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LAVENDER ESSENTIAL OIL IMPROVED DEPRESSIVE BEHAVIOR IN MICE AFTER INTERFERON-α ADMINISTRATION BUT NOT AFTER CYCLOSPORINE A ADMINISTRATION

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The purpose of this study was to assess whether Lavender essential oil (Lav) could alleviate depressive symptoms induced by Interferon-α (IFN-α) therapy, which reduces tryptophan levels, or Cyclosporine A (Cyc) treatment that leads to psychological issues by inhibiting the mammalian target of rapamycin (mTOR) receptor. The study focused on mice as the subjects for evaluation. Lav 50,100,200 mcL/kg, and Cyc 40 mg/kg (all IP) and IFN-α 1600000 IU/kg SC were administered. The tests were performed after 6 days of consecutive injections on day 7. First total activity was evaluated by the locomotor test, following the splash test and then immobility time during the forced swimming test (FST) was measured. Sucrose preference was measured in order to test anhedonia. The selected treatments did not cause noticeable changes on the locomotor activity. IFN-α increased the immobility time during FST (178.6±10.4 s vs. control 125.8±17.7 s; P < 0.05) indicating depressive-like effect, and IFN-α-lav200 decreased it to (83.3±22.2 s, vs. IFN-α; P<0.01). The grooming time during splash test increased from 36.8±6.1s in IFN-α group to 106.3±9.6 in IFN-α-lav200 group (P<0.05). Sucrose preference increased to 82% following IFN-α-Lav200 administration. However, Lav did not cause a significant change on Cyc-induced depression. Conclusion: While Lav demonstrated a beneficial effect in mitigating IFN-α-induced depression in mice, it was not able to fully reverse Cyc-induced depression. This suggests that Lav exerts its antidepressant effects through distinct mechanisms that may not involve modifications to the mTOR pathways.

Keywords: *Lavender oil, Interferon-alpha, cyclosporine A, depression, animal experiment*

INTRODUCTION

Lavender essential oil (*Lavandula angustifolia*; Lav) is an accepted herbal medicine by the European Medicines Agency to relieve stress and anxiety, and it may have pharmacological properties that modulate N-methyl-D-aspartate (NMDA) receptor, serotonin (5-hydroxytryptamine, 5-HT) reuptake transporter, and neurotoxicity caused by hydrogen peroxide[1]. According to a systematic review and meta-analysis; Lavender could decrease the depression scores compared to the control group, thus it has significant antidepressant effects[2]. Herbs and essential oils that protect against free radicals are not only useful in hypertension but also for neuroprotection[1,3].

IFN-α treatment has the potential to cause adverse effects on the central nervous system (CNS), such as depression and cognitive alterations, which may negatively impact the effectiveness of the immunotherapy. IFN-α therapy is often associated with ample neurological symptoms that involve mood, memory, cognition, and mild subcortical

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dementia[4]. The prevalence of IFN-α therapy depression is passably 50%. Depressive symptoms are common in the early stages of treatment, but typically peak between 4 and 16 weeks. IFN-α and IFN-β increases brain prostaglandin E2 levels, thereafter indolamine 2,3-dioxygenase (IDO) activity upsurges. IDO increases kynureninase, which inhibits kynurenine aminotransferase, resulting in excitotoxicity due to an imbalance between the NMDA receptor agonists (quinolinic acid) and antagonist (kynurenic acid). This neurotoxic challenge causes a reduction in the density of serotonergic and adrenergic neuron, and loss of neurons in the hippocampus. These alterations in the neurochemical and neurohistological course predispose individuals to depression[5].

Cyclosporine A (Cyc) is a Ca2+-dependent protein phosphatase, calcineurin inhibitor prescribed for preventing graft rejection in liver, heart, and kidney transplants. Other drug indications include treating autoimmune disorders and rheumatic diseases. Neurological complications such as tremor, nervousness, and depression have been reported as side effects of its chronic use[6]. It has been noted that calcineurin, is involved in neurotransmission, neuronal plasticity, and memory. Studies show that calcineurin inhibitors induced depressive-like effect by blockade of a signaling pathway the mammalian target of rapamycin (mTOR); a serine-threonine protein kinase that controls synaptic protein synthesis[6].

A meta-analysis showed that the lifetime prevalence of depression is 10.8% and the point prevalence is higher in women (14.4%)[7]. Although it is an important neuropsychiatric condition, the efficacy of medication in treating depression is insufficient, implying that roughly 40% of patients do not respond to the treatment[8]. In addition, as noted earlier some drugs may cause neurological side effects, as depression through altering various pathways[4,6]. In light of these concerns, several studies have been conducted to explore alternative therapeutic approaches aimed at improving clinical outcomes for depression. Among these approaches, phytomedicine has emerged as a primary complementary remedy to conventional drugs. Medicinal herbs have been a subject of investigation for their potential in treating depression, and significant progress has been made in this area[9]. The main objective of this behavioral animal study was twofold: firstly, to determine the effective antidepressant dose of Lav in mice, and secondly, to evaluate its antidepressant-like effects following the administration of IFN-α or Cyc, which induce depression through different pathways.

MATERIAL AND METHODS

Drug preparation and administration

Lav was purchased from TabibDaru (Kashan, Iran); IFN-α (PDferon, Pooyesh Darou 3×10^6 IU, Iran), and fluoxetine HCl (Sigma-Aldrich, India).

