

Pinetonina™
Literature Review
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Introduction

Fagron Pinetonina™ is a phyto-complex derived from the essential oils of *Lavandula Angustifolia* Mill., *Lavandula Dentata* and *Foeniculum Vulgare* Mill. Essential oils of these plants have been extensively studied for their therapeutical properties.

To support all the aspects of the use of these essential oils for their properties, this literature review is composed with abstracts of the most relevant articles. Should you have any questions or remarks, please contact your local sales representative.



Pinetonina™

Evaluation of Pinetonina™

Jardim M. Et al. (2018) *Pinetonina™, an Intranasally Administered Essential Oil Preparation, Is Effective In Decrease of Cortisol Levels and on the Glutamate Release Modulation.* *Neuroscience & Medicine.* 2018;9;135-149. <https://doi.org/10.4236/nm.2018.93014>.

Background: Integrative approaches such as aromatherapy are used in addition to medications to improve sleep quality and reduce anxiety. Thus, Pinetonina™, a phyto-complex obtained from a blend of essential oils aims to aid in the symptoms of stress and anxiety.

Methods: The cytotoxicity of Pinetonina™ was evaluated MTT assay using fibroblasts and astrocytes showed reduction in the cell viability only at high concentrations. Cultures of astrocytes treated with Pinetonina™ showed residual glutamate levels in the supernatants reducing proportionally, as well as, intracellular calcium reduction. The determination of salivary cortisol showed a significant reduction in salivary cortisol levels in the group that received Pinetonina™. The evaluation of the electroencephalogram in patients treated with Pinetonina™ had a significant increase ($P < 0.05$) in the frequency (Hz) of the alpha and beta waves.

Results: A reduction in dose-dependent cell viability was observed when compared to cultures of Pinetonina™ treated fibroblasts with control culture. When Pinetonin™ and linalool are administered in astrocytic cells, there was a reduction of the intracellular concentration of Ca^{2+} against a control group treated with DHPG agonist. The evaluation of salivary cortisol demonstrated a reduction when the patient group was treated with Pinetonina™ by purchasing the results against the group of patients treated with saline. Reinforcing the relaxed state of that group, alpha waves have been increased and reductions in beta waves.

Conclusion: The results obtained after intranasal administration of Pinetonina™ suggest that this phyto complex can help reduce the symptoms of stress and the better quality of life.



Lavender

European Medicines Agency. *Assessment report on Lavandula angustifolia Mill., aetheroleum and Lavandula angustifolia Mill., flos* EMA/HMPC/143183/2010.

Abstract: This draft Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Lavandula angustifolia* Mill., aetheroleum and of the draft monograph on *Lavandula angustifolia* Mill., flos. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monographs.

Lewith G. et al. *A Single-Blinded, Randomized Pilot Study Evaluating the Aroma of Lavandula angustifolia as a Treatment for Mild Insomnia*. *The journal of alternative and complementary medicine*. 2005;11;4;631–637. doi: 10.1089/acm.2005.11.631.

Objectives: The aims of this study were to evaluate the proposed trial methodology and the efficacy of *Lavandula angustifolia* (lavender) on insomnia.

Design: This was a pilot study with randomized, single-blind, cross-over design (baseline, two treatment periods, and a washout period, each of one-week duration). Subjects and setting: Volunteers with defined insomnia treated on a domiciliary basis participated in the study.

Results: Ten (10) volunteers (5 male and 5 female) were entered and completed the 4-week study. Lavender created an improvement of 2.5 points in PSQI ($p = 0.07$, 95% CI - 4.95 to - 0.4). Each intervention was equally credible and belief in CAM did not predict the outcome. Women and younger volunteers with a milder insomnia improved more than others. No period or carry-over effect was observed.

Conclusion: The methodology for this pilot study appeared to be appropriate. Outcomes favor lavender, and a larger trial is required to draw definitive conclusions.

Hirokawa K. et al. *Effects of lavender aroma on sleep quality in healthy Japanese students*. *Perceptual and Motor Skills*. 2012;114(1):111-122. DOI: 10.2466/13.15.PMS.114.1.111-122.

Abstract: This single-blind randomized study investigated the effectiveness of lavender aroma on quality of sleep in healthy Japanese students. The data of seven participants (2 men, 5 women) in the intervention group and eight participants (3 men, 5 women) in the control group were analyzed (M age = 19.0 yr., SD = 0.9). The total procedure comprised 3 days for pre-intervention assessment, 5 days for the intervention, and 3 days for post-intervention assessment. Lavender exposure was compared with the absence of lavender (control). Information regarding the relaxing effect of aromas was provided to examine expectancy effects. Results showed that lavender aroma improved sleepiness at awakening after the intervention. Sex differences and daily variation in quality of sleep during the intervention period were not observed. The findings suggest that nighttime exposure to lavender aroma relieves sleepiness at awakening.



