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Indian Journal of Pharmacy and Pharmacology

Journal homepage: https://www.ijpp.org.in/

Original Research Article

Antidepressant potential of *Withania somnifera* and *Ginkgo biloba*, sertraline: An experimental study in male albino mice

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Abstract

Background: Sertraline, a selective serotonin reuptake inhibitor (SSRI), serves as the first-line drug in the treatment of major depressive disorder and post-traumatic stress disorder. *Withania somnifera* and *Ginkgo biloba* have demonstrated antidepressant properties in animal studies, but no comparative studies exist in human/animal models against standard antidepressants like sertraline.

Materials and Methods: Following Institutional Animal Ethical Committee (IAEC) approval, the study evaluated antidepressant effects in albino mice across two phases using forced swim test (FST) and tail suspension test (TST). In phase I, single-dose effects (*Withania somnifera* 200mg/kg, *Ginkgo biloba* 100mg/kg, and Sertraline 20mg/kg) were tested 1 hour post administration. Phase II, tested effects after 21 days of daily dosing

Results: In phase I, there was no statistically significant difference between the groups in TST. FST showed a statistically significant reduction for the *Withania somnifera* vs vehicle (*P=0.04*).

In phase II, TST showed significant differences vs vehicle: (*Ginkgo biloba* P= 0.003, Sertraline P = 0.014 and *Withania somnifera* P = 0.043 (ANOVA with post hoc Tukeys test). FST showed significance vs vehicle (*Ginkgo biloba P = 0.001*, Sertraline P = 0.002 *Withania somnifera* P = 0.046) There was also a significant difference between *Ginkgo* and *Withania* (*P=0.008*).

Conclusion: *Withania somnifera* (200mg/kg) and *Ginkgo biloba* (100mg/kg) show antidepressant effect similar to Sertraline in mice, supporting their potential as adjunctive therapies.

Keywords: Selective Serotonin Reuptake Inhibitors, Sertraline, Ginkgo biloba, Withania somnifera, Antidepressive Agents

Received: 13-01-2026; **Accepted:** 22-01-2026; **Available Online**: 13-04-2026

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1. Introduction

Depression is one of the most prevalent and incapacitating psychiatric disorders globally. A study by Santomauro et al estimates that major depression caused 49.4 million DALYs in 2020.[1] The existing drugs for the treatment have several side effects, including anticholinergic side effects, sedation, weight gain, postural hypotension, nausea, loose stools, and sexual distress.[2] Rates of remission and response are also low. Relapse is a common problem faced in the treatment of depression. Hence, there is a need for safer, more effective treatment options. *Withania somnifera*, also known as Ashwagandha, is an herb commonly used by traditional medicine practitioners in India. Studies have shown it possesses anti-inflammatory, antioxidant, anti-stress, and adaptogenic properties.[3]

Ginkgo biloba, also known as the maidenhair tree, is the last living species of the order Ginkgoales. The extracts of Ginkgo leaves are known to be effective as nootropics or memory enhancers. Ginkgo contains flavonoid glycosides and terpene lactones, which have antioxidant and neuroprotective properties.[4]

Sertraline is a selective serotonin reuptake inhibitor (SSRI). It is the first-line drug in the treatment of major depressive disorder and post-traumatic stress disorder.

No human/animal studies have been done to compare the antidepressant effects of *Withania somnifera*, *Ginkgo biloba*, and Sertraline. Hence, this study was conducted to confirm the antidepressant effects of *Withania somnifera* and *Ginkgo biloba* and to compare them with the first-line antidepressant, Sertraline.

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https://doi.org/10.18231/j.ijpp.15273.1771667369
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2. Aim

To evaluate and compare the antidepressant effects of *Withania somnifera* (200mg/kg), Ginkgo biloba (100mg/kg), and sertraline (20mg/kg) in male albino mice using forced swim test (FST) and tail suspension test (TST) with acute (single-dose) and chronic (21-day dosing).

3. Objectives

1. To assess the duration of immobility in FST and TST following single dose administration.
2. To evaluate the same parameters after daily dosing for 21 days.
3. To compare the antidepressant effects of *Withania somnifera*, Ginkgo biloba, and Sertraline with each other and with placebo in male albino mice.

4. Materials and Methods

Approval from the Institutional Animal Ethics Committee (IAEC) was obtained vide letter number IAEC/AFMC/06/2022 prior to the commencement of the study. The study was conducted in accordance with the Committee for Control and Supervision of Experiments on Animals (CCSEA) guidelines.

