Life Sciences 128 (2015) 24–29

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Linalool and β-pinene exert their antidepressant-like activity through the monoaminergic pathway

Silvia Laura Guzmán-Gutiérrez [a,c,d], Herlinda Bonilla-Jaime [a], Rocío Gómez-Cansino [b], Ricardo Reyes-Chilpa [b,*]

[a] Laboratorio de Farmacología Conductual, Dpto. Biología de la Reproducción, D.C.B.S. Universidad Autónoma Metropolitana Iztapalapa, 09340, Iztapalapa, México D.F., México
[b] Departamento de Productos Naturales, Instituto de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510 Coyoacán, México D.F., México
[c] Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510 Coyoacán, México D.F., México
[d] Cátedra CONACYT, México

ARTICLE INFO

Article history:
Received 2 December 2014
Received in revised form 14 January 2015
Accepted 12 February 2015
Available online 11 March 2015

Keywords:
Linalool
β-Pinene
Antidepressant
Monoterpenes
Aromatic compounds

ABSTRACT

Aims: Linalool and β-pinene are two volatile monoterpenes that possess antidepressant-like activity. These are components of many aromatic plants used in folk medicine around the world to relieve anxiety and depression. In this contribution, we focused on examining the mechanism of action of these compounds.
Main methods: We used mice in the forced swimming test (FST) and antagonist drugs (i.p.) to receptors related to the depression process such as 5-HT_{1A}. To assess the possible contribution of the serotoninergic system, animals were pre-treated with WAY 100635 (a 5-HT_{1A} receptor antagonist) and PCPA (a serotonin synthesis inhibitor). To assess the participation of the noradrenergic system, the animals were pre-treated with yohimbine (an α_2 receptor antagonist), propranolol (a β receptor antagonist) and neurotoxin DSP-4 (a noradrenergic neurotoxin). In the dopaminergic system, we used SCH23390 (a D_1 receptor antagonist).
Key findings: WAY 100635 blocked the antidepressant-like effect of linalool and β-pinene. In contrast, pretreatment of mice with PCPA did not modify reductions in the immobility time elicited by the two monoterpenes. The yohimbine modified the effect of linalool on immobility time. Propranolol and neurotoxin DSP-4 reversed the anti-immobility effect of β-pinene; also, SCH23390 blocked the antidepressant-like effect of β-pinene.
Significance: Our results indicate that linalool and β-pinene produce an antidepressant-like effect through interaction with the monoaminergic system.

© 2015 Elsevier Inc. All rights reserved.

1. Introduction

Although several treatment options are available for depressive disorders, there is a need for new drugs with improved tolerability and efficacy. There are several reports describing the antidepressant activity of different plant species, and in some cases, the active components have been identified. The most notable example is *Hypericum perforatum* (St. John's Wort), which contains the active components hypericin and hyperforin [1].

Litsea glaucescens (Lauraceae) is a shrub species native to Mexico and Central America. It is known as "laurel", its leaves are commonly used as food condiment, replacing the European species *Laurus nobilis* (Lauraceae), but "laurel" is also used in traditional medicine. An infusion of leaves of *L. glaucescens* is used to treat illnesses related to the central nervous system, diarrhea, vomiting, pain in the bones, colic in children, as well as postpartum baths [2]. Our group previously determined that the essential oil of *L. glaucescens* shows antidepressant activity in mice subjected to the forced swimming test (FST). The main active compounds were identified as linalool and β-pinene [3]. Recently, the antidepressant activity of linalool was confirmed using the tail suspension test (TST) in mice [4]. However, its mechanism of action remains unknown.

Experimental and clinical evidence support the monoaminergic hypothesis of depression, which postulates that the main neurochemical process in this disorder is impairment of monoaminergic neurotransmission with a concomitant decrease in extracellular concentrations of noradrenaline and/or serotonin [5]. For this reason, the receptors, transporters or enzymes that participate in monoaminergic transmission were explored as targets of substances with potential antidepressant activity. This study was designed to explore the mechanism of action of linalool and β-pinene. To achieve this objective, we used antagonist drugs on some serotonergic, dopaminergic and noradrenergic receptors that participate in pathways modified by some antidepressant drugs, such as fluoxetine.

* Corresponding author at: Instituto de Química, Departamento de Productos Naturales, Universidad Nacional Autónoma de México, Ciudad Universitaria, Coyoacán 04510, México D.F., México. Tel.: +52 55 56224512; fax: +52 55 56162203.
E-mail address: chilpa@unam.mx (R. Reyes-Chilpa).

http://dx.doi.org/10.1016/j.lfs.2015.02.021
0024-3205/© 2015 Elsevier Inc. All rights reserved.