Atsumi T. et al. *Smelling lavender and rosemary increases free radical scavenging activity and decreases cortisol level in saliva.* Psychiatry research. 2007;150: 89-96. DOI: 10.1016/j.psychres.2005.12.012.

Abstract: Free radicals/reactive oxygen species are related to many biological phenomena such as inflammation, aging, and carcinogenesis. The body possesses various antioxidative systems (free radical scavenging activity, FRSA) for preventing oxidative stress, and saliva contains such activity. In the present study, we measured the total salivary FRSA induced after the smelling of lavender and rosemary essential oils that are widely used in aromatherapy. Various physiologically active substances in saliva such as cortisol, secretory IgA, and α -amylase activity were found to be correlated with aroma-induced FRSA. The subjects (22 healthy volunteers) sniffed aroma for 5 min, and each subject's saliva was collected immediately. FRSA was measured using 1,1-diphenyl-2-picrylhydrazyl. The FRSA values were increased by stimulation with low concentrations (1000 times dilution) of lavender or by high-concentrations (10 times dilution) of rosemary. In contrast, both lavender and rosemary stimulations decreased cortisol levels. A significant inverse correlation was observed between the FRSA values and the cortisol levels with each concentration of rosemary stimulation. No significant changes were noted in sIgA or α -amylase. These findings clarify that lavender and rosemary enhance FRSA and decrease the stress hormone, cortisol, which protects the body from oxidative stress.

Chien L.W. et al. *The Effect of Lavender Aromatherapy on Autonomic Nervous System in Midlife Women with Insomnia.* Evidence-Based Complementary and Alternative Medicine Volume 2012, Article ID 740813, 8 pages. doi:10.1155/2012/740813. DOI: 10.1155/2012/740813.

Abstract: The objective of this study is to determine the effects of 12 weeks of lavender aromatherapy on self-reported sleep and heart rate variability (HRV) in the midlife women with insomnia. Sixty-seven women aged 45–55 years, with a CPSQI (Chinese version of Pittsburgh Sleep Quality Index) greater than 5, were recruited from communities in Taiwan. The experimental group ($n = 34$) received lavender inhalation, 20min each time, twice per week, for 12 weeks, with a total of 24 times. The control group ($n = 33$) received health education program for sleep hygiene with no intervention. The study of HRV was analyzed by time and frequency-domain methods. Significant decrease in mean heart rate (HR) and increases in SDNN (standard deviation of the normal-to-normal (NN) intervals), RMSDD (square root of the mean squared differences of successive NN intervals), and HF (high frequency) of spectral powers analysis after lavender inhalation were observed in the 4th and 12th weeks of aromatherapy. The total CPSQI score of study subjects was significantly decreased in the experimental group ($P < 0.001$), while no significant difference was observed across the same time period ($P = 0.776$) in the control group. Resting HR and HRV measurements at baseline 1 month and 3 months after allocation showed no significant difference between the experimental and control groups. The study demonstrated that lavender inhalation may have a persistent short-term effect on HRV with an increase in parasympathetic modulation. Women receiving aromatherapy experienced a significant improvement in sleep quality after intervention. However, lavender aromatherapy does not appear to confer benefit on HRV in the long-term follow up.



Kritsidima M. et al. *The effects of lavender scent on dental patient anxiety levels: a cluster randomized -controlled trial.* Community Dent Oral Epidemiol 2010; 38: 83–87. DOI: 10.4103/1735-9066.170001.

Abstract: To review the effect of lavender scent on anticipatory anxiety in dental participants. Methods: In a cluster randomized-controlled trial, patients' (N = 340) anxiety was assessed while waiting for a scheduled dental appointment, either under the odor of lavender or with no odor. Current anxiety, assessed by the brief State Trait Anxiety Indicator (STAI-6), and generalized dental anxiety, assessed by the Modified Dental Anxiety Scale (MDAS) were examined. Results: Analyses of variance (anova) showed that although both groups showed similar, moderate levels of generalized dental anxiety (MDAS F (1,338) = 2.17, P > 0.05) the lavender group reported significantly lower current anxiety (STAI: F (1,338) = 74.69, P < 0.001) than the control group. Conclusions: Although anxiety about future dental visits seems to be unaffected, lavender scent reduces state anxiety in dental patients.

