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Valerian and Hops Combination Versus Escitalopram in Models of Depression and Anxiety: A Cross-talk with Oxidative Stress

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ABSTRACT

Depression and anxiety disorders are the most common mental health problems and are associated with oxidative stress. Although famous for its anxiolytic effect, the antidepressant effect of the valerian-hops combination was not previously studied, also the relationship between the sedative effect of valerian-hops and oxidative stress markers is unclear. The current research has two objectives: (1) to compare the antidepressant effect of valerian-hops with escitalopram and (2) to evaluate the sedative/anxiolytic effects of valerian-hops in relation to oxidative stress markers namely Nitric Oxide (NOx), inducible Nitric Oxide Synthase (iNOS) and Super Oxide Dismutase (SOD). Two models were employed using BALB/c mice: A normal condition depression model in which mice were divided into: control, valerian-hops-treated (100mg/kg), and escitalopram-treated (10mg/kg) groups one hour before the open field test, the elevated plus-maze test, and the forced swim test and an anxiety model in which mice were divided into: unstressed naïve, control (stressed), valerian/hops (100mg/kg), and escitalopram (10 mg/kg) groups treated for three weeks; acutely restrained for 6 hours and sacrificed, serum was obtained to detect NOx, iNOS and SOD activity. In the depression model, valerian-hops demonstrated antidepressant activity similar to escitalopram ($p>0.05$). In the anxiety model, the valerian-hops treated mice demonstrated a profound sedative effect in all behavior paradigms ($p<0.05$), and normalized the anxiety-induced NOx levels and SOD activity ($p<0.05$). Under normal conditions, the valerian-hops combination exerts an antidepressant effect similar to escitalopram while in stress/anxiety conditions it exerts profound sedative and antioxidant effects.

Keywords: Antidepressants, anxiolytics, valerian-hops, mice model, stress.

1. INTRODUCTION

Mental health disorders are becoming increasingly common among all age groups (1,2) Depression and anxiety disorders are the most common mental health problems and are dramatically increasing worldwide (3). The neurobiology of depression and anxiety is complex and multifactorial. Beyond the well-established monoamine deficiency theory of psychological disorders (4), accumulating evidence points to the role of oxidative stress(5,6). Nitrates, a nitric oxide (NO) metabolite, are a marker of oxidative stress and were shown to increase during acute anxiety (7,8). Nitric oxide (NO) is produced from L-arginine by enzymatic conversion of the enzyme NO synthase (NOS) (9). In support of the potential role of NO in depression, a growing body of evidence has demonstrated that some antidepressants exert a NO-lowering effect. For example, a study revealed that L-arginine antagonized the effects of the classic tricyclic

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antidepressant imipramine (10). Superoxide dismutase (SOD) is an abundant antioxidant enzyme responsible for superoxide (O2-) species detoxification to yield hydrogen peroxide (H_2O_2). SOD activation occurs as a response to an oxidative stress status (11).

The different classes of available antidepressants are based on the monoaminergic deficiency hypothesis, i.e. they increase the levels of the synaptic monoamines (serotonin, dopamine, and norepinephrine); these classes include Selective Serotonin Reuptake Inhibitors (SSRIs) such as escitalopram. Although considered a safe option, SSRIs have many limitations: they are effective only in 50% of cases, they could lead to weight gain or sexual impairment, and they take up to two weeks to exert a clinically acceptable effect (12,13). Therefore, herbs with psychotropic effects are gaining wide attention due to their high safety profile, minimal drug interactions, and negligible addictive potential (14–16).

Valerian and hops are perennial plants. valerian is originally native to Asia and Europe (17) and hops plants are distributed throughout North America, Europe, and Asia (18). Valerian root (*Valeriana officinalis Valerianacea*) is often combined with Hops strobile (*Humulus lupulus L., Cannabaceae*) to enhance its sedative and anxiolytic efficacy (19). The pharmacological effect of valerian depends on valerenic acid, which is assumed to be a ligand for GABA and adenosine receptors (20–24).In addition, many rodent studies on hops have shown results in terms of sedation and antidepressant activity as well. This has raised speculation about the activity of hops to extract on GABA receptors (25) In the United States, valerian is regulated by the Food and Drug Administration (FDA) as a dietary supplement (https://ods.od.nih.gov/factsheets/Valerian-HealthProfessional/).

The valerian-hops combination is commercially available worldwide as an OTC product (26). Valerian is considered to be relatively safe and well-tolerated, but gastrointestinal problems (e.g. nausea, abdominal cramps) are included as unpleasant side effects in the European Medicine Agency (EMA) monograph. Although hydroalcoholic extracts of valerian root in the prescribed dosage of 400-600 mg dry extract increase sleep latency and quality, the elements that contribute to its efficacy are unknown (27)

Previously published rodent studies used "anxiety-free" models and focus on valerian alone and not on the valerian-hops combination. For example, the mice receiving the methanolic and ethanolic extracts of *Valeriana Officinalis* demonstrated antidepressant and anxiolytic but no sedative effects, despite treatment for 16 days (28) A similar study reported an antidepressant effect of valerian after both an acute dosing and two weeks of chronic dosing of *Valeriana Wallichi* (29).The sedative properties of valerian, however, are not profound. Even using a dose of 1000mg/kg did not result in profound sedation (30).

