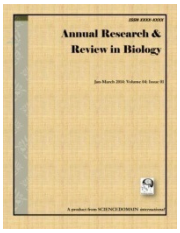

Annual Research & Review in Biology
4(14): 2396-2405, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Antidepressant-like Effects of *Elatostema umbellatum* and *Urtica dioica* in Mice Using Forced Swim Test and Tail Suspension Test

Amir Modarresi Chahardehi[1*], Darah Ibrahim[1], Farid Abolhassani[2] and Shaida Fariza Sulaiman[3]

[1]Industrial Biotechnology Research Laboratory, School of Biological sciences, Universiti Sains Malaysia, 11800 Minden, Penang Island, Malaysia.
[2]Department of Anatomy, Medical School, Tehran University of Medical Sciences, Iran.
[3]Phytochemistry Laboratory, School of Biological sciences, Universiti Sains Malaysia, 11800 Minden, Penang Island, Malaysia.

Authors' contributions

This work was carried out in collaboration between all authors. Author AMC performed the study, statistical analysis and wrote the first draft of the manuscript. Author DI designed and managed the study. Author FA prepared all the materials for antidepressant assays for this project in his laboratory. Author SFS helped us to desinged of the methods of extraction from these plants and phytochemistry of the study. All authors read and approved the final manuscript.

Original Research Article

Received 10th March 2014
Accepted 28th March 2014
Published 10th April 2014

ABSTRACT

Aims: The aim of the present study was to evaluate the antidepressant action of *Elatostema umbellatum* and *Urtica dioica* as well as comparison them with conventional antidepressant drugs and to determine the possible mechanism of its antidepressant action using two methods of study.
Study Design: Prospective.
Place and Duration of Study: Department of Anatomy, Medical School, Tehran University of Medical Sciences, Iran.
Methodology: Alcoholic extracts of *E. umbellatum* and *U. dioica* were intra-peritoneal administrated in 78 albino mice (each group contains six mice) using two different methods of extraction (Soxhhlet and partitioning extractions) and antidepressant assays.

**Corresponding author: Email: amirmch@yahoo.com;*

The antidepressant activity was examined to obtain antidepressant-like effect using Forced Swimming Test (FST) and Tail Suspension Test (TST) in mice.
Results: CEUD I and BEUD IIf_2 led to reduction of immobility time, as the selected extracts with two doses (50 and 100mg/kg) administered were different compared to the control, in the FST method by 65.55% and 72.87% for 100mg/kg, respectively. However, fraction BEUD IIf_2 showed the best result compared to our positive controls. Similar results of increased antidepressant effect, that was, of immobility time depending on the concentration administered, were obtained with the TST method. Also our data showed that there was no significant differences between doses (50 and 100mg/kg) except for HEEU I extract.
Conclusion: The results suggested that the antidepressant action of the butanol extract of *U. dioica* its fraction (BEUD IIf_2) was mediated by an interaction with 5-hydroxytrptamine (5-HT). *U. dioica* showed a potential source for the isolation of important natural products with antidepressant-like properties. However, further studies are still required.

Keywords: Urtica dioica; Elatostema umbellatum; antidepressant activity; forced swimming test (FST); tail suspension test (TST).

1. INTRODUCTION

Depression is considered as an affective disorder characterized by change in mood, lack of interest in the surroundings, psychomotor retardation and melancholia. The prevalence of depression in general population is estimated to be around 5% [1]. Numerous antidepressant compounds are now available, presumably acting via different mechanisms. Hence, over 20 animal models of depression have been developed. These assays either provide a means of screening for putative antidepressant activity, or allow theories relating to the etiology of depression to be found. Forced swimming test (FST) and tail suspension test (TST) are the models which based on the application of stress to the animal [2,3]. However, many plant extracts and different classes of phytochemicals have been shown to have useful activity [4]. The search for novel therapeutic natural plants that mitigate depressive illness has been extensively explored over the past decade [5,6].

