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Antidepressant effects of *Mentha pulegium* in mice

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Abstract

The aim of this study is to investigate the antidepressant effects of *Mentha pulegium* essential oil in BALB/c mice. Six experimental groups (7 mice each) were used. Forced swim test was performed 30 min after essential oil injection. In the groups receiving *M. pulegium* essential oil (50, 75 and 100 mg/kg), immobility duration significantly decreased compared to the control group. *M. pulegium* (50 and 75 mg/kg) resulted in significant decrease in nitrate/nitrite content in serum compared to the control group. *M. pulegium* essential oil antidepressant effect that may be due to the inhibition of oxidative stress. The results showed that decrease in nitrate/nitrite content in serum and high anti-oxidant effects of *M. pulegium* essential oil.

Introduction

Depression occurs at any ages and more frequently in women than men. The prevalence of major depressive disorder is approximately 10-25% in men and 5-12% in women (Kuczmarski et al., 1994).

Since chemical drugs are likely to be associated with many adverse effects and psychotherapy is virtually time-consuming and costly. The plants can be valuable alternative or complementary treatments of depression with greater efficacy and fewer side effects (Mirhosseini et al., 2014; Aslam and Sultana, 2015).

Mentha pulegium is from the genus Mentha and the family Lamiaceae. *M. pulegium* produces valuable secondary metabolites that are able to eliminate free radicals (Ahmad et al., 2012). *M. pulegium* is used as exter-minator, antiseptic, flavoring, food spice, mucus, and disinfectant. *M. pulegium* leaf essential oil has been used to treat ovarian cancer. This plant is sedative and refreshing. Chewing mint and *M. pulegium* is useful for fixing hiccups and is anticonvulsant and nerves-calming (Müller-Riebau et al., 1997).

Depression has been associated with increase in oxidative stress (Saki et al., 2014). Anti-oxidants have been shown to counteract this oxidative stress and reduce the complications of oxidative stress in a wide variety of diseases (Akhlaghi et al., 2011). *M. pulegium* L., is one of these plants which produces valuable secondary metabolites that are able to eliminate free radicals. The aim of this study is to investigate the antidepressant effects of *M. pulegium* in BALB/c male mice.

Materials and Methods

In this study, 42 BALB/c mice were used and assigned to six groups of seven each as follows: Intraperitoneally injected with 1 mL/kg body weight normal saline (control); administered with intraperitoneal reserpine (5 mg/kg BW); administered with reserpine 18 hours before administration of *M. pulegium* essential oil; intraperitoneally injected with *M. pulegium* essential oil (50, 75, and 100 mg/kg BW); and administered with reserpine (5 mg/kg BW) 18 hours before intraperitoneal administration of 20 mg/kg BW fluoxetine. *M. pulegium* essential oil was administered to the mice 30 min before forced swim test (FST).

Box 1: Estimation of serum nitric oxide level

Principle

Nitrite and nitrate were measured by reduction of nitrite to nitrate by cadmium.

$NO_3^- + H_2O + Cd \rightarrow NO_2^- + Cd^{2+} + 2OH^-$

Requirements

Cadmium granule; centrifuge machine; Griess 1 reagent; sodium hydroxide; spectrophotometer; zinc granule

Procedure

Step 1: The samples were deproteinized by the introduction of zinc sulfate + sodium hydroxide solution

Step 2: Centrifugation, the supernatant was isolated and glycine buffer was added to it

Step 3: Cadmium granules were rolled in zinc sulfate and glycine buffer for five min to be activated

Step 4: The activated granules were added to the samples and the solutions were stirred for 10 min

Step 5: The solutions were transferred to new tubes, Griess 1 reagent was added, and the tubes were incubated at room (25° C) temperature for 10 min

Step 6: The Griess 1 reagent was added and the samples absorbance was measured by spectrophotometer at 540 nm wavelength

References

1. Navarro-Gonzálvez et al., 1998

Forced swim test (FST) Video Clip 1 2

To investigate the effect of *M. pulegium* on depression, FST was conducted. This test is a highly reliable and commonly used animal test to examine depression. According to the FST, increased immobility duration is considered depression and decreased immobility duration represents the efficacy of antidepressants. To conduct this test, a glass container (25 × 12 × 15 cm) was filled with 25°C water and the mice were slowly placed in the water. Conventionally, stopping of the mouse's hands and feet is considered immobility.

