

Synergistic Antidepressant Effect of *Ginkgo biloba* and *Withania somnifera* Using Experimental Animals

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ABSTRACT

Aim: This study involved the antidepressant activity of *Ginkgo biloba* and *Withania somnifera* in mice. Depressive disorder is a prevalent psychiatric Condition, affecting 21% of the global population. The currently used drugs can impose a variety of side-effects including cardiac toxicity, hypotension, sexual dysfunction, weight gain and sleep disturbances. In the last decade, there has been growing interest in the therapeutic effects of natural products on mental disorders. *Ginkgo biloba* and *Withania somnifera* were investigated for their antidepressant activity. **Materials and Methods:** Antidepressant activity was investigated by using Open Field Test (OFT) and Tail Suspension Test (TST) models. Imipramine was used as reference standards. **Results and Conclusion:** Our study observed that both the *Ginkgo biloba* and *Withania somnifera* significantly reduced immobility in the tail suspension test and the open field test model of depression, comparable to Imipramine. However, further studies are needed to understand the mechanism of action and identify the active components responsible for the antidepressant-like activity.

Keywords: *Ginkgo biloba*, *Withania somnifera*, Imipramine, Antidepressant.

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INTRODUCTION

Depression is a frequent mental disorder, characterized by the presence of sadness, loss of interest or pleasure, feelings of guilt or lack of self-esteem, sleep or appetite disorders, feeling tired and lack of concentration (Leh and Lee, 2022). Depression is the leading cause of disability and is a major contributor to the disease burden worldwide (Lee *et al.*, 2020). The lifetime prevalence of depression ranges from 20% to 25% in women and 7 to 12% in men (Razzak *et al.*, 2019). Medications such as Tricyclic Antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs), selective Reversible Inhibitors of Monoamine oxidase A (RIMAs) and specific Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs) are clinically employed for drug therapy. However, these drugs can impose a variety of side-effects including cardiac toxicity, sexual dysfunction, body weight gain and sleep disorder (Wang *et al.*, 2017; Anacker and Hen, 2017; Jain, 2015; Patel and Sharma, 2014). Imipramine prevents reuptake of nor adrenaline and serotonin resulting in their increased availability in the synapse and therefore an increase in adrenergic

and serotonergic neurotransmission (Chandrasekhar *et al.*, 2012). Herbal treatments for depression have gained attention as complementary or alternative approaches to conventional treatments. *Ginkgo biloba* is one of the most commonly used herbal supplements used in the world. The name "Ginkgo" is derived from a Japanese word, while the term "biloba" refers to the characteristic two-lobed shape of its leaves. It has been used to treat various conditions, including cognitive decline, memory loss and circulatory disorders (Baldwin *et al.*, 2006; Sakakibara *et al.*, 2006). *Ginkgo biloba* is believed to exert its potential antidepressant effects through various mechanisms, including antioxidant and anti-inflammatory properties, modulation of neurotransmitter activity and improvement of cerebral blood flow. *Withania somnifera* is an herb commonly used in traditional Ayurvedic medicine, primarily known for its adaptogenic properties, which help the body cope with stress and promote overall well-being. While research on *Withania somnifera* effects on depression is still emerging, some studies suggest that it may have potential as a natural remedy for alleviating depressive symptoms (Park *et al.*, 2005).

The purpose of this study was to evaluate the synergistic antidepressant effect of *Ginkgo biloba* and *Withania somnifera* using behavioural animal models and by estimating biochemical parameters.



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MATERIALS AND METHODS

Drugs and chemicals

Ginkgo biloba and *Withania somnifera* was purchased from Heilen Biopharm, Ahmedabad India. Imipramine was purchased from Modern Pharmaceuticals, Mumbai. All other chemicals are used in the study were of analytical grade.

Experimental Animals

Male albino mice (20-25 g) were purchased from Lacsmi Biofarms, Pune, India. Animals were kept in cage at a normal laboratory temperature. The animals were maintained according to the CPCSEA guidelines for the use and care of experimental animal. The Institutional Animal Ethical Committee (IAEC) approved the protocol of this study.

Experimental Design

Animals were divided into six different groups each group contain six animals. Group I: Served as control and received distilled water. Group II: Mice received standard imipramine (10 mg/kg/ i.p) for 14 days. Group III: Mice received *Ginkgo biloba* (50 mg/kg/ p.o.) for 14 days. Group IV: Mice received *Withania somnifera* (100 mg/kg/p.o.) for 14 days. Group V: Mice received *Ginkgo biloba* (50 mg/kg/p.o.) and *Withania somnifera* (100 mg/kg/p.o.) for 14 days.