According to our knowledge, no previous studies have evaluated the psychotropic actions of the valerian-hops combination versus escitalopram in a depression and in an anxiety model in association with NO_x, iNOS and SOD.

Therefore, the current research has two objectives: (1) to compare the antidepressant effect of valerian-hops with escitalopram and (2) to evaluate the sedative/anxiolytic effects of valerian-hops in relation to oxidative stress markers namely Nitric Oxide (NOx), inducible Nitric Oxide Synthase (iNOS) and Super Oxide Dismutase (SOD).

2. MATERIALS AND METHODS

2.1 Study animals and design

Balb/C mice were used for this study. All mice were six to eight weeks old and of an equal ratio of males to females. Animals were kept individually in separate cages in order to reduce anxiety as in (5)

Temperature and humidity were controlled at 25°C, 50-60% respectively.

The research followed the international ethical standards for the Care and Use of Laboratory Animals. The study protocol was approved by the Institutional Review Board (IRB) of The American University of Madaba

approval number A20001. All procedures were in an accordance with the "International Guiding Principles for Biomedical Research Involving Animals, 2012".

The study design consisted of two models:

2.2 The normal condition depression model:

Mice were divided into three groups (n=10) as follows. Group I: control (treated with a single dose of distilled water); group II: valerian-hops (treated with a single dose of 100mg/kg); and group III: Escitalopram (treated with a single dose of 10mg/kg) escitalopram was supplied from Pharma International and the dose selection was made as in (5). After a treatment period of one hour, mice were then subjected to behavioral tests.

2.3 The anxiety model:

Mice were divided into three groups (n=10) as follows. Group I: naïve (unstressed and untreated); group II: control (treated with distilled water for 3 weeks, then stressed); and group III: valerian-hops (treated for 3 weeks, then stressed). A treatment period of 3weeks was set to evaluate the antidepressant potential, as in [14]. After 3 weeks of treatment, groups II and III were restrained for six hours, then all mice were subjected to behavioral tests, blood was collected and serum was obtained, as in(5,31).

2.4 Valerian-hops combination extraction and treatments

Valerian root of (Valeriana officinalis)-hops strobile (Humulus lupulus) aqueous extract was supplied from Roha pharmaceuticals and was prepared as follows. The dry extract valerian root in a relationship of drug to extract of 4-6:1, the extraction agent was water, and dry extract of hop stabile in a relationship of drug to extract of 3-6:1, where the extraction agent was water. The extract contained a ratio of dry extract of valerian root to hop strobile of 4:1. A daily dose of 100mg/kg of valerian-hops in 0.5ml of distilled water was administered via oral gavage as in (28) for group III for 3 weeks. The dose was selected based on previous literature(32).

2.5 Acute Immobility Stress

The acute immobility stress was employed as the anxiety model according to (5,31) with slight modifications. Animals were restrained individually for 6 hours in a restraining tube, while maintaining the animals' ventilation undisturbed. In the naïve group, the mice were kept in an animal cage with soft bedding in the same experimental conditions. After performing the immobility stress, mice were subjected to behavioral tests.

2.6 Behavioral tests

2.6.1 Forced swim test:

Forced Swim Test (FST) is the most commonly used behavioral model for screening

antidepressant-like activity in rodents(33). Mice were individually forced to swim for five minutes in an open glass chamber (25×15×25 cm3), which contained freshwater to a height of 15 cm and was maintained at 26±1°C. Floating time was defined as the time in which mice stop moving completely while in the water.

2.6.2 Elevated plus maze

The anxiolytic effects were screened through the elevated plus maze as previously

described (34) with some modifications. The apparatus was elevated 25 cm above the floor.

The maze was composed of two closed arms (30*5 *10 cm) and two open arms (30*5 cm). Mice were placed at the center facing the closed arm and allowed to move freely for10 minutes. The frequency of Open Arm Exits (OAE) and the Open Arm Time (OAT) spent were recorded.

2.6.3 Open field test

The locomotion and sedation were evaluated through the standard (72*72cm) open field test as previously described (35). In brief, mice were placed in a central square and allowed to move freely for 5 minutes. The locomotion is measured by the number of lines crossed and sedation is measured by the rearing frequency. The procedure was performed in an empty room with indirect lighting, and the field was regularly cleaned with 70% ethyl alcohol.

2.7 Biochemical Tests

Performed only for the multiple-dose, anxiety-induced model in order to study stress correlation with oxidative stress.

2.7.1 Nitric oxide measurement

The accumulation of nitrate, an indicator of the production of NO, was determined in serum using a colorimetric assay with a Griess reagent (36). Serum nitrate was assayed using a Nitric Oxide Assay Kit (cat. no. ab65328; Abcam, Cambridge, MA, USA) according to the manufacturer's instructions. The nitrate concentration was obtained according to the standard curve generated after measuring absorbance at a wavelength of 540 nm using a Multiskan™ FC Microplate Photometer (Thermo Fisher Scientific, Waltham, MA, USA). All samples and standards were processed in duplicate.

