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Original article

Anti-depressive-like effect of monoterpene *trans*-anethole via monoaminergic pathways

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ABSTRACT

Trans-anethole (ANE) is a monoterpene present in many aromatic plants, especially *Pimpinella anisum* (PA). In this regard, we previously reported the anti-depressant potential of PA. Here, we examined the anti-depressant activity of ANE and its possible mechanism in mice. In experiment 1, the animals received ANE (12.5–50 mg.kg $^{-1}$) 60 min prior to forced swimming and open-field tests. In experiment 2, the animals received several receptor antagonists to assess the possible mechanism of ANE. The administration of ANE (25 and 50 mg.kg $^{-1}$; $p < 0.01$ and $p < 0.001$, respectively) exhibited an anti-depressive-like effect in FST without any significant effect on animal locomotion($p > 0.05$). Moreover, haloperidol($p < 0.001$), SCH23390($p < 0.001$), sulpiride($p < 0.001$), ketanserin($p < 0.001$), *p*-chlorophenylalanine($p < 0.001$), WAY100135($p < 0.001$), reserpine, ($p < 0.001$) prazosin($p < 0.001$), and yohimbine($p < 0.001$) inhibited the anti-depressive-like effect of ANE. Furthermore, co-treatment of a subeffective dose of ANE with imipramine or fluoxetine induced synergistic anti-depressant-like effects($p < 0.001$). Our data mainly showed that the anti-depressive-like effect of ANE, which can be attributed to the contribution of the monoaminergic system.

1. Introduction

Major depression (MD) is a prevalent and serious health problem worldwide. According to the statistics, about 350 million persons in the world are suffering from MD (Ali et al., 2017). The main specifications of MD are low mood, poor concentration, loss of pleasure or interest, sadness, insomnia, feeling tiredness, and helplessness (Ng et al., 2016). Earlier works revealed that the monoaminergic pathway (including dopaminergic, noradrenergic, and serotonergic systems) has a crucial function in the pathogenesis of MD. On the other hand, the insufficient activity of these neurotransmitters is the main cause of MD (Boku et al., 2018). Hence, the anti-depressant agents normalize or elevate the level of these neurotransmitters by inhibiting their reuptake or preventing the metabolism. Nevertheless, certain side effects of antidepressants such as relapse, suicide, and recurrence limit their clinical use (Santarsieri & Schwartz., 2015). Nowadays, depressed patients need alternative agents (especially medicinal plants and their derivatives) with minimum side effects (Ismail et al., 2018; Setorki, 2020).

Trans-anethole (ANE) (Fig. 1) is a monoterpene present in many aromatic plants, especially *Pimpinella anisum* (PA). In this regard, we previously reported the anti-depressant potential of PA using mouse models (Shahamat et al., 2016). Apart from our findings, previous studies have shown that the monoterpenes produced anti-depressive-like effects by different mechanisms in animal models (Melo et al., 2011; Fukumoto et al., 2006; Guzman-Gutierrez et al., 2015; Deng et al., 2015; Mohaghegh et al., 2019).

ANE is utilized as a flavoring agent in food such as baked goods, candy, and ice cream (Shimoni et al., 2003). In several investigations, the anti-inflammatory (Kanget al., 2013), anticarcinogenic (Choo et al., 2011), vasoactive (Soares et al.,2007), antioxidant (Freire et al.,2005), and neuroprotective effects (Ryu et al.,2014) of ANE have been relieved. Despite the numerous pharmacological effects of ANE, its anti-depressive-like effect and possible mechanism have not yet been addressed in literature; hence, the anti-

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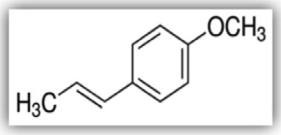

Fig 1. Structure of *trans*-anethole (ANE).

depressive activity of ANE and its possible mechanism were examined using mice forced swim test (FST).