Urticaceae family was reported as one of the effective medicinal plant [7]. This family known to possess many ethnomedical and biological properties [8]. *Urtica dioica* (stinging nettle) is annual and perennial herb which distinguished with stinging hairs. This plant is traditionally used in Northern Iran and Eastern part of Europe [9] and also have already been known for a long time as medicinal plants in many parts of the world [10]. These herbs are used to treat stomachache [11,9]. Besides, this herb is used to treat rheumatic pain and for colds and cough [12]. *Elatostema umbellatum* as an edible was found to have high antioxidant activities [13]. Although in our previous study, this species exhibited medium range of antioxidant activity by DPPH radical scavenging [8] and has kaempferol glycosides and caffeic acid as a flavonoid and simple polyphenol, respectively [14].

On the other hand, Central Nervous System (CNS)-depressant activity has been studied for *Urtica dioica*. It has been shown to produce a reduction in spontaneous activity in rats and mice [15]. Inhibition of drug-induced convulsions, and a lowering of body temperature in rats. Nettle has been reported to have no effect on the blood pressure of mice, whereas in cats it has produced a marked hypotensive effect and bradycardia [15]. The stinging hairs of most nettle species contain serotonin, formic acid and histamine [16]. Serotonin or 5-

hydroxytrptamine (5-HT) is a monoamine neurotransmitter and is primarily found in the gastrointestinal (GI) tract, platelets, and in the CNS of animals including humans [17]. However, there is no report of this plant directed to antidepressant activity. The antidepressant activity was determined by forced swimming test (FST) and tail suspension test (TST) in order to understand the importance of these extracts.

2. MATERIALS AND METHODS

2.1 Plant Materials and Extraction

The leaves of *E. umbellatum* were collected in Maxwell Hill (Bukit Larut) in Taiping, Perak, Malaysia (the geographical coordinates of sampling sites: Altitude: 4°51'31.91" N-100°48'17.81" E and altitude: 1326m) in March 2008. A voucher specimen was deposited at the Herbarium of the School of Biological Sciences, Universiti Sains Malaysia by our taxonomist Mr. Shunmugam a/l Vellosamy in April 2008 by the code of 11321.

The aerial parts of *U. dioica* including leaves and stems were collected in Iran from Salmanshahr city in Mazandaran province (the geographical coordinates given by GPS: Latitude: 36°42'34" N-51°08'57" E and altitude: 21m) and Tehran city in Tehran province (the geographical coordinates given by GPS: latitude: 35°50'21" N-51°25'22" E and altitude: 2012m) in August 2007. The Voucher specimens were deposited at the Herbarium of the School of Pharmaceutical Sciences, University of Tehran (Iran) by Mr. Kazem Mehdigholi in April 2010 by the code of 6725-TEH. The plant materials were washed; dried in shade place and ground to small pieces. The first method (Method I) of extraction included the using of four solvents by following non-polar to polar solvents (by using Soxhlet apparatus). In this method, dried powdered plant was extracted. The solvents used were hexane, chloroform, ethyl acetate and methanol. The second method (Method II) included 5 solvents system (by using partition technique). In this following method, the dried materials were extracted by using Soxhlet extractor with methanol as a solvent for 72 hours at room temperature (30°C). The methanolic extracts were further partitioned by adding distilled water in a separating funnel and then followed using chloroform, diethyl ether, ethyl acetate and butanol as described by Mellidis and Papageorgiou [18], with a slight modification. According to the order of solvents polarity which were used in the method II were hexane>chloroform>diethyl ether>ethyl acetate>butanol>methanol. The dried extracts were then weighed using microbalance and were kept at 4°C. Abbreviations for crude extract used in this paper namely.

HE I (hexane extract of method I), CE I (chloroform extract of method I), EAE I (ethyl acetate extract of method I), ME I (methanol extract of method I), ME II (methanol extract of method II), CE II (chloroform extract of method II), DEE II (diethyl ether extract of method II), EAE II (ethyl acetate extract of method II) and BE II (butanol extract of method II). However, according to our previous studies in our lab, antioxidant, antimicrobial, toxicity and anticancer activities, four of this crude extracts which are namely: chloroform extract of *U. dioica* from extraction method I (CEUD I), butanol extract of *U. dioica* from extraction method II (BEUD II), hexane extract of *E. umbellatum* (HEEU I) and methanol extract of *E. umbellatum* from extraction method II (MEEU II) were selected for antidepressant activity. The doses of the extracts and fraction were selected on the basis of our previous results from toxicity assay on mice which were showed no behavioral changes on these animals and also previously reported to enhance locomotor activity [19]. Using two different solvent systems made a possible the use of the best system for their isolation for this study.

