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Original Article

Anti-manic and Antipsychotic Effects of *Withania somnifera* Extract in Rodent Model of Bipolar Disorder

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ABSTRACT

Aim: The present study was to investigate the effects of *WSE* improve cognitive, behavioral and mood disorders in animal models of bipolar disorder. **Materials:** Animals were divided into six groups each group contain 6 wistar rats of either sex ,Behavioral and memory test were carried out followed by estimation of oxidative stress and neurotransmitters in rat brain using continuous sub anesthetic dose of Amph (1.5 mg/kg, i.p) with *Withania somnifera* extract (300 mg/kg, i.p) and Lithium chloride (100mg/kg, i.p.) administered daily for 21 days.
Results: % Alternation was decreased in rat treated with *WSE* as compared to control indicating that it also improved spatial memory and learning. various oxidative parameters were estimated, oxidative stress was observed the levels of SOD and GSH reduced and increased in TBARS level compared to control groups, but reduced ion in oxidative stress upon administration of *Withania somnifera* extract and Lithium chloride indicates ameliorating effects of *Withania somnifera* extract in oxidative stress. **Conclusion:** We concluded that *WSE* showed improvement in learning and memory as animals treated with WSE spent more time in open arms as compared to Amphetamine with *Withania somnifera* and Lithium chloride-treated rats. Overall, the findings of this work show that neurotransmitters get imbalance and change the mood and chemistry of the brain. Hence *Withania somnifera* extract improve neurotransmitter imbalance which is directly linked with mood, behavior, anxiety and manic episodes in an animal model of bipolar disorder.

Keywords: *Withania somnifera* extract, Cognitive, Behavioral, Mood disorder, Neurotransmitters, Bipolar disorder.

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INTRODUCTION

Bipolar Disorder (BD) is marked by persistent manic and depressive episodes interspersed with periods of euthymia (normal mood).[1]

The symptomatology of BD is quite diverse and highly dependent on the patient's current state. People experience euphoria, hostility, decreased need for sleep, strong reward seeking, hypersexuality, and hyperactivity during manic episodes. Anhedonia, increased sleep, diminished libido, fatigue, and a higher risk of suicide are all indicators of depression.[2]

Globally, Bipolar disorder influences 46 million population worldwide. The lifetime pervasiveness of bipolar disorder is 2.4 %, according to a survey of 11 nations. The United Nation had a one per cent prevalence of BD type I, which would have been substantially higher than the majority of other countries in this survey.[3] Every year, approximately 2.8 % of respective populations in the United States are diagnosed with bipolar disorder. Others with bipolar disorder are at the maximum possibility of being diagnosed with serious disability from every mood disorder (82.9 %) Since the previous year, males and females have the same prevalence of bipolar disorder (2.8 % and 2.9 %, respectively).[4] 25 years age is the typical age of beginning of symptoms. The National Alliance on Mental Illness (NAMI) (National Alliance on Mental Illness, 2017) persons aged group between eighteen to twenty-nine had the maximum frequency of bipolar disorder in 2001-2003 (4.7 %), subsequently by some of those aged between thirty to forty-four. (3.5 %). On average, bipolar illness decreases one's life span by 9.2 years (NIMH, 2017). 15% to 17% person who are suffering from BD are at high risk to attempt or committing suicide. The Treatment Advocacy Center (TAC), a non-profit organization seems dedicated to works on behalf of persons in treatment. Substance abuse disorders impact up to 60% of people with almost every mental disease, particularly bipolar disorder. Several persons who suffer from bipolar disorder have co-occurring health issues, the most common of which are high BP, thyroid disease, migraines, elevated cholesterol, asthma, and

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osteoarthritis have all been recognised as potential mutual health concerns.[5]

