



ORIGINAL ARTICLE

Study of Sedative, Preanaesthetic and Anti-anxiety Effects of Herbal Extract of Motherwort (*Leonuruscardiac*) in Comparison with Diazepam in rat

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ABSTRACT

Due to sedation, anticonvulsant and anti-pain effects, Leonuruscardiaca has had a special place in traditional medicine of Iran and any of countries. The chemical composition of this plant contain alkaloids (stachydrine, Leonurine), Iridoid glycosides, labdanediterpene and terpene lactones like (Leo carlin and macrobid side), flavonoids, phenolic acids and tannins that these substances may affect the plant in areas of CNS strengthen calming and soothing effect and is caused by GABA. In the present time, sedative and anxiolytic drugs such as chemical drugs are used for the, sedation and anxiolytic but due to their side effects and economic issues, the significance of research on finding sedative and anxiolytic drugs with less side effects and their ability to substitute these synthetic drugs and substituting newer sedation and anxiolytic compounds is obvious. Considering the importance of sedative and anxiolytic effects of this plant's wedecided to have a comparative study of this plant with synthetic drugs. Two different groups of male Wistar rats received herbal extract of Leonuruscardiaca with doses (150, 300, 450mg/kg, IP) and Diazepam with dose of (1.2mg/kg, IP), and Dimethyl sulphoxide with the equal volume. 30 minutes after assessing the relief sedative and preanaesthetic effects (induced sleep duration by ketamine 40mg/kg, IP) & anti-anxiety effects (using elevated plus maze) injected intra peritoneal. The results showed meaningful increase in the period of the sleep time that had been induced with Ketamine and also meaningful increase in time spent at open arms in the treatment group with the previous. The results showed that the Leonuruscardiaca extract with dose 450mg/kg has sedative, preanaesthetic& anti-anxiety effects.

Keywords: *Leonuruscardiaca, sedative, anti-anxiety, diazepam, elevated plus maze.*

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INTRODUCTION

Nowadays, medical herbs form an important part of traditional medicine in most countries as well as especial and valuable place in new treatment procedures. In the present study has been attempted to introduce the extract as a pre-anesthetic and anti-anxiety medicine which is more effective and has fewer side effects in comparison with chemical drugs. Also, the herb is used for disease treatment in traditional medicine [3, 20-21].

Motherwort (*Leonuruscardiaca*) is a herbaceous perennial plant in the mint family, Lamiaceae. Other common names include Throw-wort, Lion's Ear, and Lion's Tail. Lion's Tail also being a common name for *Leonotisleonurus*, and Lion's Ear, a common name for *Leonotisnepetifolia*. Originally from Central Asia it is now found worldwide, spread largely due to its use as a herbal remedy. *L. cardiaca* has a square stem and opposite leaves. The leaves have serrated margins and are palmately lobed with long petioles; basal leaves are wedge shaped with three points and while the upper leaves are more latticed. Flowers appear in leaf axils on the upper part of the plant and it blooms between June–August [13]. The flowers are small, pink to lilac in colour often with furry lower lips. The plant grows to about 60–100 cm in height. It can be found along roadsides and in vacant fields and other disturbed areas [4]. Motherwort has a long history of use as a herb in traditional medicine in Central Europe, Asia and North America. Like many other plants, it

has been used for a variety of ills. Midwives use it for a variety of purposes, including uterine tonic and prevention of uterine infection in women, hence the name Motherwort. The herb contains the alkaloid leonurine [1], which is a mild vasodilator and has a relaxing effect on smooth muscles. For this reason, it has long been used as a cardiac tonic, nervine and an emmenagogue. Among other biochemical constituents, it also contains bitter iridoid glycosides, diterpenoids, flavonoids (including rutin and quercetin), tannins, volatile oils, and vitamin A [2].