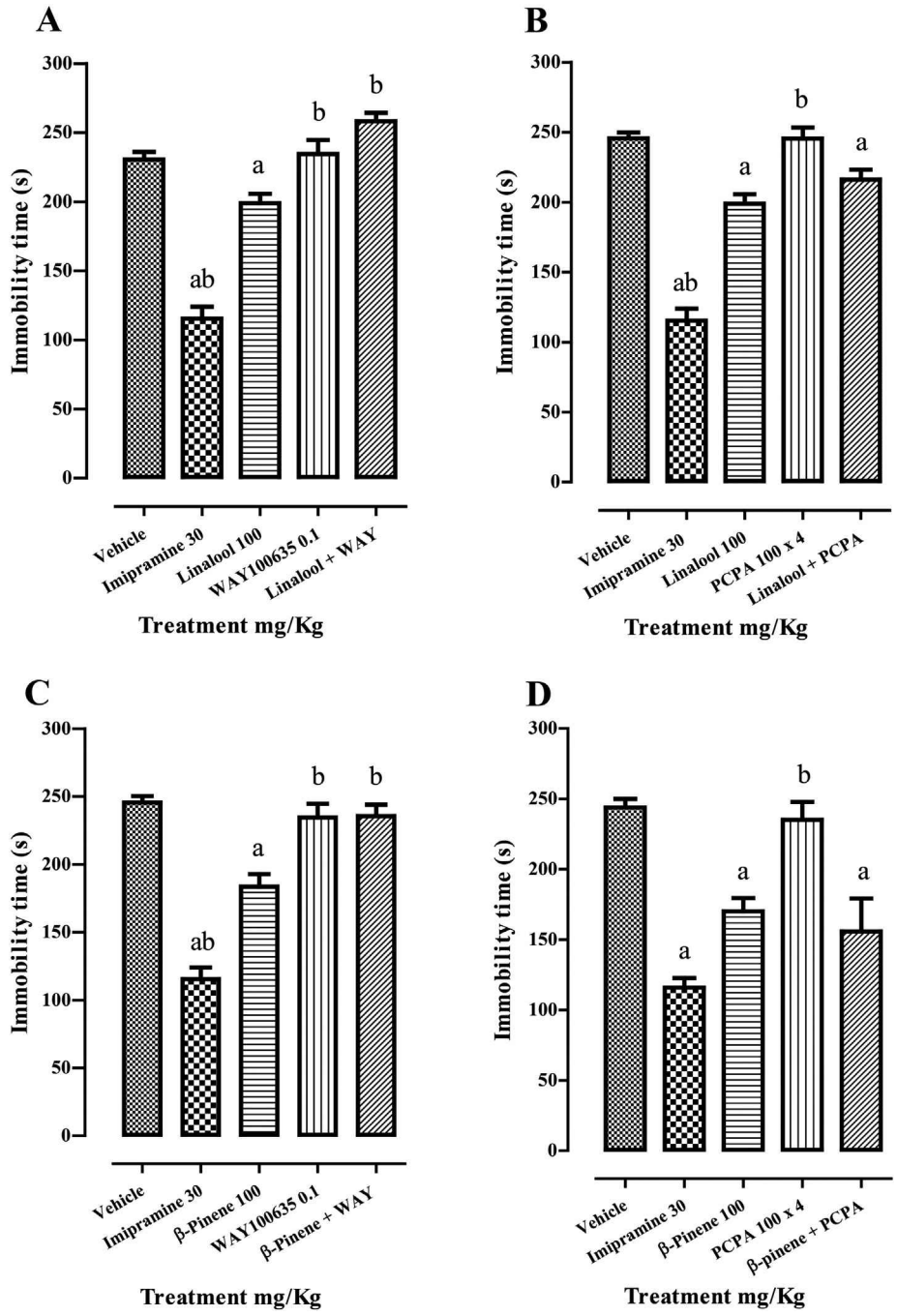

Fig. 1. Effect of the pre-treatment with WAY 100635 (1 mg/kg, i.p.) or PCPA (100 mg/kg, i.p.) on the immobility time induced by linalool (100 mg/kg, i.p.; panels A and B, respectively) or β-pinene (100 mg/kg, i.p.; panels **C** and **D**, respectively) in the FST in mice. Each column represents the mean ± SEM (n = 8–10). ANOVA followed by a Tukey's test, $p < 0.05$ with the exception of panel **C** (ANOVA Kruskal–Wallis followed by Dunn's test). Significant effect compared to the control group (**a**), and to the monoterpene group (**b**).