4.1. Animals

The study was carried out in male albino mice weighing 20-25g, fed with a standard diet and water. The animals were acclimatised to the laboratory conditions for two hrs before testing. Experiments were conducted between 0900 and 1200 hours. Food and water were removed for the duration of the test. Considering the principle of reduction in the number of animals used as per CPCSEA guidelines, six mice were used in each group. The dose was calculated using the simple practice guide for dose conversion between animals and humans.[5]

The sample size for this study was determined based on both CCSEA reduction principles and published meta-analyses of forced swim test (FST) effect sizes in rodent antidepressant studies. Given the CCSEA principle of "replacement, reduction, refinement" (3Rs), and the fact that we were testing herbal compounds and not an entirely novel class, Cohen's d = 1.0-1.5 was chosen with alpha (α) of 0.05 and beta (β) of 0.20). A total of 24 Albino mice were used. They were divided into four groups of six animals each. Using one way ANOVA with G* Power 3.1 software, effect size f was 0.38, corresponding to Cohen's d of 1.0.

1. Group One: was administered distilled water (Control)
2. Group Two: was administered 20mg/kg Sertraline orally (Standard)
3. Group Three: was administered 100mg/kg of *Ginkgo biloba* orally
4. Group Four: was administered 200mg/kg of *Withania somnifera* orally

With $\alpha = 0.05$ and $\beta = 0.20$ and 4 groups with 6 per group, statistical power of 78% for detecting f+0.38 (moderate to large effect). Animals were weighed individually, and the respective drugs were administered orally to different groups. The study was carried out in two phases. For Withania somnifera, commercial brand Carmel Organics® Ashwagandha root powder (USDA certified) manufactured by Carmel Organics, Madhya Pradesh, India, was used. For Ginkgo, commercial VitaWin® Ginkgo biloba powder manufactured by VitaWin Nutraceutical products, India, was used.

1. **Phase One** was conducted after administering a single dose of the drug. One hour after the drug administration, the mice were subjected to the forced swim test (FST) and the duration of immobility was recorded.

   After 24 hours, the mice were subjected to the tail suspension test (TST) and the duration of immobility was recorded.

2. **Phase Two** involved daily administration of the drugs for 21 days to the respective groups. On day 21, the mice were subjected to the forced swim test (FST) again, and the duration of immobility was recorded. After 24 hours, the mice were subjected to the tail suspension test (TST) and the duration of immobility was recorded.

4.2. Tests used for studying antidepressant activity

There are several animal models for testing the antidepressant activity of a given drug. The following two well-validated tests were used to measure the antidepressant activity in our study.

1. **Forced swim test (FST)[6]:** In this test, mice were forced to swim, one at a time, in a glass cylinder measuring 25cm in height and 12cm in diameter, containing water at room temperature to a depth of 15cm. The duration of immobility was recorded for each animal for four minutes after excluding the first two minutes of a six minute period. The mouse was considered immobile when it remained floating in the water without struggling, making only minimal movements of its limbs necessary to keep its head above water. This behaviour reflects a state of despair. Agents effective in depression decrease the duration of immobility. After six minutes, the mouse was taken out and dried with a towel. The water was changed after each test because urine and the other chemicals released by the first mouse would affect the swimming pattern of the next mouse.[7]
2. **Tail suspension test (TST)[6]:** In this test, mice were suspended upside down, one at a time, on a metal rod at a height of 75 cm from the ground with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. The total duration of immobility was noted during the last four minutes of a six minute

period. The mice were considered immobile when they did not show any movement of the body and hung passively.

To ensure that the alteration in immobility is not due to an effect on motor activity, each mouse was assessed for locomotor activity using a photoactometer on day zero and day 21. The animals were placed individually in the photoactometer, and their locomotor activity was recorded for six minutes after a two-minute acclimatisation period.

5. Results

The results of phases one and two are summarised in **Table 1**-**Table 4**.

Table 1: Forced swim test (FST) Phase One results (single dose administration)

Group	n	Mean Immobility (seconds)	SD	95% CI	Cohen's d vs Vehicle	p-value (vs Vehicle)
Vehicle (Control) (NS)	6	205.2	35	163–248	—	—
Sertraline (20 mg/kg)	6	184.8	43	133–237	−0.51	0.421
Ginkgo biloba (100 mg/kg)	6	195	38	148–282	−0.28	0.687
Withania somnifera (200 mg/kg)	6	129	49	67–191	−1.79	0.040*

* p < 0.05 SD-standard deviation, NS-normal saline, CI-confidence interval

Table 2: Tail suspension test (TST) Phase One results (single dose administration)