MATERIAL AND METHODS

Understudied animals

In the present study, 30 Wistar male rats of 200 ± 20 g weighting and about 3 month aged were used for laboratory experiments. Animals were kept in standard condition, at 20-25°C, 70% humidity and light cycle of 12 hours lighting and 12 hours darkness. Standard foods were used in order to feeding by method of Ad-Libitum in during 24 hours feeding. Specific dishes were used for water. The rats were divided in groups consisted of 5 animals and were placed in especial cages.

Obtaining extract:

1000 g dried Motherwort was powdered in order to obtain extract from stem and leaves. The powder was soaked in methanol and chloroform (70:30) for at least 24 hours; then, the obtained mixture was entered rotary operator system in vacuum pressure for obtaining raw extract. The resulted raw extract was dissolved in the least quantity of hot methanol followed by freezing at -15°C and was filtered immediately for obtaining fatless extract. The fat-removed extract was dissolved in chloromethane, dried by magnesium sulfate and removed solvent by operator rotary system under vacuum in order to water-remove and obtain pure extract.

Evaluating method as well as sedation and pre-anesthetic effects of Leonuruscardiaca:

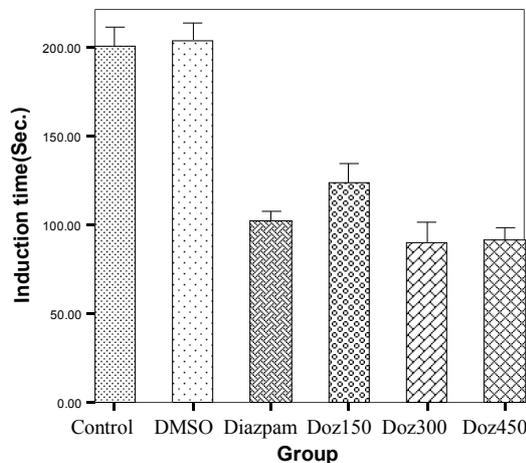
In order to evaluate the sedation and pre-anesthetic effects of hempseed extract in comparison with diazepam, 150 mg of extract per kg of body weight in first group, 300 mg of extract per kg of body weight in second group, 450 mg of extract per kg of body weight in third group, 1.2 mg diazepam per kg of body weight in fourth group, the same amount of methyl sulfoxide was injected intra peritoneal in fifth group, and sixth group did not receive any drug. 40 mg/kg BW of ketamine was injected intra peritoneal in all groups 30 minutes following of mentioned drugs. Induction time and sleeping time were measured immediately following administration of ketamine.

Elevated plus maze was used in order to evaluate anti-anxiety effects of Motherwort extract. The system consists of two arms (50×10 cm) which are open and against each other and two arms (40×10×50 cm) which are closed and against each other. They are related to each other by a central plate (10×10 cm) in a semi dark and silent. They are placed in 50 cm distance of the floor. In order to determine anti-anxiety effects of the drugs, the duration of remaining the rats on open arms is considered as non-anxiety marker and the duration of remaining the rats on closed arms is considered as anxiety marker. More duration of remaining the rats on open arms demonstrates the strong anti-anxiety effects of considered drug. Therefore, Common mallow extract with dosages of 150, 300, 450 mg/kg BW and 1.2 mg/kg BW of diazepam and dimethyl sulfoxide (as placebo) were used as intra peritoneal injection. Methyl sulfoxide was placed in maze center 30 minutes following administration of the mentioned drugs. The time duration in which the rats remained in each of maze's arms was recorded in terms of second; time duration of their presence in maze is 5 minutes [8]. SPSS software program was used in order to statistical analysis of data as well as Tokay follow up test for determining a meaningful difference among dual groups. $P < 0.01$ has been considered as meaningful. Also, data were reported as mean \pm SD.

