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Antidepressant Effects of Imipramine and Ashwagandha: A Quasi Experimental Study

Ayesha Ramzan, Mashkoor Ahmed Ansari, Sadat Memon, Sawaira Hussain, Sophia Raza Laghari, Sumeira Naeem Khan

ABSTRACT:

Objective: Tocompares the antidepressant properties of Imipramine and Ashwagandha (Withaniasomnifera)

Study Design and Setting: Experimental Observational Study. Animal House of Agriculture University, Tando Jam, collaborated with the Department ofPharmacology and Therapeutics LUMHS Jamshoro

Methodology: Three groups of rats were used: Group A received normal saline (0.9% NaCl); Group B received 32 mg/kg of imipramine; and Group C received 100 mg/kg of Ashwagandha. To evaluate the antidepressant efficacy of the medications, Forced Swimming Test (FST) and the Tail Suspension Test (TST) were used. In the TST, the duration of immobility was recorded as an indicator of behavioral despair, while in the FST, the duration of immobility, climbing and swimming time were measured to evaluate the antidepressant effects. Data was analyzed by using SPSS v26. P-value <0.05 was considered significant.

Results: TST Test Results: Immobility duration was 201± 1.3 in the Ashwagandha Group (GroupB)and 198± 1.1 in the imipramine group (Group C), compared to 225 ± 1.8 in the Control group (Group A). FST Test Results: Immobility duration was 96 ± 1 in Group B and 102 ± 1 in Group C, compared to 206.2 ± 0.8 in Group A. The climbing times were 92 ± 0.2 and 90 ± 0.8 (Group C) vs 62.8 ± 0.9 (Group A). The swimming times were 172 ± 1.3 (Group B) and 168 ± 1 (Group C) vs 91 ± 1 (Group A).

Conclusion: Findings highlighted Ashwagandha as a promising natural alternative antidepressant agent, warranting further investigation into its mechanisms and clinical applications.

Keywords: Antidepressant effects, Ashwagandha, Imipramine, ForcedSwimming Test, Tail Suspension Test.

How to cite this Article:
Ramzan A, Ansari MA, Memon S, Hussain S, Laghari SR, Khan SN. Antidepressant Effects of Imipramine and Ashwagandha: A Quasi Experimental Study. J Bahria Uni Med Dental Coll. 2025;15(2):121-126 DOI: https://doi.org/10.51985/JBUMDC2025505

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Received: 07-01-25
Accepted: 25-03-25
1st Revision: 15-01-25
2nd Revision: 22-01-25
3rd Revision: 03-03-25

INTRODUCTION:

Depression is a diverse illness that impacts an individual's conduct, mental and physical wellbeing. In today's stressful culture, the prevalence of depressive mood disorders is on the rise, which raises the risk of suicide or self-harm as well as the death rate from associated general medical diseases.[1]Depression is a debilitating mental condition that is on the rise globally and contributes to morbidity and disability. Changes in structural synapses and protein composition are increasingly associated with mental disease. In the hippocampus's cornu ammonis 1 and dentate gyrus regions, for example, there is evidence of pyramidal neurone retraction, dendritic atrophy, and reduced gene expression of synaptic proteins such synapsin, microtubule-associated protein, and AMPA receptor subunits in the depressed brain.[2]One Up to 10–15% of people with this illness have suicidal thoughts at some point in their lives.According to the World Health Organisation, depression was the third most common cause of sickness worldwide in 2018. By 2030, it is predicted to overtake all other diseases.[3] According to studies, this lowers life satisfaction and raises the likelihood of divorce as well as major illnesses like cancer, heart disease, depression[4,5]. Tricyclic antidepressants (TCAs) are a class of psychotropic drugs that are mainly used to treat serious