2. Materials and methods

2.1. Animals

All the experiments were performed with adult male ICR mice (27–33 g) obtained from the bioterium of Universidad Autónoma Metropolitana in Mexico City. Mice were maintained under a 12-h light/dark cycle (22 ± 1 °C) with free access to food and water. Procedures involving animal care were approved by the Ethics Committee and conducted in conformity with the Mexican Official Norm for Animal Care and Handling (NOM-062-ZOO-1999), and in compliance with international rules on the care and use of laboratory animals. All experiments were performed in a room isolated from external noise.

2.2. Drugs

All compounds were purchased from the Aldrich Co. (St. Louis, MO): Imipramine hydrochloride (tricyclic antidepressant), linalool, (1S)-(−)-β-pinene, WAY 100635 (a 5-HT_{1A} receptor antagonist), yohimbine (a α_2 receptor antagonist), prazosin (a α_1 receptor antagonist), propranolol (a non-selective β receptor antagonist), SCH23390 (a D_1 receptor antagonist), PCPA (a serotonin synthesis blocker), and DSP-4 (a noradrenergic neurotoxin). β-Pinene, linalool, yohimbine, PCPA, prazosin,

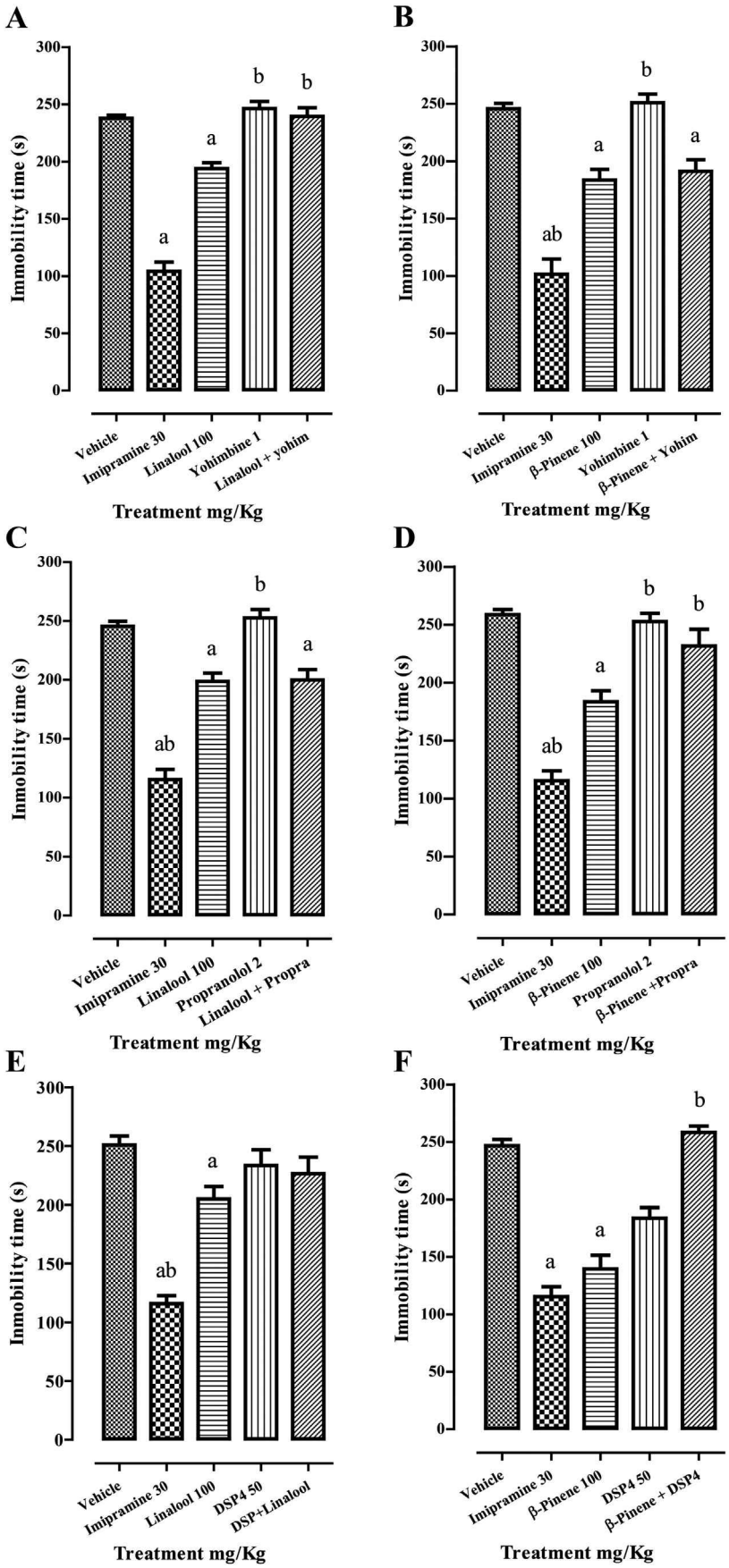

Fig. 2. Effect of the pre-treatment with yohimbine (1 mg/kg, i.p.), propanolol (2 mg/kg, i.p.) or DSP-4 (50 mg/kg, i.p.) on the immobility time induced by linalool (100 mg/kg, i.p.; panels **A**, **C** and **E**, respectively) or β-pinene (100 mg/kg, i.p.; panels **B**, **D** and **F**, respectively) in the FST in mice. Each column represents the mean ± SEM (n = 8–12). ANOVA followed by a Tukey's test, $p < 0.05$ with exception of panel **F** (ANOVA Kruskal–Wallis) followed by Dunn's test. Significant effect compared to the control group (**a**), and to the monoterpene group (**b**).

and WAY 100635 were suspended in 0.5% Tween 80 in saline solution (0.9%). Propranolol, SCH23390, imipramine hydrochloride, and DSP-4 were dissolved in saline solution (0.9%). Treatments were injected intraperitoneally (i.p.) at a volume of 0.1 mL/10 g of body weight. Control animals received the same volume of the vehicle.

2.3. Treatments

For all experiments we use imipramine hydrochloride (30 mg/kg), linalool (100 mg/kg × 3) and (1S)-(−)-β-pinene (100 mg/kg × 3) [3]. To assess the possible contribution of the serotoninergic system over linalool and β-pinene action, mice were pre-treated with PCPA (100 mg/kg × 4), WAY 100635 (0.1 mg/kg), or vehicle. For the FST, WAY 100635 was administered three times, always 15 min before administration of linalool or β-pinene. PCPA was administered once a day for four consecutive days before the FST [6].