2. Materials and methods

2.1. Drugs

Trans-anethole (ANE) was obtained from Sigma Co. (USA). Its linear formula is $CH_3CH = CHC_6H_4OCH_3$, with formula weight of 148.20. According to Sigma report, the degree of purity is > 99%. In addition, sulpiride (Sul; a specific D_2 dopamine antagonist), reserpine (Res; a vesicular monoamine depleter), SCH-23390 (SCH; a specific D_1 dopamine antagonist), WAY-100135 (WAY, a specific 5-HT_{1A} antagonist) ketanserin (Ket; a specific $5HT_{2A/C}$ blocker), and *p*-chlorophenylalanine (pCPA; a tryptophan hydroxylase inhibitor), and haloperidol (Hal; as non-specific dopamine antagonist) were obtained from Sigma Co. (USA). Yohimbine (Yoh; an α_2-adrenoceptor antagonist) and prazosin (Praz; an α_1-adrenoceptor antagonist) were obtained from Iran Daru and Razak Co. (Iran), respectively. Moreover, imipramine (Imp) and fluoxetine (Flx) were obtained from Pars Darou Co. (Iran). All drugs and ANE were given through the intraperitoneal (i.p.) route, in a volume 0.2 ml/20 g body weight. Moreover, the solvent of ANE or drugs was normal saline (0.9%) plus DMSO (5%). A vehicle-treated control received normal saline plus DMSO (5%).

2.2. Laboratory animals

Eight-week-old male NMRI mice (22–32 g) obtained from Razi Institute (Iran) and housed on a 12-hour light: dark illustration, at 24–26 °C, and with free access to water and standard rodent chow. The study protocol was in accordance with the rules of the National Institutes of Health and were evaluated by and had prior approval from the Research Ethics Board at Islamic Azad University of Pharmaceutical Sciences (IAUPS no. 22510303952100).

2.3. Assessment of LD_{50} and toxicity effects

We used Lorke's method to access ANE acute toxicity (Lorke, 1983). In summary, this method is encompassing two separate phases as follows:

Phase 1: In this phase, nine animals were assigned to three different groups (n = 3), and they *i.p.* were given 10, 100, and 1000 mg.kg $^{-1}$ of ANE.

Phase 2**:** In this phase, three mice were assigned to three groups (n = 1), and they *i.p.* received 1000, 2900, and 5000 mg.kg $^{-1}$ of the drug. Finally, any signs of toxicity and mortality in both phases were recorded for each animal for one day.

2.4. Behavioral models

2.4.1. Forced swim test (FST)

In this behavioral model, the animals were drooped separately in a cylinder-shaped jar (height 25 cm and width 10 cm), filled with 14 cm fresh water at 25 °C. The duration of immobility for each animal was registered during the 4 min after 2 min adaptation. The reduction of immobility time reflects the anti-depressive-like effect (Porsolt et al., 1977).

2.4.2. Open-field test (OFT)

To evaluate any relationship between the anti-depressive-like effect of ANE and animal locomotion, the OFT is used. In this experiment, the animals separately submit to the center of the box (60 × 50 × 40 cm dimensions). The counts of squares passed by all paws (crossing) and picked up the front paws (rearing) were recorded by a counter for 5 min (Rodrigues et al., 2002).

2.5. Experimental design and treatment protocols

In experiment 1, ANE (12.5, 25, and 50 mg.kg^{-1}) was given 60 min before the behavioral tests to examine the anti-depressive and psychostimulant effects, respectively.

In experiment 2, to assess the possible mechanism implicated in the anti-depressive-like effect of ANE, animals received several receptor antagonists in FST as follows:

To examine the contribution of the dopaminergic system in mediating the effect of ANE, the animals received different DA receptor antagonists including SCH (0.05 mg.kg^{-1}), Sul (50 mg.kg^{-1}), and Hal (0.2 mg.kg^{-1}) 60 min prior to the injection of vehicle (Veh) or ANE (50 mg.kg^{-1}). 30 min later, animals were tested.

To explore the role of the serotonergic system in mediating the effect of ANE, animals received different 5HT receptor antagonists including Ket (5 mg.kg^{-1}) and WAY (10 mg.kg^{-1}) 60 min prior to the injection of Veh or ANE (50 mg.kg^{-1}). 30 min later, animals were tested.

Moreover, distinct groups of mice were given pCPA (200 mg.kg^{-1}) or the Veh daily for three continuous days. Then, they received Veh or ANE (50 mg.kg^{-1}) and were examined 30 min later.

To study the contribution of the noradrenergic system in mediating the effect of ANE, animals were given Praz (1 mg.kg^{-1}) and Yoh (1 mg.kg^{-1}) 60 min prior to the injection of Veh or ANE (50 mg.kg^{-1}). 30 min later, animals were tested.

Furthermore, the mice received Res (2 mg.kg^{-1}) 4 h before the administration of ANE (50 mg.kg^{-1}) and were examined 30 min later.