depression, while they can also be used to treat a variety of other neurological and psychiatric conditions.[6]Depression treatment underwent a revolution in the middle of the 20th century thanks to this family of medications, which were the first to treat the condition. Although SSRIs are usually suggested as the main-stay of treatment for MDD (major depressive disorder), TCAs are endorsed for patients with chronic depression or as a backup for patients who don't respond to novel agents used for depression, according to the clinical practice guidelines for mood disorders published by the Royal Australian and New Zealand College of Psychiatrists and the National Institute for Health and Care Excellence (NICE). 7Impramine is a tricyclic antidepressant that is included in the WHO Model List of Essential Medicines. There are only two vital agents for the treatment of depression. [8] Imipramine acts primarily by inhibiting the reuptake of neurotransmitters such as serotonin and norepinephrine, which are crucial in mood regulation. It has been shown to reverse stress-induced changes in brain structures associated with depression, particularly in the amygdala and prefrontal cortex. Side effects of imipramine are notably higher compared to other antidepressants, with reports indicating that 86.7% of patients experience adverse reactions. Common side effects include: Dry mouth, Constipation, Urinary retention, Drowsiness, Weight gain, Cardiac issues, particularly in patients with pre-existing conditions.[9] The behavioral test for mouse called the tail-suspension test is significant for assessing many treatments that can influence behaviors linked to depression and for screening the agents used for depression. A Tape is used to hang mice by their tails so they are unable to flee or cling to adjacent items. This test, which typically lasts six minutes, measures the subsequent escape-oriented behaviours. An important method for high-throughput screening of possible antidepressant chemicals in drug discovery is the tail-suspension test. Another mouse behavioral test called the forced swim test is used to assess the effectiveness of antidepressant medications, novel substances, and experimental procedures intended to induce or avoid depressive-like conditions. Mice are kept in a transparent, unavoidable tank filled with water, and their movement behaviour in relation to escape is observed. The forced swim test requires little specialised equipment and is simple to perform consistently. Minimising unnecessary stress for the mice and following certain protocol guidelines are essential for a successful forced swim test.[6]

Ashwagandha is thought to have potential advantages in treating depression and anxiety, two issues that are becoming more and more prevalent in contemporary culture. Ashwagandha's bioactive ingredients, especially withanolides, may help lessen anxiety and depressive symptoms by influencing the nervous system through a number of biological processes. This may entail neurotransmitter control, anti-inflammatory properties, and assistance with stress management techniques. Ashwagandha's broad mode of action as a natural adaptogen and tendency to have less adverse effects than traditional antidepressants and anxiolytic medications offer a substantial advantage in terms of possible future treatment choices. Ashwagandha may be a natural complement in these areas, according to numerous research in the literature.

Ashwagandha, or Withaniasomnifera, is a well-known herb in India and a common ingredient in Ayurvedic medicines. Ashwagandha is also known as winter cherry, poison gooseberry, and others. The primary active ingredients of ashwagandha are withaferin and sitoindosides VII–x. Phytopharmacological research indicates that ashwagandha may have sedative, immunomodulatory, diuretic, anti-inflammatory, and cardioprotective effects.[10]Ashwagandha enhances the patients strength to manage with stress, potentially reducing anxiety and depressive symptoms. Ashwagandha modulates neurotransmitters and exhibits antioxidant properties, which may support mood regulation.[11] Many physiological effects of Withania somnifera (WS) have been extensively studied, with an emphasis on its possible application in the treatment of brain diseases, based on the close relationship between stress and neuropsychiatric diseases, the anti-stress characteristics of Withania somnifera WS are believed to play a crucial role in its potential benefits for depression, anxiety, and insomnia. Since GABA is the main inhibitory neurotransmitter in the central nervous system, GABAergic neurotransmission plays a major role in the mechanism of anxiety. GABA agonist medications are commonly given to treat anxiety disorders because they primarily act at GABA type A (GABAA) receptors, which improve GABAergic function. Substances in Withania somnifera WS actively engage and regulate GABAA receptors, according to extensive studies in non-human subjects. This could account for Withania somnifera WS's ability to reduce anxiety. The first proof that WS can imitate GABA was published in 1991 by Mehta et al. In the absence of GABA, the researchers found that a methanolic extract of WS root enhanced the flow of chloride ions in mammalian spinal cord neurones. In a way comparable to that of GABAA receptor agonists, the extract also prohibited GABA from binding to its receptor Ashwagandha has antioxidant and anti-inflammatory effects and modulates the effects of many neurotransmitters inside the brain, that may benefit mental illnesses such as anxiety, depression, obsessive-compulsive disorder, psychosis, attention deficit hyperactivity disorder, and addictive conditions.[12] Depressive disorders raise the risk of self-harm and suicide. While antidepressants have multiple side effects, herbal alternatives like ashwagandha offer better tolerance and compliance with fewer adverse effects.