Sensitization (increases in abnormal behavioral response to repeated stimuli) but instead of tolerance or downregulation are seen throughout clinical features of bipolar disorder. That involves hypersensitivity to recurring stresses, mood swings, and drug addiction episodes. The sensitization and kindling preclinical models aid in the conceptualization of many elements of biochemical, behavioral, or physiological components of aliment development in affective disorders inside this way. Drugs like lamotrigine and carbamazepine which have been beneficial in averting full-blown amygdala-kindled seizures, were inefficient in the initial stages of kindling development.[6]

After the initial manic episode, long-term prophylaxis becomes required: The sorts of interventions used to follow a first manic episode, as well as their consistency, need to be overhauled. The mental or structural abnormalities that arise with initial manic symptoms are resolved within the upcoming year only if no more episodes occur, according to studies. Preventing additional episodes, a year following a first manic episode seems to be a difficult endeavor, as well as the sorts and intensity of therapy required to achieve this goal need to be investigated further. The increased usage of lithium might be a sign of a successful strategy. A randomized controlled trial found that first-manic episode who'd been randomized to a year of quetiapine or lithium had fewer bouts of mania and depression, greater responding when given lithium in functioning as well as cognition, and fewer abnormalities on brain imaging when given lithium.[7,8] Moreover, in a long-term study, lithium was considered superior to certain other mood stabilizers, echoing the findings of Lithium medication reduced the number of individuals who had drug addiction comorbidities.[9-11]

Historically decades, the roots from *WS* have indeed been utilized as a nerve tonic and adaptogen.[12] WS seems to be a member of the Solanaceae family, sometimes known also as nightshade family.[13] WS is really a 200-800 cm tall green woody shrub that may be found across the drier portions of South East Asia, including India, Nepal, Sri Lanka, Pakistan and Bangladesh along with sections of Australia, America and Africa.[14] In India, WS is found in the states of Punjab, Madhya Pradesh, Gujarat, Rajasthan and Uttar Pradesh. WS as well as its active components are shown to provide a number of health benefits, including anticancer, anti-inflammatory anti-stress, immunomodulatory and adaptogenic effects on the nervous system, endocrine, and the cardiovascular system.[15-19] Thus, based on the role of *WS* in neuroprotective mechanisms offered in several disorders of anxiety and manic episodes associated with bipolar disorder in animal model as reported in previous studies, the present study has attempted to understand the mechanism by which the anti-oxidative, anti-inflammatory and anti-excitotoxic effects of *WS* could be involved on anxiety and manic episodes associated with bipolar disorder in animal model.

MATERIALS AND METHODS

All chemical and reagent was used A Grade (99.9%). Amphetamine (SIGMA ALDRICH, USA.), Lithium chloride (SIGMA ALDRICH, USA) and fresh root of *Withania somnifera* from Khaadi Bawli Market, Old Delhi and authenticated by Senior Botanist Dr. Rizwan and a pouch of sample submitted to the University for reference.

Animals

Wistar albino rats from either sex was employed as a prospective animal model of bipolar illness. This research lasted 21 days. The animals were divided into six groups, each one with six animals. A Wistar albino rat weighing 200-230 g was Procured from Institute for Industrial Research and Toxicology-Ghaziabad, India. Approved by Institutional Animal Ethics Committee (IAEC) [Project proposal no- IIRT/IAEC/2021/144] on dated 06 Sept 2021. The animals were maintained in polypropylene cages under typical laboratory settings (12-hr light/dark cycles) with unlimited access to a commercial pellet food and water. Its temperature inside the animal housing was kept at 25 ±2°C.

Methods of Extraction of *WS*

Withania somnifera root was air dried and then milled into a rough powder. Following that, a cold maceration process was used to extract the coarse granular powder (500 gm) with distilled water and 95% *w/v* alcohol separately for 24 and 72 hr, respectively. Both extracts were evaporated under reduced pressure and vacuum after being filtered through muslin fabric. While the alcoholic extract only produced 29% w/w, the aqueous extract produced 43% w/w. Alcoholic extract was dissolved in water, fractionated with petroleum ether, chloroform, ethyl acetate, and nbutanol, and the results were 5.8%, 3.9, 2.1, and 1.2% w/w fractional yields from each solvent, respectively.