We also tested the influence of the noradrenergic, adrenergic and dopaminergic systems on the antidepressant-like effect of monoterpenes. In this case, the animals were pre-treated with yohimbine (1 mg/kg), prazosin (1 mg/kg), DSP-4 (50 mg/kg), propranolol (2 mg/kg), SCH23390 (0.01 mg/kg) or vehicle. For the FST, each drug was administered three times, always 15 min before administration of linalool or β-pinene, except for DSP-4, which was administered only once, 7 days before the swimming test [7].

2.4. Forced swimming test (FST)

The FST method used to assess antidepressant activity was similar to that described by Herrera-Ruiz and Martínez-Vázquez [8–9]. The apparatus consisted of a glass vessel (25 cm height × 12 cm diameter) filled with water to a depth of 15 cm (24 ± 1 °C). In the pre-test session, each animal was placed individually in the vessel for 15 min, 24 h prior to the 5-min swimming test. Each drug was administered three times: immediately after the initial pre-test, and at 18 h and 1 h 15 min prior to the FST, while linalool or β-pinene was administered 15 min after each application of the drugs, except for PCPA and DSP-4 (see the Treatments section). All test sessions were video-recorded and analyzed after the experiment to register the immobility time (in seconds) for each animal. Mice were considered to be immobile when they made no further attempt to escape, only moving the minimum necessary to keep their heads above the water. A decrease in the duration of immobility time in the test group compared to controls indicated an antidepressant effect of the substance tested. Each experimental group consisted of 8–10 animals [8].

2.5. Statistical analysis

The data were analyzed by a one-way ANOVA followed by a Tukey's test, unless otherwise stated. Differences were considered significant if $p < 0.05$. Data were expressed as mean ± standard error of the mean (SEM).

3. Results

In this study, the antidepressant mechanism of the monoterpenes linalool and β-pinene were examined using antagonist drugs for serotonergic, dopaminergic and noradrenergic receptors.