METHODOLOGY:

The research study was officially approved by the Research Ethic Committee LUMHS Jamshoro. NO. LUMHS/REC/-

67. Dated: 11/05/2023. This was an Experimental Observational Study. It was conducted at Animal House of Agriculture University, Tando Jam, collaborated with the Department of Pharmacology and Therapeutics LUMHS Jamshoro. spanning a time of 6 months, i-e June 2023 to Nov 2023. A sum of 36 rats [13] (N=36) were employed as the sample size. Albino rats weighing between 200 and 250 grams. Rats were healthy, exhibiting typical conduct and activities. Rats weighing more than 250 grams and less than 200 grams, having any abnormalities in their bodies were excluded. Ashwagandha and Imipramine were purchased from local market and pharmacy respectively. Three groups of twelve albino rats each were created: In Group A's Rats received normal saline control (0.9%) 5 milliliters per kilogram. In Group B Rats received 32 mg/kg of imipramine. In Group C, Rats received 100 mg/kg Ashwagandha (WithaniaSomnifera). TST (Tail Suspension test) and FST (Force swim test) were used to assess rats' depression-like behavior. The animals were kept under particular standard settings of laboratory, through a 12-hour normal dark and light cycle, at a constant room temp: (23_+2oc), and with a 60% humidity level in accordance with CPCSEA norms. They were also given unrestricted access to food and drink as needed6. The behavioral tests were conducted between 9:00 a.m. and 11:00 p.m. after the animals had been acclimated for five days. We bought imipramine and ashwagandha from the market. All animals were housed in Sindh Agriculture University's animal home in Tando Jam in order to test for antidepressant effects.

Tail suspension test: A wooden chamber that is 70 cm high is used for the mechanical assembly of the tail suspension test (TST). A bar that was 60 cm from the ground or 10 cm from the top of the mechanical assembly was installed between the load-dividing side dividers. Sticky tape was used to hang the rats from the pole, one inch from the tip of their tails. Rats received a 15-minute pretest session for 12 days, and on day 13, they received a 5-minute test session following the administration of imipramine 32 mg/kg via nasogastric tube and normal saline (0.9% Nacl) 5 ml/kg orally to the control group. For the final 300-second test, each rat was suspended independently from the pole. Each animal's stability was recorded for a duration of 300 seconds.[6] Rats were thought to be stable when they hung motionless with bars and made an effort to escape.

Force Swim Test: Rats were forced to swim alone in a 45x40x30 cm vertical Plexiglass vessel with 20cm level of water above the surface and a temp: of 22+1UC. As a result, the rats' feet did not contact the vessel's floor and they did not climb out. Two sessions comprised the entire study.[14] PRETEST SESSION: For 12 days, rats were made to swim alone for 15mins in a vessel made of polypropylene. TEST SESSION: On day 13, each animal was once more compelled to swim. During a test session, swim for six minutes. During the first two minutes, each animal made a determined effort to leave the Plexiglas container. After that, they all became motionless and made sporadic attempts to do so, as shown by the head raising slightly above the water. Each test lasts two minutes, and the total time spent swimming, climbing, and immobility is recorded for a total of six minutes. The length of time spent swimming, climbing, and immobility was contrasted with that of the control group. All drugs were given oral by nasogastric tube.[13]

SPSS V.26 was used to analyze data. The mean and standard deviation were calculated for every numerical variable. The students's t-test were used & P-value < 0.05 regarded as statistically significant. Informed consent was not required as this study involved animals.

RESULTS:

The study evaluated the antidepressant effects of Ashwagandha (WithaniaSomnifera) and imipramine using tail suspension test (TST) and forced swim test (FST). Both treatments significantly reduced the immobility duration compared to the control group ($p<0.01$).

TST Test Results: The anti-depressant effect investigated by using Tail Suspension Test (TST) model suggested the statistically significant effect of Ashwagandha and imipramine when they are compared with the control group. There is statistically significant reduction of immobility duration in Group B & C which are treated with Ashwagandha and Imipramine respectively, as compared to Group A. Immobility duration was 201± 1.3 in the Ashwagandha Group (Group B) and 198± 1.1 in the imipramine group (Group C), compared to 225 ± 1.8 in the Control group (Group A) shown in Table 1 & Figure 1.

