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Study of Sedation, Pre-Anesthetic and Anti-Anxiety Effects of Celandine Extract Compared with Diazepam in Rats

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Abstract: Celandine with scientific name *Chelidounium majus*, spreads across the world and exists in Northern parts of Iran like Gilaan, the outskirts of Rasht, Roodbar and Mazandaran. Some of effective chemical compounds are: malic, copticine, cityicacid, chelerythrine, berberine, succinic acid and sangainarine acid. The herb's other medical properties are: calmative, narcotic, anti spasm, lowering blood pressure, antibilious, cathartic and wormroot in internal uses. Epispastics and flesh wound amneliorator in external uses. Other chemical compounds of the herb have alkaloids that some of which are toxic those alkaloids are Chelidtine hemochelidotine, cheleritrine, sangainarine and protopine. In the present study, 30 Wistar male rats of 200-230 g weight and about 3 months old were used for laboratory experiments. Animals were kept in standard condition, at 20-25°C, 70% humidity and light cycle of 12 h lighting and 12 h darkness. Standard plates were used in order to feeding by method of *ad-libitum*, i.e., 24 h feeding. It can be concluded, generally that based on different studies the extract of celandine may affect via effecting on benzodiazepine receivers connected to GABA receivers (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 400 mg kg^{-1} BW among other dosages has had more meaningful results and has a better sedation, pre-anesthetic and anti-anxiety effects compared with diazepam ($p<0.01$).

Key words: Sedation, pre-anesthetic, anti-anxiety, celandine, diazepam, rats

INTRODUCTION

Now a days, 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 the attempt was to introduce the extract as a pre-anesthetic and anti anxiety medicine which is more effective and has fewer side effects compared with chemical drugs. Also, the herd is used for disease treatment in traditional medicine (Cetto, 1999; Pellow *et al*., 1985; Racine, 1972). Celandine with scientific name *Chelidounium majus*, spreads across the world and exists in Northern parts of Iran like Gilaan, the outskirts of Rasht, Roodbar and Mazandaran. Some of effective chemical compounds are: malic, copticine, cityic acid, chelerythrine, berberine, succinic acid and sangainarine acid.

The herb's other medical properties are: calmative, narcotic, anti spasm, lowering blood pressure, antibilious, cathartic and wormroot in internal uses. Epispastics and flesh wound amneliorator in external uses. Other chemical compounds of the herb have alkaloids that some of which are toxic those alkaloids are chelidtine hemochelidotine, cheleritrine, sangainarine, protopine (Mirhaydar, 2002; Cetto *et al*., 2000; Perez *et al*., 1985). If celandine be used along with hop it will be effective in sedation gastric cancer pains. Meanwhile, Hanzlik believes that chelidonin is a material adjacent to papaverin considering chemical compound and physiological effect.

Rubbing pure celandine or mixed with water as well as its fresh and squeezed roots on infectious ulcers or ulcers occurred due to Vitamin C deficiency provide improving and healing effects. Its sap is beneficial for skin diseases such as eczema (Zargari, 1989; Lemus *et al*., 1996; Joly, 1979). Because of existing effective materials (chelidonin, sangarine, cheleritrine and protopine), pigmented material called chelidograntin, chelidonic acid, other organic acids and minerals, especially calcium phosphate, magnesium and aluminum, the herb has sedation and calmative effects. Considering the mentioned items and due to existing chelidonic acid, the herb has sedation and anti-anxiety effects. In the present study, the effect of

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different doses has been evaluated (Mirhaydar, 2002; Dos Santos *et al*., 2005; Wilson *et al*., 1998).

MATERIALS AND METHODS

Understudied animals: In the present study, 30 Wistar male rats of 200-230 g weight and about 3 months old were used for laboratory experiments. Animals were kept in standard condition at 20-25°C, 70% humidity and light cycle of 12 h lighting and 12 h darkness. Standard plates were used in order to feeding by method of *ad libitum*, i.e., 24 h feeding. Especial dishes were used for water. The rats were numbered in groups consisted of 5 animals and were placed in especial cages.

Obtaining extract: About 1000 g dried celandine 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 h 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. Then, the obtained extract was given a person who prescribes only the drugs and doesn't know anything about their nature.

