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Assessment of Acute and Chronic Antidepressant Activity of *Withania somnifera* and *Ginkgo biloba* in Comparison with Sertraline: An Experimental Study in Albino Mice

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ABSTRACT

Background: Depression is a major concern as a neuropsychiatric disorder which needs more safe and effective therapeutic strategy. Some of the herbal medicine like *Withania somnifera* and *G. biloba consisted of the* neuroprotective and psychotropic properties. The study was a comparative analysis of the activities of the acute and chronic antidepressant with the sertraline in case of albino mice.

Methods: The study was conducted with total 32 male albino mice which were randomly allocated in 4 groups of n=8, vehicle control, sertraline (20 mg/kg), *G. biloba* (100 mg/kg), and *W. somnifera* (200 mg/kg). The activity of the Antidepressant used was investigated and analysed by the use of Forced Swim Test, Tail Suspension Test, and photoactometer which was followed by the acute and chronic 21-day treatment.

Result: During the acute treatment period, *W. somnifera* caused the minimum immobility in the Forced Swim Test (126.7 ± 45 seconds; p=0.028). In the chronic treatment regime, *G. biloba* showed the maximum immobility in the Tail Suspension Test (146 ± 27 seconds; p=0.005) and Forced Swim Test (82.4 ± 24 seconds; p=0.001), which was even greater than sertraline. The locomotion results indicated that the action of these drugs was not associated with increased.

Conclusion: The study concluded that *G. biloba showed the activity of* chronic antidepressant, while acute antidepressant effects have also been shown by *W. somnifera.*

Key-words: Depression, Withania somnifera, Ginkgo biloba, Sertraline, Forced Swim Test (FST)

INTRODUCTION

Major depressive disorder is one of the top causes of disability globally and represents an important public health issue with associated economic burdens and significant increases in overall disability-adjusted life years [1]. In the past, the treatment of depression has primarily focused on the classic monoamine hypothesis of depression where it has been theorized that the pathophysiology of depression is due to localized deficits in neurotransmission through the monoamine's serotonin, norepinephrine, and dopamine [2]. The current pharmacological agents prescribed for the treatment of depression primarily enhance the function of these monoamines: for instance, serotonin reuptake inhibitors (SSRIs) enhance the reuptake of serotonin; norepinephrine reuptake inhibitors (SNRIs) enhance the reuptakes of norepinephrine, etc [2].

Selective SSRIs are a highly effective treatment for depression and anxiety disorders with sertraline as their prototype first line agent but have significant limitations due to extended therapeutic delays (multi-week) and severe tolerability issues [3]. Specifically, early onset (<2 days) of common adverse effects includes acute nausea (1-day median onset), insomnia, and dizziness; however,

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while the incidence of metabolic weight gain starts at almost the same time as the experience of nausea, its typical time to emerge following start of treatment is ~31 days [3]. As another example of the long-time course associated with tolerability issues with this class of medications, treatment-emergent sexual dysfunction occurs at a typical time point of 16.5 days after starting SSRI treatment and results in a long-term prevalence of treatment-emergent sexual dysfunction of between 30% and 60% across all participants and an incidence in some clinical samples of >73% [3, 4].

Both *W. somnifera* and *G. biloba* are commonly found in phytotherapeutic treatments for both regulating neuropsychiatric pathways, as well as for assisting in the development of coping mechanisms against an individual's stressors [5-8]. *W. somnifera* (an Ayurvedic adaptogen), contains withanolides and sitoindosides, which are bioactive compounds that prevent stimulation of the hypothalamic-pituitary-adrenal axis (HPA) and thereby, modulate levels of plasma cortisol (CORT), adrenocorticotropic hormone (ACTH), and corticotropin-releasing hormone (CRH) [5,6]. These effects include prevention of the activity of the inflammatory mediators, nuclear factor-kappa B (NF-kB); stimulation of gamma-aminobutyric acid (GABA) and serotonin signaling; and stimulation of brain-derived neurotrophic factor (BDNF) and sirtuin 1 (SIRT1) with maintenance of mitochondrial respiration and synaptic plasticity in the brain [5,6]. Ginkgo biloba, in standardized extracts (e.g., EGb 761), has been shown to exert neuroprotection due to its high concentrations of terpenoid lactones and flavonoid antioxidants, with terpenoid lactones having neuroprotective properties and flavonoids having antioxidant properties that scavenge free radicals within the body [7,8]. *G. biloba* has also reversible inhibition of monoamine oxidase (MAO) and enhancement of blood flow to the brain via the reversible inhibition of platelets activating factor (PAF), and enhancement of levels of BDNF and nerve growth factor (NGF) within the brain. The combined overall effects of these compounds will therefore optimize the neurotransmissions of serotonin (5-HT) and dopamine (DA), as well as provide neuroprotection from neurodegenerative processes and ischemic injury [7,8].

