

Hypnotic effect of *Coriandrum sativum*, *Ziziphus jujuba*, *Lavandula angustifolia* and *Melissa officinalis* extracts in mice

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Abstract

The aim of the present study was to evaluate hypnotic effect of *Coriandrum sativum*, *Ziziphus jujuba*, *Lavandula angustifolia* and *Melissa officinalis* hydroalcoholic extracts in mice to select the most effective ones for a combination formula. Three doses of the extracts (250, 500 and 1000 mg/kg of *C. sativum* and *Z. jujuba* and 200, 400 and 800 mg/kg of *L. angustifolia* and *M. officinalis*) were orally administered to male Swiss mice (20-25 g) and one hour later pentobarbital (50 mg/kg, i.p.) was injected to induce sleep. Onset of sleep and its duration were measured and compared. Control animals and reference group received vehicle (10 ml/kg, p.o.) and diazepam (3 mg/kg, i.p.), respectively. *C. sativum* and *Z. jujuba* failed to change sleep parameters. *L. angustifolia* at doses of 200, 400 and 800 mg/kg shortened sleep onset by 7.6%, 50% and 51.5% and prolonged sleep duration by 9.9%, 43.1% and 80.2%, respectively. Compared with control group the same doses of *M. officinalis* also decreased sleep onset by 24.7%, 27.5% and 51.2% and prolonged sleep duration by 37.9%, 68.7% and 131.7% respectively. Combinations of *L. angustifolia* and *M. officinalis* extracts showed additive effect and it is suggested that a preparation containing both extracts may be useful for insomnia.

Keywords: Hypnotic; Sleep; *Coriandrum sativum*; *Ziziphus jujuba*; *Lavandula angustifolia*; *Melissa officinalis*; Mice

INTRODUCTION

Sleep has a significant role in regaining mental and physical health (1). Adequate sleeping is indispensable to cognitive behaviors and accomplishes awakening (2). Insomnia is the most prevalent chief complaint in adults with sleep disorder and it means deficiency in quality or quantity of sleep relates to inadequate sleep-latency, frequent awakening, early waking or decreased sleep-efficacy (3,4). Short-term insomnia is often caused by anxiety. Usually it does not need any treatment plan but sometimes prescribing sedative or hypnotic drugs is required (1).

Some of the most popular insomnia medications include benzodiazepines, barbiturates, certain antidepressants and some of the first generation antihistamines (5). Drug dependence or drowsiness is evident as the adverse effects of these drugs. Although most

of antihistamines have sedative effect, but next day-weakness and anticholinergic complications and other side effects limit their usage (6).

Hypnotic drugs can depress the central nervous system up to varying degrees. Increasing dose lead to anesthesia and greater amounts cause medulla oblongata life centers suppression and also death can be followed. So the effects are dose-related and respectively provide comfort, sleep, unconsciousness, coma and death (7).

Benzodiazepines used to induce sleep can cause some hangover effects, such as decreased ability to do certain things that requires alertness. Sensitivity to the effects of benzodiazepines increases by increasing age. Confusion and losing muscle adaptation in older adults take these drugs may lead to increased risk of hip fractures and driving accidents (8). Severe withdrawal symptoms can appear when benzodiazepines are suddenly stopped after chronic use (9).

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Sedative effects of herbs have been considered traditionally and the efficacy of some of these plants has been demonstrated in recent studies.

Coriandrum sativum is used traditionally as a remedy for insomnia. Animal studies have shown that aqueous extract of *C. sativum* at doses of 200, 400 and 600 mg/kg and its hydroalcoholic extract at doses of 400 and 600 mg/kg increased pentobarbital-induced sleeping time compared to saline-treated group (10,11). Linalool is the major coriander monoterpene which has shown sedative and calmative effects in animal studies and it has proven its anxiolytic effects in human ones. Hypnotic effects of other *C. sativum* monoterpenes like myrsine and limonene has been demonstrated in mice. Anxiolytic effects of coriander extract (100 mg/kg) in mice have been demonstrated (10,11).