2.7.2 SOD activity measurement

SOD activity was assayed using an SOD Assay kit (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany; cat. no. 19160) as previously described (37) .In brief, the rate of the reduction with O2 is linearly associated with the xanthine oxidase activity, and is inhibited by SOD. The SOD activity, as an inhibition activity, is quantified by measuring the decrease in the color development at a wavelength of 440 nm.

2.7.3 iNOS measurement

The serum iNOS was measured by Abcam colorimetric kit according to the manufacturer's recommendations. The iNOS concentration was obtained according to the standard curve generated after measuring absorbance at a wavelength of 540 nm using a Multiskan™ FC Microplate Photometer (Thermo Fisher Scientific, Waltham, MA, USA). All samples and standards were processed in duplicate.

2.8 Data and statistical analysis

All data obtained from the behavioral tests, NOx, SOD and iNOS were analyzed with a one-way ANOVA and a subsequent Tukey post hoc test, where $p < 0.05$ was considered statistically significant. Quantitative data were presented as mean values ± SEM.

3. RESULTS

3.1 The normal condition depression model

3.1.1 Forced swim test

The valerian-hops group showed lower FT compared to the control ($p<0.05$). Moreover, it showed a significant reduction in the immobility episodes and a significant increase in the floating latency time for the control group ($p<0.05$), as shown in Figure 1A, 1B and 1 C.

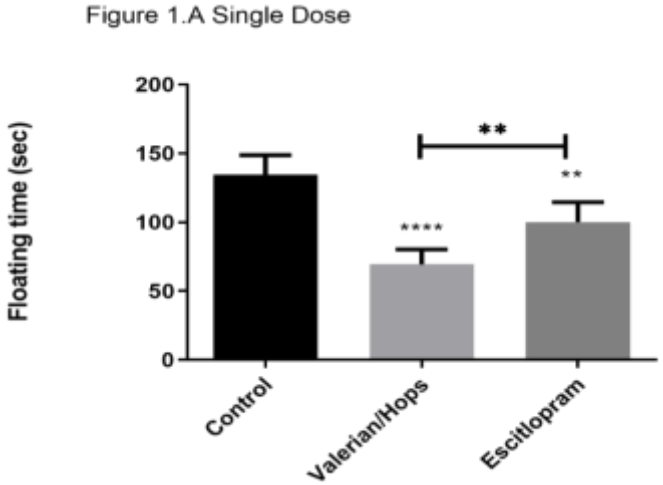
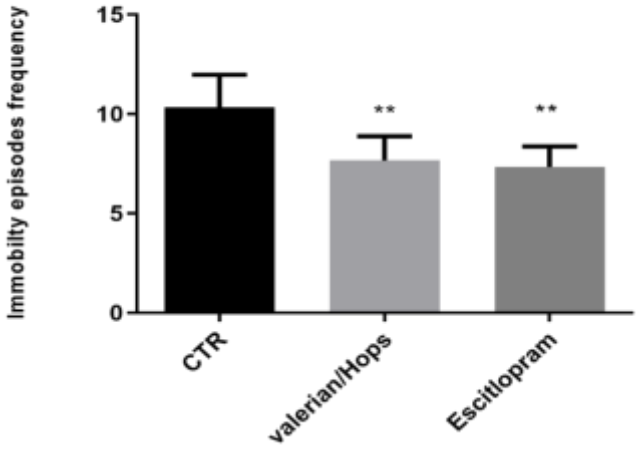


Figure 1: Forced Swim Test Single Dose Model

(A) Effect of a single dose treatment with V/H (100 mg/kg), ESC (10 mg/kg) on floating time.

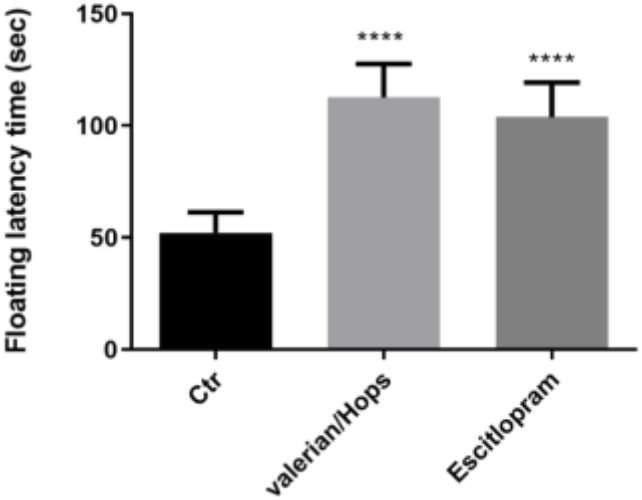
Values are expressed as the mean ± SEM (ANOVA followed by Tukey's test). F (2, 15) = 35.82 ; **p<0.001,****p<0.0001 compared to the control

Figure 1.B Single Dose



(B) Effect of a single dose treatment with V/H (100 mg/kg), ESC (10 mg/kg) on immobility episodes episodes. Values are expressed as the mean ± SEM (ANOVA followed by Tukey's test). Each bar represents the mean ± SEM (ANOVA followed by Tukey's test). F (2, 15) = 9.359; **p<0.001 compared to the control.