Group	n	Mean Immobility (seconds)	SD	95% CI	Cohen's d vs Vehicle	p-value (vs Vehicle)
Vehicle (Control) (NS)	6	218	35	178–258	—	—
Sertraline (20 mg/kg)	6	201	42	153–249	−0.43	0.487
Ginkgo biloba (100 mg/kg)	6	210	38	167–253	−0.22	0.726
Withania somnifera (200 mg/kg)	6	192	45	140–244	−0.61	0.298

SD-Standard Deviation, NS-Normal Saline, CI-confidence interval

Table 3: Tail suspension Test (TST) – Phase Two (chronic dose- 21 day administration)

Group	n	Mean Immobility (seconds)	SD	95% CI	Cohen's d vs Vehicle	p-value
Vehicle (Control) (NS)	6	226	28	197–255	—	—
Sertraline (20 mg/kg)	6	168	31	136–200	−1.92	0.014*
Ginkgo biloba (100 mg/kg)	6	142	25	116–168	−3.16	0.003**
Withania somnifera (200 mg/kg)	6	188	34	151–225	−1.21	0.043*

* p < 0.05, ** p<0.01 SD-Standard deviation, NS-normal saline, CI-confidence interval

Table 4: FST results phase two (chronic dose- 21 day administration)

Group	n	Mean Immobility (seconds)	SD	95% CI	Cohen's d vs Vehicle	p-value
Vehicle (Control) (NS)	6	220.8	32	182-260	—	—
Sertraline (20 mg/kg)	6	121.2	29	89-154	−3.18	0.002**
Ginkgo biloba (100 mg/kg)	6	78	25	55-107	−4.92	0.001**
Withania somnifera (200 mg/kg)	6	147	34	105-189	−2.22	0.046*

* p < 0.05, ** p<0.01SD-standard deviation, NS-normal saline, CI-confidence interval,

All results are expressed as mean ± standard deviation (SD). A p-value less than 0.05 is considered statistically significant.

5.1. Phase one

The p-value corresponding to the F statistic of the one-way analysis of variance (ANOVA) test is greater than 0.05 for TST. In FST, the p-value corresponding to the F statistic of a one-way analysis of variance (ANOVA) test is less than 0.05. Post hoc analysis with Tukey's test shows a statistically significant difference between group 1 (vehicle) and group 4 (*Withania somnifera*) (p = 0.04). The rest of the groups showed no significant difference.

5.2. Phase two

In TST, the p-value corresponding to the F statistic of one-way analysis of variance (ANOVA) test is less than 0.05 (P=0.003). In FST, the p-value corresponding to the F statistic of one-way analysis of variance (ANOVA) test is less than 0.05 (P=0.002).

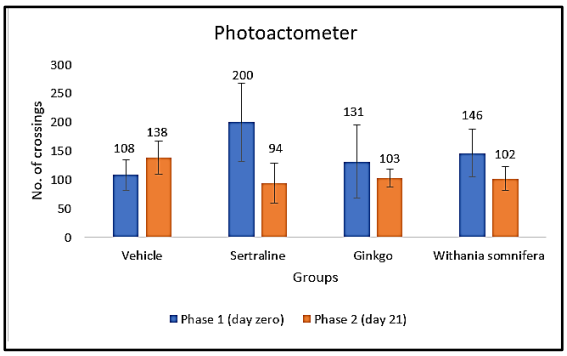

Figure 1: Graph depicting the mean number of crossings during Phase 1 and Phase 2. Values have been expressed as mean ± standard deviation (SD). * p < 0.05, # p<0.01

6. Discussion

No studies have been done comparing the effects of *Withania somnifera*, *Ginkgo biloba*, and Sertraline with each other. In our study, the effects of these compounds were tested after daily administration for a period of 21 days using the standard tests for screening antidepressant activity. This study is the first to directly compare the antidepressant effects of *Withania somnifera* and *Ginkgo biloba* with Sertraline in a systematic two phase design with acute and chronic dosing paradigms. The findings reveal a critical temporal distinction in antidepressant efficacy- acute single-dose administration produces minimal effects across all three compounds, whereas 21 days of daily treatment results in robust antidepressant effects for all three compounds, with notable differences in magnitude.

It is documented in humans that Sertraline and other SSRIs require continuous administration before the therapeutic antidepressant effect becomes clinically apparent, despite achieving peak plasma concentrations and receptor occupancy.[8] Our phase one results are consistent with the actual clinical scenario.