Moreover, it is believed that *Ziziphus spinosa* also called *Z. jujuba* has sedative effect. *In vitro* studies have shown anxiolytic and sedative effect of *Z. jujuba* extract which is due to affinity to serotonin, benzodiazepine, dopamine and GABA receptors (12). Spinosine which is found in *Z. jujuba* has decreased sleep latency and increased sleep duration. Evaluation of various compounds of Jujuba extract has proved that saponins have more hypnotic effects compared with flavonoids and polysaccharides. Studies have shown that the *Z. jujuba* extract has sedative effects by inhibiting glutamate-mediated pathway in hippocampus (12).

Lavandula angustifolia has shown analgesic effects as aromatherapy in mice (13). It has been reported that methanol extract of *L. officinalis* has hypnotic effect at doses of 800 and 1000 mg/kg and sedative effect at doses of 200, 400 and 600 mg in mice (14).

Melissa officinalis is widely used in insomnia disorders (alone or combined with other herbs). Animal studies have shown that rosmarinic acid in *M. officinalis* has hypnotic effect (15,16).

We know that herbal drugs are usually less effective in comparison with chemical ones, and they are used generally in combination with other herbs to treat insomnia all around the world. Moreover the ecological and

climate factors profoundly affect the chemical composition of herbs, so this study was conducted to find out the hypnotic effect of above plants grown in Iran alone or in combination to elucidate the possible additive or synergistic effect of a selected combination.

MATERIALS AND METHODS

Animals

Male Swiss mice weighting 20–25 g bred in animal house of School of Pharmacy (Isfahan, Iran) were used in this study. Animals were kept in standard environmental conditions of temperature and light/dark cycles and allowed free access to pelleted rodent chow and tap water. All animal experiments were approved by the Ethics Committee of Isfahan University of Medical Science and performed in accordance with National Institute of Health Guide for the Care and Use of Laboratory Animals.

Plant extracts

Hydroalcoholic extracts of the plants were provided by Barij Essence Pharmaceutical Company (Kashan, Iran). Pentobarbital was purchased from Sigma Chemical Company (USA) and diazepam was a gift from Sobhan Pharmaceutical Company (Rasht, Iran).

Sleep induction

Plant extracts were administered orally to the animals and one hour later, animals received an intraperitoneal (i.p.) injection of pentobarbital (50 mg/kg) to induce sleep. Control animals received vehicle (1% tween 80 in saline at a dose of 10 ml/kg, p.o.). Diazepam (3 mg/kg, i.p.) was injected to a group of animals which served as reference group. Sleep latency characterized by losing of righting reflex was observed and recorded (10). Afterward, sleep duration of each animal was measured in a calm and quiet environment. Each group of animals contained 6-8 mice. Three doses of each extract (250, 500 and 1000 mg/kg for *C. sativum* and *Z. jujube* and 200, 400 and 800 mg/kg for *L. angustifolia* and *M. officinalis*) were checked and based on the obtained results; the combined doses were selected to consider additive or synergism effects.

Statistics

Data are presented as Mean \pm SEM. Comparisons between the results of the treatment groups were done by one-way ANOVA followed by Duncan's test as Post Hoc. $P < 0.05$ was considered as a significant difference.