Figure 1.C Single Dose



(C) Effect of a single dose treatment with V/H (100 mg/kg), ESC (10 g/kg) on the floating latency time. Values are expressed as the mean ± SEM (ANOVA followed by Tukey's test). Each bar represents the mean ± SEM (ANOVA followed by Tukey's test) F (2, 14) = 29.92; **** p<0.001 compared to the control, V/H: Valerian/Hops; ESC: Escitalopram; SEM, standard error of the mean.

3.1.2 Elevated plus maze

The valerian-hops-treated group showed a significant increase in the OAE (open arm exits) count compared to the control ($p<0.05$) as seen in Figure 2.

3.1.3 Open field test

The valerian-hops-treated group showed similar ambulation frequency (AF, measured in lines crossed) to the control. Additionally, the valerian-hops-treated group showed a significantly higher rearing frequency compared to the control ($p<0.05$). Results are shown in Figure 3.

3.2 The anxiety model

3.2.1 Forced swim test

The antidepressant effect of valerian-hops combination was completely absent. The control showed a significantly higher FT compared to the naïve group ($p<0.05$). The valerian-hops group demonstrated a significantly higher FT compared to both the control and the naïve groups ($p<0.05$) and the escitalopram-treated group showed a significantly decreased FT compared to the control and naïve groups ($p<0.05$). Regarding the number of immobility episodes, the control group showed a significantly higher frequency compared to the naïve group. Both the valerian-hops-treated group and the escitalopram-treated group showed a significant reduction in the frequency compared to the control ($p<0.05$). In regards to the latency time, both the valerian-hops-treated group and the escitalopram-treated group showed a significant increase in LT compared to the control ($p<0.05$). Results are not shown.

3.2.2 Elevated plus maze

The OAE did not increase in the valerian-hops group compared to the control ($p>0.05$). However, the escitalopram-treated group demonstrated a higher OAE relative to the control group ($p<0.05$). As for open arm time (OAT) in seconds, the valerian-hops group did not show any increase compared to the control. Results are shown in Figure 2A and 2B.

Figure 2.A

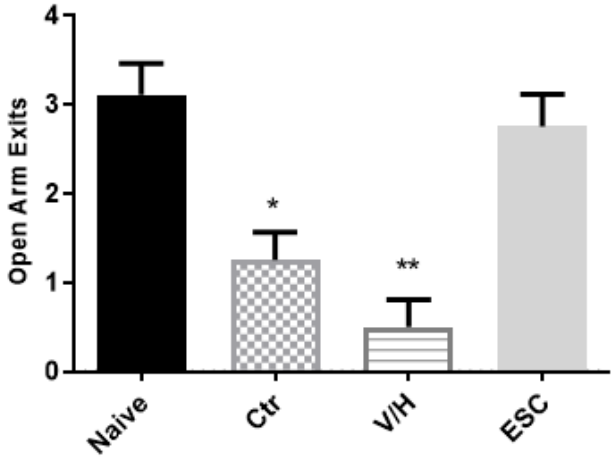
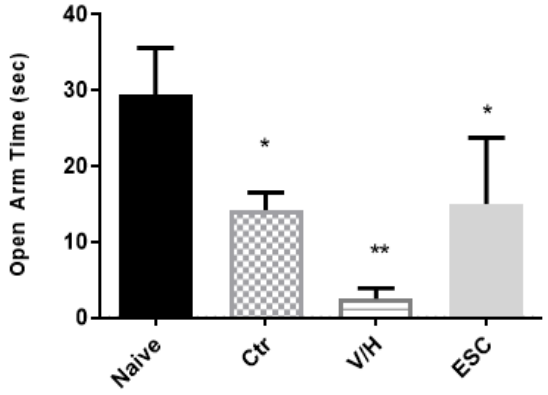


Figure 2: Elevated Plus Maze

(A) Effect of 3 weeks of treatment with V/H (100 mg/kg), ESC (10 mg/kg) on OAE following immobilization stress.

Values are expressed as the mean ± SEM (ANOVA followed by Tukey's test). F (3, 31) =14.25; *$p<0.05$, ** $p<0.0001$ versus naïve. OAE, open arm exists.

Figure 2.B



(B) Effect of 3 weeks of treatment with V/H (100 mg/kg), ESC (10 mg/kg) on OAT following immobilization stress .

ANOVA followed by Tukey's test.F (3,28)=11.10; * p<0.05, ** p<0.0001 versus naïve. OAT: open arm time. V/H: Valerian/Hops; ESC: Escitalopram; SEM, standard error of the mean.

3.2.3 Open field test

The valerian-hops-treated group did not show any increase in AF compared to the control group (p>0.05). Moreover, it significantly diminished the rearing frequency with respect to the control (p<0.05) thus indicating profound sedation. Results are shown in Figure 3A and 3 B.