In preclinical studies, a sample size of six animals per group is commonly used due to historical practices and resource limitations. Research suggests that this size is often sufficient to detect moderate to large effects in behavioral models, though larger sample sizes or power analyses may be needed in future studies for greater robustness. Generally, a sample size of 6 to 10 animals can reliably achieve statistical significance for moderate to large effect sizes, particularly in antidepressant activity evaluations. Using six animals also aligns with the ethical principle of minimizing animal use while enabling meaningful data collection (Gupta *et al.*, 2015; Sharma *et al.*, 2017; Govindappa *et al.*, 2019). The animals were randomly assigned to six treatment groups to ensure unbiased distribution across the various interventions. This randomization helps eliminate selection bias and ensures that differences observed in the outcomes can be attributed to the treatments rather than pre-existing differences among the animals

Understanding the pathogenesis of altered mood, impaired concentration and neuro-vegetative symptoms in major depression has largely relied on animal models. However, creating valid models for human depression is challenging due to its complex nature. Current models combine ethologically valid behavioural assays with advanced molecular biology and automated video-tracking. Popular models include acute stress tests (e.g., forced swim test), prolonged stress models (e.g., social defeat), secondary depression models, genetic models and

experiments on antidepressant mechanisms. These paradigms are evaluated for their ease, validity, replicability, molecular insights and potential to develop new depression therapies.

Estimation of general Parameters

Body weight, water consumption and feed intake were recorded at the conclusion of the treatment period.

Assessment of behavioural Parameters

Open Field Test Apparatus

Male albino mice weighing about 20-25 g were used. The animals were then administered their respective treatment 30 min before the study. Each animal was placed individually in one corner square of the open field and observed for 5 min. The parameters noted were ambulation (number of squares crossed), rearing (number of times the animals stood on their rear paws) and grooming (number of times grooming occurred) (Antai-Otong, 2004).

Tail Suspension Test Apparatus

Treatment was administered 60 min prior to the study, as described by the study design. Mice were suspended at the edge of the table, 50 cm above the floor, using adhesive tape placed approximately 1 cm from the tip of the tail. The total duration of immobility induced by tail suspension was recorded during a 6-min period within a 10-min observation window. An animal was considered immobile when it showed no body movement, hung passively and remained completely motionless (Trick *et al.*, 2004).

Estimation of Biochemical Parameters in serum

Using a glass capillary, blood was extracted from the retro orbital plexus and a high-speed centrifuge was used to separate the serum. Serum was used to measure the amount of Glucose, Total Cholesterol, Triglycerides and Corticosterone levels on a biochemistry analyser (Rai *et al.*, 2003).

Statistical analysis

The results are given as Mean±SEM ($n=6$). ANOVA was used for analysis and then the Bonferroni test was applied. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared to negative control group. ^a $p<0.05$, ^{aa} $p<0.01$, ^{aaa} $p<0.001$, they showed relation with combination group and imipramine. ^b $p<0.05$, ^{bb} $p<0.01$, ^{bbb} $p<0.001$ they showed relation with combination group and *Ginkgo biloba*. ^c $p<0.05$, ^{cc} $p<0.01$, ^{ccc} $p<0.001$ they showed relation with combination group and *Withania somnifera*.

This study employs a one-way ANOVA (Analysis of Variance) to compare the means of six different animal groups based on a single independent variable: the treatment received (control, imipramine, *Ginkgo biloba*, *Withania somnifera*, or their combination). The dependent variable is the measure of behavioral

or physiological response to these treatments. A one-way ANOVA will identify any statistically significant differences in outcomes compared to the control group.

The Bonferroni test was utilized in the study to conduct multiple comparisons among the treatment groups. It assessed whether significant differences existed between each treatment group (imipramine, *Ginkgo biloba*, *Withania somnifera* and the combination group) and the negative control group that received distilled water. Additionally, it evaluated relationships between the combination group and the individual treatments: imipramine, *Ginkgo biloba* and *Withania somnifera*. This approach helped control for errors during the analysis.

RESULTS

Estimation of General Parameters

Following the treatment period, each group's body weight, food consumption and water intake were tracked. As indicated in Table 1 at the end of 14 days, body weight from all the groups was monitored. It was noticed that depressed mice displayed a significant ($p<0.001$) reduction in body weight, food intake and water intake. Administration of imipramine, a standard antidepressant drug showed significant ($p<0.001$) increase in the body weight, food intake and water intake when compared to the negative control group. Mice receiving *Ginkgo biloba* and *Withania somnifera* alone and combination of both displayed a significant ($p<0.001$) elevation in the body weight compared to the negative control group.