3.1. Involvement of the serotonergic system

Regarding the serotonergic pathway, Fig. 1A ($F_{4,35} = 53.13$, $p < 0.05$) and B ($F_{4,35} = 56.50$, $p < 0.05$) show that linalool and imipramine decreased the immobility time of mice when compared with control on the FST. A similar result is showed for β-pinene and imipramine in Fig. 1C ($F_{4,35} = 42.06$, $p < 0.05$) and D ($H(4) = 32.56$, $p < 0.05$). Concerning the exploration of the mechanism of action of these two monoterpenes, previous administration of WAY 100635 (a 5-HT_{1A} receptor antagonist) blocked the antidepressant-like effect of both linalool ($F_{4,35} = 53.13$, $p < 0.05$) and β-pinene ($F_{4,35} = 42.06$, $p < 0.05$). In contrast, pretreatment of mice with PCPA (tryptophan hydroxylase inhibitor) did not modify the reduction in immobility time elicited by linalool (Fig. 1C) or β-pinene (Fig. 1D).

3.2. Involvement of the noradrenergic and dopaminergic systems

In relation to noradrenergic and dopaminergic pathways, Fig. 2A ($F_{4,55} = 89.09$, $p < 0.05$), C ($F_{4,35} = 41.71$, $p < 0.05$) and E ($F_{4,55} = 23.84$, $p < 0.05$) show that linalool and imipramine decreased the immobility time of mice compared to control. Similarly, Fig. 2B ($F_{4,35} = 41.71$, $p < 0.05$), D ($F_{4,35} = 40.79$, $p < 0.05$) and F ($H(4) = 32.93$, $p < 0.05$) show that β-pinene and imipramine decreased immobility time. Concerning the mechanism of action, pre-treatment with yohimbine (an α_2 receptor antagonist) modified the effect of linalool ($F_{3,41} = 11.07$, $p < 0.05$) (Fig. 2A), but not β-pinene (Fig. 2B).

Regarding β-pinene, Fig. 2D ($F_{4,35} = 40.79$, $p < 0.05$) and F ($H(4) = 32.93$, $p < 0.05$), show that propranolol and neurotoxin DSP-4, respectively, were able to prevent its anti-immobility effect; whereas linalool was not affected by the administration of either treatment (Fig. 2C and E). Prazosin had no effect on the activity of either monoterpene.

Fig. 3 ($F_{4,45} = 61.49$, $p < 0.05$) shows that β-pinene and imipramine decreased the immobility time of mice with respect to control. Pretreatment with SCH23390 (a D_1 receptor antagonist) blocked the antidepressant-like effect of β-pinene.

4. Discussion

Although current antidepressants offer both short- and long-term benefits, important problems persist, such as tolerance, delayed therapeutic onset, limited efficacy of common treatments in milder and resistant depression [10]. For these reasons, patients need new therapeutic alternatives that could be provided by medicinal plants and natural products.

Linalool is a monoterpene that acts on the central nervous system; for example, it has shown anticonvulsive and sedative effects in animals, and humans [11–13]. It is present in several aromatic plants, such as *Lavandula augustifolia*, *Melissa officinalis* and *L. glaucescens* [3,14–15]. Previously we have demonstrated that linalool produces antidepressant activity. Regarding β-pinene, a common constituent of several essential plant oils, its antidepressant activity has also been reported in FST on mice [3].

In the current work, imipramine, linalool and β-pinene decreased the immobility time of mice when compared with control on the FST. These results are in agreement with a previous report [3]. Concerning the mechanism of action, the serotoninergic pathway is implicated, since WAY 100635 reversed the antidepressant effect of linalool and β-pinene, these data suggest that the 5-HT_{1A} receptors are involved in the mechanism of action of monoterpenes. Preceding studies have shown that 5-HT_{1A} receptor agonists, such as buspirone and gepirone, have antidepressant activity, and these drugs act on presynaptic and postsynaptic receptors [16]. However, PCPA did not reverse the antidepressant activity of monoterpenes, this suggests that they could act through postsynaptic type receptors [17]. A similar effect was observed for 8-hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT), an 5-HT_{1A} receptor agonist, suggesting that its antidepressant-like effect is exerted through the postsynaptic 5-HT_{1A} receptors [18]. Furthermore, a progressive sensitization of postsynaptic 5-HT_{1A} receptors in the dorsal hippocampus, after long-term treatment with a tricyclic antidepressant has been observed experimentally [19].