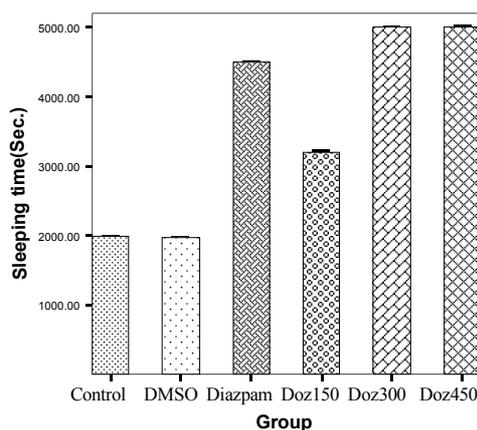
RESULTS

Following the injection of pre-anesthetic drugs and anesthetic inductive drugs, recorded of induction time and sleeping time are considered as markers of the sedation rate effects of a pre anesthetic drug. The results demonstrated that the injection of different dosages of the extract caused to increase sleeping time. The results of dual Tokay follow up test showed a meaningful difference between intra peritoneal injections of 450 mg/kg BW of Motherwort extract and 1.2 mg/kg BW of diazepam. Based on diagrams 1 and 2, intra peritoneal injections of 450 mg/kg BW of Motherwort extract has lower induction time and higher sleeping time in comparison with 1.2 mg/kg BW of diazepam; so that there is a meaningful difference ($P < 0.01$). In other words, the extract has better sedation and pre anesthetic effects in comparison with diazepam. But dosages of 150 and 300 mg/kg BW of the extract don't show a meaningful difference with diazepam. Dosages of 150 and 300 mg/kg BW of the extract have weaker and identical functions, respectively, in comparison with diazepam. The significant differences between of extract dosages of 300 and 450 mg/kg BW suggest that the increase of extract dose leads to increase the sedation and anti-anxiety effect. Based on diagram 3, the results show that hempseed extract in dosage of 450

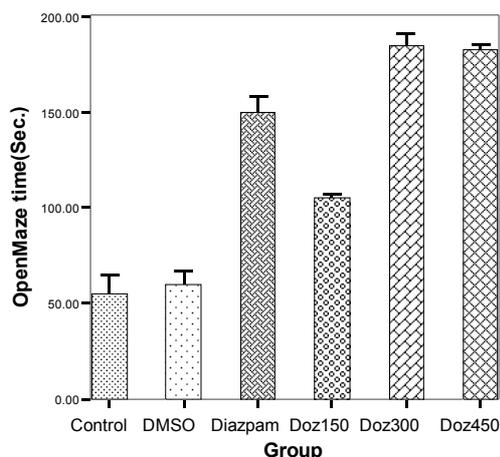
mg/kg BW has a better anti-anxiety effect in comparison with 1.2 mg/kg BW of diazepam. Also, they show a statistical significant difference. In other words it causes to decrease the anxiety and increase of the time spent on open maze arms as well as increases the numbers of traverse on open arms. But, the extract dosages of 150 and 300 mg/kg BW demonstrate a significant difference, it means that they have a weak function ($P < 0.01$).



Figures 1: Mean of induction time obtained from understudied groups plant *Leonuruscardiaca*



Figures2: Mean of sleeping time obtained from understudied groups plant *Leonuruscardiaca*



Figures 3: Mean of Maze data obtained from understudied groups plant *Leonuruscardiaca*

DISCUSSION

Motherwort is especially valuable in the treatment of female weaknesses and disorders, allaying nervous irritability, inducing quiet and passivity of the whole nervous system [11]. It is also seen as a remedy for

heart palpitations, it has a strengthening effect, especially on a weak heart [5]. The antispasmodic and sedative effects promote relaxation rather than drowsiness [7]. The leaves are antispasmodic, astringent, cardiac, diaphoretic, emmenagogue, nervine, sedative, stomachic, tonic and uterine stimulant[4, 9 and 12]. They are taken internally in the treatment of heart complaints (notably palpitations) and problems associated with menstruation, childbirth and menopause, especially of nervous origin[6]. Although an infusion can be used, the taste is so bitter that the plant is usually made into a conserve or syrup[14]. An alcoholic extract is said to possess superior action to valerian (*Valeriana officinalis*)[20]. The plant has been found effective in the treatment of functional heart complaints due to autonomic imbalance, and also as an anti-thyroid treatment, though it needs to be taken for several months for these effects to be noticed[16]. The whole herb is harvested in August when in flower and can be dried for later use. It should not be prescribed in the earlier stages of pregnancy or where periods are heavy[17, 19]. A homeopathic remedy is made from the plant[18]. It is used in the treatment of heart complaints, amenorrhoea, menopausal problems and flatulence[10]. The German Commission E Monographs, a therapeutic guide to herbal medicine, approve *Leonurus cardiaca* Motherwort for nervous heart complaints.

