative to positive control group. Furthermore, mice treated with EETS (1 and 2 g / kg) induced a substantial decrease (P < 0.001) in brain NA levels relative to positive control animals [Figure 2a].

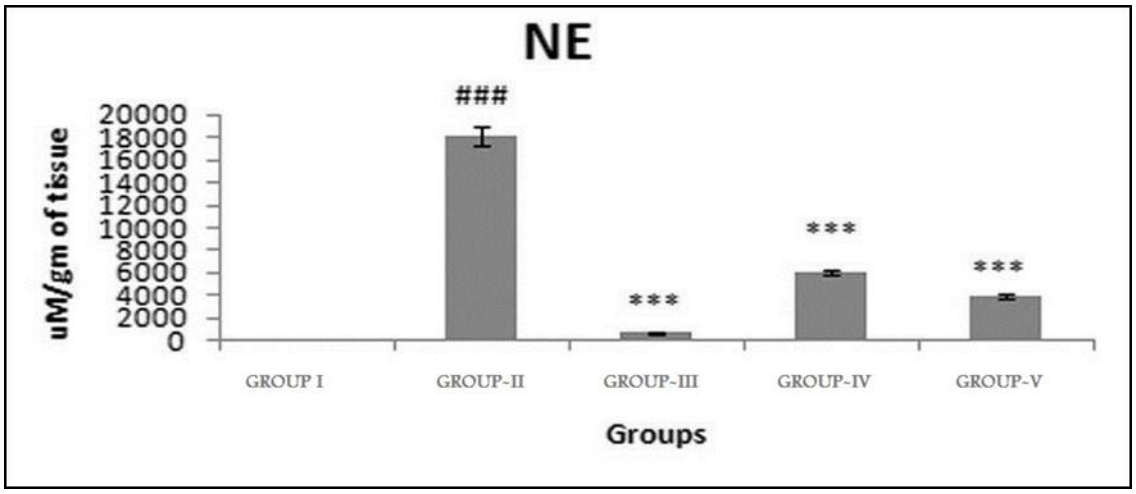

Figure: 1 Effect of EETS on the brain NE level on MK‑801 induced psychosis in mice.

Effect of EETS on dopamine levels in mice brain

In positive control animals, the DA levels in mice brain were significantly (P < 0.001) higher than in normal control animals. However, when treating animals with EETS (1 and 2 g / kg), they induced a marked decrease in brain DA levels (P < 0.05; P < 0.01) compared with positive control animals [Figure 2].