To examine the potential synergistic effects, distinct groups of mice were given co-treatments of ANE and Imp or Flx (in subeffective doses of 12.5, 5 and 5 mg.kg^{-1}, respectively). 30 min later, animals were tested. All drug doses were selected based on our earlier works and literature data (Shahamat et al., 2016; Abbasi-Maleki and Maleki, 2021; Yan et al., 2015; Kaur et al., 2015; Ishola et al., 2014; Moradi et al., 2014; Koriem et al., 2016).

2.6. Data analysis

Data are shown as mean ± S.D, n = 7. To compare the groups, we used one or two-way ANOVA followed by Tukey's test. The probability of $p < 0.05$ was considered a significant level. The analyses were carried out using Prism 8.0 software.

3. Results

3.1. LD_{50} and toxicity effects

Following Lorke's method, the LD_{50} of ANE was 1.3 g.kg $^{-1}$. The main toxic effects in doses higher than 1.3 g.kg $^{-1}$, first for the early period (4 h) followed by a late period (24 h) were ataxia, dyspnea, muscular relaxation, wheezing sounds, irritability, and confusion.

3.2. Anti-depressive-like effect of ANE in FST

As shown in Fig. 2, ANE (25 and 50 mg.kg^{-1}) reduced the immobility time [23.09 and 54.81 %, respectively; $F_{6, 42} = 76.7$, $p < 0.001$]. The peak decrease was observed at 50 mg.kg-1. Hence, this dose was selected for further experiments. Moreover, fluoxetine (20 mg/kg) and imipramine (30 mg/kg) also reduced immobility time (59.51% and 84.05%, respectively; $F_{6, 42} = 76.7$, $p < 0.001$) *vs* the Veh group.

3.3. Open filed-test (OFT)

As shown in Fig. 3 (A) and 3 (B), all ANE doses (12.5–50 mg.kg^{-1}) cannot produce psychostimulant effects *vs* the Veh group ($p > 0.05$).

3.4. Assessment of monoaminergic system antagonists on the anti-depressive-like effect of ANE

3.4.1. Participation of dopaminergic system

Fig. 4 (A), (B) and (C) reveal that the pre-treatment with SCH [($F_{1,24}$ = 83.6, $p < 0.001$); ANE ($F_{1,24}$ = 138.1, $p < 0.001$); ANE × SCH ($F_{1,24}$ = 164, $p < 0.001$)], Sul [($F_{1,24}$ = 68.93, $p < 0.001$); ANE ($F_{1,24}$ = 154.5, $p < 0.001$); ANE × Sul ($F_{1,24}$ = 130.8, $p < 0.001$)]and Hal [($F_{1,24}$ = 71.2, $p < 0.001$); ANE ($F_{1,24}$ = 107.8, $p < 0.001$); ANE × Hal ($F_{1,24}$ = 132.7, $p < 0.001$)] prevented the anti-depressive-like effect of ANE (50 mg.kg^{-1}).

3.4.2. Participation of serotonergic system

As shown in Fig. 5 (A), 5(B) and 5(C), the pre-treatment with WAY [($F_{1,24}$ = 75.22, $p < 0.001$); ANE ($F_{1,24}$ = 149.6, $p < 0.001$); ANE × WAY ($F_{1,24}$ = 154, $p < 0.0001$)], Ket [($F_{1,24}$ = 69.18, $p < 0.001$); ANE ($F_{1,24}$ = 118.2, $p < 0.001$); ANE × Ket ($F_{1,24}$ = 132.8, $p < 0.001$)]and pCPA [($F_{1,24}$ = 72.91, $p < 0.001$); ANE ($F_{1,24}$ = 128, $p < 0.001$); ANE × pCPA ($F_{1,24}$ = 143, $p < 0.001$)] abolished the anti-depressive-like effect of ANE (50 mg.kg^{-1}).

3.4.3. Participation of noradrenergic system

As shown in Fig. 6 (A) and 6(B), the pre-treatment with Praz [($F_{1,24}$ = 29.52, $p < 0.001$); ANE ($F_{1,24}$ = 97.42, $p < 0.001$); ANE × Praz ($F_{1,24}$ = 59.72, $p < 0.001$)], and Yoh [($F_{1,24}$ = 76.87, $p < 0.001$); ANE ($F_{1,24}$ = 96.71, $p < 0.001$); ANE × Yoh ($F_{1,24}$ = 97.14, $p < 0.001$)] prevented the anti-depressive-like effect of ANE (50 mg.kg^{-1}).