The total duration of the FST is seven min. In the first two min, namely habituation phase, the immobility duration was not recorded. Rather, the immobility duration was recorded within the later five min.

Data analysis

The data were analyzed by SPSS 16 and expressed as mean (standard deviation). To investigate the significance of differences between the treatments, one-way ANOVA was used. Tukey's post-hoc test was used and to compare the means. $p<0.05$ was considered the level of statistical significance.

Results

Forced swimming test

Figure 1 illustrates the findings on the mice's immobility duration (efficacy or inefficacy of treatment with antidepressants) in the FST in different groups.

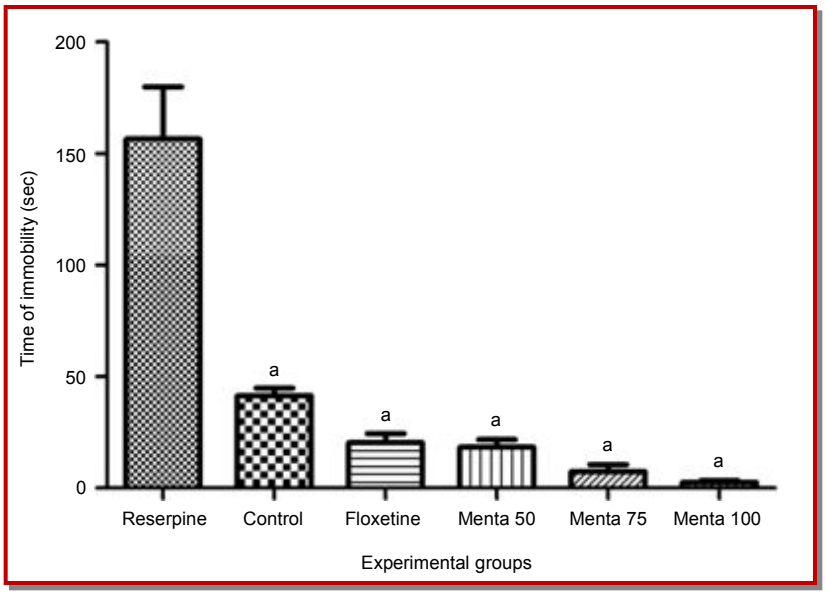

Figure 1: The effect of intraperitoneal injection with different doses of *Mentha pulegium* on the mice's immobility duration in forced swim test ($^a p \leq 0.01$)

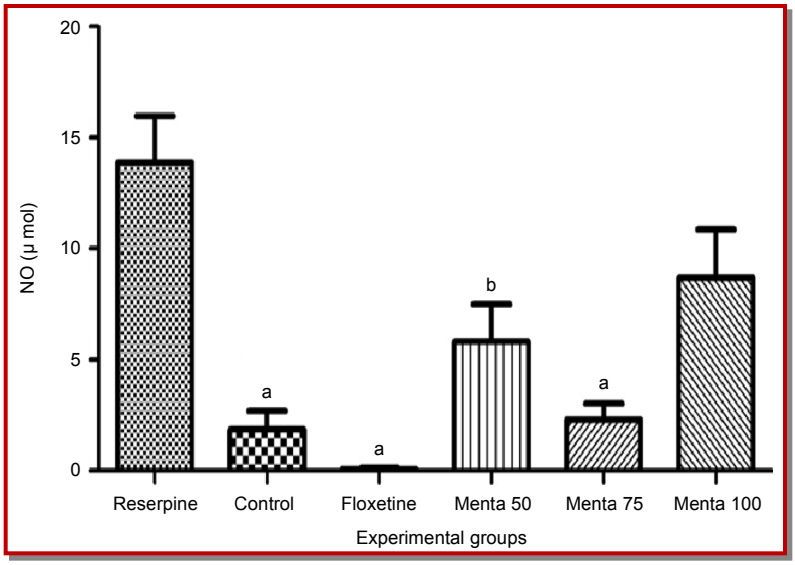

Figure 2: The total serum levels of nitrate and nitrite of the groups treated with different concentrations of *Mentha pulegium* essential oil compared to the reserpine group ($^{a}p\leq0.01$ and $^{b}p\leq0.05$)

Regarding the immobility duration in the FST, a significant difference was observed between the negative controls and controls, positive controls, and all the *M. pulegium*-treated groups ($p<0.01$). Furthermore, the findings on *M. pulegium* effect was not dose-dependent in treating the depression symptoms of the BALB/c mice because no significant difference was derived in the immobility duration in the FST among the groups treated with different doses of *M. pulegium*.