Behavioural Parameters

Outcome of concurrent administration of *Ginkgo biloba* and *Withania somnifera* on locomotor activity using OFT.

At the end of 14 days locomotor activities like no. of crossings, grooming and rearing were evaluated using OFT. It was observed that no. of crossings was decreased in control group (negative control). The animals treated with *Ginkgo biloba* and *Withania*

somnifera showed increase in no. of crossing. It was found that the mice treated with their combination (*Ginkgo biloba*+*Withania somnifera*) displayed noteworthy elevation ($p<0.01$) in no of crossing when contrast with negative control group (Figure 1).

Alone treatment of *Ginkgo biloba* and *Withania somnifera* displayed significant ($p<0.01$) increase in no. of crossing as compared with the combination of both drugs.

Locomotor activity like rearing was decreased in control group. After the administration of *Ginkgo biloba* and *Withania somnifera* individually showed increased in the rearing in mice whereas those mice administered with concurrent of *Ginkgo biloba* and *Withania somnifera* showed better increased ($p<0.01$) in rearing in contrast to the group under negative control.

It was observed that administration of *Withania somnifera* showed more significant ($p<0.001$) elevation in rearing activity than the standard imipramine and *Ginkgo biloba* drug treatment compared to the combination group.

It was also found that grooming activities were increased in control group. Administration of combination of *Ginkgo biloba* and *Withania somnifera* showed more noteworthy ($p<0.01$) decreased in grooming activities than the individual treatment of drug when compared to the control group due to their synergistic anti-depressant activity.

It was observed that *Ginkgo biloba* showed more ($p<0.01$) significant reduction in grooming activity than the imipramine and the *Withania somnifera* ($p<0.05$) drug treatment as compared to the combination group of (*Ginkgo biloba*+ *Withania somnifera*).

Outcomes of concurrent administration of *Ginkgo biloba* and *Withania somnifera* in TST

As shown in Figure 2, administration of Imipramine significantly reduces ($p<0.001$) the immobility time in the TST-using animals. Administration of *Ginkgo biloba* and *Withania somnifera* significantly reduces the immobility time, whereas their combination showed more considerable ($p<0.01$) decrease in immobility duration in contrast to the control group.

Table 1: Effect of combined administration of *Ginkgo biloba* and *Withania somnifera* on Body weight, food intake and water intake.

Treatment group	Body Weight (g)	Food intake (g)	Water intake (mL)
G-I (Negative Control group)	12.83±1.24	2.1±0.18	2.73±0.47
G-II (Imipramine 10 mg/kg)	24.83±1.10***	5.9±0.47***	7.43±0.70**
G-III (<i>Ginkgo biloba</i> 50 mg/kg, G.b)	21.33±1.30***	4.3±0.58*	6.28±0.74*
G-IV (<i>Withania somnifera</i> 100 mg/kg, W.s)	19.83±1.60**	4.5±0.53**	6.53±0.75**
G-V (G.b 50 mg/kg+W.s 100 mg/kg)	23.67±1.20***abcc	5.1±0.52***abbc	6.90±0.94**aabc

It was observed that standard imipramine drug treatment showed beneficial ($p < 0.01$) reduction in immobility time compared to the combination group.

Based on the analysis of the graph, the control Group (G-I) exhibited the highest immobility duration at approximately 180 sec. In contrast, the imipramine-treated Group (G-II) showed the most significant reduction in immobility, with duration of around 30 sec, reflecting a reduction of about 150 sec. The *Ginkgo biloba* Group (G-III) reduced immobility to approximately 100 sec, indicating a reduction of 80 sec compared to the control. The *Withania somnifera* Group (G-IV) showed a reduction to roughly 120 sec, amounting to a 60-second decrease. Finally, the combination of *Ginkgo biloba* and *Withania somnifera* (G-V) resulted in a further reduction of immobility to about 90 sec, corresponding to a 90-second decrease. These results highlight the magnitude of reduction across the different treatment groups, with imipramine showing the most substantial effect, followed by the combination treatment, *Ginkgo biloba* and *Withania somnifera* individually.

Biochemical Estimation

Outcomes of concurrent administration of *Ginkgo biloba* and *Withania somnifera* on Blood Glucose level, Triglyceride's level, Total Cholesterol level and Corticosterone level.