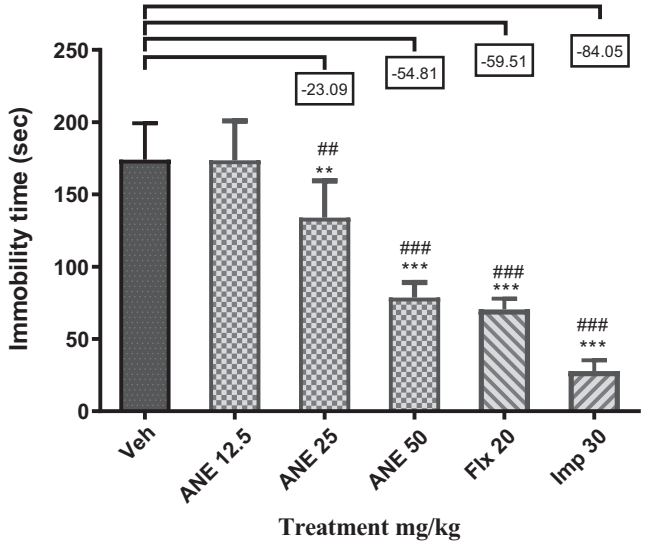

Fig 2. The anti-depressive-like effect of ANE, imipramine (Imp) and fluoxetine (Flx) in FST (mean ± S.D, n = 7). p^{**}<0.01 and p^{***}<0.001 *vs.* Veh (vehicle) group. p##<0.01 and p###<0.001 *vs.* ANE (12.5 mg.kg-1) group.

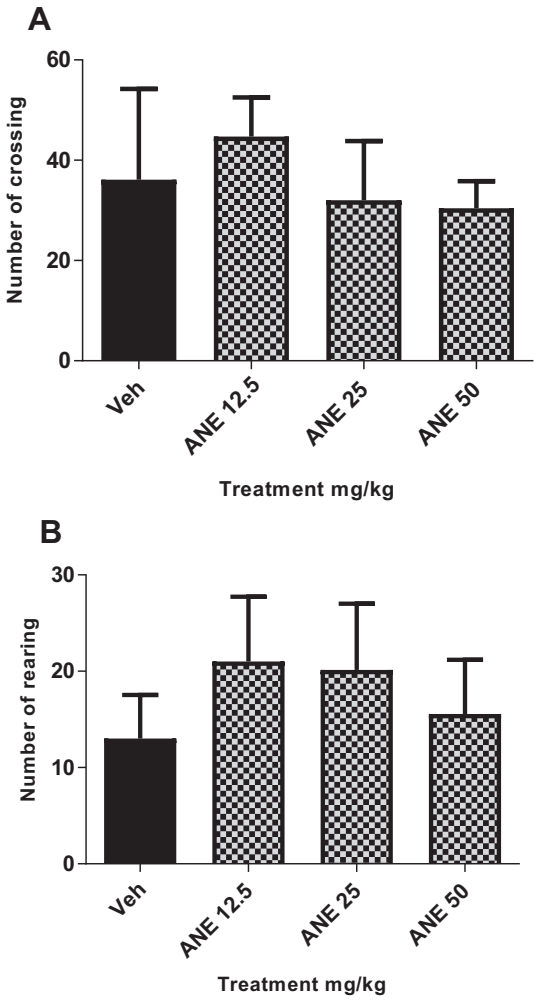

Fig. 3. Effects of ANE on the number of crossing (Panel A) and rearing (Panel B) in the OFT (mean ± S.D, n = 7). $p > 0.05$ *vs.* Veh (vehicle) group.

3.4.4. Effect of reserpine (Res) on anti-depressive-like effect of ANE

As shown in Fig. 7, the pre-treatment with Res [($F_{1, 24}$ = 72.69, $p < 0.001$); ANE ($F_{1, 24}$ = 142.9, $p < 0.001$); ANE × Res] ($F_{1, 24}$ = 154.8, $p < 0.001$)] abolished the anti-depressive like effect of ANE (50 mg.kg^{-1}).

3.4.5. Effects of the co-treatment of subeffective dose of ANE with Flx or Imp

As shown in Fig. 8(A) and 8 (B), the concurrent use of a subeffective dose of ANE and Flx [($F_{1,24}$ = 134.5, $p < 0.001$); ANE ($F_{1,24}$ = 384.8, $p < 0.001$); ANE × Flx ($F_{1,24}$ = 142.6, $p < 0.001$)] or Imp [($F_{1,24}$ = 86.93, $p < 0.001$); ANE ($F_{1,24}$ = 282.2, $p < 0.001$); ANE × Imp ($F_{1,24}$ = 145.8, $p < 0.001$)] induced a synergistic anti-depressive-like effect [($F_{1,24}$ = 134.5, $p < 0.001$); ANE ($F_{1,24}$ = 384.8, $p < 0.001$); ANE × Flx ($F_{1,24}$ = 142.6, $p < 0.001$)].