Lav 50,100,200 mcL/kg was injected intraperitoneal (IP), at room temperature, Lav was diluted with normal saline containing 1% tween80[10]. IFN-α 1600000 IU/kg was injected subcutaneously (SC)[11]. Cyc was injected IP 40 mg/Kg and diluted in normal saline ethanol 2%[12]. Fluoxetine HCl 20mg/kg was administered IP as the reference antidepressant for validating FST. All the injections were performed for 10 ml/kg mice body weight for 6 consecutive days the tests were performed on day seven.

Chemical composition of the essential oil

Gas chromatography–mass spectrometry analysis of the essential oil by Quality Control TabibDaru Company reported the main contents as follow: 37.95 % linalyl acetate, 35.19% linalool, 3.06% lavandulyl acetate, 0.77% lavandulol, 0.19% camphor, 4.33 % terpinen 4-ol.

Animals

Male albino mice that weighted 27 ± 2 g (6-8 weeks' old) were kept at room temperature with freely accessing standard mice chow and tap-water in a 12-hrs light and 12-hrs dark cycle. The animals were acclimated to the behavioral laboratory 48 hrs before the experiments, and the experiments were conducted in compliance with the guidelines of The National Ethical Committee of Iran (Ethical No: IR.MUI.RESEARCH.REC.1400.537) aiming to minimize animal distress and the number of animals used in the research. In order to eliminate interventions on the animal's

behavior, the test was performed between 8am and 2pm.

Fourteen animal groups (6 mice in each group) were applied: four groups that received Lav 50,100,200 mcL/kg, or normal saline containing 1% tween80; two groups received IFN-α r normal saline; two groups received Cyc or ethanol 2% in saline (Cyc diluent); two groups received IFN-α-Lav (100 or 200 mcL/kg); two groups received Cyc-Lav (100 or 200 mcL/kg); two groups received IFN-α-fluoxetine or Cyc-fluoxetine. The results of Lav 50 mcL/kg are omitted since it was not effective.

Locomotor test

This approach utilized an enclosure with dimensions of 40.40.40 cm^3. The rodents were placed in the chamber and given 3 minutes to explore while oriented towards the wall. The frequency of the animals standing on their hind legs was recorded manually during this time. The device recorded the animals' horizontal movements by detecting interruptions in the infrared beams. The overall movement of each animal, taking into account both horizontal and vertical motions, was calculated.

Splash test

The examination was conducted following the locomotion assessment. Every mouse was individually positioned in a plexiglass enclosure and a 10% sucrose solution was scattered on the animal's back. The latency of grooming, and the overall time spent cleaning for five minutes was recorded. Hesitation for cleaning is an indicator of depressive like behavior, it is correlated with symptoms of apathy and disinterest as a phenotype of depression[13]. After animals were cleaned they were ready for the forced swimming test.

Forced swimming test

The forced swimming test (FST) relies on the observation that an animal's unwillingness to struggle when faced with aversive conditions is connected with another depressive phenotype, i.e. hopelessness behavior[14,15]. To execute this assessment, the mice were put inside a 2-liter glass container filled with 15 cm of water at a temperature ranging from 23 to 25 degrees Celsius. The whole test was 6 minutes, the first 2 minutes were considered to adapt the animal to the environment, and in the last 4 minutes, the duration of immobility, swimming and climbing were recorded. The period during which the animals ceased to move their limbs was referred to as the duration of immobility, i.e. animal does not make any attempt to escape. In the basic state, the duration of immobility in mice is about 2 minutes, which drugs reduce this time with antidepressant effect[16,17]. These data were measured using a stopwatch, animals were dried in warm room to avoid hypothermia.

Sucrose preference test

The sucrose preference test is a supplementary test of anhedonia to complete the depression test. Normal mice prefer sucrose solution over water, but this preference is compromised when inducing depression. In order to familiarize the animal with sucrose solution at first two bottles of 2% sucrose solution were placed in each cage for 24h (day 4), then one bottle was replaced with water for the next 24h (day5), and finally, one bottle of water and one bottle of sucrose solution were measured and placed in each cage (day 6). The consumption of water and sucrose solution in the last 24 hrss (day7) was recorded, and the percentage of preference for sucrose solution consumption was calculated. Percentages above 65% were considered as preference for sucrose consumption[13,18].

Data processing and statistical analysis

The results of all groups were expressed as mean ± standard error of the mean (Mean ± SEM). Data were analyzed using one-way analysis of variance (ANOVA) with the complementary Tukey's multiple comparison tests for comparisons between two groups the unpaired t-test was used. P-values less than 0.05 were considered as significant results. The software programs used for data analyzing and making graphs were Excel 2020 and the Graphpad Prism 8.

RESULTS AND DISCUSSION

Results

Effect of Lav alone and in combination with IFN-α on depressive behavior

As shown in **Fig. 1a**, locomotor results did not change significantly after administration of

different doses of Lav. Similarly, co-administration with IFN-α, Lav or fluoxetine demonstrated little change in locomotor which was not a notable difference from control.