Treatment Schedule

Animals were divided into six groups each group contain 6 wistar rats of either sex, Normal saline was given to the control group, Amphetamine 1.5 mg/kg, I.p, daily administered for 21 days to induce Bipolar like symptoms (Amphetamine Model), 300mg/kg of *WSE* was given I.p for 21 days to the third group, combination of *WSE* and amphetamine was given i.p for 21 days to the fourth group, Lithium chloride 100mg/kg alone was injected i.p for 21 days as a gold standard comparative study. 100mg/kg Lithium chloride in combination with Amphetamine 1.5mg/kg, i.p was given to the sixth group.

Statistical analysis

Data was expressed as the mean ± SEM. Regarding analysis of data, one-way analysis of variance (ANOVA) would be used to

compare group means, followed more by Tuckey-Kramer multiple comparison test, which could be used to make distinctions across groups. $p < 0.05$ was considered significant.

RESULTS

Behavioural Parameters

Spontaneous Alternation Behavior

There was slightly change in the percentage alternation of animals in *WSE* treated groups as compared to control group. Furthermore, as compared with the control group, that percentage change in the Amphetamine (Amph) treated group was significantly lower (p<0.05). A significant possible alternation was observed in Amphetamine (Amph) *per se* and *WSE* combination treated groups in comparison to control (Figure 1).

All the values were expressed as mean +SEM and each data point was the average of 6 animals in each groups (n=6). Statistical analysis was carried out using analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison test. p<0.05 was considered significant. * p<0.05, **p<0.01, *** p<0.001 when compared with control, # p<0.05, ## p<0.01, ### p<0.001 when compared with Amphetamine (Amph).

Elevated Plus Maze Test

Administration of *WSE* (300 mg/kg body weight, i.p. for 21 days) When compared to Amphetamine (Amph) treated (1.5 mg/kg daily for 21 days) groups, the time spent in open arms rose while the time spent in closed arms decreased. Closed arm entrance were statistically significant (p<0.001) in comparison with the control group. In compared to control groups, the total number of open arm entries fell in Amphetamine (Amph) treated groups, and *WSE per se* groups revealed extremely significant findings p <0.001 (Figure 2(a), 2(b)).

All the values were expressed as mean +SEM and each data point was the average of 6 animals in each groups (n=6). Statistical analysis was carried out using analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison test. p<0.05 was considered significant. * p<0.05, **p<0.01, *** p<0.001 when compared with control, # p<0.05, ## p<0.01, ### p<0.001 when compared with Amphetamine (Amph).

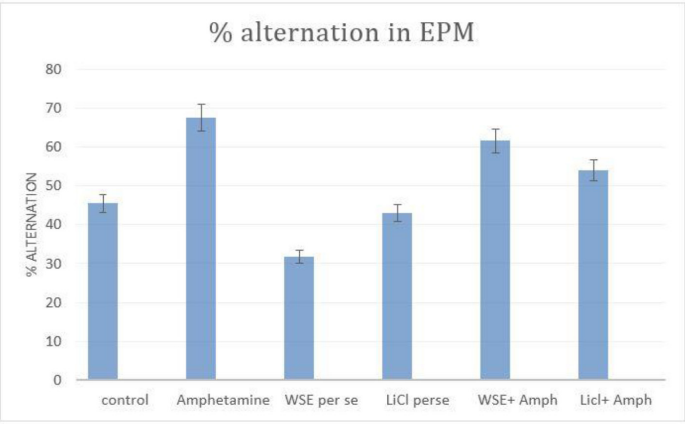

Figure 1: Effects of *Wthania somnifera* extract (WSE) on % alteration in elevated plus maze test in rats.