4. Discussion

Our results for the first time, to the best knowledge of the researchers, show that acute systemic (*i.p.*) administration of ANE (25 and 50 mg.kg^{-1}) is efficient in decreasing the duration of

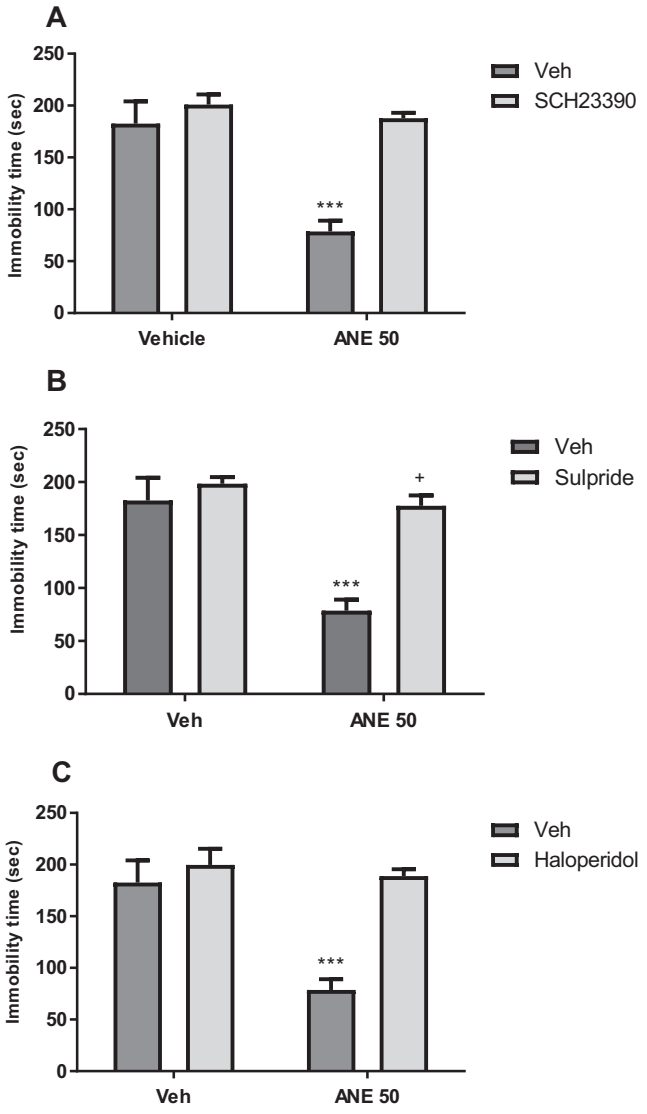

Fig. 4. Effects of SCH23390 (Panel A), sulpiride (Panel B) and haloperidol (Panel C) on the anti-depressive-like effect of ANE FST (mean ± S.D, n = 7). p^{***}<0.0001 *vs.* Veh (vehicle) group. p^{+}<0.05 *vs* ANE-treated group.