Post hoc analysis with Tukey's test shows a statistically significant difference between group one (vehicle) and group three (*Ginkgo biloba*) (p = 0.003), group one (vehicle) and group two (Sertraline) (p = 0.014), and between group one (vehicle) and group four (*Withania somnifera*) (p = 0.043). Similarly, for FST, post hoc analysis with Tukey's test shows a statistically significant difference between group 1 (vehicle) and group 3 (*Ginkgo biloba*) (p = 0.001), group 1 (vehicle) and group 2 (Sertraline) (*P = 0.002*) and between group 1 (vehicle) and group 4 (*Withania somnifera*) (*P = 0.046*). There is also a statistically significant difference between groups 3 and 4 (*P=0.008*).

Withania somnifera showed a statistically significant FST effect in Phase One (Cohen's d = -1.79, *P= 0.040*) but negligible TST effect. Both *Withania somnifera and Ginkgo biloba* showed significant improvement in Phase two. This pattern is consistent with the concept of bioaccumulation, time-dependent receptor sensitization and pathway activation. Herbal compounds, particularly withanolides in *Withania somnifera*, have relatively long half-lives (18-27 hrs). Plasma concentration of the same accumulates with daily dosing, reaching steady state by 5 to 7 days. We hypothesize that by day 21 of the study, steady state bioaccumulation may be allowing higher tissue concentration and possible downstream adaptive changes from persistent engagement with molecular targets, BDNF upregulation, inhibition of monoamine oxidase, and upregulation of serotonin synthesis. These mechanisms need biochemical studies for confirmation. The anti-neuroinflammatory effect also possibly requires weeks to take effect. Herbal extracts, in comparison to single-molecule drugs, contain several active compounds. Bioactive compounds may be subject to extensive first pass metabolism with higher doses saturating these pathways. The cumulative effect on multiple pathways may be another reason why chronic exposure is required for significant antidepressant effects.

Chronic Ginkgo biloba administration produced significantly greater reduction in immobility compared to *Withania somnifera* in both FST (*P= 0.008* and Cohen's d= 2.07) and TST (*P=0.087*). This could be due to better intestinal absorption of *Ginkgo* compared to *Withania* and higher bioavailability. Further studies with larger samples are necessary to further understand the possible reason for this difference in results.

There is no statistically significant difference between the groups in locomotor activity using the photoactometer, in both phases one and two, as depicted in **Figure 1**.

Withania somnifera, or winter cherry, is a shrub belonging to the *Solanaceae* family of plants. It is widely used in traditional medicine systems such as Ayurveda for its anti-anxiety properties and is considered a nervine tonic. Research has suggested that this plant has potent adaptogenic and antioxidant properties, which could play a role in preventing free radical damage. Biologically active components which have been identified in *Withania somnifera* include saponins, anahygrine, cuseohygrine, acylsterylglucosides, isopelletierine and sitoindosides. Acylsterylglucosides, sitoindosides and withaferin have shown statistically significant anti-stress activity in acute forms of experimental stress.[9]

Apart from action on serotonergic transmission, other mechanisms which may be responsible for the antidepressant action of *Withania somnifera* include an increase in expression of trophic factors such as brain-derived neurotrophic factor (BDNF), a decrease in nitric oxide levels by inhibition of Nitric oxide synthase (NOS), N-methyl-D-aspartate (NMDA) antagonism, inhibition of pro-inflammatory cytokines and inhibition of indoleamine-2,3 dioxygenase.[10] Lopresti et al suggested that the stress-

relieving activity of *Withania somnifera* may be attributed to the modulation of the hypothalamic-pituitary-adrenal (HPA).[11] The HPA axis plays an important role in the regulation of stress responses in the body. It is a complex neuroendocrine system involving, as the name suggests, interaction between the hypothalamus, pituitary gland, and adrenal glands. A study by Juruena et al has suggested the role of dysregulation of the HPA axis in depression.[12] Dysregulation may be hyperactivity or hypoactivity of the HPA axis, depending on the type of depression, but some common findings are increased levels of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. The normal response to stress in the human body is the release of CRH from the hypothalamus, which stimulates the release of ACTH from the pituitary, which in turn triggers the release of cortisol from the adrenal glands. Prolonged exposure to high levels of cortisol can impair the functioning of the prefrontal cortex and hippocampus, thus affecting mood regulation. This can lead to the typical symptoms of depression, such as low mood and anhedonia. On the other hand, hypoactivity of the HPA axis can lead to a blunted response to stress and may be associated with atypical depression.