2.2 Animals

A total of seventy-eight mice of either sex (BALB/c strain) purchased from animal house, School of Medical Sciences, University of Tehran (Iran), and weighing 25–35g were used. Animals were placed at Animal house, Department of Anatomy, School of Medical Sciences, University of Tehran, housed 6 per cage under a normal 12h/12h light/dark schedule with the lights on at 07:00 a.m. and they were fed with commercial mice food pellets and tap water ad libitum. They were allowed at least 1 week to adapt to the laboratory prior to the administration. All efforts were made to minimize animal suffering and to reduce the number of animal used. All the drugs were administered intra-peritoneally (i.p.) 30min prior to FST.

2.3 Forced Swimming Test (FST)

The forced swimming test was administered in a similar manner and has been used as a model predictive of antidepressant effect [19]. Mice of either sex were individually forced to swim in an open cylindrical container (diameter 10cm, height 25cm), containing 19cm of water at 25±1℃. The immobility time, defined as the absence of escape-oriented behaviors, such as swimming, was scored during 6 min with the help of stop-watch, as described previously by [19-21]. All the mice of either sex were divided in thirteen different groups (shown in Table 1) and all BALB/c mice were exposed to the forced swim stressor in a cylinder that had been cleaned and disinfected prior to the session. The first group assigned as control receiving only vehicle (0.9%NaCl 5ml/kg body mass). The other groups received acute dose of extracts (50,100mg/kg). The positive groups (group 2 and 3) received standard drugs such as haloperidol (diluted with sterile water) and fluoxetine (diluted with normal saline) (1 and 10mg/kg, respectively). The total duration of immobility was recorded during the last 6 min of the 10-min period. Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. A decrease in the period of immobility is indicative of an antidepressant-like effect. This experiment was injected for two days later with same the doses of selected crude extracts of *U. dioica* (Third day) with a bit modification [22].

2.4 Tail Suspension Test (TST)

The total duration of immobility induced by tail suspension test was measured according to the method described by Steru et al. [3]. Mice both acoustically and visually isolated were suspended 70cm above the floor by adhesive tape placed approximately 1cm from the tip of the tail. The total immobility period was scored manually during 6 minutes test session with the help of stopwatch. Immobility was defined as the absence of any limb or body movements, except for those caused by respiration or when they hung passively and completely motionless. The parameter obtained was the number of seconds spent immobile. Parameter used was the number of seconds spent immobile.

2.5 Experimental Procedure

The thirteen animal groups received intra-peritoneally (i.p.) route at first day and third day for FST and one day for TST.

Group 1: Control group used normal saline as a vehicle
Group 2: Positive control using haloperidol 1mg/kgb.w., i.p.;

Group 3: Positive control using fluoxetine 10mg/kgb.w., i.p.;
Group 4 and 5: CEUD I extract at dose of 50 and 100mg/kg, respectively, b.w., i.p.;
Group 6 and 7: BEUD II extract at dose of 50 and 100mg/kg, respectively, b.w., i.p.;
Group 8 and 9: BEUD IIf2 fraction at dose of 50 and 100mg/kg, respectively, b.w., i.p.;
Group 10 and 11: HEEU I extract at dose of 50 and 100mg/kg, respectively, b.w., i.p.;
Group 12 and 13: MEEU II extract at dose of 50 and 100mg/kg, respectively, b.w., i.p.

2.6 Statistical Analysis

Data were expressed as the mean±standard deviation of mean (S.D.). Comparisons between experimental and control groups were performed by one-way analysis of variance (ANOVA) followed by Tukey`s HSD test when appropriate. $P<0.001$ and $p<0.01$ was considered significant.