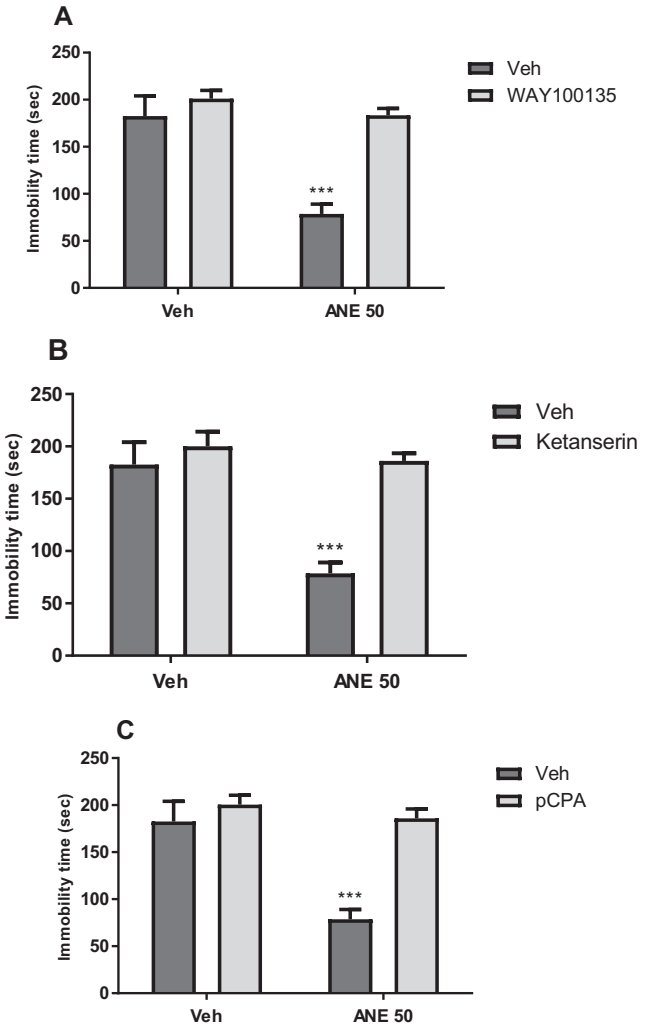

Fig. 5. Effects of WAY-100135 (Panel A), ketanserin (Panel B), and pCPA (Panel C) on the anti-depressive-like effect of ANE in FST (mean ± S.D, n = 7). p^{***}<0.001 *vs.* Veh (vehicle) group.

immobility in FST as a predictor of anti-depressive-like effect. Moreover, in contrast to previous findings (Shahamat et al., 2016), 50 mg/kg of ANE was comparable to 100 and 200 mg/kg of *Pimpinella anisum* (PA) extracts in terms of efficacy. The anti-depressive effects of ANE were, however, more potent than those of PA extracts. The present findings suggested the high dose of ANE (50 mg/kg) shortens immobility in the FST as in the case of fluoxetine, despite its weaker effect compared to imipramine.

In line with our results, Porsolt et al. (1977) noted that the anti-depressant agents reduced the immobility time in mouse FST. This rodent model is a behavioral method used for the assessment of all major classes of anti-depressant agents, including tricyclic anti-depressants (e.g., Imp) and selective serotonin reuptake inhibitors (e.g., Flx). Furthermore, FST is the main tool to assess neurobiological mechanisms that participated in the anti-depressive-like effect of different drugs (Porsolt et al., 1977).

Since the psychostimulant effect of agents may give rise to a false positive response in FST (Yi et al., 2010), locomotor activity was also assessed following pretreatment with ANE. Our findings disclosed that the pretreatment of the animals with ANE induced no psychostimulant activity in OFT, suggesting that the decrease of immobility time in FST with ANE cannot be attributed to its psychostimulant effects.

Previous studies proved the pivotal function of the monoaminergic system in the pathogenesis and treatment of MD (Boku et al., 2018). The findings revealed that the anti-depressive-like effect produced by ANE was reversed by the pre-treating of mice with different DA, 5-HT, and NA receptor antagonists. Additionally, we found out that the subeffective dose of ANE could enhance the anti-depressive-like effect of common anti-depressants (e.g., Flx and Imp).

Trans-anethole (ANE) is a monoterpene isolated from different aromatic plants (Hussain et al., 1990). It has been reported that monoterpenes have different pharmacological and biological properties, including anticonvulsant, anti-Alzheimer, analgesic, anti-inflammatory and anti-Parkinsonian effects (Salakhutdinov Nariman et al., 2017). Furthermore, previous studies demonstrated that different monotrepens (including β-pinene, linalool and thymol) exert the anti-depressive-like effect in rodent models of depression (Guzman-Gutierrez et al., 2015; Deng et al., 2015). In this regard, previous investigations have documented the effects of monoterpenes on the monoaminergic system (Fukumoto et al., 2006; Guzman-Gutierrez et al). Similarly, another research showed that the volatile monoterpenes (such as linalool) produced their anti-depressive-like effect by modulation of the monoaminergic