FST Test Results: The anti-depressant effect investigated by using Forced swim test (FST) model suggested the statistically significant effect of Ashwagandha and imipramine when they are compared with the control group. There is statistically significant reduction of immobility duration in Group B & C which are treated with Ashwagandha and Imipramine respectively, as compared to Group A. The climbing time and swimming time were increased statistically significant in Group B and C as compared to Group A. The climbing times were 92 ± 0.2 and 90 ± 0.8 (Group C) vs 62.8 ± 0.9 (Group A) shown in Table 2 & Figure 2. The swimming times were 172 ± 1.3 (Group B) and 168 ± 1 (Group C) vs 91 ± 1 (Group A) shown in Table 3 & Figure 3.

DISCUSSION:

In a preclinical context, the current study examined ashwagandha's potential as an antidepressant. According to our research, ashwagandha significantly decreased immobility time in the forced swim test (FST) and tail suspension test (TST), demonstrating antidepressant-like effects. A previous research by Jayshree Dawane et al concluded that Ashwagandha (Withania somnifera) exhibited significant

Table 1: Mean Duration of Immobility Time of Tail Suspension Test

Group	Dose (mg kg^{-1})	Mean Duration of Immobility	P-Value
Group A (Control)	Normal saline 5ml/kg	225 ± 1.8	<0.01
Group B (Ashwagandha)	Ashwagandha 100mg/kg	201 ± 1.3	
Group C (Imipramine)	32mg/kg	198 ± 1.1	

p < 0.05 is significantly different from control group

Table 2: Mean Climbing Time of Forced Swim Test

Group	Dose (mg kg^{-1})	Climbing Time (sec)	P-Value
Group A (Control)	Normal saline 5ml/kg	62.8 ± 0.9	<0.05
Group B (Ashwagandha)	Ashwagandha 100mg/kg	92 ± 0.2	
Group C (Imipramine)	32mg/kg	90± 0.8	

p < 0.05 is significantly different from control group

Table 3: Mean Swimming Time of Forced Swim Test.

Group	Dose (mg kg^{-1})	Swimming Time (sec)	P-Value
Group A (Control)	Normal saline 5ml/kg	91 ± 1	<0.01
Group B (Ashwagandha)	Ashwagandha 100mg/kg	172 ± 1.3	
Group C (Imipramine)	32mg/kg	168± 1	

p < 0.05 is significantly different from control group

Figure 1: Mean Duration of Immobility Time of Tail Suspension Test

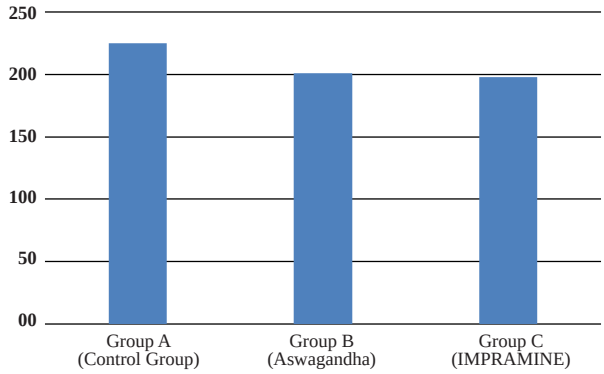


Figure 2: Mean Climbing Time of Forced Swim Test

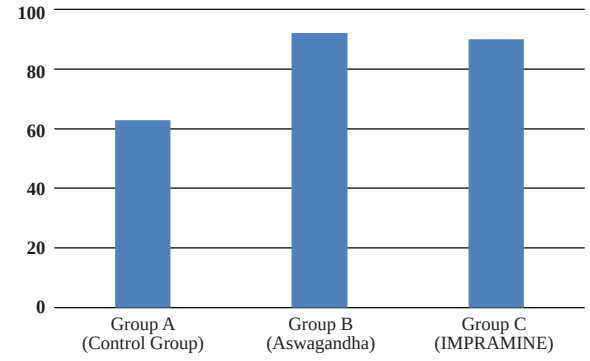
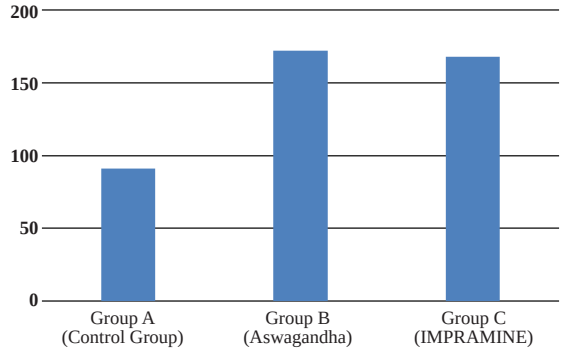