It was found that negative control mice exhibited significant ($p < 0.001$) increased glucose level due to persistent hyperglycemia. Mice administered with *Ginkgo biloba* and *Withania somnifera*

and their concurrent more significantly ($p < 0.001$) declined the elevated glucose amount when compared to negative control groups (Table 2).

It was observed that standard imipramine drug treatment displayed more significant ($p < 0.001$) reduction in BGL than the alone treatment of *Ginkgo biloba* and *Withania somnifera* ($p < 0.05$) as compare with the combination group.

Triglycerides levels in serum were monitored in all groups (Table 2). There were notable modifications observed in the number of triglycerides at the end of 14 days. The level of triglycerides was significantly ($p < 0.001$) decreased in mice treated with standard imipramine drug as contrast to control group. After the treatment with *Ginkgo biloba* and *Withania somnifera*, it was found that level of triglyceride was significantly ($p < 0.05$) declined contrasted with the control group. Combination treatment of *Ginkgo biloba* and *Withania somnifera* showed more notable ($p < 0.01$) declined in number of triglycerides.

Imipramine and *Withania somnifera* showed ($p < 0.01$) reduction in triglycerides level when compared with the combination group, whereas *Ginkgo biloba* showed less ($p < 0.05$) significant reduction in triglycerides level when compared with the combination group.

Total cholesterol level in serum was monitored in all groups (Table 2). There was a major alteration observed in the level of total cholesterol. It was noted that negative control group showed increased in cholesterol level. The level of total cholesterol was significantly ($p < 0.001$) declined in mice administered with

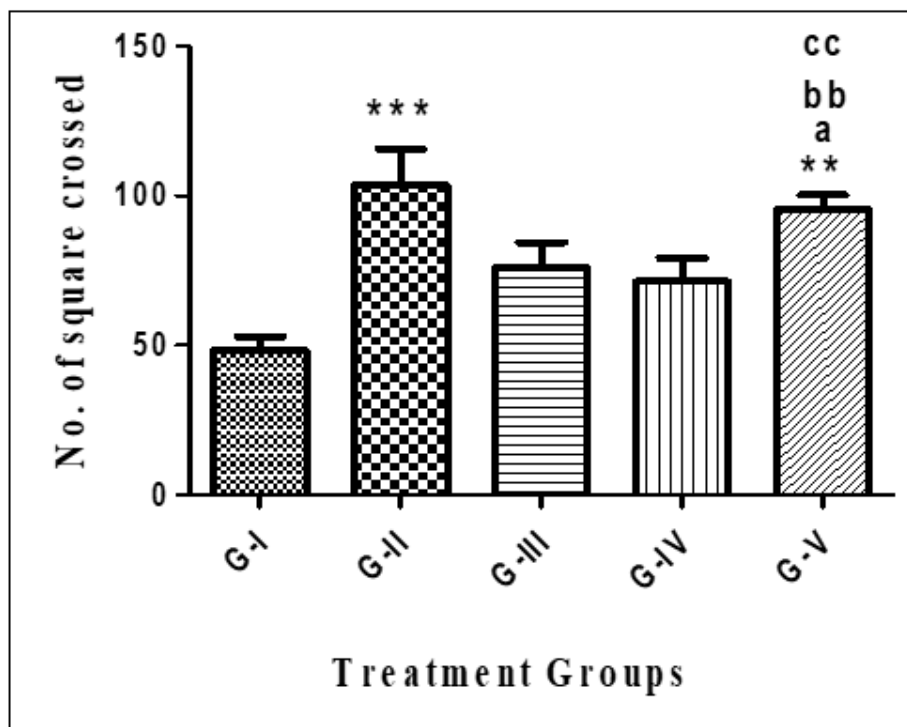


Figure 1: Effect of combined administration of *Ginkgo biloba* and *Withania somnifera* on no. of square crossing in OFT.

imipramine as contrast to control group. The treatment with *Ginkgo biloba* and *Withania somnifera* showed significant ($p < 0.001$) declined in level of elevated total cholesterol when compared to control group. Mice administered with combination of both drugs (*Ginkgo biloba* and *Withania somnifera*) showed more beneficial ($p < 0.001$) declined in the level of Total Cholesterol.

It was observed that *Ginkgo biloba* showed more ($p < 0.01$) significant decrease in Cholesterol level than the imipramine and *Withania somnifera* ($p < 0.05$) drug treatment when compared to the combination group.

