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Comparative Study of Sedative, Pre-Anesthetic and Anti-Anxiety Effect of *Origanum majorana* Extract with Diazepam on Rats

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Abstract: In the present study, sedative and anti-anxiety drugs such as chemical drugs are used for the sedation and anti-anxiety but due to their side effects and economical issues, the significance of research on finding sedative and anti-anxiety drugs with less side effects and their ability to substitute these synthetic drugs and substituting newer sedation and anti-anxiety compounds is obvious. *Origanum majorana* is one of the plants that have the effect sedation and anti-anxiety. The aim of this research was to examine the effects of sedative, pre-anesthetic and anti-anxiety of *Origanum majorana* with diazepam in rats to different groups of male Wistar rats received herbal extract *Origanum majorana* with doses (100, 200, 400 mg kg^{-1}, IP) and diazepam with dose of (1/2 mg kg^{-1}, IP) and dimethyl sulfoxide with the equal volume. About 30 min after assessing the relift/sleep inducing effect (induced sleep duration by ketamine 40 mg kg^{-1}, IP) anti-anxiety effects (using elevated plus maze). The results show meaningful increase in the period of the sleep that had been made with ketamine and also meaningful increase in the spend time at open arms in the patient group with the previous. The results show that the dose of extract *Origanum majorana* 200 mg kg^{-1} relieving effects of sedative, pre-anesthetic and anti-anxiety and before.

Key words: Sedation, anesthesia, anxiety, *Origanum majorana* extract, diazepam, rat

INTRODUCTION

Anxiety is some kind of internal response to the threatening conditions people's material and spiritual conditions. Anxiety disorders are the most common spiritual-mental disorder so that the prevalence of these disorders is estimated at 10-30% (Kandel and Squire, 2000). Thus, anti-anxiety and sedative drugs such as drugs high consumers are considered. Since, most of the anti-anxiety drugs have effects of sedative (sedating), hypnotics and muscle relaxants on the central organs and on the other hand lead to being physical dependence and mentally well can cause addiction (Rabbani *et al*., 2004). Also because of the increasing desire of people to use herbal medicines, in this study been try to anti-anxiety effect of *Origanum majorana* (medicinal plants of Iran) that grows at the North of the country grows amount of enormous is evaluated on the model of anti-anxiety in the rat. Marjoram plant with scientific names of *Origanum majorana* of the families are lamiaceae that has world-wide distribution these plant are seen in part of the wide Europe, especially in the Southern this continent, North Africa and also wide parts of Asia.

In Iran, there is more scattered in the North and North West. The most important compounds in this plant, include monoterpenes phenolic thymol and carvacrol, p-hydrocarbon simin, α and γ trypnn (Youdim and Deans, 1999a, b) and other important compounds can be compounds oxygen such as pointed borneol and acid ursalic (Heo *et al*., 2002; Kulisic *et al*., 2004). The marjoram plant in some countries such as Morocco is used as a muscle relaxant also this plant in patient with diabetes mellitus is cause significant therapeutic effects and in traditional medicine against respiratory diseases and also used for dispel catarrh (Kulisic *et al*., 2004; Lemhadri *et al*., 2004) and also used to treat leukemia (Goun *et al*., 2002), also this plant is due to ursolic acid pharmacological properties such that has additive effect pattern of exploratory movements, muscle tone and sleep induced by anesthetic agents (Chattopadhyay *et al*., 2003), also marjoram is a herb rich in phenolic antioxidants and is considered an important source for food additive (Kulisic *et al*., 2004).

According to these studies, it is possibility that this plant due to phenolic aromatic compounds contain the sedative and anti-anxiety effects. And the purpose of

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this study, investigate the effects the sedative and anti-anxiety extract of marjoram is in comparison with diazepam. In this study, the effect of different doses intraperitoneally. According to the above studies, it is possibility that this plant due to flavonoids and alkaloids contain the sedative and anti-anxiety effects that in this study have been investigated effect of different doses.