Figure 3.A

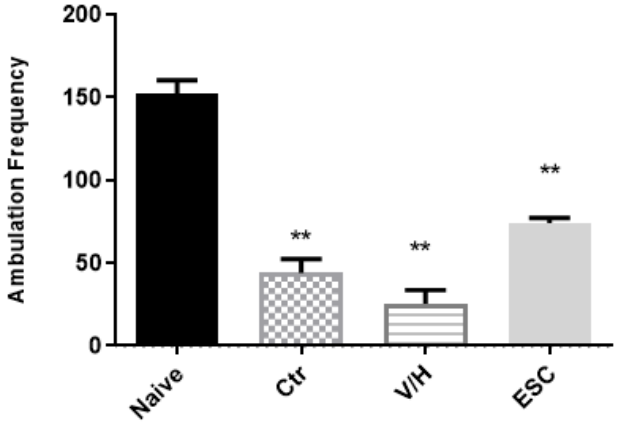
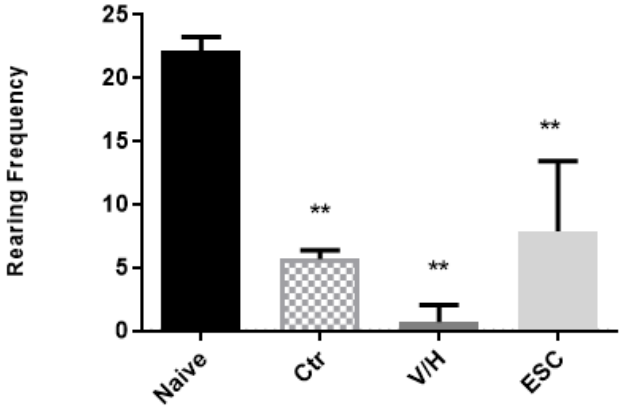


Figure 3: Open Field Test

(A) Effect of 3 weeks of treatment with V/H (100 mg/kg), ESC (10 mg/kg) following immobilization stress on the ambulation frequency.

Values are expressed as the mean ± SEM (ANOVA followed by Tukey's test). F(3,33)=57.91; **p<0.0001 versus naïve.

Figure 3.B



(B) Effect of 3 weeks of treatment with V/H (100 mg/kg), ESC (10 mg/kg) following immobilization stress on the rearing frequency.

Values are expressed as the mean ± SEM (ANOVA followed by Tukey's test). F(3, 34)=69.19;**p<0.0001 versus naïve. V/H : Valerian/Hops ; ESC: Escitalopram; SEM, standard error of the mean

3.3 Biochemical tests

3.3.1 NO_x & iNOS

The AIS increased NO_x ($p<0.05$), and this increase was significantly normalized with the valerian-hops ($p<0.001$); similarly escitalopram showed a NO_x lowering effect in respect to the stressed group ($p<0.001$), results are shown in Figure 4. The iNOS levels did not vary throughout the study (data are not shown).

Figure 4

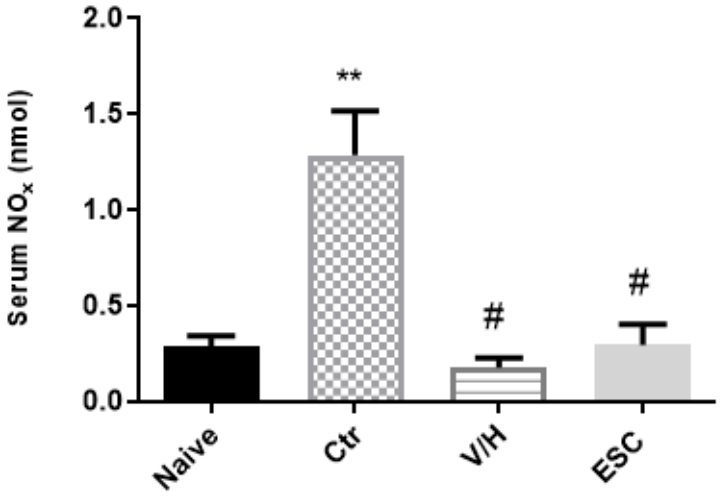


Figure 4: Nitric Oxide levels Effect of 3 weeks of treatment with V/H (100 mg/kg), ESC (10 mg/kg) following immobilization stress on serum NO_x levels.

Values are expressed as the mean ± SEM (ANOVA followed by Tukey's test). F(3, 30)=19.21;**p<0.0001 versus naïve # p<0.0001 versus control. V/H: Valerian/Hops; ESC: Escitalopram; SEM, standard error of the mean.

3.3.2. SOD activity

The AIS increased SOD activity ($p<0.05$) in the stressed group with respect to the naïve , valerian-hops treated group showed a significant decrease in respect to the stressed group ($p<0.001$); however, escitalopram did not show any change in SOD activity. Figure 5

Figure 5

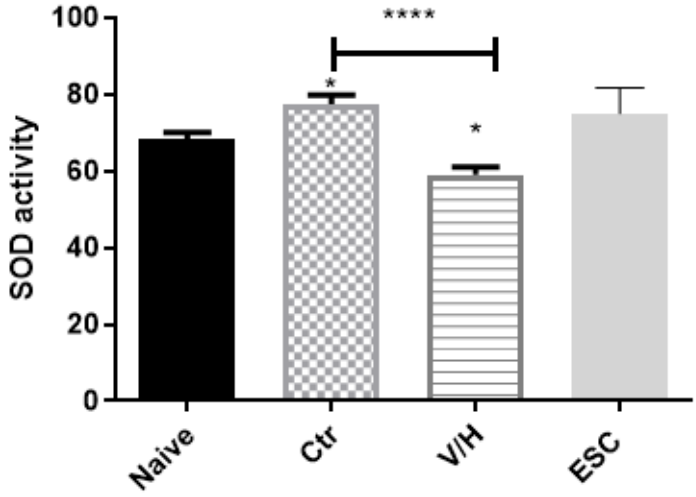


Figure 5: SOD activity

The effect of 3 weeks of treatment with V/H (100 mg/kg), ESC (10 mg/kg) following immobilization stress on SOD activity levels.