It was found that negative control group animals showed increased corticosterone level. Administration of standard imipramine medication exhibited a significant ($p < 0.001$) drop in corticosterone levels in comparison to the group receiving no treatment.

Mice receiving *Ginkgo biloba*, *Withania somnifera* alone and combination of both (*Ginkgo biloba* + *Withania somnifera*) displayed a noteworthy ($p < 0.001$) reduced in corticosterone level in water intake compared to the control group, due to their antidepressant activity.

It was observed that *Ginkgo biloba* showed more ($p < 0.01$) significant decrease in corticosterone level than the imipramine and *Withania somnifera* ($p < 0.05$) drug treatment when compared to the combination group.

It was found that mice treated with combination of *Ginkgo biloba* and *Withania somnifera* showed more significant ($p < 0.001$) reduction in corticosterone level due to their antidepressant activity when compared to the negative control group.

The effects of the treatments on blood glucose, triglycerides, total cholesterol and corticosterone levels varied across the groups. The negative control Group (G-I) exhibited the highest levels of all these parameters. In the imipramine Group (G-II), there was a significant reduction across all markers, with blood glucose levels decreasing to 84.98 mg/dL, triglycerides to 72.16 mg/dL, total cholesterol to 75.44 mg/dL and corticosterone to 114.3 ng/mL, indicating a strong effect of imipramine on metabolic and stress markers.

The *Ginkgo biloba* Group (G-III) also showed significant reductions in glucose (266 mg/dL) and total cholesterol (112.5 mg/dL), but the reduction in triglycerides (139.1 mg/dL) and corticosterone (211.3 ng/mL) was less pronounced compared to the imipramine group. *Withania somnifera* (G-IV) produced a similar trend, with significant reductions in glucose (280 mg/dL) and cholesterol (106.4 mg/dL), but less impact on triglycerides (156.5 mg/dL) and corticosterone (202.3 ng/mL).

The combination of *Ginkgo biloba* and *Withania somnifera* (G-V) demonstrated the most consistent reductions across all parameters, with glucose levels at 234.3 mg/dL, triglycerides at 116 mg/dL, cholesterol at 87.1 mg/dL and corticosterone at 154.0

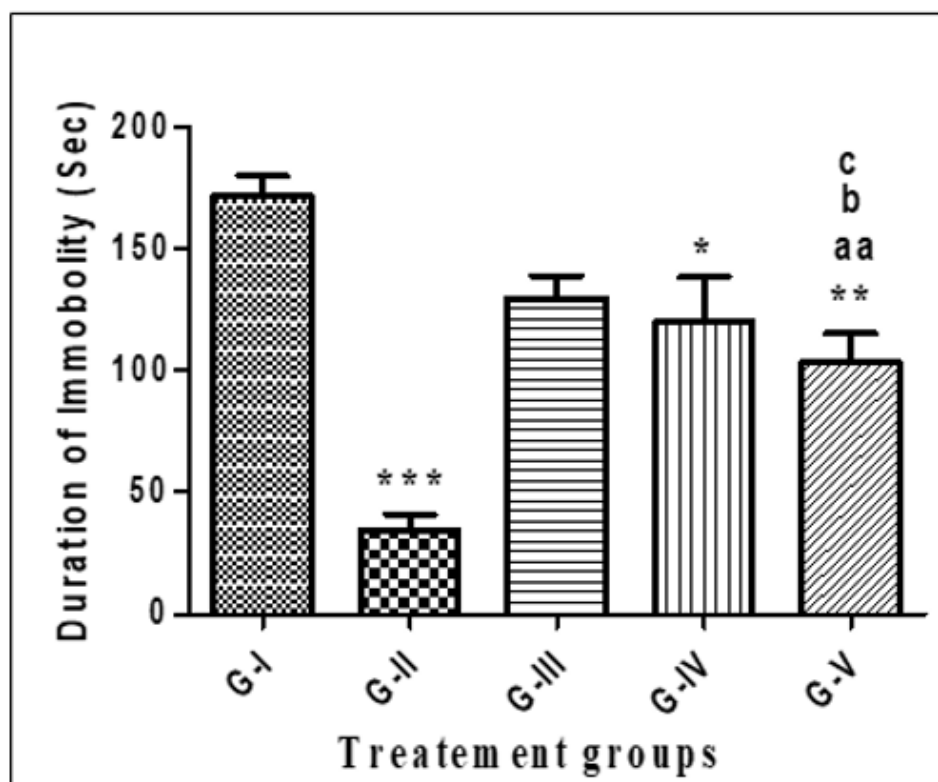


Figure 2: Effect of combined administration of *Ginkgo biloba* and *Withania somnifera* on no. of square crossing in TST.