Figure 3: Mean Swimming Time 0f Forced Swim Test



anxiolytic and antidepressant effects in a rat model of chronic stress. Treatment with Ashwagandha root extract increased serotonin and BDNF levels while reducing CRH, ACTH, cortisol, IL-6, and TNF-á. These findings suggest its potential as a prophylactic and therapeutic agent for stress-related disorders.[15] A previous study by Shaista Yousuf et al. reported that Acorus calamus L. rhizome extract exhibits dose-dependent antidepressant activity in mice using the Tail Suspension Test (TST), which is consistent with our findings.[16] Likewise, Ridho Islamie et al. demonstrated that the ethanolic leaf extract of Ocimum sanctum L. has an antidepressant-like effect in the TST, further supporting our study.[17] However, Devesh D. Gosavi et al. found that the alcoholic extract of Withania coagulans fruits did not exhibit antidepressant properties; instead, it had a depressive effect in the TST, which contradicts the above studies.[18] Kosar Asadi et al. reported that components of Cuminum cyminum essential oil exhibited antidepressant-like activity similar to imipramine in both the Forced Swimming Test (FST) and Tail Suspension Test (TST), aligning with our findings.[19] In contrast, Hemant Tanwani et al. found that cinnamaldehyde

(CNM) at lower doses, alone or with escitalopram, showed antidepressant effects in both acute and chronic studies, while higher doses (200/400 mg/kg) did not. Additionally, CNM (200 mg/kg) combined with escitalopram reduced antidepressant effects upon chronic administration. Since their study used SSRIs while ours focused on TCAs, it does not align with our findings.[20] Another previous research stated that Ashwagandha had significant antidepressant effects., they have used Bramhi along with Ashwagandha. They stated that the Combination of these two indigenous drugs with Imipramine showed high efficacy in animal model. [21] a study by concluded that WS produced significant decrease in MIT (mobility time) in mice which could be mediated partly through á adrenoceptor as well as alteration in the level of central biogenic amines. [22]

An important and well-liked Indian medicinal herb, ashwagandha has strong anti-aging, immunomodulatory, anti-anxiety, and stress-relieving properties. Ashwagandha is a widely used Indian medicinal herb that has strong anti-aging, immunomodulatory, anti-anxiety, and stress-relieving properties. It works by boosting glutathione peroxidase activity and normalising elevated lipoxygenese (LPO) activity. According to our research, it has a noticeable antidepressant effect and enhances the effects of imipramine when taken in small doses. This outcome is consistent with Elhassaneen YA [23]findings. While this study is animal-based and employs behavioural tests like TST and FST, Majeed, M. et al[24]. previously showed that a 60-day passage of treatment with Withaniasomnifera root extract standardised for 2.5% of the withanolide compounds found in WS improved depression in normal grownups showing minor to modest symptoms of those endpoints. However, this study works on ashwagandha powder form rather than root extract.

Previously Lopresti AL et al [25] demonstated that Ashwagandha's impact on depression, anxiety reduction, and sleep quality whereas our research solely examines the impact of antidepressants They have also observed its manner of action, whereas our study has observed it as well. In contrast, they have used a number of medicines, whereas in our study we have just compared it with TCAs.

Our study does, however, have a number of limitations First, our findings may not be as broadly applicable as they may be due to the limited sample size. Second, because the study was preclinical in nature, more investigation is required to extrapolate these results to clinical populations. Third, we did not evaluate the possible interactions between ashwagandha and imipramine, which could be crucial for further research.

CONCLUSION:

Our research suggests that Ashwagandha is a safe and effective alternative for depression, potentially matching imipramine with fewer side effects. Its adaptogenic properties may enhance well-being and stress resilience, making it a promising stand-alone or adjunct treatment for mental health. Further studies are needed to confirm its long-term efficacy and safety.

Authors Contribution:
Ayesha Ramzan: conception, analyzed and interpreted the study data
Mashkoor Ahmed Ansari: conception, analyzed and interpreted the study data
Sadat Memon: conception, analyzed and interpreted the study data
Sawaira Hussain: contributor in writing the manuscript
Sophia Raza Laghari: contributor in writing the manuscript
SumeiraNaeem Khan: contributor in writing the manuscript

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