RESULTS

Hypnotic effect of *Coriandrum sativum*

As it is seen in Fig. 1, *C. sativum* extract at doses of 250, 500 and 1000 mg/kg did not

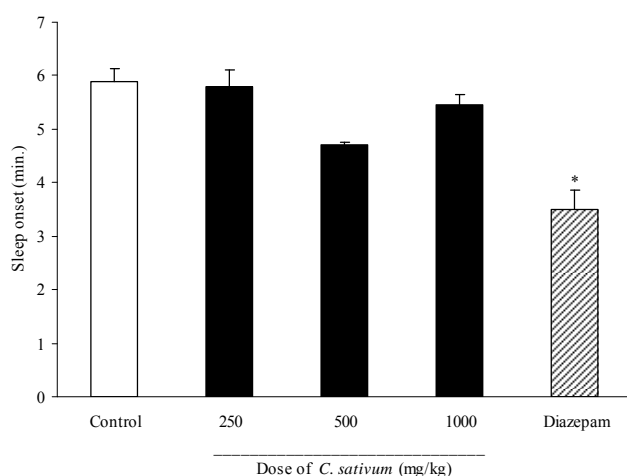


Fig. 1. Effect of different doses of *Coriandrum sativum* seed extract on sleep onset in mice. *Coriandrum sativum* seed extract (250, 500 and 1000 mg/kg, p.o.) was administered to animals and one hour later, animals received an intraperitoneal injection of pentobarbital (50 mg/kg) to induce sleep. Control animals received vehicle (10 ml/kg, p.o.). Diazepam (3 mg/kg, i.p.) was injected to the reference group. Sleep latency characterized by losing of righting reflex was observed and recorded. Data show mean \pm S.E.M. of 6-8 mice in each group. * $P < 0.05$ compared with control group.

produce any significant change in sleep onset. Diazepam (3 mg/kg, i.p.) significantly ($P < 0.05$) reduced pentobarbital-induced sleep onset (3.5 ± 0.9 min in diazepam group vs. 5.9 ± 0.6 min in control group). Results of the effect of *C. sativum* on sleep duration are demonstrated in Fig. 2. Again the three administered doses of *C. sativum* could not change the duration of sleep, while diazepam as the reference drug significantly ($P < 0.001$) increased the sleep duration. The percent increase in sleep duration for diazepam was 101.8% compared with control group (Fig. 2).

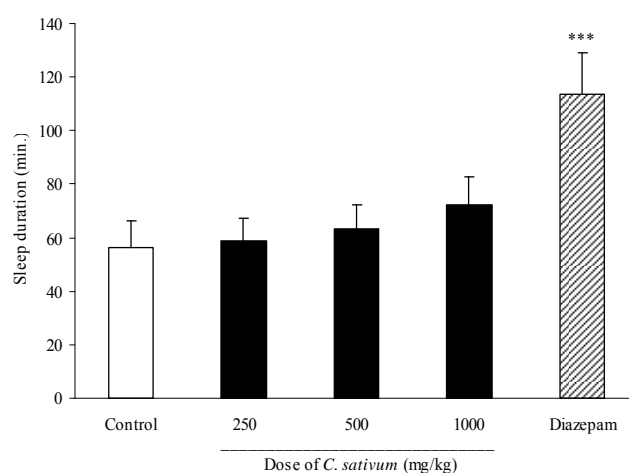


Fig. 2. Effect of different doses of *Coriandrum sativum* seed extract on sleep duration in mice. *Coriandrum sativum* seed extract (250, 500 and 1000 mg/kg, p.o.) was administered to animals and one hour later, animals received an intraperitoneal injection of pentobarbital (50 mg/kg) to induce sleep. Control animals received vehicle (10 ml/kg, p.o.). Diazepam (3 mg/kg, i.p.) was injected to reference group. Data show mean \pm S.E.M. of sleep duration of 6-8 mice in each group. *** $P < 0.001$ compared with control group.

Table 1. Hypnotic effect of combinations of *L. angustifolia* and *M. officinalis* extracts.