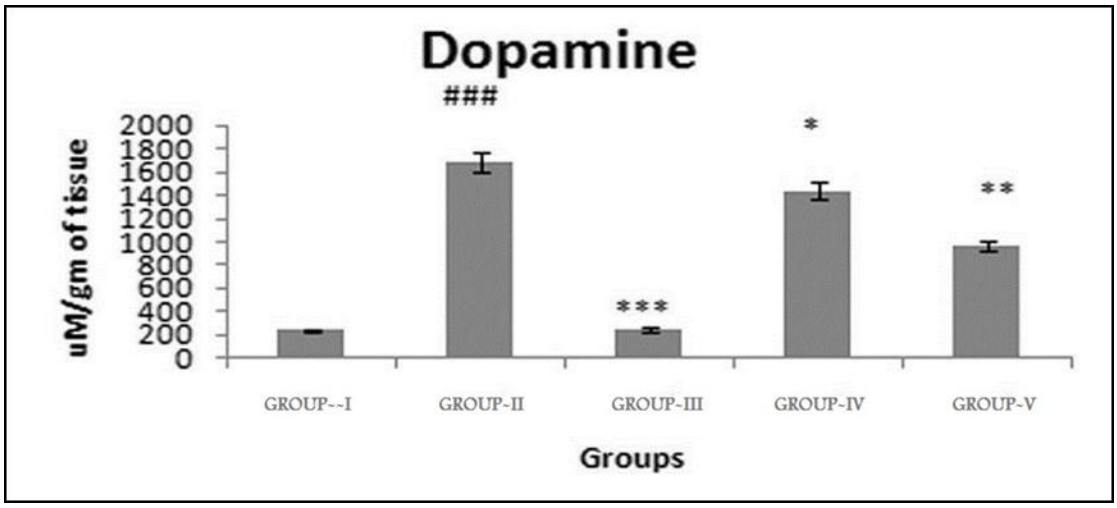

Figure 2: Effect of EETS on the brain dopamine level on MK-801 induced psychosis in mice.

Effect of EETS on 5-hydroxytryptamine levels in mice brain

The 5-HT amount in the positive control mice was significantly ($P < 0.001$) higher than the normal control mice. However, EETS-treated mice (1 and 2 g / kg) induced a substantial reduction in brain 5-HT levels ($P < 0.01$ and $P < 0.001$) as opposed to positive control animals [Figure 3].

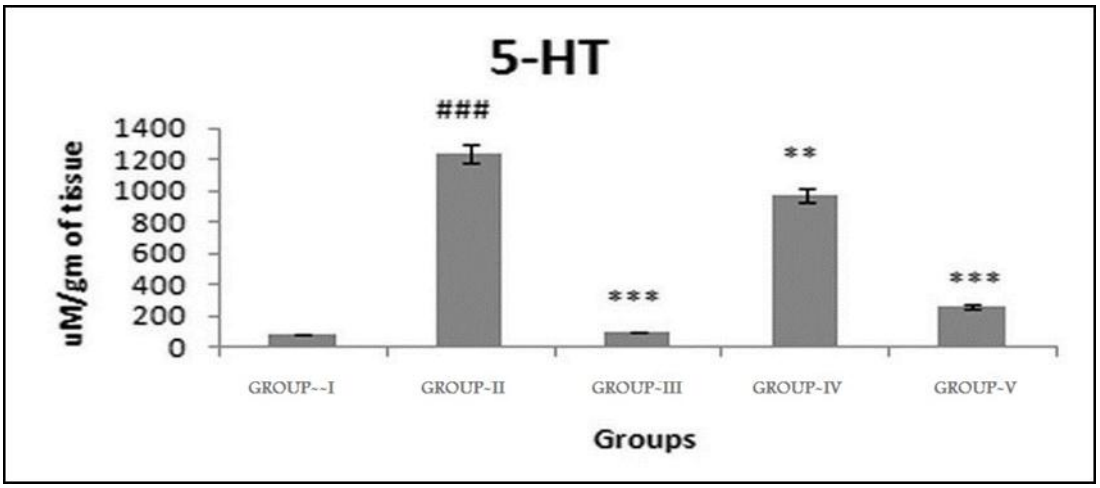

Figure 3: Effect of EETS on the brain 5 -hydroxytryptamine level on MK-801 induced psychosis in mice.

Effect of EETS on glycine levels in mice brain

Positive test mice showed a substantial reduction ($P < 0.001$) in brain glycine levels compared with the standard control group. This decrease in the brain glycine levels caused by MK-801 was significantly prevented by clozapine ($P < 0.01$). Also significantly increased brain glycine levels with EETS (1 and 2 g / kg) ($P < 0.05$ and $P < 0.001$) relative to positive control animals [Figure 4].