Hudson R. *The value of lavender for rest and activity in the elderly patient.* Complementary Therapies in Medicine. 1996;4: 52-57. DOI: 10.1089/acm.2014.0327.

Abstract: Symptoms of tiredness, lack of muscle co-ordination and dysarthria, and difficulty in maintaining attention in elderly people may be wrongly labelled as part of the ageing process and so ignored. 1 If adequate sleep can reduce these symptoms and restore therapeutic activity, it is of enormous value to elderly people in retaining their independence and quality of life. Safe promotion of sleep without daytime lethargy is needed. In order to test the hypotheses that Essential Oil of Lavender has a sedative effect, and that the resultant sleep promotes therapeutic activity, a pilot study was arranged with acutely ill elderly people. This was followed by a more detailed trial with long-term patients. The results show a positive trend towards improvement with lavender.

Kasper, S. et al. (2010) *Efficacy and safety of silexan, a new, orally administered lavender oil preparation, in subthreshold anxiety disorder – evidence from clinical trials.* Wiener Medizinische Wochenschrift December 2010;160;21–22: 547–556. DOI: 10.1007/s10354-010-0845-7.

Abstract: We review the data on the efficacy and tolerability of silexan, a novel preparation from lavender oil for oral use, in the treatment of anxiety disorders and related condition with particular attention to subthreshold generalized anxiety disorder (GAD). Three randomized, double-blind clinical trials were identified which investigated the efficacy of silexan in subsyndromal anxiety disorder (vs. placebo; 10 weeks' treatment), in GAD (vs. lorazepam; 6 weeks), and in restlessness and agitation (vs. placebo; 10 weeks) according to DSM-IV and ICD-10 criteria. All trials assessed the participants' anxiety levels using the Hamilton Anxiety Scale (HAMA). Across all trials 280 patients were exposed to silexan 80 mg/ day, 37 were treated with lorazepam 0.5 mg/day and 192 received placebo. Average within group HAMA total scores at baseline ranged between 24.7 and 27.1 points. Patients treated with silexan showed average HAMA total score decreases by between 10.4±7.1 and 12.0±7.2 points at week 6 and by between 11.8±7.7 and 16.0±8.3 points at week 10. In GAD silexan and lorazepam showed comparable HAMA total score reductions (90% CI for mean value difference: -2.3; 2.8 points).



Koulivand P.H. et al. *Lavender and the Nervous System. Evidence-Based Complementary and Alternative Medicine. Volume 2013, ArticleID681304, 10 pages. DOI: 10.1155/2013/681304.*

Abstract: Lavender is traditionally alleged to have a variety of therapeutic and curative properties, ranging from inducing relaxation to treating parasitic infections, burns, insect bites, and spasm. There is growing evidence suggesting that lavender oil may be an effective medicament in treatment of several neurological disorders. Several animal and human investigations suggest anxiolytic, mood stabilizer, sedative, analgesic, and anticonvulsive and neuroprotective properties for lavender. These studies raised the possibility of revival of lavender therapeutic efficacy in neurological disorders. In this paper, a survey on current experimental and clinical state of knowledge about the effect of lavender on the nervous system is given.

Hritcu L. et al. *Effects of lavender oil inhalation on improving scopolamine-induced spatial memory impairment in laboratory rats. Phytomedicine. 2012;19;6: 529-534. DOI: 10.1016/j.phymed.2012.02.002.*

Abstract: Lavender is reported to be an effective medical plant in treating inflammation, depression, stress and mild anxiety in Europe and the USA. The present study investigated the effects of two different lavender essential oils from *Lavandula angustifolia* ssp. *angustifolia* Mill. (Lamiaceae) and *Lavandula hybrida* Rev. (Lamiaceae) on neurological capacity of male Wistar rats subjected to scopolamine (0.7 mg/kg)- induced dementia rat model. Chronic exposures to lavender essential oils (daily, for 7 continuous days) significantly reduced anxiety-like behavior and inhibited depression in elevated plus-maze and forced swimming tests, suggesting anxiolytic and antidepressant activity. Also, spatial memory performance in Y-maze and radial arm-maze tasks was improved, suggesting positive effects on memory formation. Taken together, multiple exposures to lavender essential oils could effectively reverse spatial memory deficits induced by dysfunction of the cholinergic system in the rat brain and might provide an opportunity for management neurological abnormalities in dementia conditions.