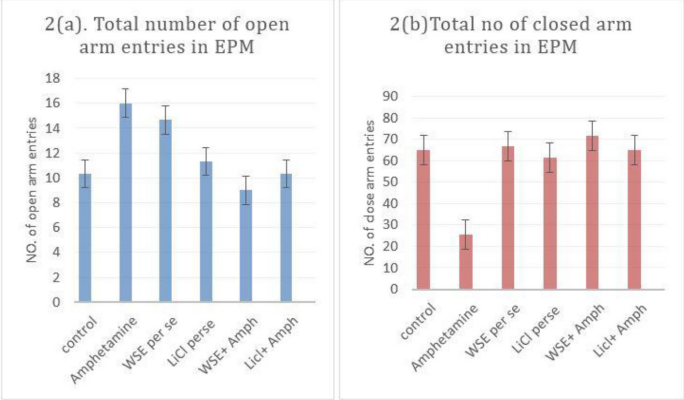

Figure 2: Effect of *Wthania somnifera* extract (WSE) on Total no. of open arm and closed arm entries in elevated plus maze test in rats.

Locomotor Activity Monitoring

Total movement time was increased in Amphetamine (Amph) treated groups as compared with control groups, where *WSE per se* groups showed highly significant as compared with Amphetamine (Amph) group (P<0.001). Rest time was increased in *WSE* treated groups as compared to Amphetamine (Amph) treated groups showed hyperlocomotion activity. Horizontal locomotor activity was increased in Amphetamine (Amph) treated group as compared to control groups (Table 1).

All the values were expressed as mean ±SEM. Statistical analysis was carried out using analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison test. p<0.05 was considered significant. * p<0.05, **p<0.01, *** p/0.001 when compared with control, # p<0.05, ## p<0.01, ### p<0.001 when compared with Amphetamine (Amph).

Biochemical Parameters

Reduced glutathione GSH

WSE extract (300 mg/kg body weight, i.p. for 21 days) treatment showed significant increase in GSH levels (p<0.05) and Amphetamine (Amph) administration (1.5mg/kg daily for 21 days) as compared with their separate controls, resulted in a drop in GSH level, and when combined, resulted in a rise in GSH level (Figure 3(a)).

TBARS

WSE extract (300 mg/kg body weight, i.p. for 21 days) When compared with the control group, there was a decrease in TBARS levels (p0.05). When compared to a control group, Amphetamine (Amph) generated a higher TBARS score (p<0.01). The combination of *WSE* and Amphetamine (Amph) treatment

Table 1: Effects of *WSE and* Lithium chloride on Amphetamine (Amph) induced locomotor activity in rats by using Open Field Activity Monitoring System.

Groups (*n*=6)	Treatment	Horizontal activity(cm)	Move time (s)	Rest time (s)	Average dist/ move (cm)	Mean velocity (cm/s)	Total movement
I	Control (1ml/kg,i.p) saline (0.9%)	2068.37±98.65	243± 15.68	682.57±14.98	2.58 ±0.17	2.73±0.11	563.38±23.78$^{\#}$
II	Amphetamine (Amph) (1.5 mg/kg,i.p)	6082.62±252.70**	738±16.87**	246±15.94**	5.16±0.35**	8.19±0.07**	1689±78.26**
III	*WSE per se* (300 mg/kg,i.p)	1974.71±92.51$^{**\#\#}$	165±8.79$^{**\#\#}$	671±8.57*#	1.89±0.06$^{*\#\#}$	2.81±0.06$^{\#}$	452.93±26.31$^{*\#\#}$
IV	LiCl *per se* *(100mg/kg, i.p.)*	1052±35.69$^{**\#\#\#}$	232±25.68$^{\#\#}$	693.67±10.31$^{*\#\#\#}$	2.36±0.04$^{*\#\#}$	2.63±0.02$^{\#\#\#}$	611.52±11.04$^{**\#\#\#}$
V	(*WSE* + Amph 300 mg/kg,i.p. +1.5 mg/kg, i.p.)	3032±203.54	308±15.73	612.65±15.54	3.15±0.13	3.18±0.12	862.73±27.54
VI	LiCl + Amph (100mg/kg,i.p. +1.5 mg/kg ,i.p)	4031±263.27	302±24.78	602.70±25.73	3.24±0.24	3.82±0.21	903.21±22.13