Turning to FST results, the immobility time decreased as the dosage of Lav increased **(Fig. 1b)**. In Lav200 group the immobility time significantly declined to 75±17.7 s compared with the control ip group 134.4±7.9 s (P=0.027, F(2,19)=4.8). According to table1, the time spent on swimming in FST did not noticeably differed among different doses of administration of Lav alone. Climbing in Lav200 group faced a rise comparing with IP control (P=0.005, F(2,18)=10.25). Similarly, grooming time in lav200 (170.6±16.9) was more than IP control (69.3±19.9, P=0.0114, F(2,16)=5.11) which indicates antidepressant effect of Lav200. There was also a rise in sucrose preference up to 81 % in Lav alone groups **(table 1).**

Depression was induced in IFN-α-treated mice as shown in **Fig. 1b** in the FST animals were more immobile than the SC control group (178.6±10.4s vs 125.8±17.7s respectively, P=0.009). IFN-α showed a significant fall in swimming time compared with SC control group (table 1, P=0.011). Sucrose preference showed indifference between water and sucrose solution, i.e 65% of sucrose intake that is a manifestation of depression and anhedonia.

The depressant effect of IFN-α was altered by administrating Lav200 (83.3±22.2s, P=0.0022) and fluoxetine (88.5±22.8s, P=0.0041, F(4,30)= 6.08) compared with Lav alone group which indicates the antidepressant-like effect of Lav200 **(Fig..1b)**. Fluoxetine-IFN-α group experienced more swimming time (P=0.040 vs IFN-α alone group) **(Table 1)**. While IFN-α alone and together with Lav had less swimming time compared with control SC group. Although Lav100 did not manifest a remarkable rise in IFN-α treated mice climbing time compared with IFN-α alone **(table1)**, Lav200-IFN-α caused a significant rise (P<0.001). Additionally, IFN-α-Lav200 climbing time was notably different from SC control (P<0.001). fluoxetine with IFN-α showed an increase in climbing time compared to IFN-α alone (P=0.021). Likewise, IFN-α-Lav200 demonstrated an increase in the grooming times in comparison with IFN-α (106.3±9.6 vs 36.83±6.11, P=0.014 F(4,27)=4.32)**(Fig. 1c),** the same result was observed with fluoxetine. The sucrose preference also rose up to 82% following Lav administration with IFN-α, as fluoxetine co-administration also increased the sucrose preference **(table 1).**

Table 1: The effect of Lav alone and in combination with IFN-α on swimming and climbing time in FST, and sucrose preference test.

Group (n=6)	FST		Sucrose preference (%)
	Climbing time (s)	Swimming time (s)	
Control IP	37.7±6.5	76.5±9.3	76.3
Lav (100 mg/kg)	28.67±6.2	86.8±19.1	81
Lav (200 mg/kg)	75.8±9.4^^	97.6±10.5	77.5
Control SC	38.7±12.1	94.5±16.2	69
IFN-α	17.6±6.1***	43.8±8.5 *	65
IFN-Lav (100 mg/kg)	51.6±11.4	50.0±6.1*	82
IFN-Lav (200 mg/kg)	133.0±9.2###,***	40.5±12.2*	75
IFN-FLX (20 mg/kg)	63.0±11.5#	101.8±24.9 #	70

IFN-α = interferon-α (1600000 IU/kg), Lav=Lavender essential oil, FLX = fluoxetine. The control groups received normal saline. Results of FST are expressed as group mean ± SEM and analyzed by ANOVA followed by Tukey's comparison test. Results of sucrose preference presents preference percentage in each cage containing 6 mice. ^^ P <0.01 compared with control ip, * P <0.05 and *** P < 0.001 compared with the control group sc. ## P < 0.01 and ### P < 0.001 compared with IFN-α group.