MATERIALS AND METHODS

Research design- The study was an experimental animal study which was conducted as a randomized controlled design to evaluate the activity of the Acute and Chronic Antidepressants *W. somnifera* and *G. biloba* comparatively with the Sertraline, by the use of FST. Total 32 male mice of weight 20 to 25 g were taken and divided into 4 different groups, containing 8 mice in each group-Vehicle Control, Sertraline (20 mg/kg), *G. biloba* (100 mg/kg), and *W. somnifera* (200 mg/kg). The study was conducted under the CCSEA guidelines and ethical approval was taken from the Institutional Animal Ethics Committee (IAEC). Certain inclusion and exclusion criteria were selected for the study.

Inclusion criteria

- Healthy albino male mice of weight 20 to 25 kg were selected for the study.
- Those animals were acclimatized under certain laboratory conditions prior the study.
- All mixed were maintained with standard diet and was provided with ad libitum.
- Forced Swim Test (FST) and Tail Suspension Test (TST) were conducted for behavioural analysis of the animals.
- Mice were randomly allocated in both of the groups.

Exclusion criteria

- If any signs of illness, injury, infection, or abnormal behavioural pattern noticed was excluded.
- Diagnosed with severe adverse effects were excluded.
- Animal with impaired motor part or physical disabilities which can put hindrance to the analysis study by FST and TST were excluded.
- Those mice which did not complete the protocol of the study or did not receive the proper treatment regimen were excluded.

Procedure- All healthy mice of weight 20 to 25 gram were selected on the basis of the criteria, and all mice were randomly allocated into four different groups: Vehicle Control, Sertraline (20 mg/kg), *G. biloba* (100 mg/kg), and *W. somnifera* (200 mg/kg). All test treatments were administered orally. The study composed of 2 phases, Phase I as acute study is a single dose of study which was evaluated and the FST was

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conducted after 1 hour. This was followed by TST after 24 hours. In Phase II (chronic study), all treatments were administered for 21 days. At the end of the 21st day, all of the selected animals underwent the FST. This was followed by the TST after 24 hours. The photoactometer was used to assess the activity of locomotion at day 0 and day 21, which had excluded the impaired motor as a confounding factor. The duration of FST and TST was estimated as the primary outcome to measure the activity of antidepressants.

Statistical Analysis- Data entry was done in the Microsoft Excel and SPSS version 27 was used for analysis. Data were represented in the form of mean ± standard deviation (SD). Comparative analysis was done for the four different groups by the use of the one-way Analysis of Variance (ANOVA), which was followed by the post-hoc testing. Cohen's d and the 95% confidence intervals (CI) were calculated to estimate the effect size. The p-value of less than 0.05 was maintained for statistical analysis.

RESULTS

Table 1 showed that the vehicle group provides the highest mean value for the immobile duration, which indicated the high depressive-like behavioural pattern. Some of the treatment options like sertraline and *G. biloba* have provided reduction in the duration of immobility, rather than the control group. The groups which was treated with the *W. somnifera* showed the lowest value of duration of immobility, (126.7 ± 45 seconds), which represented the reduction specific to the control group. Highest effect size was noted (Cohen's d = -1.85), with the statistical significance (p = 0.028).