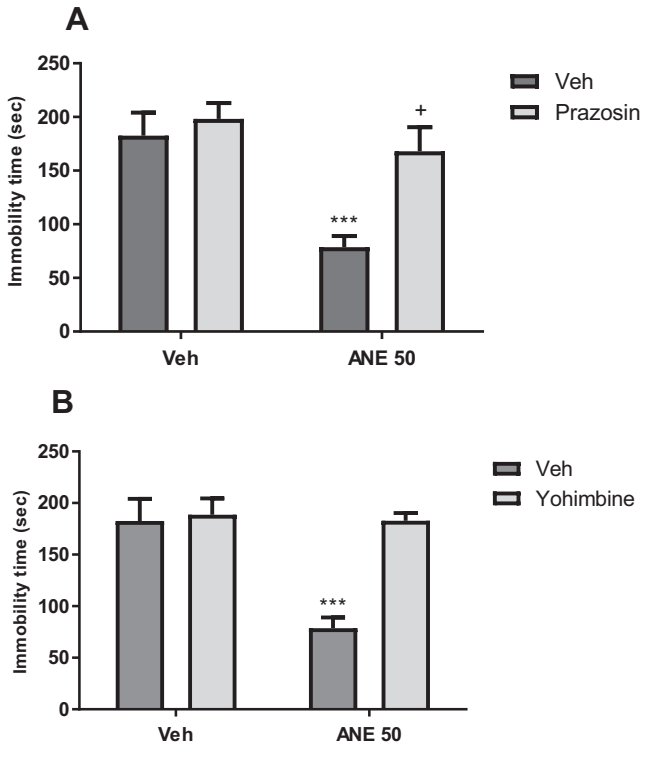

Fig. 6. Effects of prazosin (Panel A) and yohimbine (Panel B) on the anti-depressive-like effect of ANE in FST. (mean ± S.D, n = 7). p^{***}<0.001 *vs.* Veh (vehicle) group. p^{+}<0.05 *vs* ANE-treated group.

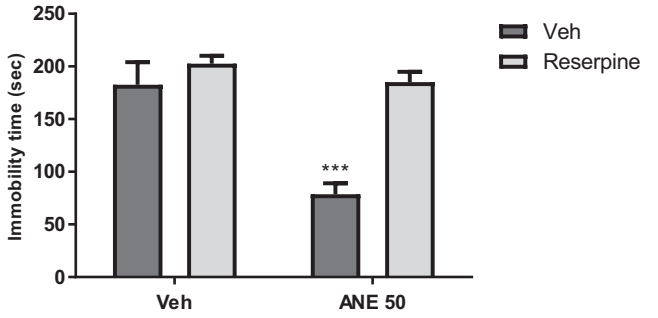

Fig. 7. Effects of reserpine on the anti-depressive-like effect of ANE in FST (mean ± S.D, n = 7). p^{***}<0.001 *vs.* Veh (vehicle) group.

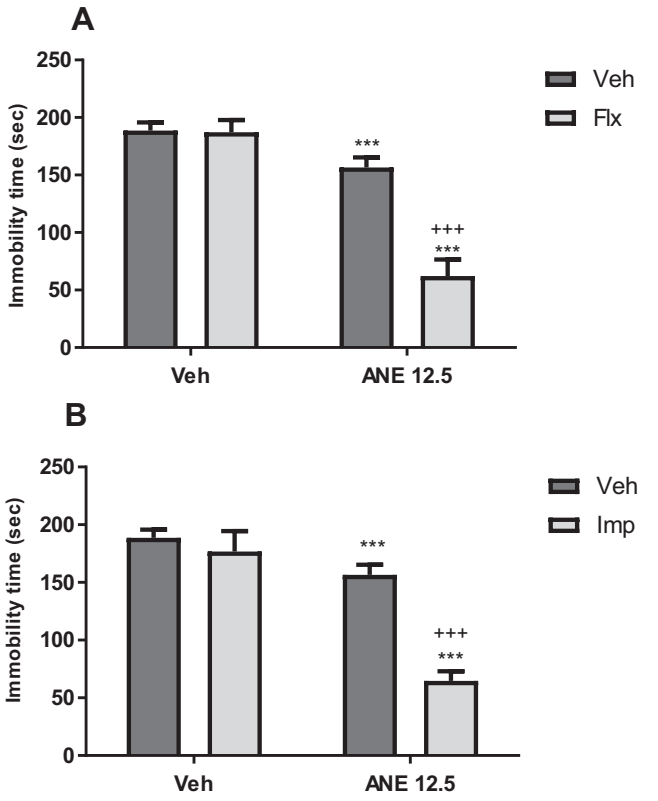

Fig. 8. Effects of the non-effective doses of Flx (Panel A) and Imp (Panel B) on the subeffective dose of ANE in FST (mean ± S.D, n = 7). p^{***}<0.001 *vs.* Veh (vehicle) group. p^{+++}<0.001 *vs* ANE-treated group.

system (Guzman-Gutierrez et al., 2015). Moreover, Fukumoto et al. also noted that the rats' brain monoamines increased after prescribing monoterpenes, such as γ-terpinene (Fukumoto et al., 2006). The findings of another work showed that carvacrol (as another monoterpene) induced their anti-depressive-like effect via modulation of the dopaminergic system, but not noradrenergic and serotonergic neural systems (Melo et al., 2011). Moreover, recent work demonstrates that menthol (as another monoterpene) exerts an anti-depressive-like effect through the dopaminergic system (Mohaghegh Daghigh et al., 2019). A study by Deng et al (2015) has shown that thymol, a bioactive monoterpene, produces an anti-depressive-like effect probably by increasing the effect of serotonergic and noradrenergic systems (Deng et al.,2015). Taken together, monoterpenes seem to have different mechanisms of action.