3. RESULTS AND DISCUSSION

The present study demonstrated that the selected crude extract of *U. dioica* given systemically (Intra-peritoneal route), are effective in producing significant antidepressant-like effects, when assessed in the FST and in the TST. The antidepressant-like effects of these extracts in the FST and TST were comparable to haloperidol and fluoxetine as positive controls.

Behavioral studies have been shown to play an important part in the evaluation and development of antidepressant drugs [23]. Forced swimming test (FST) and tail suspension test (TST) are among behavioral models that widely and routinely used for screening new antidepressant compound [24].

In this study, albino mice treated with CEUD I, BEUD II and fraction BEUD IIf_2 at 100mg/kg in groups (six per cage) displayed high levels of immobility in the tail suspension test. HEEU I at dose of 50mg/kg did not show any significant compared with negative control (without treatment). However, for FST, CEUD I, BEUD II and fraction BEUD IIf_2 exhibited significant ($P=.05$).

According to TST results from Table 1, a robust effect of chloroform extract of *U. dioica* (CEUD I) and fraction BEUD IIf_2 at dose 100mg/kg were determined. The per cent of change of these extract in time of immobility were recorded at -67.82% and -65.98%, respectively, which it was near to fluoxetine as a positive control (-69.97%). Similar findings of increased antidepressant effect which is immobility time depending on the dose concentration of HEEU I extract administered for the TST.

In this study, a variation of the original Porsolt test was used [2], which means placing the mice in the water tank in two occasions separated by different days and recording swimming activity automatically. Also comparing the results between two methods of antidepressant activity which employed in this study, use different stress situations to induce states of despair, it can be found that the effect of the crude extract on the reduction and of immobility time was achieved more strongly in the FST than in the TST [25]. According to Bach-Rojecky et al. (2004), FST is more sensitive assay and could better reflects the state of depression which means that when comparing both models [26].

Table 1. Antidepressant effect of selected crude extracts of *E. umbellatum* and *U. dioica*

Name of extract	Dose (mg/kg)	Forced swimming test				Tail suspension test	
		Immobility time[a] (s) at first day	Change (%)	Immobility time[a] (s) at third day	Change (%)	Immobility time[a] (s)	Change (%)
Control	0	379.00±31.50	-	387.00±52.80	-	326.30±30.40	-
Haloperidol	1	106.70±4.50***	-71.84	75.00±8.20***	-80.62	64.00±15.10***	-80.39
Fluoxetine	10	203.70±6.10***	-46.25	201.00±7.00***	-48.06	98.00±11.50***	-69.97
CEUD I	50	225.33±25.01***	-40.55	134.67±6.11***	-65.20	139.33±8.51***	-57.30
	100	168.67±35.57***	-55.50	133.33±30.92***	-65.55	105.00±13.08***	-67.82
BEUD II	50	296.67±3.51**	-21.72	178.33±8.08***	-53.92	140.00±6.00***	-57.09
	100	266.67±4.51***	-29.64	176.00±31.75***	-54.52	127.33±2.52***	-60.98
BEUD IIf_2	50	276.00±12.29***	-27.18	122.67±8.02***	-68.30	135.00±5.37***	-58.63
	100	193.00±19.97***	-49.08	105.00±9.64***	-72.87	111.00±3.64***	-65.98
HEEU I	50	292.00±13.08**	-22.96	196.67±32.00*	-49.18	287.67±15.28ns	-11.84
	100	260.67±12.50***	-31.22	180.33±17.50***	-53.40	252.33±27.50**	-22.67
MEEU II	50	268.67±41.63***	-29.11	110.33±12.22***	-71.49	308.33±33.98ns	-5.51
	100	206.33±7.37***	-45.56	100.33±10.2***	-74.07	275.00±18.68ns	-15.72