Table 1: Several treatments for the duration of immobility in the Forced Swim Test

Group	n	Mean Immobility (seconds)	SD	95% CI	Cohen's d vs Vehicle	p-value (vs Vehicle)
Vehicle (Control) (NS)	8	208.4	33	180–237	—	—
Sertraline (20 mg/kg)	8	181.6	40	148–215	-0.68	0.312
G. biloba (100 mg/kg)	8	189.8	36	160–220	-0.5	0.478
W. somnifera (200 mg/kg)	8	126.7	45	89–164	-1.85	0.028

Table 2 stated highest mean value of the duration of immobility was noted for the vehicle control group, which indicated the depressive-like behaviour. The treatment with Sertraline with the mean value of the duration of immobility was 198.7 seconds. *G. biloba* showed the reduced duration as 206.4 seconds. Lowest duration of immobility was noted in case of the *W. somnifera* group, which suggested the highest impact of antidepressant. The effect size was highest for the *W. somnifera* (Cohen's d = -0.74), and then the Sertraline and *G. biloba*.

Table 2: The comparative analysis of the Immobility Time in the tail suspension test among different Treatment Groups

Group	n	Mean Immobility (seconds)	SD	95% CI	Cohen's d vs Vehicle	p-value (vs Vehicle)
Vehicle (Control) (NS)	8	220.5	34	184–257	—	—
Sertraline (20 mg/kg)	8	198.7	40	156–241	-0.55	0.412
G. biloba (100 mg/kg)	8	206.4	37	167–246	-0.36	0.598
W. somnifera (200 mg/kg)	8	188.9	43	143–235	-0.74	0.221

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Table 3 stated that the vehicle control group had showed the highest mean value of the immobility time, which indicated high depressive-like behavioural pattern. All of the groups of treatment had showed reduction in the duration of immobility rather than the control group. *G. biloba* resulted in highest reduction (146 ± 27 seconds), and also large effect size with significant improvement. Sertraline and the *W. somnifera* showed reduction in the duration of immobility, with the p-value of 0.018 and 0.047. *G. biloba* resulted to produce the highest antidepressant like impact.

Table 3: The impact of the Sertraline, *G. biloba*, and *W. somnifera* on the duration of immobility in TST-Phase Two

Group	n	Mean Immobility (seconds)	SD	95% CI	Cohen's d vs Vehicle	p-value
Vehicle (Control) (NS)	8	228	29	198–258	—	—
Sertraline (20 mg/kg)	8	171	32	138–204	-1.84	0.018*
G. biloba (100 mg/kg)	8	146	27	118–174	-3.02	0.005**
W. somnifera (200 mg/kg)	8	191	35	154–228	-1.15	0.047*

Table 4 stated that the highest mean time was for the vehicle control group, with 223.5 ± 31 seconds. All treatments were administered, which showed reduction in the duration of immobility compared with the control group. *G. biloba* showed reduction, which revealed the highest effect size and strong statistical significance. Sertraline showed the reduction in the duration of immobility, while the *W. somnifera* showed the moderate reduction. These result findings indicated that the most potent and effective antidepressant-like effect like Ginkgo biloba, which was followed by the 21 days of treatment.

Table 4: FST outcome at the time of Phase II Following Chronic 21-Day Treatment

Group	n	Mean Immobility (seconds)	SD	95% CI	Cohen's d vs Vehicle	p-value
Vehicle (Control) (NS)	8	223.5	31	190–257	—	—
Sertraline (20 mg/kg)	8	125.8	28	96–156	-3.05	0.003**
G. biloba (100 mg/kg)	8	82.4	24	57–108	-4.76	0.001**
W. somnifera (200 mg/kg)	8	151.3	33	116–187	-2.15	0.041*

Table 5 stated that the highest activity of crossing was in case of phase 1 was noted in the Sertraline group with 195 crossings, which was followed by the149 crossings of *W. somnifera* and 136 crossings of Ginkgo biloba. Contrastingly, the vehicle group showed the lowest activity in phase 1, with 112 crossings. The activity of crossing reduced during the phase 2, and highest value of about 136 crossings were noted for the vehicle group. *G. biloba* (106 crossings) showed the highest activity in phase 2, which was followed by the *W. somnifera* (105 crossings).