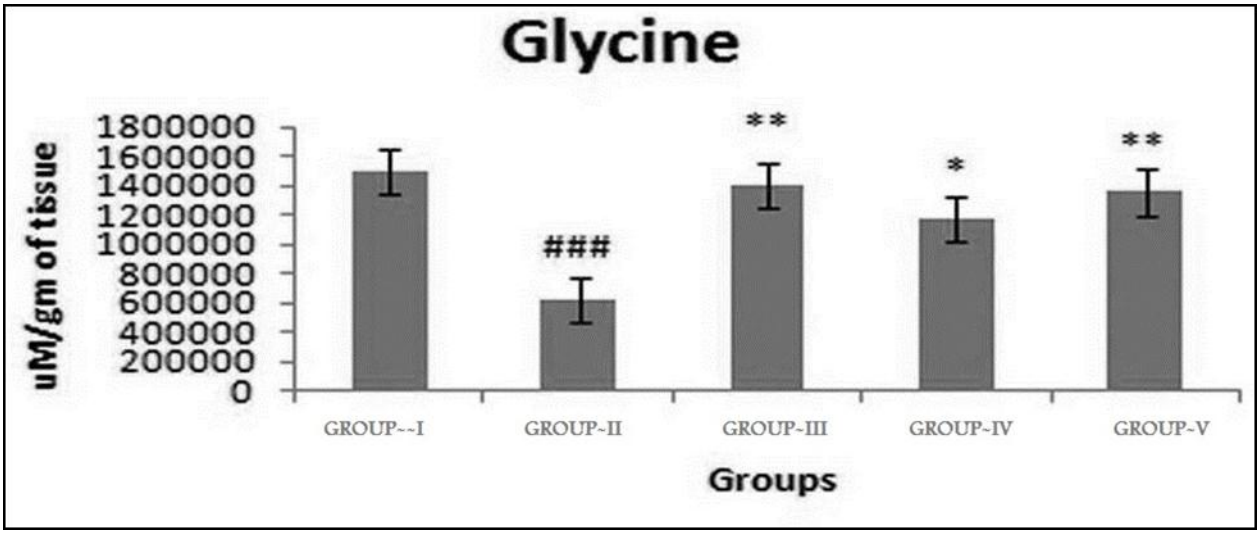

Figure 4: Effect of EETS on the brain glycine level on K-801-induced psychosis in mice.

Effect of EETS on glutamate levels in mice brain

Positive control animals reported a substantial decrease ($P < 0.001$) in brain glutamate levels compared with normal control animals. On the contrary, EETS treatment (1 and 2 g / kg) induced a pronounced ($P < 0.01$) elevation of the levels of brain glutamate relative to positive control animals [Figure 5].

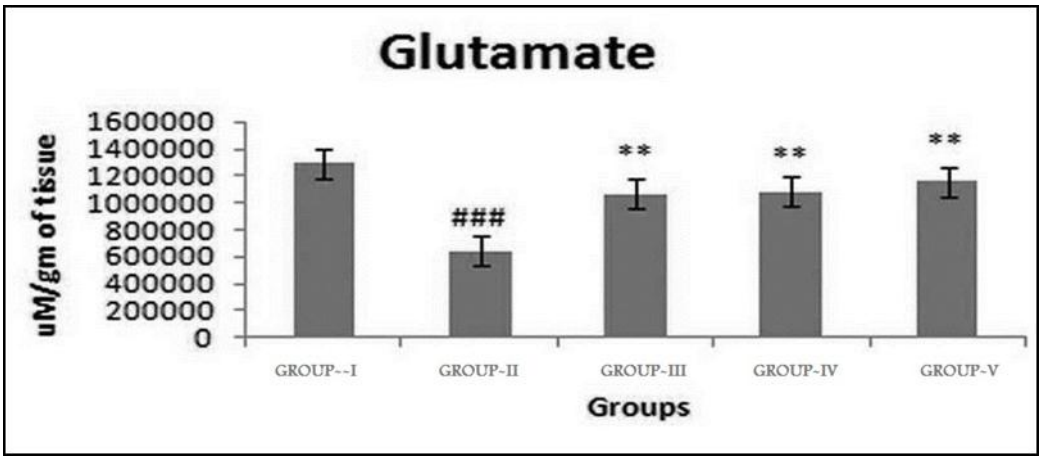

Figure 5: Effect of EETS on the brain glutamate level on K-801-induced psychosis in mice

Effect of EETS on gamma-aminobutyricacid levels in the brain

Brain GABA level in MK-801-treated mice decreased significantly ($P < 0.001$) compared with the normal control group. However, EETS care (1 and 2 g / kg) has induced a marked rise in brain GABA levels ($P < 0.05$ and $P < 0.01$) as opposed to positive control animals [Figure 6].