Plant extract	Dose (mg/kg)	% increase in sleep duration
<i>M. officinalis</i>	200	38.0%
	400	68.5%
<i>L. angustifolia</i>	200	11.1%
	400	43.1%
<i>M. officinalis</i> + <i>L. angustifolia</i> (observed)	200 + 200	53.0%
<i>M. officinalis</i> + <i>L. angustifolia</i> (Expected)	200 + 200	49.9%
<i>M. officinalis</i> + <i>L. angustifolia</i> (observed)	400 + 400	96.0%
<i>M. officinalis</i> + <i>L. angustifolia</i> (Expected)	400 + 400	111.6%

Hypnotic effect of *Ziziphus jujuba*

Results of *Z. jujuba* effect on sleep onset have been shown in Fig. 3. *Z. jujuba* extract at doses of 250, 500 and 1000 mg/kg did not make any significant change in sleep onset. Diazepam (3 mg/kg, i.p.) significantly ($P < 0.05$) reduced pentobarbital-induced sleep onset (3.5 ± 0.9 min. in diazepam group and 5.9 ± 0.6 min. in control group). Also the three administered doses of *Z. jujuba* could not change the duration of sleep (Fig. 4).

Hypnotic effect of *Lavandula angustifolia*

As it is shown in Fig. 5, *L. angustifolia* extract at doses of 400 and 800 mg/kg significantly ($P < 0.05$) reduced sleep onset latency (3.4 ± 0.9 min. in 400 mg/kg administered group, 3.2 ± 1.5 min in 800 mg/kg administered group and 5.9 ± 0.6 min in control group). Sleep duration results are demonstrated in Fig. 6. Doses of 400, 800 mg/kg and also diazepam (3 mg/kg) could change significantly the duration of sleep.

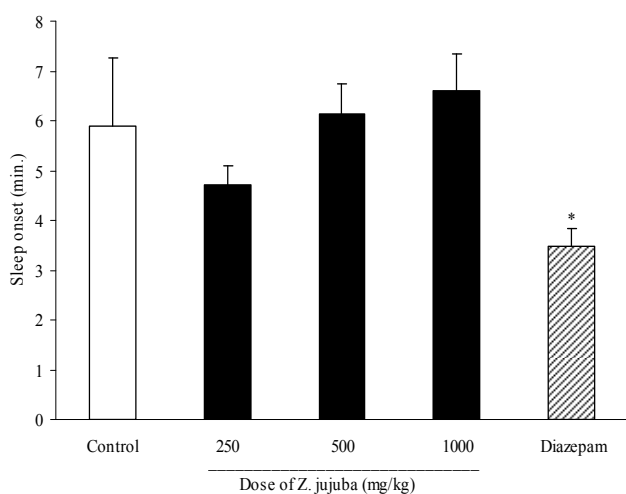


Fig. 3. Effect of different doses of *Ziziphus jujuba* extract on sleep onset in mice. *Ziziphus jujuba* extract (250, 500 and 1000 mg/kg, p.o.) was administered to animals and one hour later, animals received an intraperitoneal injection of pentobarbital (50 mg/kg) to induce sleep. Control animals received vehicle (10 ml/kg, p.o.). Diazepam (3 mg/kg, i.p.) was injected to reference group. Sleep latency characterized by losing of righting reflex was observed and recorded. Data show mean \pm S.E.M. of 6-8 mice in each group. * $P < 0.05$ compared with control group.

Hypnotic effect of *Melissa officinalis*

M. officinalis extract at a dose of 800 mg/kg and diazepam (3 mg/kg, i.p.) significantly ($P < 0.05$) reduced pentobarbital-induced sleep onset (3.5 ± 1.23 min. in test group, 3.5 ± 0.9 min. in diazepam group and 5.9 ± 0.6 min. in control group) (Fig. 7).

Sleep duration results are illustrated in Fig. 8. Doses of 400, 800 mg/kg and also diazepam (3 mg/kg) could change significantly the duration of sleep. The effect of *M. officinalis* extract on sleep duration was dose dependent and the effect of a dose of 800 mg/kg of the plant extract was nearly equal to that of diazepam (3 mg/kg).