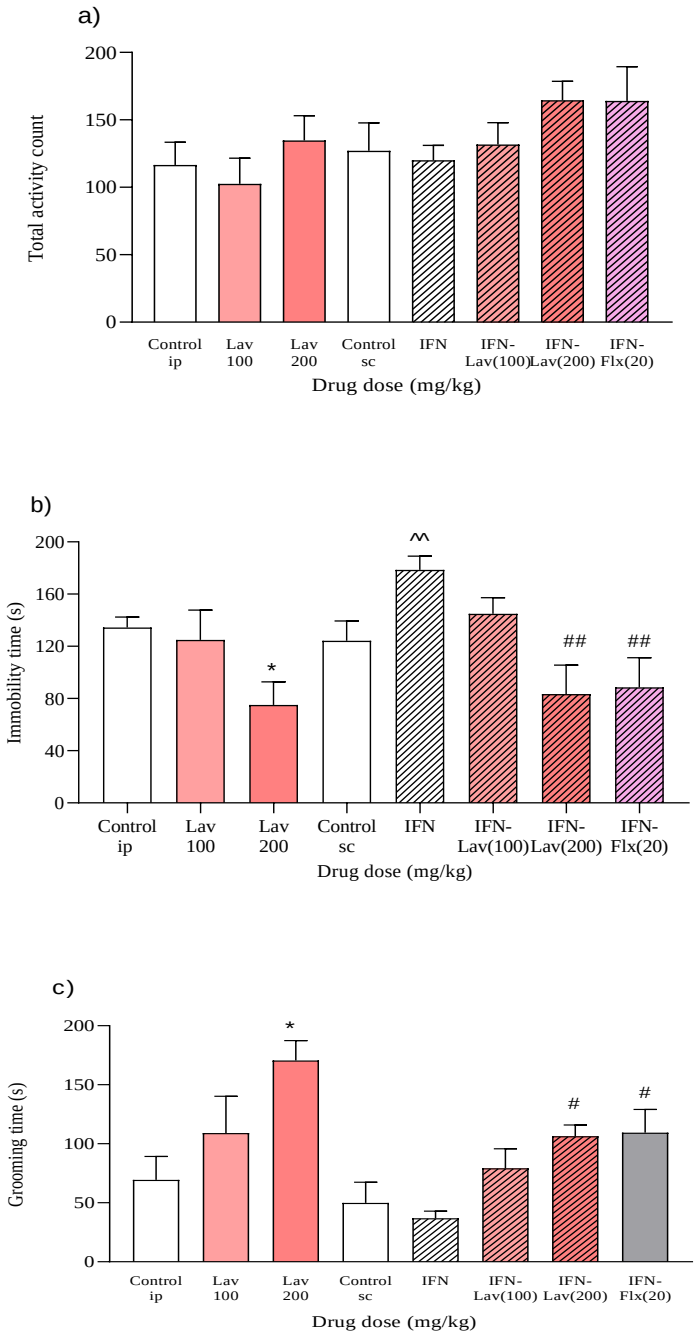

Fig. 1: The effect of Lavender essential oil (Lav) alone and together with Interferon-α (IFN-α) on the total activity count (horizontal activity +vertical activity) in locomotor activity test (a), immobility time during FST (b), and grooming time in splash test (c). Control animals received normal saline solution. IFN-α was injected SC (1600000 IU/kg) all other drugs were injected IP. The results present mean ± SEM, and analyzed by ANOVA followed by Tukey's multiple comparison tests (n=6). ^^ P <0.01 compared with control sc group; * P<0.05 compared with the control ip group, #P<0.05, ##P<0.01 compared with IFN-α alone group.

Effect of Lav combination with Cyc on depressive behavior

As shown in **Fig. 2a**, Cyc injection alone or in combination with Lav, or fluoxetine demonstrated little change in locomotor activity compared to the control group (EtOH 2%) which were insignificant. Around 62 % of animals that were treated concomitantly with Cyc-Lav 200mg/kg died during the experiments therefore they were excluded from the results.

After Cyc administration depressive was induced in animals as shown in **Fig.. 2**. Immobility time significantly increased during FST (178.5±10.5s vs 110.3±22.3; P=0.0095, F(3,22)=18.3) **(Fig. 2b)**. As shown in table 2 climbing time declined significantly compared with control (EtOH 2%) group, changes in the swimming time were insignificant. There was no sucrose preference following Cyc injection that showed anhedonia (table 2). Although fluoxetine showed antidepressant effect in Cyc-injected mice, Lav100 effect on depressive behavior were insignificant during the FST compared with Cyc alone group **(Fig. 2b)**. However, Lav 100 significantly improved the grooming time (94.3±11.9s vs Cyc alone 28.6±6.6s, P=0.0056; F(3,22)=8.53) similar to fluoxetine. Sucrose preference also showed increase preference for sucrose solution over water **(table 2)**.

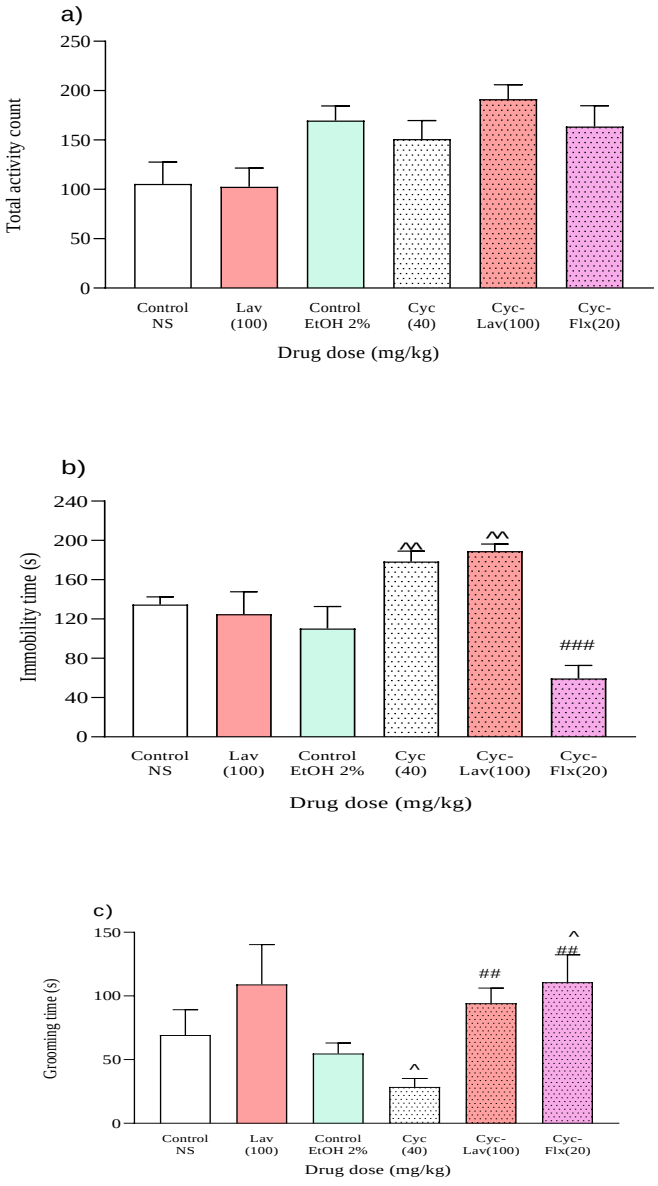

Fig. 2: The effect of Lavender essential oil (Lav) alone and together with cyclosporine A(Cyc) on the total activity count (horizontal activity +vertical activity) in locomotor activity test (a), immobility time during FST (b), and grooming time in splash test (c). Control animals received (NS) normal saline, or normal saline ethanol 2% solution. All drugs were injected IP. The results present mean ± SEM, and analyzed by ANOVA followed by Tukey's multiple comparison tests (n=6). ^ P<0.05, ^^P<0.01, compared with the control EtOH 2% group, ###P<0.001 compared with Cyc alone group.