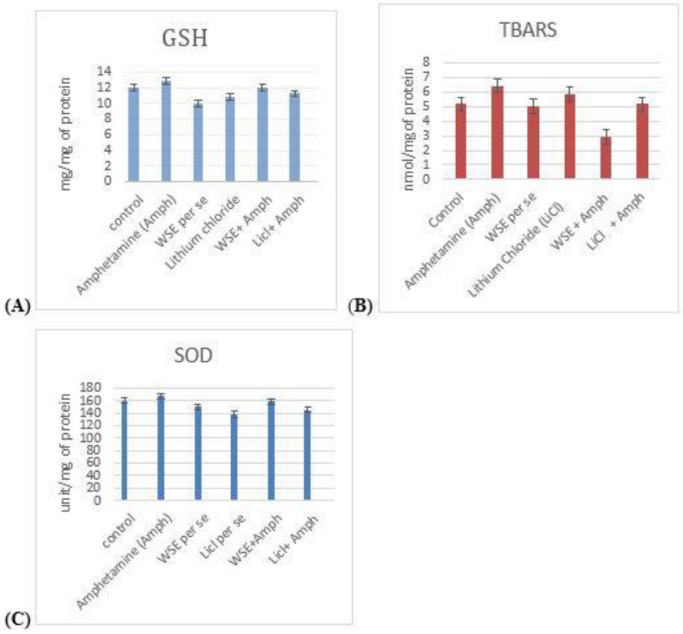

Figure 3: Effects of *Withania somnifera* extract (WSE) on GSH, TBARS and SOD level in rat brain sample.

resulted in a somewhat higher decrease of TBARS than just the control groups (Figure 3(b)).

SOD activity

SOD values showed significant increase in *WSE* extract groups as compared to Amphetamine (Amph) group (P< 0.001), while *WSE* extract showed slightly difference as compared to control group (p<0.05). However, when combination of *Withania somnifera* and Amphetamine (Amph) administered showed marked decreases in SOD value as compared to control groups (Figure 3(c)).

All values are expressed as mean + SEM. And each data point is the average of 6 animals in each group. The data show significant

Table 2: Effects of *WSE and* Lithium chloride on acetylcholinesterase in elevated plus maze test in rat.

Groups (*n*=6)	Drug treatment (21 days)	Dosage (mg/kg)	Acetylcholinesterase mole/mg/protein
I	Control (NS)	1 ml	18.48 ± 1.05
II	Amphetamine (Amph)	1.5	27.37 ± 2.02*
III	*WSE per se*	11.86	6.74 ±1.04$^{**\#\#}$
IV	Lithium Chloride (LiCl) per *se*	100	3.06 ±0.68$^{**\#\#\#}$
V	*WSE* + Amph	11.86 + 1.5	10.03 ±0.93$^{*\#\#\#}$
VI	LiCl+ Amph	100+1.5	11.90 ± 1.28

decrease in TBAR, SOD and GSH level in drug treated and Lithium Chloride (LiCl) treated groups, as measured by one way ANOVA followed by Tukey- Kramer multiple comparison test. P value greater than 0.05 is considered as significant, there is significant difference between control group and Amphetamine (Amph) treated group (P<0.01). WSE have shown significance (p<0.01) as compared with toxic group.

Acetylcholinesterase Activity

Amphetamine (Amph) (100mg/kg daily for 21 days) When contrasted to their control, there was a substantial rise in acetyl cholinesterase activity (p0.05). *WSE* extract administration resulted in a reduction in acetyl cholinesterase levels when compared to the control (Table 2).

All results have been presented as mean + SEM, and ANOVA and Tukey-Kramer multiple comparison tests are being used to analyze them. p values of less than 0.05 were considered significant, while P values of less than 0.001 were regarded very significant. The total number of animals within every group is n=6* p<0.05, **p<0.01, *** p<0.001 when compared with control, # p<0.05, 4# p<0.01, ### p<0.001 when compared with Amphetamine (Amph).