*[a]Mean±SD, n=6; Statistically significant difference compared to the control group of animals: *** P=.05, ** P<.010, * P<0.001 and ns=Data are not different significant compared to control (vehicle). CEUD I: chloroform extract of U. dioica from extraction method I; BEUD II: butanol extract of U. dioica from extraction method II; BEUD IIf_2: fraction number 2 from the butanol extract of U. dioica from extraction method II; HEEU I: hexane extract of E. umbellatum from extraction method I and MEEU II: methanol extract of E. umbellatum from extraction method II*

Regarding to high antioxidant, antimicrobial, anticancer activities of these crude extracts, BEUD II was subjected to get fractions and developed by PC chromatograms using butanol:acetic acid:water ratio (BAW) as mobile phase. Four bands obtained in three colours in visible light. BE IIf_1 and BE IIf_2 were appeared in light yellow, BE IIf_3 in dense yellow and BEUD IIf_4 in dark green colour. However, first band (BEUD IIf_1) exhibited yellow colour, BEUD IIf_2 in blue (sea green), BEUD IIf_3 in yellow-green and BEUD IIf_4 in green colour under UV light. Majority of bands under visible light represented in yellow colour except the last band (fourth band) appeared in dark green colour. These bands (BEUD IIf_1, BEUD IIf_2 and BEUD IIf_3) could be in flavonols group. According to R_f value of serotonin was 0.34 (34) in TLC chromatogram and same R_f with 35.15±1.27 in BEUD IIf_2 and also showed blue (sea green) under UV light. BEUD IIf_2 could be 5-hydroxytryptamine (5-HT).

According to Harborne [27], flavonols are appeared in bright yellow and bright yellow fluorescent. Although some highly methylated flavonols behave similarly. On the other hand, according to our previous results, CEUD I showed high anticancer activity against breast cancer and fibrosarcoma cancer cell line [28]. Regarding to some literature, the antidepressant like potential involved to the presence of alkaloids, flavonoids and glycosides. HEEU I showed moderate total flavonoid contents following by CEUD I extract [8]. However, transportation these metabolites into the brain tissue through the blood brain barrier and their effect on the CNS has been discussed [29]. It seems one of the antidepressant mechanisms of CEUD I and HEEU I is thought to involve flavonoid glycosides which reach the brian tissues through the metabolizing process, protecting brain function from CNS disturbance and consequently, exerting an antidepressant effect. An et al. [30] found out that active flavonoid contents may attributed to initial antidepressant action which may appearance of Depression-like symptoms. Generally, most of cancer patients during their treatment need some antidepressant drugs. This crude extract beside may have anticancer activity showed antidepressant activity which may useful for further investigation.

Some diterpenoids and triterpenoids isolated from natural sources like plants. In this among, several species of the genus antimicrobial and as an antimicrobial remedy. Also many of them are able to influence the central nervous system investigate [31]. From previous study revealed that one of the main constituent of *Salvia divinorum* is diterpenoids which may have antidepressant activity. Yu et al. [32] found that course treatment with diterpene alkaloids of *Aconitum baicalense* in mice reduced that time of immobilization in the TST [33].

Rocha et al. [34] found out that *Cecropia glazioui* (Urticaceae family) as same as *U. dioica*, had Antidepressant-like activity. The effect was enhanced after purification of the active extract. Catechins, procyanidins and flavonoids were the main constituents of the purified active fraction. So far, *In vitro* studies showed that catechin (4α→8) ent-catechin (Procyanidiin B3 isomer), catechin and epicatechin (4α→8) epicatechin (Procyanidin B2) inhibited 5-HT, NA and DA uptakes in brain synaptosomes but the flavonoids isoorientin and isovitexin did not. Rocha et al. found that chatechin and procyanidins are the major active substances *In vitro* and may contribute to the antidepressant-like effect produced by *C. glazioui*.

Fluoxetine (Prozac) which it used in this study, in pharmacologic treatments for depression in cancer patients at doses 10-20mg as starting dose and 20-60mg as therapeutic range has common side-effect such as varying degrees of gastrointestinal [35].