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Table 5: Evaluation of the Phototactometer for the crissing activity during both of phases

Group	Phase 1 (Day 20) Mean No. of Crossings	Phase 2 (Day 21) Mean No. of Crossings
Vehicle	112	136
Sertraline	195	98
Ginkgo biloba	136	106
W. somnifera	149	105

DISCUSSION

Studies show that root extracts of *W. somnifera* containing withanolide A protect brains from damage due to stress [9,10]. A study of HT-22 human neural cells demonstrated that withanolide A-containing extracts (100 ug/mL and 200 ug/mL) protect against stress-induced cellular damage by reducing oxidative damage, as demonstrated by decreases in indicators such as oxidized monoamines, total oxidative stress, and madonialdehyde and increasing levels of BDNF, TrkB and p-AKT, as well as HO-1 transcript expression [9]. For both mice and rats subjected to chronic unpredictable stress, daily doses of the extract from 27 mg/kg up to 108 mg/kg have been shown to reverse behaviors related to despair, restore the ability to move freely in an open area, and restore their preference for sweet substances such as sucrose [9,10]. This extract also reduced HPA (hypothalamic pituitary adrenal) axis activity by decreasing systemic CRH, ACTH, and corticosterone levels, as well as increasing serotonin levels, and reducing neuro-inflammatory markers (e.g., IL-6, IL-1β, and TNF-α) [9,10].

Clinical data regarding the efficacy of *W. somnifera* (WS) for depression suggests it produces acute and short-term antidepressant-like effects; however, the number of recently published studies comparing WS to sertraline (an SSRI) in a head-to-head fashion is limited [11,12]. For example, in a 6-week randomized trial, patients taking 1 g/day of WS (co-administered with their current SSRIs) experienced a decrease in Hamilton Anxiety Rating Scale (HARS) scores of 14 points compared to 8 points for the placebo group ($p < 0.05$) [11]. The 2025 meta-analysis of 14 RCTs revealed WS to have substantial improvements compared to placebo for depression (SMD = -1.28; 95% CI -2.40 to -0.16) and anxiety (SMD = -1.13; 95% CI 1.65 to 0.60) [12]. These cumulative data suggests that WS provides a statistically significant therapeutic effect for the treatment of both depression and anxiety overall despite considerable heterogeneity [11,12].

Studies assessing the efficacy of *G. biloba* as an antidepressive drug have yielded little evidence to support Ginkgo as a standalone antidepressant. Yet little research has been published about the efficacy of Ginkgo in comparison with sertraline (Zoloft). According to a multi-centre study published in 2024 with 72 subjects with comorbid stable major depressive disorder taking adjunct Ginkgo to their usual antidepressants showed significant post-treatment reductions in their Hamilton Scores (p-value < 0.05) but no significant difference between Ginkgo and placebo when using an analysis of variance (ANOVA) [13,14]. Although only short-term data is currently available for the safety of Ginkgo, there are no published direct comparisons with the established SSRIs [13,14].

Research has shown that the herb *W. somnifera* (ashwagandha) and the *G. biloba* tree may provide an alternative means of managing depression in response to chronic stress. In animal models of stress, *W. somnifera* has been found to significantly reduce the effects of stress-related hormonal activity, while *G. biloba* promotes positive neurologic changes affecting metabolism and decreases the activity of oxidative pathways. However, while the evidence is encouraging and suggests positive effects of the herbs on the brain, all of the evidence to date has come from studies using rodents, so clinical benefit to humans or the equivalence to human antidepressant medications like sertraline remains uncertain. Therefore, these herbal treatments should be viewed as potentially useful adjuncts to standard antidepressant therapy, but not as a substitute.

CONCLUSIONS

The study concluded that the *W. somnifera* and *G. biloba* had antidepressant-like effects relative to the control vehicle group of albino mice. For the acute phase, the best antidepressant-like effect of *W. somnifera* was observed by the most substantial reduction of immobility time in the Forced Swim Test (126.7 ± 45 seconds) as

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well as a strong effect size (Cohen's d = -1.85; p = 0.028). For the Tail Suspension Test within the acute phase, all treatment groups revealed reductions of immobility time compared with the control but without significance. After 21 days of chronic administration, both interventions of the herbs displayed a better antidepressant effect. The best antidepressant effect was seen by the use of *G. biloba* since it showed a significant reduction of immobility time in both tests, the Tail Suspension Test (146 ± 27 seconds; p = 0.005) and Forced Swim Test (82.4 ± 24 seconds; p = 0.001) better than the sertraline standard drug.

CONTRIBUTION OF AUTHORS

Research concept- Avijit Ganguly
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Supervision- Avijit Ganguly, Purnendu Mandal
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