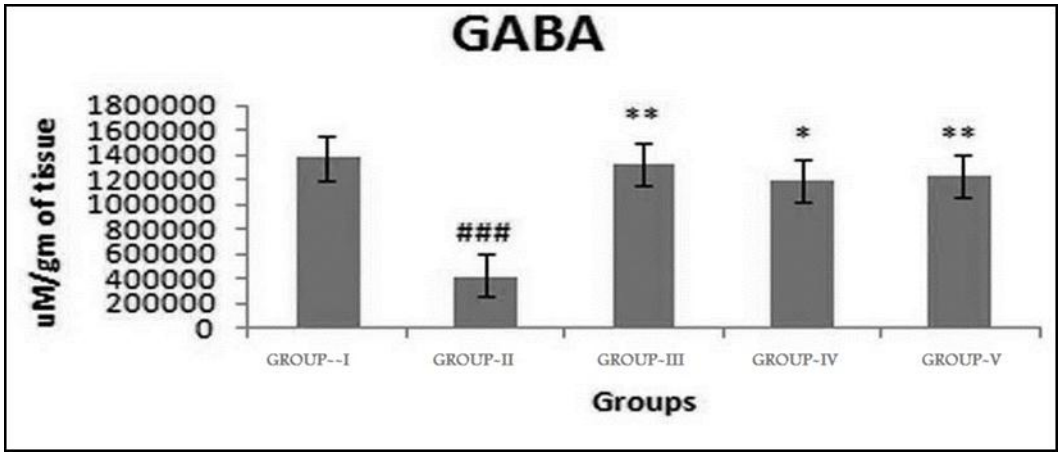

Figure 6: Effect of EETS on the brain GABA **level on K-801-induced psychosis in mice**

DISCUSSION

Since synthetic antipsychotics cause many adverse effects, an alternative treatment is required to manage the psychotic symptoms in humans. Medicinal plants have been important sources of possible medicinal action for unknown chemical constituents. It was therefore decided to pick the herbal plant that is reported to be having some effect on the dopaminergic system. The effect of EETS against MK-801-induced psychosis has been assessed in this research. MK-801 administration developed 14-day psychosis that was characterized by numerous behavioral symptoms and neurochemical anomalies.

The rise in the duration of immobility following the administration of antagonist N-methyl-D-aspartic acid (NMDA) has been used as a model for determining negative symptoms of psychosis, e.g., effect flattening and avolition. Additionally, antipsychotic medications have stopped NMDA receptor antagonist-induced behavioral anomalies. [23] Immobility time in the forced swim test was significantly increased upon repeated treatment with MK-801. On the contrary, the test drug at both the therapeutic doses was shown to decrease the immobility time significantly whin MK-801 treated mice.

MK-801 administration in animals has impaired performance on tasks which appear to rely on hippocampal or amygdalar function. With these results, the effect of both EETS doses in mice on the activity of pole climbing was assessed. EETS demonstrated a substantial improvement in the duration of escape latency measured by Cooke's pole apparatus relative to the positive control mice at both the therapeutic doses. The study drug retarded pole climbing time against the positive control mice.

Moreover, according to previous reports, MK-801 in animals developed hyperlocomotion, ataxia, impaired social interactions, and stereotyping [24] due to the dopaminergic pathway interaction. Treatment with EETS at doses of 1 and 2 g / kg demonstrated motor incoordination correction by increasing the time of permanence measured by rota-rod devices compared to the positive control group.