Evaluating method as well as sedation and pre-anesthetic effects of celandine: In order to evaluate the sedation and pre-anesthetic effects of celandine extract compared with diazepam, 100 mg of extract per kg of body weight in first group, 200 mg of extract per kg of body weight in second group, 400 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 6th group did not receive any drug. About 40 mg ketamine per body weight was injected intra peritoneal in all groups 30 min following 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 celandine extract. The system consists of two arms (10×15 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 from the earth. 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, celandine extract with dosages of 100, 200, 400 and 1.2 mg kg^{-1} BW diazepam of diazepam and dimethyl sulfoxide (as placebo) were used as intra peritoneal injection. Methyl sulfoxide was placed in maze center 30 min 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 min (Wilson *et al*., 1998). SPSS Software program was used in order to analysis statistical 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±SD (Fig. 1).

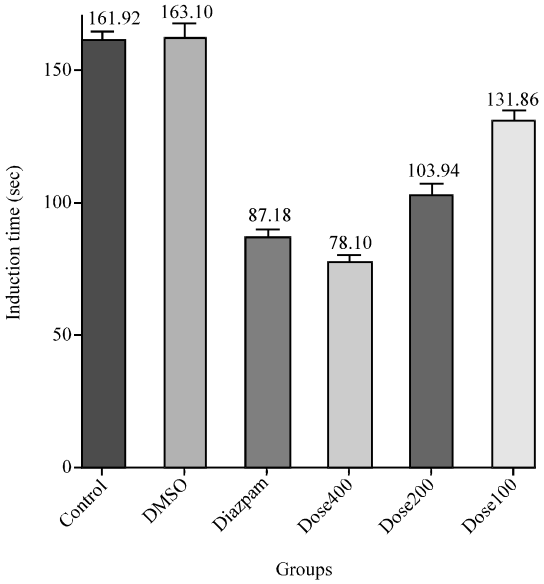

Fig. 1: Mean of induction time obtained from understudied groups plant celandine

RESULTS AND DISCUSSION

Following the injection of pre anesthetic drugs, the injection of anesthetic inductive drugs, recording of induction time and sleeping time are considered as markers of the rate of sedation effects of a pre anesthetic drug (Fig. 2). The results demonstrate that the injection of different dosages of the extract causes to increase sleeping time. The results of dual Tokay follow up test show a meaningful difference between intra peritoneal

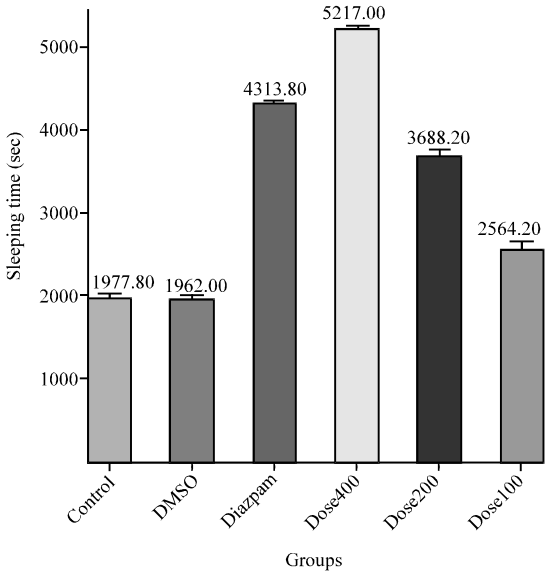

Fig. 2: Mean of sleeping time obtained from understudied groups plant celandine

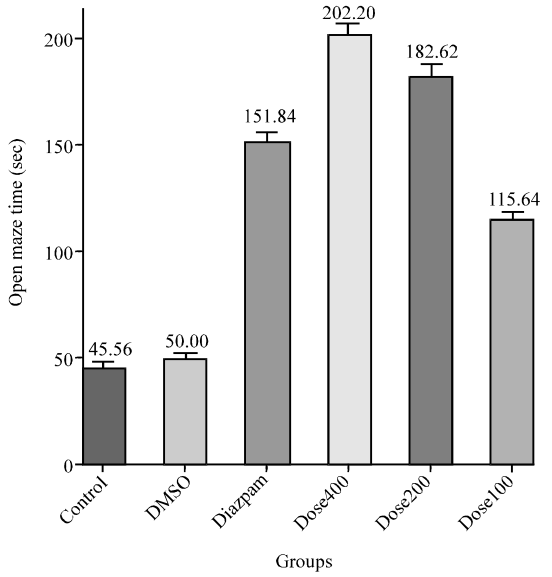

Fig. 3: Mean of maze data obtained from understudied groups plant celandine

injections of 400 mg kg^{-1} BW of celandine extract and 1.2 mg kg^{-1} BW of diazepam. Based on Fig. 1 and 2 intra peritoneal injections of 400 mg kg^{-1} BW of celandine extract has lower induction time and higher sleeping time compared with 1.2 mg kg^{-1} 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 compared with diazepam. But dosages of 100 and 200 mg kg^{-1} BW of the extract do not show a meaningful difference with diazepam. Dosages of 100 and 200 mg kg^{-1} BW of the extract have weaker and identical functions, respectively compared with diazepam.