Table 2: Effect of Lav and Cyc administration the FST.

Group (n=6)	FST		sucrose preference (%)
	Climbing(s)	Swimming (s)	
Control NS	42.67±6.08	79.86±8.56	76.3
Lav100	28.67±6.20	86.83±19.07	81
Control EtOH 2%	31.5±7.65	83.83±28.35	71
Cyc	5.37±1.77^	56.13±11.35	64
Cyc-Lav100	7.83±4.08	43.17±3.99	73
Cyc-FLX	79.5±11.95^^^	84.33±6.27	68

Cyc= Cyclosporin 40mg/Kg, EtOH = Ethanol 70% normal saline, Lav=Lavender essential oil, NS= normal saline, FLX = fluoxetine (20 mg/kg). Results are expressed as group mean ± SEM and analyzed by ANOVA followed by Tukey's comparison test. ^ $P<0.05$, ^^^ $P < 0.001$ compared with the control (EtOH 2%) group.

Discussion

This study aimed to examine the impact of Lav on depression induced by IFN-α and Cyc. The results revealed a promising antidepressant effect of Lavender in managing depression caused by IFN-α. However, it did not demonstrate a consistent antidepressant effect on Cyc-induced depression. This marks the first investigation of Lavender's potential effects on these specific forms of depression.

In our experiment there was no significant difference among tested groups and their control group in their locomotor activity hence, the difference in immobility time in FST is not caused by changes in the locomotor activity. The locomotor activity test is used in behavioral experiments in order to avoid result bias[17].

Commonly the FST is used to assess depressive-like behavior in animal models for pharmaceutical screening, and designing new antidepressants[19,20]. By measuring the active behavior, swimming and climbing, during FST could help differentiate between serotonergic and noradrenergic antidepressant effects[14]. Our results assessed different phenotypes of depression, despair, apathy, and anhedonia. Additionally, grooming is a complex behavior in mice that is responsive to stress and various genetic and pharmacological interventions, that could alter its activity and pattern. By using cleaning behavior patterns as a behavioral endpoint, this method enables the evaluation of stress levels in individual animals, and has broad implications in biological psychopharmacology, genetics, and experimental modeling of mood disorders[21].

Lavender is widely utilized in aromatherapy and phytotherapy to address various central nervous system disorders, including stress and sleep problems. This natural essential oil is recognized as a commercial remedy for headaches, anxiety, and depression[22]. Its pleasant taste and aroma contribute to reducing mental exhaustion and fatigue. In our study, Lav exhibited antidepressant effects in mice, as evidenced by a dose-dependent decrease in immobility time during the FST. Moreover, grooming time and sucrose preference also increased, indicating its potential as an effective antidepressant. Following Lav200 injection swimming time and climbing time increased although climbing increased significantly, the time spent for swimming was more than the climbing time. These are in agreement with previous results that Lav has serotonergic effects, Lavandula aqueous and hydroalcoholic extracts were found to significantly reduce immobility time and increase swimming time without affecting climbing time[23]. Additionally, it has also been proven that Lav induces its potential effects through NMDA receptor antagonist, and inhibiting the 5-HT transporter1.

In agreement with previous studies, IFN-α induced depressive-like behavior in mice, during FST the immobility time increased and grooming time and sucrose preference decreased[11,12]. IFNs are thought to interfere with the neurochemical pathways associated with depression by disrupting the central adrenergic, serotonergic, and neuroendocrine systems. Research has indicated that selective 5-HT reuptake inhibitors (such as fluoxetine)

can be effective in treating depression symptoms associated with IFN-α therapy[24]. 5-HT that is essential in the neurobiology of mood disorders is synthesized from tryptophan via tryptophan hydroxylase. A decrease in blood tryptophan levels can lead to reduced accessibility of 5-HT in the CNS, that potentially initiates depression in vulnerable subjects[25.26]. In previous research, lower plasma concentrations of tryptophan were observed in untreated depressed patients compared to healthy control subjects[25,27]. Meanwhile, Tryptophan deficiency plays a role in the development of depressive symptoms associated with IFN-α treatment[28]. Since, IDO induction by IFN-α, causes 5-HT deficiency because of the shift of tryptophan metabolism to kynurenine formation[28]. Kynurenine, which is capable of crossing the blood-brain barrier, can be metabolized into quinolinic acid - a neurotoxic agent that stimulates the NMDA receptor[29]. In our investigation, Lav200 altered depressive-like behavior caused by IFN-α and the results were comparable with fluoxetine. All the phenotypes of depressive behavior (despair, apathy, and anhedonia) were altered by Lav 200. Lav mainly consists of monoterpenes like linalool and linalyl acetate, that are capable of neurological efficacy according to the previous research[30,.31]. As the CNS molecular mechanisms have shown the potency of lav to interact with 5-HT reuptake transporter and ionotropic NMDA receptors in addition it has shown neuroprotective efficacy against H2O2 toxicity in the PC12 cell line1.32. In our animal study, we demonstrated that the administration of IFN-α interferes with serotonin synthesis, and the co-administration of Lav improved depression through mechanisms independent of the 5-HT system. This was evident from the observed increase in climbing time in the study subjects (Table 1). Another significant finding from our animal study was the neuroprotective effect of Lav when used in conjunction with IFN-α. This effect is likely attributed to Lavender's ability to prevent the neurotoxic impact of NMDA overactivity caused by quinolinic acid.