MD is linked to the hypofunction of the dopaminergic system. According to previous studies, DA concentration decreased in depressed patients (Belujon & Grace., 2017; Camardese et al.,2014). Accordingly, antidepressants with dopaminergic activity are effective in the treatment of MD(Franco-Chaves et al.,2013; Hori and Kunugi, 2013). Moreover, the administration of Flx or Imp increases the concentration of DA in nucleus accumbence (NAcc) (Ichikawa et al., 1998). Further, previous studies have relieved the important role of different dopamine (D_1 & D_2) receptors in the pathogenesis of MD (Cannon et al., 2009; Montgomery et al., 2007). In the support of this view, the antagonism of these receptors blocks the anti-depressive- like effect of some agents in rodent models of depression (Ishola et al.,2014;Abbasi-Maleki and Maleki,2021; Fedotova., 2012; Umukoro et al.,2018). Similarly, our results illustrated that the pretreatment of animals with SCH, Hal, and Sul significantly stopped the anti-depressive-like effect of ANE in FST. Consistent with the other findings, our findings suggest that the dopaminergic system could partly involve in the anti-depressive-like effect of ANE (Abreuet al., 2018; Melo et al., 2011).

Apart from the dopaminergic system, a series of works shows the pivotal function of the serotonergic system in the pathogenesis of MD (Köhler et al., 2016; Nautiyal and Hen, 2017). On the other hand, different 5HT receptors (e.g. 5-HT_{1A} and 5-HT_2) contributed to the action of the different anti-depressants (Kaufman et al., 2016; Celada et al., 2004). Similarly, the antagonism of these receptors blocks the anti-depressive-like effect of some agents in mouse models of depression (Ishola et al.,2014; Abbasi-Maleki and Maleki 2021; Fedotova, 2012). In this regard, our results illustrated that pretreatment of the animals with WAY, pCPA and Ket reversed the anti-depressive-like effect of ANE in FST. Furthermore, a recent study suggested the antioxidant activities of ANE (Shahriari et al.,2018). Earlier works have also revealed that antioxidants could stop the reuptake of serotonin(5HT) (Khanzode et al.,2003), thus increasing the concentration of 5-HT in synaptic clefts. Consistent with the other findings, our findings showed that the sero-

tonergic system could partly involve in the anti-depressive-like effect of ANE.

Furthermore, reserpine, a vesicular monoamine depleter, could block the anti-depressive-like effect of ANE, suggesting that ANE may regulate the brain monoamine neurotransmitters.

Apart from dopaminergic or serotonergic neural systems, the noradrenergic system also has a crucial function in MD pathogenesis and the mechanism action of different anti-depressive agents (Fedotova.,2012; Páez-Pereda, 2005). On the other hand, some common anti-depressants such as selective noradrenaline reuptake inhibitors could enhance the concentration of NA in the synaptic clefts (Kurita, 2016). In line with earlier findings, we concluded that the pretreatment of animals with different adrenoceptor antagonists such as Praz and Yoh reversed the anti-depressive-like effect of ANE.

Besides, our findings also indicated that the co-treatment of a subeffective dose of ANE with Flx or Imp could potentiate each other's effects; hence, both ANE and common anti-depressants could be utilized for the treatment of MD at non-therapeutic doses with no dangerous adverse reactions.

5. Conclusion

Our findings for the first time documented the anti-depressive-like effect of ANE by using FST. To this end, ANE induced their effects partly by modulation of dopaminergic (D_1 and D_2 receptors), serotonergic (5-HT_{1A}, 5-HT_{2A} receptors), and noradrenergic (α_1 and α_2 adrenoceptors) systems. Moreover, ANE could potentiate the anti-depressive-like effect of fluoxetine and imipramine, proposing that this compound might improve the efficiency of these antidepressants. Accordingly, *trans*-anethole (ANE) may have potential therapeutic value for the control of MD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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