In the present study two methods, evaluating the sedation and pre anesthetic effect and evaluating of anti-anxiety effects, were used for comparing Motherwort extract in comparison with diazepam. Some other researches were conducted in the past; for example,

Based on reported studies, different compounds were identified and isolated from Motherwort which were mentioned previously. The presence of alkaloid and flavonoid compounds in the herb cause to increase sleeping time due to injection of anesthetic drug that conforms the present study. Based on observations, it can be said that sedation effect of the extract is related to these compounds [7]. Diazepam, on one hand, is as a benzodiazepine drug has sedation and pre anesthetic effects on central neural system and on the other hand is considered as an anti-anxiety drug. So, it causes to some sedation and anti-anxiety effects by interaction with GABA receptors presented in brain especially in reticular part of middle brain [22]. Adverse effects of diazepam include anterograde amnesia (especially at higher doses) and sedation, as well as paradoxical effects such as excitement, rage or worsening of seizures in epileptics. Benzodiazepines also can cause or worsen depression. Long-term effects of benzodiazepines such as diazepam include tolerance, benzodiazepine dependence and benzodiazepine withdrawal syndrome upon dose reduction. After cessation of benzodiazepines, cognitive deficits may persist for at least six months and it was suggested that longer than six months may be needed for recovery from some deficits [4]. Diazepam also has physical dependence potential and can cause serious problems of physical dependence with long term use.

Based on obtained results, among administered dosages, 450 mg/kg BW of the extract has a meaningful difference with diazepam during sedation process ($P < 0.01$) and has better sedation and pre anesthetic effects in comparison with Diazepam, in fact it has shorter induction time and longer sleeping time in comparison with diazepam so it can be used as pre anesthetic drug instead of diazepam. But, 450 and 150 mg/ kg BW of the extract don't show meaningful difference over diazepam ($P < 0.01$). Extract dosage of 150 mg/kg BW has a weaker function in comparison with diazepam and the extract dosage of 300 mg/kg BW has an identical function in comparison with diazepam. Based on different study in the present study, in order to obtain suitable dosages, the extract dosages of 150, 300, 450 mg/kg BW were used. Also, in the second part of the study, based on obtained results, it has demonstrated that 450 mg/kg BW of the herb has better anti-anxiety effect in comparison with 1.2 mg/kg BW of diazepam. That is, by administrating 450 mg/kg BW the rats remain more time on maze open arm in comparison with diazepam; also their traverse on open arms is greater which is as an anti-anxiety marker. Considered of the herb's flavonoid and alkaloid compounds and obtained results it can be concluded that hempseed has sedation, pre-anesthetic and anti-anxiety effects [12, 13].

Nowadays, the studies on traditional medicine have been increased. But, Motherwort has remained unknown in spite of traditional uses from its stems and leaves. Consideration and observations about the extract's sedation and anti-anxiety effects, are require more studies about identification and extraction of the herb's constituents.

CONCLUSION

It can be concluded, generally, that based on different studies the extract of Motherwort may affect via effecting on benzodiazepine receptors connected to GABA receptors (considering its flavonoid content). Based on the obtained results by the present study it can be said that according to sedation process the extract dosage of 450 mg/kg BW, among other dosages, has had more significant results and has a better sedation, pre-anesthetic and anti-anxiety effect in comparison with diazepam ($P < 0.01$).

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