In agreement with previous investigations, Cyc induced depressive behavior[5,12,33]. It has been proved that depressive induced efficacy of calcineurin inhibitors is performed by prevention of the mTOR function, thus preventing synapses protein synthesis[34]. Meanwhile studies have shown a interaction between mTOR signaling distraction, and synaptic proteins deficiency in depressive symptoms35. Thus, stimulation of the mTOR function pathway could be considered to decrease the risk of depressive initiation in individuals' pharmacotherapy with calcineurin inhibitors (Cyc). Additionally, the NMDA receptors influences and controls the mTOR pathway functioning[36].

It should be noted that, more than half of the animals that received Cyc-Lav 200 died. This could be a result of drug interaction between Cyc and Lav 200. Other Lav drug interactions have been shown previously it could make the effects of CNS depressants (ex, narcotics and sedatives) stronger[37]. In addition previously it was investigated that the lethal 50 dose (LD 50) in rats is 3.55 g/kg[38].

However, when Lev 100 was administered with Cyc, it did not show improvement in immobility time during the FST. However, it did enhance grooming time and sucrose preference. These results suggest that since IFN-α and Cyc induce depressive behavior through different mechanisms, Lav was not fully effective in reversing Cyc-induced depression, unlike its effect on IFN-α-induced depression. This indicates that Lavender's action on the NMDA receptor might not be directly linked to inducing mTOR activity. Though, it may improve some stressful behavior as observed in the grooming test and sucrose preference test. The drug interaction was possibly caused following the co-administration with Lav200 that needs further evaluation.

On the downside, this study did not evaluate the cellular and molecular effects of Lav following Cyc or IFN-α administration, and did not measure the neurotransmitter level in the blood. Yet, the findings were encouraging, indicating the need for future experiments to assess Lav antidepressant efficacy in patients receiving IFN-α.

Conclusion

When administered alone, Lav demonstrated a notable antidepressant effect in mice. Additionally, when combined with IFN-α, Lav showed anti-depressive efficacy comparable to that of a conventional

antidepressant (fluoxetine). However, Lav could not entirely counteract the depressive effects induced by Cyc. This can be attributed to the fact that IFN-α and Cyc initiate depressive effects through distinct mechanisms, and Lavender's action may not be effective in mitigating the impact of calcineurin inhibitors on mTOR function and synaptic protein synthesis.

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REFERENCES

1. V. Lópe, z B. Nielsen, M. Solas, M.J. Ramirez, and AK. Jäger, "Exploring pharmacological mechanisms of lavender (Lavandula angustifolia) essential oil on central nervous system targets", ***Front. Pharmacol,*** 8, 280 (2017).
2. T.S. Firoozeei, A. Feizi, H. Rezaeizadeh , A. Zargaran, H.R. Roohafza, and M. Karimi, "The antidepressant effects of lavender (Lavandula angustifolia Mill.): A systematic review and meta-analysis of randomized controlled clinical trials", ***Complement Ther Med,*** 59, 102679 (2021).
3. L. Safaeian, N. Ghasemi-Dehkordi, S.H. Javanmard, and H. Namvar, "Antihypertensive and antioxidant effects of a hydroalcoholic extract obtained from aerial parts of Otostegia persica (Burm.) Boiss", ***Res Pharm Sci,*** 10(3), 192-199 (2015).
4. C.L. Raison, A.S. Borisov, M. Majer, D.F. Drake, G. Pagnoni, B.J. Woolwine, *et al.*, "Activation of central nervous system inflammatory pathways by interferon-alpha: relationship to monoamines and depression", ***Biol Psychiatry,*** 65(4), 296–303 (2009).
5. A. Mesripour, and M. AghamohsenI, "Melatonin prevented depressive-like behavior following cyclosporine A or interferon-α administration in mice. Hacettepe", ***Univ J Fac Pharm,*** 42(4), 209–217 (2022).
6. A. Azarfar, Y. Ravanshad, H. Mehrad-Majd, M. Esmaeeli, S.B. Aval, M. Emadzadeh, *et al.*, "Comparison of tacrolimus and cyclosporine for immunosuppression after renal transplantation: An updated systematic review and meta-analysis", ***Saudi J kidney Dis Transplant,*** 29(6), 1376–1385 (2018).
7. L.K. Sharp, and M.S. Lipsky, "Screening for depression across the lifespan: A review of measures for use in primary care settings", ***Am Fam Physician,*** 66(6), 1001-1008 (2002).
8. J.P. Kiss, "Theory of active antidepressants: A nonsynaptic approach to the treatment of depression", ***Neurochem Int,*** 52(1-2), 34-39 (2008).
9. G. Lee, and H. Bae, "Therapeutic effects of phytochemicals and medicinal herbs on depression", ***Biomed Res Int,*** 2017,6596241 (2017).
10. V. Hajhashemi, A Ghannadi, and B. Sharif, "Anti-inflammatory and analgesic properties of the leaf extracts and essential oil of Lavandula angustifolia Mill", ***J Ethnopharmacol,*** 89(1), 67–71 (2003).
11. A. Mesripour, and M. Almasi, "Flaxseed prevents interferon-alpha induced depressive behavior in mice: the α-linolenic acid is essential", ***Res J Pharmacogn,*** 8(1), 63–71 (2021).
12. O. Hajhashemi, A. Mesripour, and V. Hajhashemi, "Vanillic acid prevents interferon-alpha and cyclosporine A-induced depressant-like behavior in mice", ***J Reports Pharm Sci,*** 11(1), 59-64 (2022).
13. A. Mesripour, S. Shahnooshi, and V. Hajhashemi, "Celecoxib, ibuprofen, and indomethacin alleviate depression-like behavior induced by interferon-alfa in mice", ***J Complement Integr Med,*** 17(1), 20190016 (2019).
14. J.F. Cryan, A.Markou, and I. Lucki, "Assessing antidepressant activity in rodents: recent developments and future needs", ***Trends Pharmacol Sci,*** 23(5), 238–245 (2002).
15. J.M. Deussing, "Animal models of depression", ***Drug Discov today Dis Model,*** 3(4), 375–383 (2006).