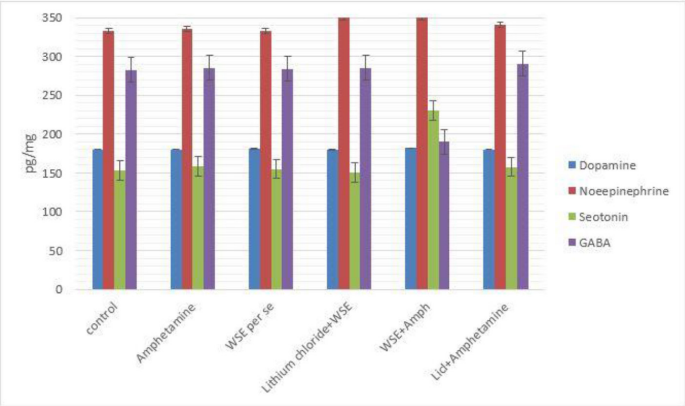

Figure 4: Effects of *Withania somnifera* extract (WSE) on various neurotransmitters in brain tissue.

Estimation of Neurotransmitters in Rat Brain

Figure 4, illustrates the neurotransmitter levels were in the brain of experimental groups. A significant (p<0.001) increase in the DA levels was observed in brains exposed to Amphetamine. LiCl alone treated rat significantly decreased the DA levels than rat treated with combined LiCl and Amphetamine in brain tissue. In contrast, a significant increase was observed in WSE alone in DA levels than Amphetamine administration alone. In Amphetamine treated rat, Norepinephrine levels significantly (p<0.05) increased in brain tissue were observed. Combined LiCl and Amphetamine treated animals showed significantly (p<0.05) decreased norepinephrine levels. LiCl alone treatment reversed the levels of norepinephrine when compared to control rat. WSE alone treatment shows increased levels of NE than Amphetamine administered rat. Serotonin (5-HT) levels was significantly (p<0.05) increased in brain tissue of control animals treated with Amphetamine and also in WSE alone treated rat. Combined LiCl and Amphetamine alone treatment showed partial decrease compared to LiCl alone treatment in rat brain tissue. A significant (p<0.001) decrease in the GABA levels was observed in brains exposed to Amphetamine. Rat treated with LiCl and WSE combination showed a partial increase in GABA levels in brain tissue. Whereas, WSE alone significantly (p<0.001) increased the GABA levels than Amphetamine administered rat (Figure 4).

All results presented as mean ± SEM and ANOVA and Duncan multiple range test [DMRT] are being used to analyze difference between them. *P* value less than 0.05 were considered significant. Each group contain 6 animals.

DISCUSSION

The impact of *WSE* extract on behavioral symptoms and memory impairment caused by either a two-week intraperitoneal injection of numerous subanesthetic doses of Amphetamine (Amph) (0.5-4.0 mg/kg, i.p). Wistar rats were taught to self-administer ethanol (10%) by prodding their noses. Its effects of *WSE* (75-300 mg/kg) on provision and maintenance, ethanol breakpoint under a progressive-ratio reinforcement schedule, of deprivation impact and resumption of seeking behaviors was investigated. There in elevated plus maze test and spontaneous alternation behavior, including locomotor activity in rats, behavioral characteristics was recorded. As during elevated plus maze test, total time spent throughout closed arm, total time spent on site arms, percent preference to closed arm as well as open arm were recorded. Animals inside the Amphetamine (Amph) group spent much more time throughout closed arm than open arm, though there was an increase in the time spent in open arms as tried to compare to closed arm because once treated with *WSE* extract, indicating that rats have had an aversion to open arm entries. Other symptoms have already been reported in high plus mazes, such as freezing to open space for an extended period of time. *WSE* extract was shown to relieve tension and anxiety with in current investigation, suggesting that it might be effective in treating bipolar disorder symptoms. GSH is the most important nonprotein antioxidant and redox regulator in the neurological system, shielding it from reactive oxygen species (Armstrong 2002) and modifying redox sensitive locations, such as NMDA receptors. GSH level has been significantly (p <0.001) lower in the Amphetamine (Amph) treated group comparison to the control group, but it was expanded within a week of *WSE* administration. Combination of *WSE* and Amphetamine (Amph) showed higher GSH levels than Amphetamine (Amph), suggesting that the drug has neuroprotective and/or anti-oxidant properties. SOD seems to be an important enzyme throughout decreasing oxidative stress; in this study, it was found to be lower in Amphetamine (Amph) treated rats, but significantly higher in *WSE* extract treated rats, indicating that neurosteroids play a significant role throughout preventing oxidative damage, neuronal cell death, and apoptosis in bipolar disorder whilst also restoring the above enzyme. Moreover, oxidative stress affects the lipid-rich white matter.[20] As a result, oxidative stress could be to blame for myelin-related deficits in bipolar disorder.[21] Its pathophysiology of illness may well be influenced by oxidative stress, which could also disrupt cellular signaling cascades.[22]