The meaningfulness of differences compared with extract dosages of 200 and 400 mg kg^{-1} BW suggests that the increase of extract dose leads to increase the sedation and anti anxiety effect. Based on Fig. 3, the results show that celandine extract in dosage of 400 mg kg^{-1} BW has a better anti anxiety effect compared with 1.2 mg kg^{-1} BW of diazepam. Also, they show a meaningful difference statistically 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 100 and 200 mg kg^{-1} BW demonstrate a meaningful difference, i.e. have a weak function ($p<0.01$). In the present study two methods, evaluating the sedation and pre anesthetic effect and evaluating of anti anxiety effects were used for comparing celandine extract against diazepam. Some other researches were conducted in the past for example in 1914 and 1920, Hanzlik suggested that anti spasm effect had caused to its administration in angina, asthma, gastric muscular fibers' contraction and disorders related to unstriated muscles' spasms. Capla in 1936 demonstrated in his studies that celandine is counted as a good drug for removing cerebral stimulations in hysteria and people who suffered from cerebral weakness such as insomnia along with stress as well as hardening of cerebral arteries. Ghorbanli in conducted a study in which the seasonal changes of alkaloid rates and phenolic compounds of celandine were evaluated in two regions, Ghorghan and Ziarat in Autumn and Winter they concluded that there is a meaningful difference considering phenolic, alkaloid and flavonoid compounds in each of seasons.

There is maximum rate of alkaloid in the herb's roots located in Ziarat (in Spring) and maximum phenolic compounds in the herb's roots located in Ghorghan (in Winter) (Fisher, 1989; Joly, 1979). Monavari conducted as study called evaluation of anti viral effects of fife species from various herbs' families they characterized that celandine has anti viral effect (Dunham and Miya, 1957; Ferrini *et al*., 1974). Based on reported studies different compounds were identified and isolated from celandine 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 (Dos Santos *et al*., 2005; Broudiscou and Lassalas, 2000; Fisher, 1989). Diazepam on one hand is as a benzodiazepine drug has

sedation and preanesthetic effects on central neural system and on the other hand is considered as an anti anxiety drug. So causes to some sedation and anti anxiety effects by interaction with GABA receivers presented in brain, especially in reticular part of middle brain (Katzung, 2004). Based on obtained results among administered dosages, 400 mg kg^{-1} BW of the extract has a meaningful difference with diazepam during sedation process ($p<0.01$) and has better sedation and pre anesthetic effects compared with Diazepam, i.e. has shorter induction time and longer sleeping time compared with diazepam so can be used as pre anesthetic drug instead of diazepam. But 100 and 200 mg kg^{-1} BW of the extract show no meaningful difference over diazepam ($p<0.01$).

Extract dosage of 100 mg kg^{-1} BW has a weaker function compared with diazepam and the extract dosage of 200 mg kg^{-1} BW has an identical function compared with diazepam. Based on different study in the present study in order to obtain suitable dosages, the extract dosages of 100, 200, 400 mg kg^{-1} BW were used.

Also in the second part of the study based on obtained results, it has demonstrated that 400 mg kg^{-1} BW of the herb has better anti anxiety effect compared with 1.2 mg kg^{-1} BW of diazepam that is by administrating 400 mg kg^{-1} BW the rats remain more time on maze open arm compared with diazepam also, their traverse on open arm is greater which is as an anti anxiety marker. Considered with the herb's flavonoid and alkaloid compounds and obtained results it can be concluded that celandine has sedation, pre anesthetic and anti anxiety effects (Kang *et al*., 2002; Fathiazad and Lotifipour, 2003; Archer, 1973). Generally, now a days the studies on traditional medicine have been increased. But celandine has remained unknown in spite of traditional uses from its stems and leaves. Considered with observations about the extract's sedation and anti anxiety effects more studies are required about identification and extraction of the herb's constituents (Pellow *et al*., 1985; Racine, 1972; Rodgers *et al*., 1997).

CONCLUSION

It can be concluded, generally that based on different studies the extract of celandine may affect via effecting on benzodiazepine receivers connected to GABA receivers (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 400 mg kg^{-1} BW among other dosages has had more meaningful results and has a better sedation, pre-anesthetic and anti-anxiety effects compared with diazepam ($p<0.01$).

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