16. R. Yankelevitch-Yahav, M. Franko, A. Huly, and R. Doron, "The forced swim test as a model of depressive-like behavior", ***J Vis Exp,*** (97) , e52587 (2015).
17. A. Mesripour, and T. Ahmadi, "Depression-like effects of levetiracetam was halted by pretreatment with n-methyl-d-aspartate receptor (NMDAR) blockers in mice", ***Bull Pharm Sci Assiut,*** 46(1), 517-527 (2023).
18. A. Mesripour, and S. Golchin, "Vitamin B6 Antidepressant Effects Are Comparable to Common Antidepressant Drugs in Bacillus-Calmette-Guerin Induced Depression Model in Mice", ***Iran J Psychiatry,*** 17(2), 208–216 (2022).
19. O.V. Bogdanova, S. Kanekar, K.E. D'Anci, and P.F. Renshaw, "Factors influencing behavior in the forced swim test", ***Physiol Behav,*** 118, 227–39 (2013).
20. A. Mesripour, E. Jafari, M.R Hajibeiki, and F. Hassanzadeh, "Design, synthesis, docking, and antidepressant activity evaluation of isatin derivatives bearing Schiff bases", ***Iran J Basic Med Sci,*** 26(4), 438-444 (2023).
21. A.V. Kalueff , J.W. Aldridge, J.L. LaPorte, D.L. Murphy, and P. Tuohimaa, "Analyzing grooming microstructure in neurobehavioral experiments", ***Nat Protoc,*** 2(10), 2538–2544 (2007).
22. J. Luo, and W. Jiang, "A critical review on clinical evidence of the efficacy of lavender in sleep disorders", ***Phyther Res,*** 36(6), 2342–2351 (2022).
23. S. Abbasi Maleki, R. Bekhradi, J. Asgharpanah, F. Abbasi Maleki, and N. Maleki Ahanghari, "Antidepressant-like effect of aqueous and hydroalcoholic extracts of lavandula angustifolia mill in forced swim test and tail suspension test in male mice", ***J Arak Univ Med Sci,*** 16(9), 65–75 (2013).
24. M. Laguno, J. Blanch, J. Murillas, J.L. Blanco, A. León, M. Lonca, *et al.*, "Depressive symptoms after initiation of interferon therapy in human immunodeficiency virus-infected patients with chronic hepatitis C", ***Antivir Ther,*** 9(6), 905–909 (2004).
25. Y.A. Fashi, A. Mesripour, and V. Hajhashemi, "Evaluation of the effect of soybean diet on interferon-α-induced depression in male mice", ***Avicenna J Phytomedicine,*** 7(5), 436-443 (2017).
26. F.A. Moreno, G.R. Heninger, C.A. McGahuey, and P.L. Delgado, "Tryptophan depletion and risk of depression relapse: a prospective study of tryptophan depletion as a potential predictor of depressive episodes", ***Biol Psychiatry,*** 48(4), 327–329 (2000).
27. P. Moore, H.P. Landolt, E. Seifritz, C. Clark, T. Bhatti, J. Kelsoe J, et al, Clinical and physiological consequences of rapid tryptophan depletion", ***Neuropsychopharmacology,*** 23(6), 601–622 (2000).
28. E. Franscina Pinto, and C. Andrade, "Interferon-related depression: a primer on mechanisms, treatment, and prevention of a common clinical problem", ***Curr Neuropharmacol,*** 14(7), 743–748 (2016).
29. C.W. Fischer, A. Eskelund, D.P. Budac, S. Tillmann, N. Liebenberg, B. Elfving , et al, Interferon-alpha treatment induces depression-like behaviour accompanied by elevated hippocampal quinolinic acid levels in rats", ***Behav Brain Res,*** 293, 166–172 (2015).
30. M. Linck V de , A.L. da Silva, M. Figueiró, E.B. Caramao, P.R.H. Moreno, and E. Elisabetsky, "Effects of inhaled Linalool in anxiety, social interaction and aggressive behavior in mice", ***Phytomedicine,*** 17(8–9), 679–683 (2010).
31. F.N. Souto-Maior, F.L. de Carvalho, L.C.S.L de Morais, S.M. Netto, D.P. de Sousa, and R.N. de Almeida, Anxiolytic-like effects of inhaled linalool oxide in experimental mouse anxiety models", ***Pharmacol Biochem Behav,*** 100(2), 259–263 (2011).
32. P. Xu, K. Wang, C. Lu, L. Dong, L. Gao, M. Yan, *et al.*, "Protective effect of lavender oil on scopolamine induced cognitive deficits in mice and H2O2 induced cytotoxicity in PC12 cells", ***J Ethnopharmacol,*** 193, 408–415 (2016).
33. A. Mesripour, M. Golbidi, and V. Hajhashemi, "Dextromethorphan improved cyclosporine-induced depression in mice model of despair", ***Res Pharm***