LiCl alone treated rat significantly decreased the DA levels than rat treated with combined LiCl and Amphetamine in brain tissue. In contrast, a significant increase was observed in WSE alone in DA levels than Amphetamine administration alone. In Amphetamine treated rat, Norepinephrine levels significantly (p<0.05) increased in brain tissue were observed. Combined LiCl and Amphetamine treated animals showed significantly (p<0.05) decreased norepinephrine levels.

CONCLUSION

It is all too common that bipolar disorder does not receive the respect and care it needs to be treated as a serious, potentially fatal medical condition. Bipolar disorder may gradually advance

to a harmful and treatment-resistant state. Such a trend can include the buildup of stressors, sensitivity to them, and cross-sensitization, as well as mood swings and episodes of substance misuse. Each of these appears to have neurological underpinnings that are regulated by epigenetic modifications to DNA, histones, and microRNA. These changes are caused by the environment, therefore efforts at prevention and treatment are feasible. Preventing a malignant change of bipolar disorder from a tolerable condition to an incapacitating and treatment-resistant one would seem to need early attempts at stress reduction and regulation, as well as episode and substance misuse treatment and prevention. The concluded have that the Continuous sub anesthetic low dose of Amphetamine (Amph) (1.5 mg/kg, i.p) with *WSE* (300 mg/kg, i.p) and LiCl (100 mg./kg, i.p.) administered daily for 21 days showed significant changes in behavior impact on bipolar disorder. It may induce negative symptoms as well as cognitive memory impairment. In EPM, *WSE* extract showed improvement in learning and memory as animal treated with *WSE* extract spent more time in open arm as compare to Amphetamine (Amph) treated rats. Percentage alteration was decreased in rat treated with *WSE* extract as compare to control indicate that it also improved spatial memory and learning. Various oxidative parameters were estimated, oxidative stress was observed the levels of SOD and GSH reduced and increased in TBARS level as compared to control groups, but reduced ion in oxidative stress upon administration of *WSE* extract indicates ameliorating effects of *WSE* in oxidative stress. Our results showed that *WSE* extract and LiCl increased learning and memory in the raised plus maze, spontaneous altering behavior, locomotor activity, enhance brain impact via lowering AchE, and lower oxidative stress. WSE extract showed Neurotransmitters modulation activity when using alone but highly effective when combined with Lithium chloride and lowering the effects of Amphetamine inducing hyperactive mania associated with bipolar disorder alone and more significant when combined with WSE. Over all, WSE cause increased Dopamine, increased GABA, serotonin and norepinephrine. To better effectively and properly treat this illness, fresh research, academic focus, and public health attention will be needed. Given the possibility that this won't be easily accomplished in the near future, each doctor should make an effort to offer the kind of comprehensive early therapy that has been shown to be necessary for a more benign outcome.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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