On the other hand, experimental studies indicate that the hypofunction of the noradrenergic system is implicated in the pathophysiology of depression [20]. There is evidence for the participation of α_1 and α_2 receptors in the mechanism of action of antidepressant agents [21]. The pretreatment of mice with yohimbine reversed the effect of linalool, but not

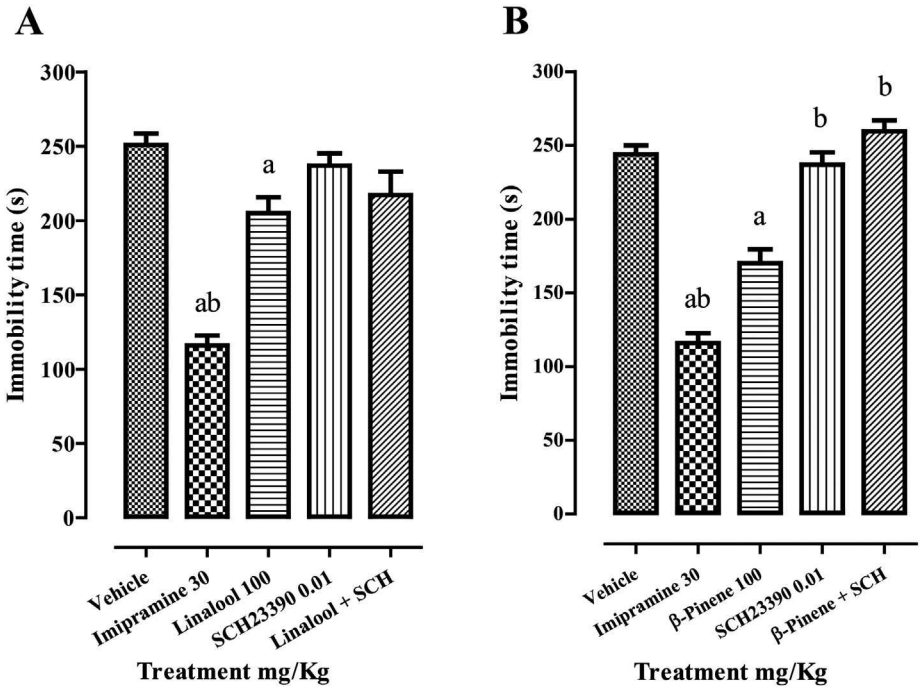

Fig. 3. Effect of the pre-treatment with SCH23390 (0.01 mg/kg, i.p.) on the immobility time induced by linalool or β-pinene (100 mg/kg, i.p.; panels **A** and panel **B**, respectively), in the FST in mice. Each column represents the mean ± SEM (n = 10). The data were analyzed by ANOVA followed by a Tukey's test, $p < 0.05$. Significant effect compared to the control group (**a**), and to the monoterpene group (**b**).

that of β-pinene. These results suggest that α_2 adrenergic receptors are involved in the antidepressant mechanism of linalool. In other studies, clonidine, an adrenergic agonist with high affinity for α_2 adrenoceptors, presented antidepressant-like effects on the FST [22], and is proposed that through central alpha 2-adrenoceptors outside the locus coeruleus and presumably postsynaptically to noradrenaline-containing neurons [23], this effect was reversed by yohimbine [24]. O'Neill et al. reported that desipramine and reboxetine are successfully used to treat depression in clinical medicine by increasing the availability of noradrenaline in the synaptic cleft. Their findings indicate that increasing the stimulation of postsynaptic noradrenergic receptors is associated with relief of depressive symptoms. Therefore, part of activity of linalool maybe due to the modulation of adrenergic function, such as clonidine [24].

On the other hand, propranolol reversed the effect of β-pinene, suggesting that the antidepressant activity of β-pinene was partly due to its action on β receptors. The antidepressant effect exerted by the drug desipramine determined in an unpredictable chronic mild stress model in mice was reversed by propranolol [25]. Furthermore, according to several studies, β-adrenoceptors may be involved in the action of antidepressants [26–29].

Regarding dopaminergic pathway, pre-treatment of mice with SCH23390 blocked the antidepressant-like effect of β-pinene. It has been documented that dopaminergic neurons originating in the ventral tegmental area which project their nerve terminals into different telencephalic areas, including the prefrontal cortex and the nucleus accumbens, are involved in the control of reward-related behavior and incentive motivation, both of which are impaired in depression [30]. The published evidence supports the hypothesis that chronic antidepressant treatments potentiate dopamine transmission, and that this potentiation results from an increased sensitivity of the postsynaptic dopamine receptors. This potentiation might be responsible for the involvement of dopamine in the control of reward-related behavior and incentive motivation. Available evidence shows that the increased sensitivity to dopamine receptor stimulation induced by chronic antidepressant treatment is related to an increased dopamine D_2-like receptor function, and a decrease in the number and sensitivity of dopamine D_1 receptors. It should be noted that these changes are more prominent in the limbic areas, which supports the view that they might indeed be important in the therapeutic effect of these drugs [31].