Wang D. et al. *Neuroprotective activity of lavender oil on transient focal cerebral ischemia in mice. Molecules. 2012;17;8: 9803–9817. DOI: 10.3390/molecules17089803.*

Abstract: The air-dried aerial parts of *Lavandula angustifolia* Mill, a traditional Uyghur herbal drug, is used as resuscitation-inducing therapy to treat neurodysfunction, such as stroke. This study was designed to assess the neuroprotective effects of lavender oil against ischemia/reperfusion (IR) injury in mice. Focal cerebral ischemia was induced by the intraluminal occlusion method with a nylon string. The neurodysfunction was evaluated by neurological deficit and the infarct area was showed by 2,3,5-triphenyltetrazolium chloride (TTC) staining. The histopathological changes were observed by hematoxylin and eosin staining. The levels of mitochondria-generated reactive oxygen species (ROS), malondialdehyde (MDA) and carbonyl, the ratio of reduced glutathione (GSH)/glutathione disulfide (GSSG), the activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) in brain tissue were measured to estimate the oxidative stress state. Neurological deficit, infarct size, histopathology changes and oxidative stress markers were evaluated after 22 h of reperfusion. In comparison with the model group, treatment with lavender oil significantly decreased neurological deficit scores, infarct size, the levels of MDA, carbonyl and ROS, and attenuated neuronal damage, upregulated SOD, CAT, GSH-Px activities and GSH/GSSG ratio. These results suggested that the neuroprotective effects of lavender oil against cerebral ischemia/reperfusion injury may be attributed to its antioxidant effects.



Schuwald A.M. et al. *Lavender Oil-Potent Anxiolytic Properties via Modulating Voltage Dependent Calcium Channels*. PLoS ONE. 2013;8;4: e59998. DOI: 10.1371/journal.pone.0059998.

Abstract: Recent clinical data support the clinical use of oral lavender oil in patients suffering from subsyndromal anxiety. We identified the molecular mechanism of action that will alter the perception of lavender oil as a nonspecific ingredient of aromatherapy to a potent anxiolytic inhibiting voltage dependent calcium channels (VOCCs) as highly selective drug target. In contrast to previous publications where exorbitant high concentrations were used, the effects of lavender oil in behavioral, biochemical, and electrophysiological experiments were investigated in physiological concentrations in the nanomolar range, which correlate to a single dosage of 80 mg/d in humans that was used in clinical trials. We show for the first time that lavender oil bears some similarities with the established anxiolytic pregabalin. Lavender oil inhibits VOCCs in synaptosomes, primary hippocampal neurons and stably overexpressing cell lines in the same range such as pregabalin. Interestingly, Silexan does not primarily bind to P/Q type calcium channels such as pregabalin and does not interact with the binding site of pregabalin, the $\alpha 2\delta$ subunit of VOCCs. Lavender oil reduces non-selectively the calcium influx through several different types of VOCCs such as the N-type, P/Q-type and T-type VOCCs. In the hippocampus, one brain region important for anxiety disorders, we show that inhibition by lavender oil is mainly mediated via N-type and P/Q-type VOCCs. Taken together, we provide a pharmacological and molecular rationale for the clinical use of the oral application of lavender oil in patients suffering from anxiety.

Moeini, M. et al. *Effect of aromatherapy on the quality of sleep in ischemic heart disease patients hospitalized in intensive care units of heart hospitals of the Isfahan University of Medical Sciences*. Iranian Journal of Nursing and Midwifery Research. 2010;15(4):234–239.

Background: Nowadays, the complementary medicine is highly considered because of its effectiveness and safety. Aromatherapy is one of the holistic nursing cares which sees human beings as a biological, mental and social unit while the psychological dimension has the central role. Each of these dimensions is dependent on each other and is affected by each other. Therefore, it is fundamental for nurses to provide aromatherapy in their clinical performance. Aromatherapy helps treatment of diseases by using vegetable oils and it seems to be effective in reducing sleeplessness.

Methods: This was a clinical trial on 64 patients (male and female) hospitalized in CCU in Al-zahra and Chamran hospitals. The intervention included 3 nights, each time 9 hours aromatherapy with lavender oil for the experiment group, while the controls received no intervention. Both groups filled out the SMHSQ that includes 11 items to assess sleep quality before and after intervention.

Results: Data analysis showed that the mean scores of sleep quality in the two groups of experiment and control were significantly different after the aromatherapy with lavender oil ($p < 0.001$).

Conclusions: Quality of sleep in ischemic heart disease patients was significantly improved after aromatherapy with lavender oil. Therefore, using aromatherapy can improve the quality of their sleep and health.