When administered chronically, NMDA antagonists induced hyperactivity and increased locomotion in animals. [25] Therefore, in animals with a positive control group, a hyperlocomotive syndrome was observed that was restored to EETS treatment at both doses in the treatment groups. Excess nitric oxide (NO) is considered neurotoxic due to the formation of peroxynitrite, a highly reactive anion produced by protonation. [26] The measurement of nitrite levels as a measure of NO concentration was performed to determine the outcome of MK-801 administration on NO metabolism. In the positive control community the nitrite level was substantially elevated. At all treatment doses the groups treated with EETS demonstrated a substantial decrease in brain nitrite levels compared with the positive control groups. A decrease in the amount of nitrite may be due to EETS 'antioxidant potential through activation of neuronal nitric oxide synthase.

Acetylcholine (ACh) was found to be responsible for the mediation of stimulus identification,

collection and processing within the cortex. Various levels of acetylcholine were correlated with visual hallucination, or distortion of reality. Reports have suggested the Ach's metabolism may involve itself in cognitive functions. Therefore, calculation of the AChE function inhibition was performed. In the present research, treatment with EETS was shown to substantially decrease brain AChE activity as opposed to positive control animals.

The enzyme DAO metabolizes D-Serine. Recent studies indicate that this enzyme is associated with susceptibility to schizophrenia. [27] Co-administration of D-serine with traditional neuroleptics demonstrated substantial improvement in schizophrenic subjects with negative, positive, and cognitive symptoms. This serves the function of cranberry selection as a treatment choice for model psychosis. There is also evidence suggesting the cranberry produces benzoic acid, a potent DAO inhibitor. As a result, EETS has been found to inhibit DAO enzyme activity and significantly decrease enzyme levels in the mice brain as opposed to model control animals.

Several studies have shown that MK-801 administration modifies expression of few proteins in the hypothalamus. Moreover, MK-801 treatment hoists presynaptic dopaminergic neuron action and in an indirect way stimulates DA discharge in the brain. [28] Based on those results, different levels of neurotransmitters were estimated in the homogeneous mice brain. It was found that the group treated with MK-801 showed a substantial increase in the levels of DA, 5-HT and NE compared with that of the standard control group at the end of the test. The EETS treatment at both the therapeutic doses was shown to substantially decrease the concentrations of DA, NE, and 5-HT in the brain relative to the positive control group elevated as a result of psychosis induced.

Studies have shown that GABA is responsible for enhancing the cognitive symptoms of schizophrenia and reduces the extrapyramidal side effects that arise as a result of DA blockade. Anatomical, histochemical, biochemical and genetic studies of schizophrenia have shown that there are both morphological changes in interneurons and their interactions with pyramidal cells, as well as differences in the GABA metabolism, including decreased levels of GABA in addition to decreased activity of a glutamic acid decarboxylase isoform, the rate-limiting enzyme in GABA. [29] Reports have also suggested that a plummeting glutamatergic pathway anticipating from cortical pyramidal neurons to the ventral tegmental region through GABA interneurons hinders DA discharge from mesolimbic DA pathway. [30] Thus, the present neurochemical study has shown that EETS at both the doses caused a significant reduction of the DA, 5-HT, and NA levels in the mice brain against the positive control group.

In 1980, glutamate was found to be decreased in schizophrenic patients 'cerebrospinal fluid, suggesting the role of this major excitatory neurotransmitter throughout the treatment of schizophrenia. The effect of EETS on concentrations of GABA, glutamate, and glycine neurotransmitters in the brain of mice was studied on this basis. Interestingly, the EETS substantially increased the brain concentrations of these neurotransmitters relative to the mice treated with MK-801.

CONCLUSIONS

EETS (1 and 2 g / kg, p.o.) substantially enhanced the behavioral symptoms of xperimentally induced psychosis once daily for 14 days, triggered neuromodulation and reduced oxidative stress.

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