MATERIALS AND METHODS

In this study, 30 male Wistar rats weighted 200-230 g and aged 3 months old were selected. All animals were kept in same situation (temperature 24°C and humanity 70%) and food and water were provided *ad libitum*. Animals were divided into 6 groups of 5 rats. To assessment of sedative and pre-anesthetic effects of extract in comparison with diazepam, group 1 received extract at the dose of 100 mg kg^{-1} BW, group 2 received extract at the dose of 200 mg kg^{-1} BW, group 3 received extract at the dose of 400 mg kg^{-1} BW, group 4 received diazepam at the dose of 1.2 mg kg^{-1} BW, group 5 received dimethyl sulfoxide at the dose of 1.2 mg kg^{-1} BW and group 6 as control group not received any medicines. About 30 min after administration of above procedures, ketamine at the dose of 40 mg kg^{-1} BW was administrated to all 6 groups through intra peritoneal immediately. After ketamine, induction time and sleeping times were calculated. To assessment of anti-anxiety effects of *Origanum majorana* extract, researchers used from elevated plus Maze test (Wilson *et al*., 1998). The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), Version 13.0 was used for statistical analysis. All data are presented as mean±SEM. Before statistical analysis, all variables were checked for normality and homogeneity of variance by using the Kolmogorov-Smirnoff and Levene tests, respectively. The data obtained were tested by ANOVA followed by Tukey's post-hoc multiple comparison test. $p<0.01$ was considered statistically significant.

RESULTS AND DISCUSSION

After administration of the anesthetic drug, recording of low induction and high sleeping times are consider as one of the good markers in detection of sedative effects of an anesthetic drug. Data shows that injection of different doses of mentioned extract yields to increase in sleeping time resulted from anesthetic drug. Tukey's test result showed that injection of extract at the dose of 200 mg kg^{-1} BW has shown significant difference than 1.2 mg kg^{-1} BW diazepam ($p<0.01$). Based on data, IP injection of extract at the dose of 200 mg kg^{-1} BW has lower induction time and higher sleeping time than diazepam at 1.2 mg kg^{-1} BW ($p<0.01$) to wit, *Origanum majorana* extract has better sedative and pre-anesthetic effects than diazepam. But extract at the doses of 100 and 400 mg kg^{-1} BW has not show significant difference than diazepam.

Thus can be conclude that efficacy of *Origanum majorana* extract is dose-independent. Based on data, it revealed that extract at the dose of 200 mg kg^{-1} BW has better anti-anxiety effect than diazepam ($p<0.01$). But doses of 100 and 400 mg kg^{-1} BW have not showed statistical significance ($p<0.01$) (Fig. 1-3).

In this study, sedative and the anti-anxiety effects of marjoram extract compared with diazepam in rats was studied. The results showed that intraperitoneal injection of marjoram extract with doses of 200 mg kg^{-1} BW with anti-anxiety was better and increased animal stay time on the open arms of the maze. There are several species of the genus marjoram plant that chemical composition of plant also depends on the species, height and the plant