Itai T. et al. *Psychological effects of aromatherapy on chronic hemodialysis patients.* Psychiatry and Clinical Neurosciences. 2000;54: 393-397. DOI: 10.1046/j.1440-1819.2000.00727.x.

Abstract: Effects of aromatherapy (odourless condition, lavender, and hiba oil) on mood and anxiety were investigated in 14 female patients who were being treated with chronic haemodialysis. A control period consisting of natural hospital smells was established before each test session, and then aromatic test conditions were systematically evaluated for odourless conditions as well as aromatic conditions containing lavender and hiba oil aromas. The effects of aromatherapy were measured using the Hamilton rating scale for depression (HAMD) and the Hamilton rating scale for anxiety (HAMA). Hiba oil aroma significantly decreased the mean scores of HAMD and HAMA, and lavender aroma significantly decreased the mean scores of HAMA. The mean scores of HAMD and HAMA in an odourless condition were not significantly different from those of the control conditions. These results indicate that in chronic haemodialysis patients hiba oil is an effective, non-invasive means for the treatment of depression and anxiety, and that lavender alleviates anxiety.



Linalool: main constituent of lavender oil.

Brum L.F.S. et al. *Effects of Linalool on Glutamate Release and Uptake in Mouse Cortical Synaptosome*. *Neurochemical Research*. 2001;26;3: 191–194.

Abstract: Linalool, a monoterpene compound prevalent in essential oil of plant species traditionally used as sedatives, has been characterized as anticonvulsant in several experimental models. Linalool inhibits the binding of [3H] glutamate and [3H] dizocilpine to brain cortical membranes, indicating a participation of the glutamatergic transmission its mechanism of action. In this study, we investigated the effects of linalool on [3H] glutamate release (basal and potassium-stimulated) and [3H] glutamate uptake in mice cortical synaptosomes. Linalool significantly reduced potassium-stimulated glutamate release as well as glutamate uptake, not interfering with basal glutamate release. The data indicates that linalool may interfere with several relevant elements of the glutamatergic transmission, including detriment of the K1-stimulated glutamate release.

Brum L.F.S et al. *Effects of Linalool on [3H] MK801 and [3H] Muscimol Binding in Mouse Cortical Membranes*. *Phytother*. 2001;15: 422–425.

Abstract: Linalool is a monoterpene compound reported to be a major component of essential oils of several aromatic species. Several linalool-producing species are used in traditional medical systems for sedative purposes, including the interruption and prevention of seizures. Previous studies in mice revealed that linalool modulates glutamatergic (competitive antagonism of L-[3H] glutamate binding, delayed intraperitoneal NMDA-induced convulsions and blockade of intracerebroventricular Quin-induced convulsions) and GABAergic transmission (protection against pentylenetetrazol and picrotoxin-induced convulsions). To further clarify the anticonvulsive mechanisms of linalool, we studied the effects of linalool on binding of [3H] MK801 (NMDA antagonist) and [3H] muscimol (GABAA agonist) to mouse cortical membranes. Linalool showed a dose dependent non-competitive inhibition of [3H]MK801 binding ($IC_{50} = 2.97 \text{ mM}$) but no effect on [3H] muscimol binding. The data suggest that the anticonvulsant mode of action of linalool includes a direct interaction with the NMDA receptor complex. The data do not, however, support a direct interaction of linalool with GABAA receptors, although changes in GABA-mediated neuronal inhibition or effects on GABA release and uptake cannot be ruled out.



Fennel

Badgujar B.S. et al. *Foeniculum vulgare Mill: A Review of Its Botany, Phytochemistry, Pharmacology, Contemporary Application, and Toxicology*. BioMed Research International. 2014; vol. 2014; Article ID 842674; 32 pages. DOI: 10.1155/2014/842674.