However, on studies using FST and TST to approach to model of depression, some other techniques except these models should be assessed due to some differences among clinical

studies in human and experimental animals. It has been reported that the TST is less stressful than FST and has greater pharmacological sensitivity. Remarkably, TST detects the anti-immobility effects of a wide array of antidepressants. Hence, *E. umbellatum* did not show any significant result from TST test compare with other extracts of *U. dioica* and positive controls. Thus, the activity of *U. dioica* could involve one of the mechanisms of the antidepressant.

4. CONCLUSION

In conclusion, the present study indicates that *U. dioica* compared with *E. umbellatum* extracts, produces a specific antidepressant-like effect in animal models predictive of antidepressant properties, forced swimming test and tail suspension test. Moreover, the effect of the acute or repeated administration of this extract was similar to the action produced by the classical antidepressant fluoxetine and haloperidol. Further studies are needed to further characterize the mechanism of the antidepressant effect of *E. umbellatum* and *U. dioica* as potential natural drug with antidepressant activity.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Richelson E. Pharmacology of antidepressants. Mayo. Clin. Proc. 2001;76:516-27.
2. Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: A primary screening test for antidepressants. Arch. Int. Pharmacodyn Ther. 1977;229:327-336. PMID: 596982.
3. Steru L, Chemat R, Thierry B, and Simon P. The tail suspension test: A new method for screening antidepressants in mice. Psychopharmcalogy, 1985;85:367-370. PMID: 3923523.
4. Ahangar N, Mirfetros S, Ebrahimzadeh MA. Antidepressant activity of polyphenol fraction of *Artemisia absinthium* L. Pharmacologyonline. 2011;1:825-832.
5. Zhang Z. Therapeutic effects of herbal extracts and constituents in animal models of psychiatric disorders. Life Sci. 2004;75:1659-1699. DOI:10.1016/j.1fs.2004.04.014.
6. Kwon S, Lee B, Kim M, Lee H, Park HJ, Hahm DH. Antidepressant-like effect of the methanolic extract from *Bupleurum falcatum* in the tail suspension test. Psychiatry. 2010;34:265-70. DOI: 10.1016/j.pnpbp.2009.11.015.
7. Gunther RT. The Greek herbal of dioscorides. Hafner Publishing, New York. 1959:491.
8. Modarresi Chahardehi A, Ibrahim D, Sulaiman SF. Antioxidant activity and total phenolic content of some medicinal plants in Urticaceae family. Journal of Applied Biological Sciences. 2009;2(3):1-5.
9. Pourmorad F, Hosseinimehr SJ, Shahabimajd N. Antioxidant activity, phenol and flavonoid contents of some selected Iranian medicinal plants. Afr. J. Biotechnol. 2006;5(11):1142-5.