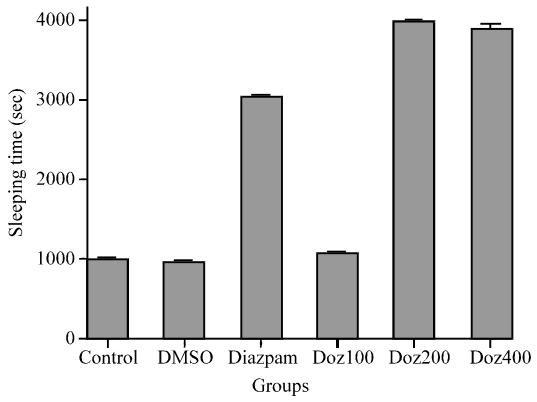

Fig. 1: Data mean of induction time in understudying groups

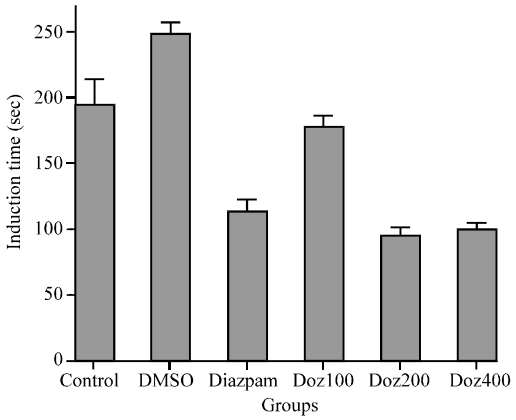

Fig. 2: Data mean of sleeping time in understudying groups

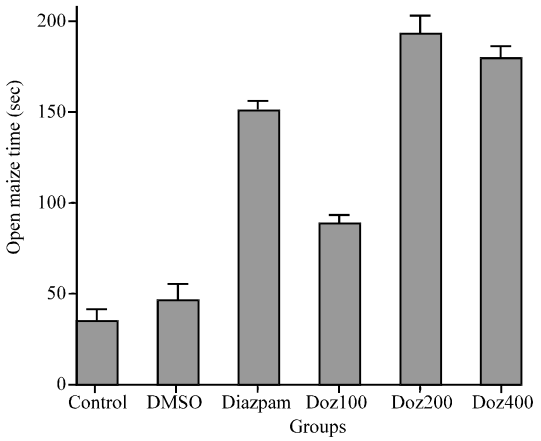

Fig. 3: Data mean of Maze test in understudying groups

has time to collect. According to compounds in this plant that containing borneol that it is an monoterpene double loop with effects of analgesic and is increase that GAGA receptor and also acid ureasalic in the inhibition of hemolytic blood factors and also has anti-cancer and anti-inflammatory effects but much of the chemical composition, this plant make up from material phenol fragment aromatic means carvocrol and thymol, these compounds have the ability to enter brain and through effects on calcium-dependent potassium channels actions effects on the activity neural and endocrine light (Youdim and Deans, 1999a, b; Economakis *et al*., 2005) phenolic compounds and marjoram extracts of ursolic acid in the brain have the ability to cross the BBB so suggested that this compounds due to effect of oxidative anti-stress in the nervous system may have anti-anxiety properties (Shivji *et al*., 2005) also ureaslic on the exploration of movement and muscle tone and induced sleep have effect by anesthetic drugs (Chattopadhyay *et al*., 2003). Diazepam is a abuse as a benzodiazepine drug have sedation and pre-anesthetic effects proved on the control nervous system and the other hand is considered as anti-anxiety drug.

Diazepam through interaction with GABA reseptors in the brain especially in the mid brain reticular formation because of sedation and anti-anxiety effects (Katzung, 1992). Based on results obtained during the sedative process in the doses used dose of 200 mg kg^{-1} BW had a statistically significant with diazepam ($p<0.01$) and have better sedation and pre-anesthetic effect than diazepam. Other words have less induction time and more sleeping time than diazepam and can be used as pre-anesthetic drug in place of diazepam and marjoram extract in doses of 100 and 400 have weaker sedation and pre-anesthesia effects than diazepam. In this study, to obtain the appropriate doses according to suggested doses in the various articles was used of doses of 100, 200 and 400 (Abbasnejad *et al*., 2005). Also in another part of study, according to results obtained marjoram extract dose of 200 mg kg^{-1} BW have better anti-anxiety than diazepam dose of 1/2 mg kg^{-1} BW. Means dose of 200 mg kg^{-1} BW have more time on the open arms of the maze than diazepam and also number of sweep in the open arms are more and this is as a indictor of anti-anxiety and according to flavonoid and alkaloid compounds in this plant and the results obtained can be concluded that thisplant has a sedation and pre-anesthetic and anti-anxiety effects.

CONCLUSION

From present study, it can be said that marjoram extract injection intraperitoneally with a dose of 200 mg kg^{-1} BW provides as a pre-anesthetic drug before injection ketamin duration induction is less and duration anesthetic is more than diazepam with a dose of 1/2 mg kg^{-1} BW and shows significant difference ($p\leq0.0$). Also injection of marjoram extract with dose of 200 mg kg^{-1} BW intraperitoneal in order to evaluate the anti-anxiety effects cause increased stay time of animals on the open arms of the maze and provides abetter effect than diazepam and shows a significant difference ($p\leq0.0$). Therefore, there is the possibility that flavonoids in the extract of marjoram this plant through the effect on benzodiazepine receptor binding to GABA-A receptors is caused sedative and anti-anxiety effects. Of course proof of this need to separate each of the active and anti-anxiety that this field is requires further study and extraction and identify the chemical structure plant ingredients.

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