Values are expressed as the mean ± SEM (ANOVA followed by Tukey's test). F (3, 30) = 15.88;*$p<0.05$ versus naïve **** $p<0.0001$ versus control. V/H : Valerian/Hops ; ESC: Escitalopram; SEM, standard error of the mean.

4. DISCUSSION

The current study aimed at comparing the antidepressant effect of valerian-hops to escitalopram on short and long terms use using different models and to correlate the findings with NOx changes.

In the normal condition depression model, the valerian-hops demonstrated antidepressant and anxiolytic activities similar to escitalopram, but with no sedative effect. This result was expected and is consistent with previous studies that used the herb for short-term treatment(28,29). This effect is thought to be caused by agonizing the GABAA receptor, thus leading to a soothing/anxiolytic effect due to valerenic acid, the main active constituent(22,23).

The findings of the anxiety model demonstrate a profound sedative effect with no anxiolytic or antidepressant effect. These findings seem to contradict previous studies showing that valerian exerts no sedative action after five days of administration in an anxiety model(38) or after 16 days in an anxiety-free model(28). However, one explanation of this finding could be the longer duration of treatment and the synergistic sedative properties of hops(39).

The AIS resulted in a significant elevation in NOx and SOD activity in the stressed group compared to the naïve group, and valerian-hops restored NOx to normal.

As seen, the NOx elevation under AIS and the decline

by valerian-hops are not related to iNOS expression. NO can be synthesized from other enzymes; hence further investigations of the neuronal nNOS and the endothelial eNOS (9,40) are required to clarify this finding.

While the AIS enhanced SOD activity in the stressed mice, the SOD activity in the valerian-hops treated group was lower. This could be explained by the direct scavenging activity of the flavonoids and phenolic compounds in the extract(30,41) that neutralized the generated free radicals and therefore did not result in SOD activation.

The treatment of depression and anxiety is challenging due to the inadequate and inconsistent response of many classical antidepressants in addition to the associated lag and adverse effects (4,42,43).

Our findings demonstrated that the herb exerts antidepressant properties at a single dose similar to escitalopram however this effect has vanished and has been replaced by strong sedation in the anxiety model. This raises several questions behind the different mechanism underlying the two responses. Perhaps acute antidepressant property is mediated by some "fast acting" GABAergic constituents of the extract as valerenic acid and upon the chronic dosing in an anxiety model other "sedating" constituents are largely involved. The next step is to isolate and characterize the important active constituents of the valerian-hops combination.

The main strength of this study is the use of two different mice models to evaluate the antidepressant and anxiolytic/sedative role of valerian-hops. On the other hand, limitations include the use of the whole extract and the study of markers only in the anxiety model.

In conclusion, valerian-hops combination showed acute antidepressant effect similar to escitalopram when given as a single dose, whereas upon the long term use and as shown in the anxiety model valerian-hops produced only a strong sedative effect with a marked decrease in NO_x and SOD activity.

REFERENCES

1. Regehr C., Carey M., Wagner S., et al. Prevalence of PTSD, Depression and Anxiety Disorders in Correctional Officers : A Systematic Review Prevalence of PTSD , Depression and Anxiety Disorders in Correctional O ffi cers : A Systematic Review. Corrections [Internet]. 2019;0(0):1–13. Available from: https://doi.org/10.1080/23774657.2019.1641765
2. Taher YA, Samud AM, Hashemi MM, et al. Prevalence of depression, anxiety and stress among Libyan primary and secondary Schoolteachers: a cross-sectional study. Jordan J. Pharm. Sci. 2016; 403(3972):1–12.
3. Hawgood J., De Leo D. Anxiety disorders and suicidal behavior: An update. Vol. 21, Current Opinion in Psychiatry. 2008. p. 51–64.
4. Hasin D.S., Sarvet A.L., Meyers J.L. et al. Epidemiology of Adult. 2018; 75(4):336–46.
5. Gammoh O., Mayyas F., Darwish Elhajji F. Chlorpheniramine and escitalopram: Similar antidepressant and nitric oxide lowering roles in a mouse model of anxiety. Biomed Reports. 2017 Jun;6(6):675–80.
6. Sowa-ku M., Stycze K., Siwek M., et al. Lipid Peroxidation and Immune Biomarkers Are Associated with Major Depression and Its Phenotypes, Including Treatment-Resistant Depression and Melancholia. 2018;448–60.
7. Gammoh OS, Al-Smadi A, Al-Awaida W.et al. Increased Salivary Nitric Oxide and G6PD Activity in Refugees with Anxiety and Stress. Stress Heal. 2016 Oct 1;32(4):435–40.
8. Jin L., Qin L., Xia D., et al. Active secretion and protective effect of salivary nitrate against stress in human volunteers and rats. Free Radic Biol Med. 2013 Apr;57:61–7.