Sci, 15(5), 447-453 (2020).

34. J.J Yu, Y. Zhang Y, Y. Wang, Z.Y. Wen, X.H. Liu, J. Qin, *et al.,* "Inhibition of calcineurin in the prefrontal cortex induced depressive-like behavior through mTOR signaling pathway", ***Psychopharmacology (Berl).***, 225(2), 361–372 (2013).
35. H.M. Abelaira, G.Z. Réus, M.V. Neotti, and J. Quevedo, "The role of mTOR in depression and antidepressant responses", ***Life Sci,*** 101(1–2), 10–14 (2014).
36. R. Gong, C.S. Park, N.R. Abbassi, and S.J. Tang, "Roles of glutamate receptors and the mammalian target of rapamycin (mTOR) signaling pathway in activity-dependent dendritic protein synthesis in hippocampal neurons", ***J Biol Chem,*** 281(27), 18802–18815 (2006).
37. C. Gyllenhaal, S.L. Merritt, S.D. Peterson, K.I. Block, and T. Gochenour, Efficacy and safety of herbal stimulants and sedatives in sleep disorders", ***Sleep Med Rev,*** 4(3), 229–251 (2000).
38. G.L. Silva, C. Luft, A. Lunardelli, R.H. Amaral, D.A. MELO, M.V.F. Donadio, *et al.,* "Antioxidant, analgesic and anti-inflammatory effects of lavender essential oil", ***An Acad Bras Cienc,*** 87, 1397–1408 (2015).

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نشرة العلوم الصيدلية
جامعة أسيوط

زيت اللافندر العطرى يحسن السلوك الاكتئابي لدى الفئران بعد تناول الإنترفيرون ألفا ولكن ليس بعد تناول السيكلوسبورين أ

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الغرض من هذه الدراسة هو تقييم ما إذا كان زيت اللافندر العطرى (Lav) يمكن أن يخفف من أعراض الاكتئاب الناتج عن علاج Interferon-α (IFN-α) ، الذي يقلل من مستويات التربتوفان، أو علاج السيكلوسبورين أ (Cyc) الذي يؤدي إلى مشاكل نفسية عن طريق تثبيط هدف الثدييات لمستقبلات الرابامايسين (mTOR). ركزت الدراسة على الفئران كمواضيع للتقييم. تم إعطاء Lav ٢٠٠، ١٠٠،٥٠ ميكرولتر/كجم، و Cyc ٤٠ مجم/كجم (داخل الصفاق) و IFN-α ١٦٠٠٠٠٠ وحدة دولية/كجم (تحت الجلد). تم إجراء الاختبارات بعد ستة أيام من الحقن المتتالية في اليوم السابع. تم تقييم النشاط الإجمالي الأول بواسطة الاختبار الحركي، بعد اختبار الرش ثم تم قياس وقت عدم الحركة أثناء اختبار السباحة القسري (FST). تم قياس تفضيل السكروز من أجل اختبار انعدام التلذذ. لم تسبب العلاجات المختارة تغيرات ملحوظة في النشاط الحركي. زاد IFN-α وقت عدم الحركة أثناء FST (١٠,٤ ± ١٧٨,٦ ثانية مقابل التحكم١٢٥,٨ ±١٧,٧ ثانية؛ P <٠,٠٥) مما يشير إلى تأثير يشبه الاكتئاب، وقد قلله IFN-α-lav200 إلى (٨٣,٣٨ ± ٢٢,٢ثانية، مقابل IFN -α؛ P <٠,٠١). زاد وقت الاستمالة أثناء اختبار الرش من٣٦,٨ ± ٦,١ ثانية في مجموعة IFN-α إلى ١٠٦,٣± ٩,٦ في مجموعة ٢٠٠ IFN-α-lav (P <٠,٠٥). ارتفع تفضيل السكروز إلى ٨٢% بعد تناول ٢٠٠ IFN-α-Lav. ومع ذلك، لم يسبب Lav تغييرًا كبيرًا في الاكتئاب الناتج عن Cyc. الاستنتاج: في حين أظهر Lav تأثيرًا مفيدًا في تخفيف الاكتئاب الناتج عن IFN-α في الفئران، إلا أنه لم يكن قادرًا على عكس الاكتئاب الناتج عن Cyc بشكل كامل. يشير هذا إلى أن Lav يمارس تأثيراته المضادة للاكتئاب من خلال آليات متميزة قد لا تتضمن تعديلات على مسارات mTOR.