Hypnotic effect of combination of *M. officinalis* and *L. angustifolia*

As indicated in Table 1, when combination of *M. officinalis* and *L. angustifolia* extracts was administered, the percent increase in sleep duration was close to the mathematical sum of the effects when the extracts were used alone

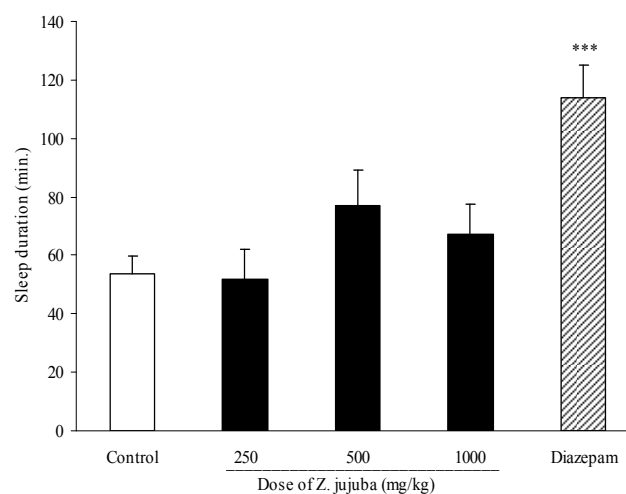


Fig. 4. Effect of different doses of *Ziziphus jujuba* extract on sleep duration in mice. *Ziziphus jujuba* extract (250, 500 and 1000 mg/kg, p.o.) was administered to animals and one hour later, animals received an intraperitoneal injection of pentobarbital (50 mg/kg) to induce sleep. Control animals received vehicle (10 ml/kg, p.o.). Diazepam (3 mg/kg, i.p.) was injected to reference group. Data show mean \pm S.E.M. of sleep duration of 6-8 mice in each group. *** $P < 0.001$ compared with control group.

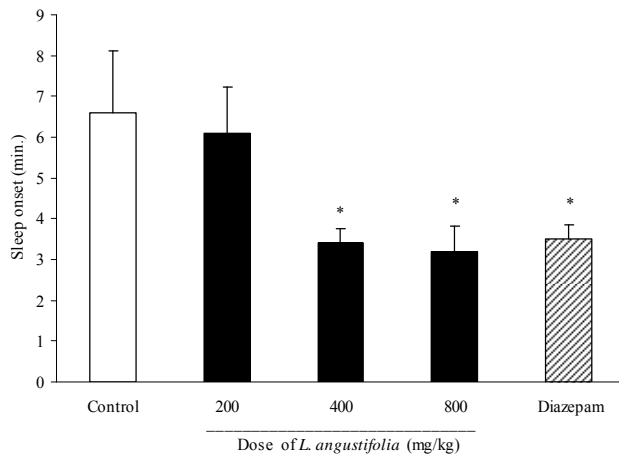


Fig. 5. Effect of different doses of *Lavandula angustifolia* extract on sleep onset in mice. *Lavandula angustifolia* extract (200, 400 and 800 mg/kg, p.o.) was administered to animals and one hour later, animals received an intraperitoneal injection of pentobarbital (50 mg/kg) to induce sleep. Control animals received vehicle (10 ml/kg, p.o.). Diazepam (3 mg/kg, i.p.) was injected to reference group. Sleep latency characterized by losing of righting reflex was observed and recorded. Data show mean \pm S.E.M. of 6-8 mice in each group. * $P < 0.05$ compared with control group.