Abstract: *Foeniculum vulgare* Mill commonly called fennel has been used in traditional medicine for a wide range of ailments related to digestive, endocrine, reproductive, and respiratory systems. Additionally, it is also used as a galactagogue agent for lactating mothers. The review aims to gather the fragmented information available in the literature regarding morphology, ethnomedicinal applications, phytochemistry, pharmacology, and toxicology of *Foeniculum vulgare*. It also compiles available scientific evidence for the ethnobotanical claims and to identify gaps required to be filled by future research. Findings based on their traditional uses and scientific evaluation indicates that *Foeniculum vulgare* remains to be the most widely used herbal plant. It has been used for more than forty types of disorders. Phytochemical studies have shown the presence of numerous valuable compounds, such as volatile compounds, flavonoids, phenolic compounds, fatty acids, and amino acids. Compiled data indicate their efficacy in several in vitro and in vivo pharmacological properties such as antimicrobial, antiviral, anti-inflammatory, antimutagenic, antinociceptive, antipyretic, antispasmodic, antithrombotic, apoptotic, cardiovascular, chemo modulatory, antitumor, hepatoprotective, hypoglycemic, hypolipidemic, and memory enhancing property. *Foeniculum vulgare* has emerged as a good source of traditional medicine and it provides a noteworthy basis in pharmaceutical biology for the development/formulation of new drugs and future clinical uses.

Ghazanfarpour M. et al. *Effect of Foeniculum vulgare (fennel) on symptoms of depression and anxiety in postmenopausal women: a double-blind randomized controlled trial*. J Obst et Gynaecol. 2018 Jan; 38; 1:121-126. DOI: 10.1080/01443615 2017.

Abstract: The aim of this study was to evaluate the effect of *Foeniculum vulgare* (fennel) on anxiety and depression symptoms in postmenopausal women. This study was a double-blind, randomized, placebo-controlled trial, in which 60 eligible postmenopausal women were selected and then randomly assigned to fennel and placebo groups. Then, symptoms of anxiety and depression were measured using Hospital Anxiety and Depression Scale (HADS) and Zung's Self Rating Depression Scale (SDS). Following the intervention, the score of HADS (depression and anxiety subgroups) and SDS did not show any significant decrease in the sample under study. However, the analysis of patients with depression or anxiety disorder showed a borderline or significant improvement. Further studies with a larger sample size are required to confirm the findings.



Rahimikian F. et al. *Effect of Foeniculum vulgare Mill. (fennel) on menopausal symptoms in postmenopausal women: a randomized, triple - blind, placebo- controlled trial.* Menopause. 2017 Sep;24(9):1017-1021. DOI: 10.1097/GME.0000000000000881.

Objective: Preliminary data suggest that Foeniculum vulgare (fennel) can be an effective treatment for menopausal symptoms. This trial was designed to assess the efficacy of fennel in the management of menopausal symptoms in postmenopausal women.

Methods: In this triple-blind, placebo-controlled trial, 90 postmenopausal women aged 45 to 60 years in Tehran were randomly assigned to treatment (n¼45) or placebo (n¼45) groups. The participants received 8 weeks of treatment with soft capsules containing 100 mg fennel or a placebo (2 per day for each group). The participants were followed for 2 weeks postintervention to assess the continuance of the effect of intervention. The Menopause Rating Scale (MRS) questionnaire was used to assess changes in menopausal symptoms at baseline and at 4, 8, and 10 weeks after onset of intervention.

Results: The groups recorded similar mean scores on the MRS questionnaire before intervention. After intervention, the treatment group showed a significant decrease in the mean MRS score. The results of the Friedman test showed significant differences between the mean score at baseline and those at 4, 8, and 10 weeks after onset of intervention in the treatment group (P<0.001), whereas there were no significant differences in the placebo group. When the fennel and the placebo groups were compared, the independent t test showed significant differences in mean scores between groups at 4, 8, and 10 weeks (2 weeks postintervention; P<0.001).

Conclusions: Fennel is an effective and safe treatment to reduce menopausal symptoms in postmenopausal women without serious side effects. More clinical trials with larger populations are required to confirm this result.

Singh J. et al. *Anxiolytic Activity of Fennel Fruit Soxhlet in Mice.* Pharmacologyonline. 2010;1: 580-582. DOI: 10.1186/1472-6882-14-310.

Abstract: Rotarod test was the screening test used to assess the anxiolytic activity of the Fennel fruit soxhlet on mice. Diazepam (4 mg/kg) served as the standard anxiolytic agent. Fennel extract was administered at 250, 500, 750 and 1000mg/kg doses in different groups respectively. Diazepam and Fennel extract shows decrease in fall off time particularly fennel extract at 750 and 1000mg/kg doses (P<0.01). Soxhlet of Fennel fruits produces prominent anxiolytic activity in mice.