5. Conclusion

This study determined that the antidepressant-like effect of linalool and β-pinene occurs through interaction with the serotonergic pathway through postsynaptic 5-HT_{1A} receptors. In addition both monoterpenes interact with the adrenergic system through different receptors, the α_2 for linalool, and β for β-pinene. Furthermore, β-pinene interacts with the dopaminergic systems through D_1 receptors; interestingly the mechanism of action of some of the most frequently prescribed antidepressant drugs involves also the monoaminergic system.

Conflict of interest statement

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by Universidad Autónoma Metropolitana and Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica, Dirección General de Asuntos del Personal Académico (Project IG 200513), Universidad Nacional Autónoma de México. Dr. Silvia Laura Guzmán Gutiérrez was funded by a post-doctoral fellowship from the Instituto de Ciencia y Tecnología del Distrito Federal (ICyTDF) and Consejo Nacional de Ciencia y Tecnología (CONACyT). The authors also thank Antonio Nieto Camacho for the technical assistance and Edgar Antonio Estrella Parra for the animal care.

References

[1] P. Blier, N.M. Ward, Is there a role for 5-HT_{1A} agonists in the treatment of depression? Biol. Psychiatry 53 (2003) 193–203.
[2] N.D.C. Jimenez-Perez, F.G. Lorea-Hernandez, C.K. Jankowski, R. Reyes-Chilpa, Essential oils in Mexican bays (*Litsea* spp., Lauraceae): taxonomic assortment and ethnobotanical implications, Econ. Bot. 65 (2011) 178–189.
[3] S.L. Guzman-Gutierrez, R. Gomez-Cansino, J.C. Garcia-Zebadua, N.C. Jimenez-Perez, R. Reyes-Chilpa, Antidepressant activity of *Litsea glaucescens* essential oil:

identification of beta-pinene and linalool as active principles, J. Ethnopharmacol. 143 (2012) 673–679.
[4] V. Coelho, L. Mazzardo-Martins, D.F. Martins, A.R. Santos, L.F. da Silva Brum, J.N. Picada, P. Pereira, Neurobehavioral and genotoxic evaluation of (−)-linalool in mice, J. Nat. Med. 67 (2013) 876–880.
[5] J.J. Schildkraut, The catecholamine hypothesis of affective disorders: a review of supporting evidence, J. Neuropsychiatr. Clin. Neurosci. 7 (1995) 524–533.
[6] R. Wang, Y. Xu, H.L. Wu, Y.B. Li, Y.H. Li, J.B. Guo, X.J. Li, The antidepressant effects of curcumin in the forced swimming test involve 5-HT_1 and 5-HT_2 receptors, Eur. J. Pharmacol. 578 (2008) 43–50.
[7] T. Cassano, S. Gaetani, M.G. Morgese, T. Macheda, L. Laconca, P. Dipasquale, J. Taltavull, T.S. Shippenberg, V. Cuomo, G. Gobbi, Monoaminergic changes in locus coeruleus and dorsal raphe nucleus following noradrenaline depletion, Neurochem. Res. 34 (2009) 1417–1426.
[8] M. Herrera-Ruiz, Y. Garcia-Beltran, S. Mora, G. Diaz-Veliz, G.S. Viana, J. Tortoriello, G. Ramirez, Antidepressant and anxiolytic effects of hydroalcoholic extract from *Salvia elegans*, J. Ethnopharmacol. 107 (2006) 53–58.
[9] M. Martinez-Vazquez, R. Estrada-Reyes, A. Martinez-Laurrabaquio, C. Lopez-Rubalcava, G. Heinze, Neuropharmacological study of *Dracocephalum moldavica* L. (Lamiaceae) in mice: sedative effect and chemical analysis of an aqueous extract, J. Ethnopharmacol. 141 (2012) 908–917.
[10] E. Penn, D.K. Tracy, The drugs don't work? Antidepressants and the current and future pharmacological management of depression, Ther. Adv. Psychopharmacol. 2 (2012) 179–188.
[11] E. Elisabetsky, L.F. Brum, D.O. Souza, Anticonvulsant properties of linalool in glutamate-related seizure models, Phytomedicine 6 (1999) 107–113.
[12] E. Elisabetsky, J. Marschner, D.O. Souza, Effects of linalool on glutamatergic system in the rat cerebral cortex, Neurochem. Res. 20 (1995) 461–465.
[13] Y. Sugawara, A. Shigetho, M. Yoneda, T. Tuchiya, T. Matumura, M. Hirano, Relationship between mood change, odour and its physiological effects in humans while inhaling the fragrances of essential oils as well as linalool and its enantiomers, Molecules 18 (2013) 3312–3338.
[14] C. Da Porto, D. Decorti, Analysis of the volatile compounds of flowers and essential oils from *Lavandula angustifolia* cultivated in northeastern Italy by headspace solid-phase microextraction coupled to gas chromatography–mass spectrometry, Planta Med. 74 (2008) 182–187.
[15] J. Patora, T. Majda, J. Gora, B. Klimek, Variability in the content and composition of essential oil from lemon balm (*Melissa officinalis* L.) cultivated in Poland, Acta Pol. Pharm. 60 (2003) 395–400.
[16] F.D. Yocca, Neurochemistry and neurophysiology of buspirone and gepirone: interactions at presynaptic and postsynaptic 5-HT1A receptors, J. Clin. Psychopharmacol. 10 (1990) 6S–12S.
[17] X.O. Zhu, N. McNaughton, The interaction of serotonin depletion with anxiolytics and antidepressants on reticular-elicited hippocampal RSA, Neuropharmacology 33 (1994) 1597–1605.
[18] G.P. Luscombe, K.F. Martin, L.J. Hutchins, J. Gosden, D.J. Heal, Mediation of the antidepressant-like effect of 8-OH-DPAT in mice by postsynaptic 5-HT1A receptors, Br. J. Pharmacol. 108 (1993) 669–677.
[19] N. Haddjeri, P. Blier, C. de Montigny, Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT1A receptors, J. Neurosci. 18 (1998) 10150–10156.
[20] B. Dell'Osso, M.C. Palazzo, L. Oldani, A.C. Altamura, The noradrenergic action in antidepressant treatments: pharmacological and clinical aspects, CNS Neurosci. Ther. 17 (2011) 723–732.
[21] M.J. Millan, The role of monoamines in the actions of established and "novel" antidepressant agents: a critical review, Eur. J. Pharmacol. 500 (2004) 371–384.
[22] M. Bourin, M.-C. Colombel, M. Malinge, J. Bradwejn, Clonidine as a sensitizing agent in the forced swimming test for revealing antidepressant activity, J. Psychiatry Neurosci. 16 (1991) 199–203.
[23] L. Cervo, R. Samanin, Clonidine causes antidepressant-like effects in rats by activating alpha 2-adrenoceptors outside the locus coeruleus, Eur. J. Pharmacol. 193 (1991) 309–313.
[24] M.F. O'Neill, D.J. Osborne, S.M. Woodhouse, M.W. Conway, Selective imidazoline I2 ligands do not show antidepressant-like activity in the forced swim test in mice, J. Psychopharmacol. 15 (2001) 18–22.
[25] I. Yalcin, F. Aksu, S. Bodard, S. Chalon, C. Belzung, Antidepressant-like effect of tramadol in the unpredictable chronic mild stress procedure: possible involvement of the noradrenergic system, Behav. Pharmacol. 18 (2007) 623–631.
[26] B.E. Leonard, Noradrenaline in basic models of depression, Eur. Neuropsychopharmacol. 7 (1997) S11–S16.
[27] A. Harkin, R. Nally, J.P. Kelly, B.E. Leonard, Effects of reboxetine and sertraline treatments alone and in combination on the binding properties of cortical NMDA and beta1-adrenergic receptors in an animal model of depression, J. Neural Transm. 107 (2000) 1213–1227.
[28] M. Papp, V. Klimek, P. Willner, Effects of imipramine on serotonergic and beta-adrenergic receptor binding in a realistic animal model of depression, Psychopharmacology 114 (1994) 309–314.
[29] A. van Waarde, W. Vaalburg, P. Doze, F.J. Bosker, P.H. Elsinga, PET imaging of beta-adrenoceptors in human brain: a realistic goal or a mirage? Curr. Pharm. Des. 10 (2004) 1519–1536.
[30] S.E. Hopwood, C.A. Owesson, L.F. Callado, D.P. McLaughlin, J.A. Stamford, Effects of chronic tramadol on pre- and post-synaptic measures of monoamine function, J. Psychopharmacol. 15 (2001) 147–153.
[31] P.S. D'Aquila, A.T. Peana, V. Carboni, G. Serra, Exploratory behaviour and grooming after repeated restraint and chronic mild stress: effect of desipramine, Eur. J. Pharmacol. 399 (2000) 43–47.