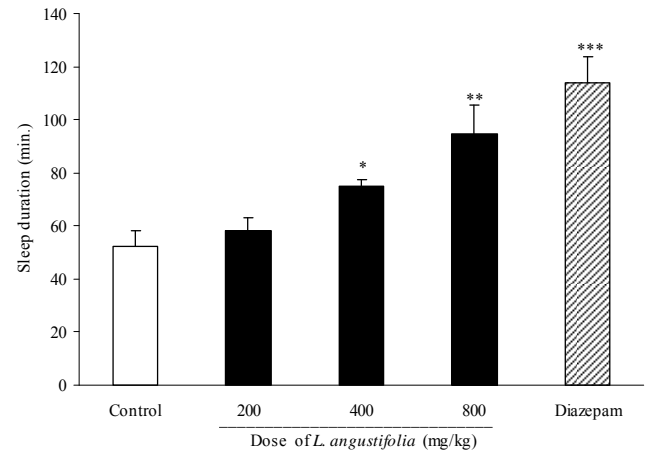


Fig. 6. Effect of different doses of *Lavandula angustifolia* extract on sleep duration in mice. *Lavandula angustifolia* extract (200, 400 and 800 mg/kg, p.o.) was administered to animals and one hour later, animals received an intraperitoneal injection of pentobarbital (50 mg/kg) to induce sleep. Control animals received vehicle (10 ml/kg, p.o.). Diazepam (3 mg/kg, i.p.) was injected to reference group. Data show mean \pm S.E.M. of sleep duration of 6-8 mice in each group. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ compared with control group.

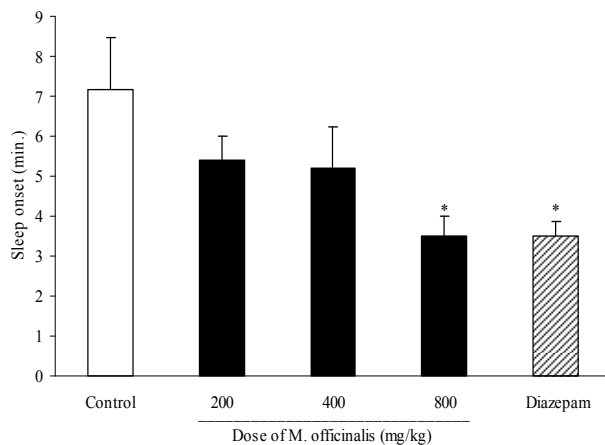


Fig. 7. Effect of different doses of *Melissa officinalis* extract on sleep onset in mice. *Melissa officinalis* extract (200, 400 and 800 mg/kg, p.o.) was administered to animals and one hour later, animals received an intraperitoneal injection of pentobarbital (50 mg/kg) to induce sleep. Control animals received vehicle (10 ml/kg, p.o.). Diazepam (3 mg/kg, i.p.) was injected to reference group. Sleep latency characterized by losing of righting reflex was observed and recorded. Data show mean \pm S.E.M. of 6-8 mice in each group. * $P < 0.05$ compared with control group.

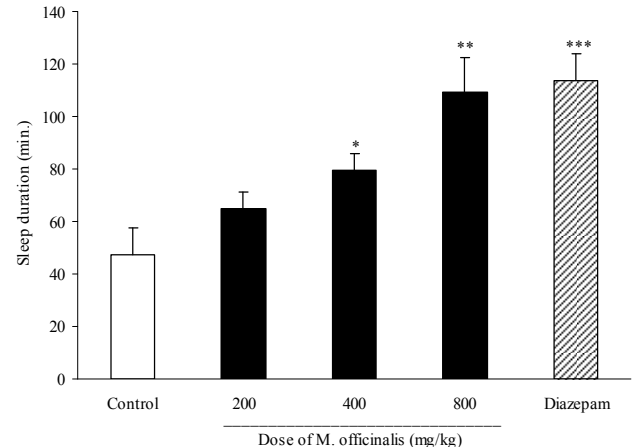


Fig. 8. Effect of different doses of *Melissa officinalis* extract on sleep duration in mice. *Melissa officinalis* extract (200, 400 and 800 mg/kg, p.o.) was administered to animals and one hour later, animals received an intraperitoneal injection of pentobarbital (50 mg/kg) to induce sleep. Control animals received vehicle (10 ml/kg, p.o.). Diazepam (3 mg/kg, i.p.) was injected to reference group. Data show mean \pm S.E.M. of sleep duration of 6-8 mice in each group. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ compared with control group.