EGb761, an extract of *Ginkgo biloba* leaves, is being used in some countries for the treatment of cerebrovascular insufficiency and dementia.[13] It contains several bioactive compounds, including flavonoid glycosides such as quercetin, isorhamnetin, and terpene lactones such as ginkgolides. These compounds have significant antioxidant action. Studies have suggested that they are neuroprotective due to their antioxidant action.[14] Serotonin plays a crucial role in mood regulation. Studies by Chimakurthy et al and Machado et al have suggested that Ginkgo biloba may have a role in serotonin, dopamine and norepinephrine neurotransmission.[15,16] Chronic inflammation is one of the factors that is believed to contribute to the development of depression. Ginkgo has also been shown to possess anti-inflammatory properties by inhibiting the release of pro-inflammatory cytokines.[17] Studies have shown that depression may be associated with reduced blood flow to certain regions of the brain. Ginkgo has been shown to improve blood flow to the brain, potentially alleviating symptoms of depression.[18]

A study conducted at JSS Medical College, Mysore, by Jayanthi et al used mice to compare the fat extract of *Withania somnifera* at two doses (20mg/kg and 40mg/kg) with imipramine (15mg/kg) in acute and chronic studies (7 days).[19] The chronic study with both doses of *Withania somnifera* showed statistical significance when compared to Imipramine, and in the acute study, only the combination of *Withania somnifera* with Imipramine showed statistical significance in FST. With TST, the results were similar for the chronic study, but none of the groups showed statistically significant results in the acute study. The higher dose and longer chronic period in our study may explain more robust effects. The fat extract preparation in Jayanthi et al. may have different bioavailability than the root powder prepared in our study.

A study conducted in Iran by Atari et al, compared two doses of *Withania somnifera* (WS) (200mg/kg and 400mg/kg) i.p with Fluoxetine i.p (20mg/kg) to check for the involvement of nitric oxide using FST, TST, and open field tests.[20] The results showed statistical significance between WS and saline, but not with Sertraline in FST and TST. There were no significant results in the open field test. There was found to be no effect on antidepressant activity from blocking the action of nitric oxide.

Another study compared by Rojas et al, *Ginkgo biloba* (5mg/kg, 10mg/kg and 20mg/kg) i.p to Sertraline i.p injections for 17 days using FST and evaluated the role of oxidative stress.[21] Their results suggested that the effect against oxidative stress may have some role in the neuroprotective effect of Ginkgo. The effect of a 5mg/kg dose was similar to the effect of Imipramine on FST. The dose and route used in our study is different from (oral vs i.p injection).

6.1. Strengths of this study

The study was conducted in two phases, acute and chronic, to strengthen the findings. Two well-established behavioural models were used to increase the validity. Locomotor activity was tested to ensure no confounding effect on the motor function of the test animals.

6.2. Limitations of the study

The study used commercially available powders. Phytochemical standardization was not performed, and the contents were not verified for active compounds. There may be variability in active compound content between batches, and this may limit reproducibility. The study does not include biochemical markers. Hence, the exact mechanism of action of these compounds cannot be ascertained from this study. The sample size chosen was adequate to detect moderate to large effects consistent with FST and TST literature. While the effect sizes achieved (Cohen's d = −2.22 for FST, −1.21 for TST) are consistent with the FST literature norms for effective antidepressants (d = 1.5–2.5), the statistical power is 78%, which is slightly lower than the ideal 80-90%. This may potentially limit the detection of smaller effects (Cohen's d< 0.8). The smaller number was chosen in consideration of the CCSEA principle of reduction, but warrants confirmation in larger cohorts of n= 12 to 15/group.

7. Conclusion

In this study, *Withania somnifera* (200 mg/kg) and Ginkgo biloba (100 mg/kg) demonstrated antidepressant effects similar to Sertraline (20 mg/kg) after 21 days of daily oral

administration in male albino mice, as assessed by forced swim test and tail suspension test.

Ginkgo biloba produced significantly greater reduction in depression-like behaviour (45% reduction in FST immobility) compared to Withania somnifera ($p = 0.008$). The acute antidepressant effects of these compounds were minimal or absent, consistent with the delayed therapeutic onset typical of SSRIs and highlighting the importance of chronic administration for antidepressant efficacy. Further studies that measure relevant biomarkers, such as brain BDNF, plasma cortisol/ACTH for HPA axis status, oxidative stress markers, pro-inflammatory cytokines and monoamine levels at the hippocampus and prefrontal cortex, would help establish which mechanisms account for the observed effects. The findings of phase two must be confirmed with a larger sample (n=12 to 15) to achieve 95% power to detect a Cohen's d of 0.8. Studies may be conducted with female mice to compare the effects between genders.

8. Source of Funding

None.

9. Conflict of Interest

None.

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Cite this article: Shyam S, Dahiya N, Dev D, Sunny S. Antidepressant potential of *Withania somnifera* and Ginkgo biloba, and Sertraline: An experimental study in male albino mice. *Indian J Pharma Pharmacol.* 2026;13(1): 11-16.