9. Guix F.X., Uribesalgo I., Coma M., et al. The physiology and pathophysiology of nitric oxide in the brain. 2005;76:126–52.
10. Harkin A.J., Bruce K.H, Craft B, et al. Nitric oxide synthase inhibitors have antidepressant-like properties in mice 1 . Acute treatments are active in the forced swim test. 1999;207–13.
11. Blokhina O, Virolainen E, Fagerstedt K V. Antioxidants, oxidative damage and oxygen deprivation stress: a review. Ann Bot. 2003;91(2):179–94.
12. Rakesh G., Pae CU, Masand P.S. Beyond serotonin: newer antidepressants in the future. Expert Rev Neurother [Internet]. 2017;17(8): 777–90. Available from: http://dx.doi.org/10.1080/14737175.2017.1341310
13. Versus A.M.C.W., Papakostas G.I., Fava M., et al. Treatment of SSRI-Resistant Depression : Across-Class Switches. 2008; 0–5.
14. Unbehaun T, Spiegelhalder K, Hirscher V, et al. Nature and Science of Sleep Dovepress Management of insomnia: update and new approaches. Nat Sci Sleep [Internet]. 2010;2–127. Available from: www.dovepress.com
15. Gammoh OS, Al-Smadi A, Turjman C, et al. Valerian: An underestimated anxiolytic in the community pharmacy? J Herb Med [Internet]. 2016;6(4):193–7. Available from: http://dx.doi.org/10.1016/j.hermed.2016.09.001
16. Paul PP, Kundu P, Karmakar UK. Chemical and Biological Investigation of Sanchezia nobilis Leaves Extract. Jordan j. pharm. sci. 2022;15(1):121–31.
17. Patočka J, Jakl J. Biomedically relevant chemical constituents of Valeriana officinalis. J Appl Biomed. 2010;8(1):11–8.
18. Torkamani M.R.D, Abbaspour N., Jafari M., et al. Elicitation of valerenic acid in the hairy root cultures of Valeriana officinalis L (Valerianaceae). Trop J Pharm Res. 2014;13(6):943–9.
19. Attele A.S., Xie J.T., Yuan C.S. Treatment of insomnia: An alternative approach. Altern Med Rev. 2000; 5(3):249–59.
20. Becker A, Felgentreff F, Schröder H, et al. he anxiolytic effects of a Valerian extract is based on Valerenic acid. BMC Complement Altern Med. 2014;14:1–5.
21. Abourashed EA, Koetter U, Brattström A. In vitro binding experiments with valerian, hops and their fixed combination extract (Ze91019) to selected central nervous system receptors. Phytomedicine. 2004;11(7–8):633–8.
22. Yuan C, Mehendale S, Xiao Y, et al. The Gamma-Aminobutyric Acidergic Effects of Valerian and Valerenic Acid on Rat Brainstem Neuronal Activity. 2004.
23. Khom S., Khom S., Khom S., et al. Valerenic acid potentiates and inhibits GABA A receptors : Molecular mechanism and subunit specificity Related papers.
24. Dimpfel W., Brattström A., Koetter U. Central Action of A Fixed Valerian -Hops Extract Combination (Z E 91019) in freely moving rats. 2006;496–500.
25. Shah BN, Panchal MA, Gohil N, et al. PHYTO-PHARMACOLOGICAL PROFILE OF HUMULUS LUPULUS.
26. Wazaify M, Elayeh E, Tubeileh R, et al. Assessing insomnia management in community pharmacy setting in Jordan: A simulated patient approach. PLoS One. 2019;14(12):1–10.
27. Committee on Herbal Medicinal Products (HMPC). European Union herbal monograph on Valeriana officinalis L., flos. Eur Med Agency [Internet]. 2016; 31(February): 1–9. Available from: https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-valeriana-officinalis-l-radix_en.pdf
28. Hattesohl M., Feistel B., Sievers H., et al. Extracts of Valeriana officinalis L. s.l. show anxiolytic and antidepressant effects but neither sedative nor myorelaxant properties. Phytomedicine. 2008 Jan 25;15(1–2):2–15.