Table 2: Effect of combined administration of *Ginkgo biloba* and *Withania somnifera* on Blood Glucose level, Triglyceride's level, Total Cholesterol level and Corticosterone level.

Treatment group	Blood-glucose level (mg/dL)	Triglyceride level (mg/dL)	Total Cholesterol (mg/dL)	Corticosterone (ng/mL)
G-I (Negative Control group)	435.1±26.22	190.8±23.54	144.3±4.59	301.5±18.63
G-II (Imipramine 10 mg/kg)	84.98±4.68***	72.16±18.1***	75.44±4.87***	114.3±16.89***
G-III (<i>Ginkgo biloba</i> 50 mg/kg, G.b)	266.0±10.66***	139.1±23.14	112.5±6.64**	211.3±30.33*
G-IV (<i>Withania somnifera</i> 100 mg/kg, W.s)	280.0±11.39***	156.5±45.9	106.4±6.67***	202.3±30.33**
G-V (G.b 50 mg/kg+W.s 100 mg/kg)	234.3±12.85***aabc	116±25.40**aabcc	87.1±3.82***abbc	154.0±14.86***abbc

ng/mL. This suggests a synergistic effect of the combination treatment, resulting in more pronounced improvements compared to either treatment alone.

The combination treatment of *Ginkgo biloba* and *Withania somnifera* was more effective than individual treatments, significantly improving body weight, food and water intake, locomotor activity and biochemical markers like glucose, triglycerides and cholesterol. It notably enhanced locomotor activities and reduced immobility in the tail suspension test, indicating stronger antidepressant effects. Additionally, the combination led to greater reductions in glucose and lipid levels, showcasing its synergistic potential. Importantly, no specific adverse effects were reported, suggesting that the combination provides superior therapeutic benefits without increasing risks.

DISCUSSION

The administration of *Ginkgo biloba* and *Withania somnifera* in combination produced a more potent antidepressant effect than the individual treatments. This was evidenced by significant improvements in locomotor activity and reduced immobility time in the tail suspension test. The enhanced effect is linked to the alleviation of depressive symptoms, which restores energy levels and decreases passive behavior by normalizing neurotransmitter activity and lowering stress hormones. Moreover, the combination treatment led to substantial reductions in biochemical markers such as blood glucose, triglycerides and total cholesterol. Elevated blood glucose and corticosterone levels in depressed mice are associated with stress hormones that impair glucose uptake. Thus, the observed reductions in these levels with the combination

treatment suggest a normalization of stress-related biochemical imbalances, further reinforcing its antidepressant potential.

Given these promising effects, future research should investigate the underlying mechanisms of this synergistic interaction, focusing on the molecular pathways influenced by the combined agents. Clinical trials in humans will be essential to confirm the efficacy and safety of this combination therapy for managing depression and associated metabolic issues. Exploring various dosages and treatment durations could also optimize the therapeutic protocol.

However, the study's limitations include the lack of data on potential side effects or toxicity over longer periods. Although no increased side effects were noted in the short term, further studies are necessary to ensure long-term safety. Additionally, results from animal models may not fully translate to humans and the direct relationship between observed biochemical improvements and antidepressant effects remains to be clarified.

CONCLUSION

The present investigation suggests that herbal drugs such as *Ginkgo biloba* and *Withania somnifera* have the ability to modulate depressive behaviour, stress-related hormonal and metabolic pathways that are dysregulated in depression. The simultaneous treatment of both *Ginkgo biloba* and *Withania somnifera* displayed Behavioural parameters, Biochemical estimation, contributing to improved mood and cognitive function. The combination of each herbal drug was found more effective than alone drug. The findings of this investigation demonstrated that the combined effect of *Ginkgo biloba* and *Withania somnifera* were due to

their strong neuroprotective and adaptogenic properties which modulate stress.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

OFT: Open field test; **TST:** Tail suspension test; **TCAs:** Tricyclic antidepressants; **SSRs:** Selective serotonin reuptake inhibitors; **RIMAs:** Selective reversible inhibitors of monoamine oxidase A; **SNRIs:** Specific serotonin-noradrenaline reuptake inhibitors; **IAEC:** Institutional animal ethical committee.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

K.B.H.S.S Trusts Institute of Pharmacy, Malegaon, Nashik. Registration No: 1566/PO/Re/S/11/CPCSEA, Date: 23/12/2011. Study registration No.: CPCSEA No. 1277.

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