DISCUSSION

The overall objective of the current study was to compare the effect of different doses of four medicinal plants including *C. sativum*, *Z. Jujuba*, *L. angustifolia* and *M. officinalis* on the duration and onset of pentobarbital-induced sleep in laboratory mice. Traditionally these plants have been used as sleep aid (17) and so far several studies have been conducted to confirm these claims. According to the results obtained from our study, doses of 250, 500 and 1000 mg/kg of *C. sativum* and *Z. jujuba* could not produce significant changes in the duration and onset of sleep while *L. angustifolia* and *M. officinalis* significantly increased the duration of sleep and led to a decrease in the onset of sleep in tested animals in a shorter duration. Rakhshandeh and coworkers (18) reported sleep prolonging effect of hydroalcoholic, ethyl acetate, and n-butanol fractions prepared from *C. sativum* aerial parts in mice. In another study conducted by Emamghoreishi and colleagues (11) i.p. administration of aqueous extract of *C. sativum* seeds showed antianxiety effect in a plus maze model.

In our study *C. sativum* seed extract administered orally to mice failed to exert sleep-prolonging effect which may be due to the low absorption or high hepatic biotransformation of active constituents via oral route. *Z. spinosa* has shown hypnotic effect in rats (19) and it is a common ingredient of traditional herbal preparations used to treat insomnia (20). Our findings clearly demonstrated that the extract of this plant even at high doses (e.g. 1000 mg/kg) could not prolong pentobarbital-induced sleep duration and it indicates that extracts of this species are not suitable to be incorporated in sleep aid formulas.

Sedative, antioxidant, antispasmodic, carminative, antibacterial, antiviral and anti-inflammatory activities are amongst the most common therapeutic properties of *M. officinalis* (21,22). Our results clearly demonstrated that *M. officinalis* extract at a dose of 800 mg/kg potentiated pentobarbital-induced sleep duration and confirmed a previous study conducted by Souleimani and

coworkers. They evaluated the sedative and hypnotic effects of *M. officinalis* and reported that the plant extract induced the sleep in mice after treatment with an infra-hypnotic dose of pentobarbital and potentiated the sleep induced by a hypnotic dose of pentobarbital (23). Also in agreement with our findings in another study, 600 mg of *M. officinalis* L. leaf extract per day improved sleep parameters in healthy volunteers (24). Our findings are also consistent with the German Commission E recommendations on the approval of *M. officinalis* L. extract use for nervous insomnia (25).

Several pharmacological properties including analgesic and anti-inflammatory (26), antibacterial (27), anti-allergic, and anti-asthma (28) have been reported for lavender. It has also a long history of medicinal use for CNS disorders and is believed to possess anticonvulsant, antidepressive, anxiolytic, sedative, and calming properties (29,30). In the present study, lavender shortened pentobarbital sleep induction and also prolonged its hypnotic effect which confirm the sedative and hypnotic effects reported previously (29,30).

Since both Melissa and lavandula showed hypnotic effect, combinations of 200 + 200 mg/kg and 400 + 400 mg/kg of these two plant extracts were also evaluated for the first time. As it is seen in Table 1, combinations produced an additive effect. Physicochemical interaction of active constituents, competition for oral absorption, pharmacodynamic interaction at receptor binding sites and also pharmacokinetic interaction especially at the level of metabolism may explain the lesser effect of a combination of 400 mg/kg of both extracts in comparison with mathematical sum of effects. However further investigation are needed for a definitive elucidation.

CONCLUSION

Results obtained from the present study indicate that *L. angustifolia* and *M. officinalis* have considerable hypnotic activity. Combination of these two plant extracts resulted in an increase in sleep time that is very close to mathematical sum of effects and

shows a nearly additive effect. It is suggested that a combination of *L. angustifolia* and *M. officinalis* may be useful for the treatment of insomnia. Clinical trials are recommended to evaluate the possible superiority of this combination over single application of them.

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