29. Sah S.P., Mathela C.S., Chopra K. Elucidation of possible mechanism of analgesic action of Valeriana Wallichii DC chemotype (patchouli alcohol) in experimental animal models. Indian J Exp Biol. 2010; 48(3):289–93.
30. Chow N.K., Fretz M., Hamburger M., et al. Telemetry as a tool to measure sedative effects of a valerian root extract and its single constituents in mice. Planta Med. 2011;77(8):795–803.
31. Machawal L., Kumar A. Possible involvement of nitric oxide mechanism in the neuroprotective effect of rutin against immobilization stress induced anxiety like behaviour, oxidative damage in mice. Pharmacol Reports. 2014;66(1):15–21.
32. Sah S.P., Mathela C.S., Chopra K. Involvement of nitric oxide (NO) signalling pathway in the antidepressant activity of essential oil of Valeriana wallichii Patchouli alcohol chemotype. Phytomedicine. 2011 Nov 15; 18(14): 1269–75.
33. Porsolt R.D., Bertin A, Blavet N., et al. Immobility induced by forced swimming in rats: Effects of agents which modify central catecholamine and serotonin activity. Eur J Pharmacol. 1979 Aug 1; 57(2–3):201–10.
34. Rodgers RJ, Dalvi A. Anxiety, defence and the elevated plus-maze. Neurosci & Biobehav Rev. 1997; 21(6):801–10.
35. Dishman R.K., Armstrong RB, Delp M.D., et al. Open-field behavior is not related to treadmill performance in exercising rats. Physiol Behav. 1988;43(5):541–6.
36. Green L.C., Wagner DA, Glogowski J, et al. Analysis of nitrate, nitrite, and [15N] nitrate in biological fluids. Anal Biochem. 1982;126(1):131–8.
37. Omori A, Yoshimura Y, Deyama Y, et al. Rosmarinic acid and arbutin suppress osteoclast differentiation by inhibiting superoxide and NFATc1 downregulation in RAW 264.7 cells. Biomed Reports. 2015 Jul;3(4):483–90.
38. Mag P, Kim JS, Ahn JD, et al. Effects of Valerianae Radix et Rhizoma extract on psychological stress in mice. 2015.
39. Franco L., Sánchez C., Bravo R., et al. The sedative effects of hops (Humulus lupulus), a component of beer, on the activity/rest rhythm. Acta Physiol Hung. 2012.
40. Vila-Verde C, Marinho ALZ, Lisboa SF et al. Nitric oxide in the prelimbic medial prefrontal cortex is involved in the anxiogenic-like effect induced by acute restraint stress in rats. Neuroscience. 2016 Apr 21;320:30–42.
41. Dyayiya N.A., Oyemitan IA, Matewu R., et al. Chemical analysis and biological potential of Valerian root as used by herbal practitioners in the Eastern Cape Province, South Africa. African J Tradit Complement Altern Med. 2016;13(1):114–22.
42. Kessing L.V., Hansen HV, Demyttenaere K., et al. Depressive and bipolar disorders: Patients' attitudes and belief towards depression and antidepressants. Psychol Med. 2005 Aug;35(8):1205–13.
43. Wen X.J., Wang L.M., Liu Z.L., et al. Meta-analysis on the efficacy and tolerability of the augmentation of antidepressants with atypical antipsychotics in patients with major depressive disorder. Brazilian J Med Biol Res. 2014; 47(7):605–16.

مقارنة فاعلية مزيج عشبة النارين والجنجل بعقار الإيسيتالوبرام على نماذج قلق وإكتئاب حيوانية والعلاقة المحتملة مع الأكسدة

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ملخص

تعتبر اضطرابات الاكتئاب والقلق من أكثر مشاكل الصحة العقلية شيوعًا وترتبط بالأكسدة إتباطاً وثيقاً. على الرغم من أنه يشتهر بتأثيره المزيل للقلق، إلا أن التأثير المضاد للاكتئاب لتركيبة عشبة الجنجل لم تتم دراسته مسبقًا، كما أن العلاقة بين التأثير المهدئ لتركيبة النارين والجنجل ومؤشراتالأكسدة غير واضحة. البحث الحالي له هدفان: (1) مقارنة التأثير المضاد للاكتئاب لمزيج عشبة النارين والجنجل مع عقار الإيسيتالوبرام و(2) تقييم التأثيرات المهدئة / المزيلة للقلق لمزيج عشبة النارين والجنجل وعلاقته بمؤشرات الأكسدة وهي أكسيد النيتروجين (NOx)، إنزيم تصنيع أكسيد النيتروجين (iNOS) وإنزيم مضاد الأكسدة .Super Oxide Dismutase (SOD)تم استخدام نموذجين باستخدام الفئران :BALB / c نموذج اكتئاب للحالة الطبيعية تم فيه تقسيم الفئران إلى: مجموعة التحكم، مجموعة مزيج النارين والجنجل (100 مجم / كجم)، ومجموعات المعالجة بالإسيتالوبرام (10 مجم / كجم) قبل ساعة واحدة من الاختبار الميداني للقلق، واختبار المتاهة المرتفع للقلق، واختبار السباحة القسري للإكتئاب. النموذج الثاني هو ونموذج القلق الذي تم فيه تقسيم الفئران إلى: غير مضغوطة، والتحكم (مضغوطة)، مجموعة مزيج النارين والجنجل (100 مجم / كجم)، وإسكيتالوبرام (10 مجم / كجم). تم معالجة المجموعات لمدة ثلاثة أسابيع ؛ تم تقييده لمدة 6 ساعات وتم التضحية به، وتم الحصول على مصل للكشف عن نشاط NOx و iNOS و .SOD في نموذج الاكتئاب، أظهرت مجموعة مزيج النارين والجنجل نشاطًا مضادًا للاكتئاب مشابهًا لإسيتالوبرام. في نموذج القلق، أظهرت الفئران التي عولجت مجموعة مزيج النارين والجنجل تأثيرًا مهدئًا عميقًا في جميع نماذج السلوك، وقامت بتثبيط مستويات أكاسيد النيتروجين المرتفعة الناتجة عن القلق ونشاط انزيم ال .SOD في ظل الظروف العادية، تمارس تركيبة مزيج النارين والجنجل تأثيرًا مضادًا للاكتئاب مشابهًا لـ لإسكيتالوبرام بينما تمارس في ظروف التوتر / القلق تأثيرات مهدئة ومضادة للأكسدة.

الكلمات الدالة: القلق، الإكتئاب، إسيتالوبرام، النارين، الجنجل.

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