Cioanca et al. *Essential oils from Apiaceae as valuable resources in neurological disorders. Foeniculi vulgare aetheroleum. Industrial Crops & Products. 2016; 88: 51-57. DOI :10.1016/j.indcrop.2016.02.064.*

Abstract: Used as a spice and to improve the palatability of different meat and vegetable dishes, common fennel, *Foeniculum vulgare* Mill. (Apiaceae), was a traditional remedy for the relief of spasms and colic due to gas accumulation, to stimulate gastrointestinal motility, to alleviate productive coughs as well as for the induction of menstruation and lactation. Fennel essential oil extracted from fennel fruits is used as traditional medicine to improve eyesight, promote courage and mental strength, reduce stress/nervousness and produce calming. Therefore, we wanted to reinforce some of the folk uses with scientific proves. The present study analyzed the anxiolytic and antidepressant of the fennel essential oil in beta-amyloid (1-42) rat model of Alzheimer's disease (AD). The antioxidant activity of the essential oil was tested in vitro. The anxiolytic-and antidepressant-like effects of the fennel essential oil were studied by means of in vivo (elevated plus-maze and forced swimming tests) approaches. The beta-amyloid (1-42)-treated rats exhibited the following: decrease of the exploratory activity, the percentage of the time spent and the number of entries in the open arm within elevated plus-maze test and decrease of swimming time and increase of immobility time within forced swimming test. Inhalation of the fennel essential oil significantly exhibited anxiolytic- and antidepressant-like effects. Results suggest that the fennel essential oil inhalation ameliorates beta-amyloid (1-42)-induced anxiety and depression in laboratory rats. Thus, the results of the present study indicate that the fennel essential oil may have potential clinical applications in the management of anxiety and depression related to AD conditions.

Kishore N.R. et al. *Evaluation of anxiolytic activity of ethanolic extract of foeniculum vulgare in mice model. International Journal of Pharmacy and Pharmaceutical Sciences. 2012;4(3). DOI: 10.1186/1472-6882-14-310.*

Abstract: The present study was designed to investigate the anxiolytic activity of ethanolic extracts of *Foeniculum vulgare* fruit. The anxiolytic activity was evaluated by elevated plus maze, rotarod, open field test, and hole board models. The efficacy of extract (100-200mg/kg) was compared with standard anxiolytic drugs diazepam (1mg/kg). Extract administered animals showed exploratory behavior with all tests similar to diazepam. The results showed that the extract significantly increased the number of entries and time spent in the open arm in the elevated plus maze apparatus. In open field test, the extract showed significant increase in number of rearings, assisted rearing and number of square crossed. Furthermore, the extract produced skeletal muscle relaxant affect assessed by rota rod. Altogether these results suggest that the ethanolic extract of *Foeniculum vulgare* may possess anxiolytic activity and provide a scientific evidence for its traditional claim.



Mesfin M. et al. Evaluation of anxiolytic activity of the essential oils of the aerial part of *Foeniculum vulgare* Miller in mice. BMC Complementary and Alternative Medicine 2014;14: 310. DOI: 10.1186/1472-6882-14-310.

Background: *Foeniculum vulgare* locally known as ensilal, is an aromatic plant widely cultivated in temperate and tropical regions. The anti-anxiety activity of the crude extract of *F. vulgare* has been reported. However, the fraction responsible for anxiolytic activity is not known and there is no any report on the anti-anxiety activity of the essential oil of *F. vulgare*. The objective of study was to evaluate the anxiolytic activity of the essential oil of *Foeniculum vulgare* Miller.

Methods: Adult Swiss albino male mice were randomly divided into six groups (n = 6). Groups I and II received Tween 80 (5%, v/v) and diazepam (0.5 mg/kg, ip), respectively, while groups III to V received orally 50, 100, and 200 and 400 mg/kg doses of the essential oil of *F. vulgare*, respectively. The mice were then individually placed in animal anxiety models: elevated plus maze (EPM), staircase test (SCT) and open field test (OFT) and evaluated for various parameters.

Results: In EPM test, 100 and 200 mg/kg doses of the essential oil significantly increased percent number of entries and time spent in open arms compared to control. In SCT these doses also reduced rearing significantly compared to controls, while only the 200 mg/kg dose significantly increased number of squares crossed at the center in the OFT test.

Conclusion: The essential oil of *F. vulgare* was found to exhibit a promising anxiolytic activity.

Koppula S. et al., *Foeniculum vulgare* Mill (Umbelliferae) Attenuates Stress and Improves Memory in Wister Rats. Tropical Journal of Pharmaceutical Research August 2013;12 (4): 553-558. DOI: 10.4314/tjpr.v12i4.17.

Purpose: To evaluate the anti-stress and memory-enhancing properties of *F. vulgare* extract in experimental rats.