Serum NO levels

Figure 2 illustrates the findings on the total serum levels of nitrate and nitrite. The administration of 50 and 75 mg/kg BW of *M. pulegium* essential oil caused a significant decrease in the total serum levels of nitrite and nitrate compared to the control treatment ($p<0.01$). The serum NO levels in group that received reserpine significantly increased compared with control group.

Discussion

Because of the current prevalence and significance of depression in community and adverse effects of chemical drugs, a wide acceptance of plant-based compounds has recently emerged. Therefore, we conducted this study to investigate the antidepressant effect of *M. pulegium* in BALB/c mice. For this purpose, we conducted the FST to evaluate the sedative effects of the drugs to examine depression.

The findings demonstrated that all the studied doses of *M. pulegium* had considerable antidepressant effects because the administration of *M. pulegium* caused a significant decrease in the immobility duration of the mice in the FST compared to the negative controls (depressed with reserpine alone and left untreated).

The effect of *M. pulegium* was not dose-dependent on the depression symptoms of the mice because no significant difference was observed in the immobility duration in the FST among the groups treated with different doses of *M. pulegium*. In addition, the effect of *M. pulegium* on the depression symptoms was not significantly different from that of fluoxetine (a standard treatment for depression) because there was no significant difference in the immobility duration of the mice in the FST between the *M. pulegium*-treated groups and fluoxetine-treated group.

Besides that, fluoxetine was significantly effective in treating the symptoms of depression in the mice because it caused a significant decrease in the immobility duration of the mice in the FST compared to the negative controls.

Deng et al. studied the antidepressant effects of thymol, an antidepressant, on depression due to unpredictable mild stress in mice and found that thymol exerted antidepressant effects through increasing neurotransmitters in the brain and inhibiting inflammatory cytokines (Deng et al., 2015).

Moreover, Daniele et al investigated the antidepressant effect of rosemary essential oil and demonstrated that 1, 8-cineol, found in rosemary essential oil, had antidepressant effect (Machado et al., 2013). Regarding such findings, we can argue that the antidepressant effects of *M. pulegium* essential oil is due to its main compounds, thymol, carvacrol, and 1, 8-cineol.

Nitric oxide (NO) is a free radical and has several biological functions in different physiological and pathological processes, especially vascular pathophysiology. Although NO has some useful effects, if produced excessively, it may exert toxic effects

because of producing reactive nitrogen species and nitrolyzing proteins. The products derived from NO (nitrate + nitrite) can exert both peroxidant and anti-oxidant effects on lipids peroxidation depending on the conditions (Djordjević et al., 2010).

Some studies have demonstrated that inhibiting nitric oxide synthase (NOS) causes antidepressant effects in BALB/c mice in laboratory model of the FST. Furthermore, administration of NOS substrate and NO precursor, L-arginine, can overcome the antidepressant effects of NOS inhibitors. This finding supports the involvement of NO pathway in these behavioral responses (Djordjević et al., 2010).

Investigations have indicated that NO may contribute to causing behavioural, hormonal, and neurochemical changes that are associated with stress and anxiety. After persistent stress, an mRNA up-regulation, associated with neuronal NOS, was apparently seen in paraventricular nucleus. Pharmacological investigations suggest that NO may play a role in modulating protective responses (Cummings et al., 1994).

According to the findings of this study, the mice treatment with *M. pulegium* essential oil caused the serum levels of nitrite and nitrate to decrease. This indicates the neuroprotective effects of this essential oil and therefore *M. pulegium* essential oil may be able to prevent oxidative stress and associated outcomes because of having anti-oxidant properties. It should be noted that depression, anxiety and most of degenerative diseases are associated with increase in oxidative stress.

Conclusion

Administration of *M. pulegium* caused a significant decrease in the immobility duration of BALB/c mice in the FST. But, the antidepressant effect of *M. pulegium* essential oil did not increase with increase in its dose, because no significant difference was seen in the immobility duration of BALB/c mice in the FST among the groups treated with 50, 75, and 100 mg/kg BW of *M. pulegium*. Therefore, the antidepressant effect of *M. pulegium* was not dose-dependent.

Acknowledgement

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Conflict of Interest

The authors have no conflict of interest.

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