Methods: *F. vulgare* plant extract was obtained using Soxhlet extraction technique. The extract, at doses of 50, 100 and 200 mg/kg body weight, was administered orally with an orogastric tube. Urinary levels of vanillylmandelic acid (VMA) and ascorbic acid in rats were used to evaluate anti-stress activity. Conditioned avoidance response was measured in normal and scopolamine-induced amnesic rats to study the memory-enhancing effects. Lipid peroxidation inhibition assay in liver and brain homogenates of rats was used to evaluate antioxidant activity.

Results: Daily administration of *F. vulgare* extract (50, 100 and 200 mg/kg body weight) 1 h prior to induction of stress significantly ($p < 0.05$) altered the stress-induced urinary biochemical levels of VMA from 395.79 ± 11.23 to 347.12 ± 12.28 , 311.21 ± 12.48 and 258.86 ± 10.26 $\mu\text{g}/\text{kg}$, respectively, in 24 h, as well as ascorbic acid excretion levels from 65.74 ± 9.42 to 78.59 ± 8.44 , 108.41 ± 15.62 and 125.82 ± 16.94 $\mu\text{g}/\text{kg}$ also within the same period, respectively. These changes occurred in a dose-dependent fashion, and the levels in the control groups were unchanged within the same period. The memory deficits induced by scopolamine (1mg/kg, i.p.) in rats was reversed by *F. vulgare* dose-dependently. The extract also exhibited potent antioxidant effect by inhibition of lipid peroxidation in both rat liver and brain homogenates to a greater extent than the standard antioxidant, ascorbic acid.

Conclusion: *F. vulgare* may be useful in the management of stress and stress-related disorders on account of its multiple actions such as anti-stress, memory-enhancing and antioxidant effects.



Pourabbas et al., Study of the anxiolytic effects of fennel and possible roles of both GABAergic system and estrogen receptors in these effects in adult female rat. Physiology and Pharmacology. 2011; 15 (1), 134-143, ABSTRACT.

Introduction: Fennel is rich in phytoestrogens and is used for estrogen deficiency disorders. Estrogens affect anxiety through neurochemical systems such as GABA-A receptors. In this study the effects of fennel on GABA-A and estrogen receptors in anxiety were investigated.

Methods: Adult female Wistar rats weighing (180±20 g) were divided into 8 groups. Groups received saline, fennel (200, 500, 750 mg/kg), tamoxifen (15 mg/kg) + fennel (500 mg/kg), picrotoxin (1 mg/kg) + fennel (500 mg/kg). A control group was also used. Elevated plus maze was used for evaluation of anxiety by measuring the time spent in the open arm. All drugs were administered intraperitoneally.

Results: The results showed that fennel only at the dose of 500 mg/kg had significant anxiolytic effects and increased the time spent in open arms (P<0.01). Picrotoxin (GABA-A antagonist) significantly prevented anxiolytic effect of 500 mg/kg of fennel (P<0.001). Tamoxifen, an estrogen receptor antagonist, also abolished the anxiolytic effect of fennel (P<0.001).

Conclusion: Fennel reduced anxiety in rats and picrotoxin, a non-competitive antagonist of GABA-A receptors, as well as tamoxifen, an antagonist/agonist of estrogen receptors, reduced this anxiolytic effect. Thus, fennel as herbal drug seems to have an anxiolytic effect and it probably acts through GABA-A and estrogen receptors.

Perveen T. et al. Involvement of altered serotonergic responses in fennel oil induced antidepressant, anxiolytic and antinociceptive effects in rats. World J Pharm Sci 2014; 2(5): 493-498.

The usage of herbs as a natural drug has mount up all over the world. Fennel (*Foeniculum Vulgare* Mill) it is a common herb. Traditionally it is used as a carminative agent, antioxidant, diuretic, anti-inflammatory, antihirsutism and many more. Present study is designed to evaluate the behavioral effects of fennel oil in rats. In the present study antidepressant, anxiolytic and analgesic effects of repeated administration of fennel oil has been monitored in rats. Forced swim test and elevated plus maze test has been used to monitor the antidepressant and anxiolytic effect respectively. However analgesic effect of fennel oil has been monitored by hot plate test. Rats treated with fennel oil showed significant increase in struggling time in Forced Swim Test (FST). Increased locomotor activity in novel environment and a significant increase in the time spent in open arm in elevated plus maze (EPM) was exhibited by fennel oil treated rats. Analgesic activity monitored by hot plate test showed significant increase in latency time in test compared to control rats. Results of present study show that fennel oil has potential antidepressant, anxiolytic and analgesic activity.

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