10. Chaurasia N, Wichtl M. Flavonol glycosides aus *Urtica dioica.* Planta Med. 1987;53: 432-4. DOI: 10.1055/s-002-5517.
11. Gülçin İ, Küfrevioğlu Öİ, Oktay M. Büyükokuroğlu MF Büyükokuroğlu MF. Antioxiant, antimicrobial, antiulcer and analgesic activities of nettle (*Urtica dioica* L.). J. Pharmacol. 2004;90:205-15. Doi: 10.1016/j.jep.2003.09.028.
12. Sezik E, Yeşilda F, Tabata M, Honda G, Takaishi Y, Fujita T, Tanaka T, Takeda Y. Traditional medicine in Turkey VIII. Folk medicine in East Anatolia Erzurum Ağrı, Kars, Iğdır provinces. Econ. Bot. 1997;51:195-211.
13. Umegaki K, Kajiki L. Component analysis of cultivated Shi-o-de an edible wild plant. Japanese Journal of Nutrition and Dietetics. 2007;65(2):81-3.
14. Sakakibara H, Honda Y, Nakagawa S, Ashida H, Kanazawa K. Simultaneous determination of all polyphenols in vegetables, fruits, and teas. J. Agiric. Food Chem. 2003;51(3):571-81. DOi:10.1021/jf020926l.
15. Broncano J, Rebuelta M, Vivas JM, Diaz MP. Estudio de diferentes preparados de *Urtica dioica* L. sobre SNC. An Real Acad. Farm. 1987;53:284-91.
16. Fu HY, Chen SJ, Chen RF, Ding WH, Kuo-Huang LL, Huang RN. Identification of oxalic acid and tartaric acid as major persistent pain-inducing toxins in the stinging hairs of the nettle, *Urtica thunbergiana*. Annals of Botany (London). 2006;98(1):57-65. DOI:10.1093/aob/mcl089.
17. Young SN. How to increase serotonin in the human brain without drugs. Rev. Psychiatr. Neurosci. 2007;32(6):394–99. PMID: 18043762.
18. Mellidis AS. Papageorgiou VP. Phenolic constituents from *Onosma heterophylla*. J. Nat. Prod. 1993;56:949-52. Doi: 10.1021/np50096a023.
19. Zomkowski ADE, Santos ARS, Rodrigues ALS. Putrescine produces Antidepressant-like effects in the forced swimming test and in the tail suspension test in mice. Prog. Neuro-psychopha. 2006;30:1419-25. PMID:16822602.
20. Eckeli AL, Dach F, Rodrigues ALS. Acute treatments with GMP produce antidepressant-like effects in mice. Neuro Rep. 2000;11:1839-1843. DOI: 10.1097/00001756-200006260-00008.
21. Kaster MP, Raupp I, Binfaré RW, Andreatini R, Rodrigues SAC. Antidepressant-like effect of Lamotrigine in the mouse forced swimming test: Evidence for the involvement of noradrenergic system. Euro. J. Pharmacol. 2007;565:119-24. PMID: 17433291.
22. Deak T, Bellamy C, D`Agostino GL, Rosanoff M, McElderry NK, Bordner KA. Behavioral responses during the forced swim test are not affected by Anti-Inflammatory agents or acute illness induced by lipopolysaccharide. Behavioural Brain Research. 2005;160:125-34. PMID: 15836907.
23. Xu Q, Yi LT, Pan Y, Wang X, Li YC, Li JM, Wang CP, Kong LD. Antidepressant-like effects of mixture of honok iol and magnolol from the barks of *Magnolia officinalis* in stressed rodents. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2008;32:715-25. PMID: 18093712.
24. Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model to assessing antidepressant activity: Review of pharmacological and genetic studies in mice. Neurosci. Biobehav. Rev. 2005;29:571-625. Doi: 10.1016/j.neubiorev.2005.03.009.
25. Porsolt, RD. Animal models of depression: Utility for transgenic research. Rev. Neurosci. 1987;11:53-8. PMID: 204499.
26. Bach-Rojecky L, Kalodera Z, Samarzija I. The antidepressant activity of *Hypericum perforatum* L. measured by two experimental methods on mice. Acta Pharm. 2004;54:157-162. PMID: 15274759.
27. Harborne JB. Phytochemical Methods: A guide to modern techniques of plant analysis. Third Edition. Chapman and Hall, UK. 1998;292-3.

28. Modarresi Chahardehi A, Ibrahim D, Abolhassani F, Fariza Sulaiman S. Cytotoxicity activity of *Elatostema umbellatum* against cancer cell lines. The 2nd Annual International Conference in conjunction with The 8th IMT-GT UNINET Bioscience Conference, 22-24 November 2012, Darussalam, Banda Aceh, Indonesia; 2012.
29. Umadevi P, Murugan S, Suganthi SJ, Subakanmani S. Evaluation of antidepressant like activity of *Cucurbita pepo* seed extracts in rats. Int. J. Curr. Pharmaceutical Res. 2011;3:108-13.
30. An L, Zhang YZ, Yu NJ, Liu XM, Zhao N. Role for serotonin in the Antidepressant-like effect of a flavonoid extract of Xiaobuxin-Tang. Pharmacol. Biochem. Behav. 2008;89:572-580. Doi:10.1016/j.pbb.2008.02.014.
31. Bonito MC. Pharmacological characterization of terpenic secondary metabolites isolated from *Salvia* species. Tesi di dottorato in scienza del farmaco. 2009:45.
32. Hanes KRJ. Antidepressant effects of the herb *Salvia divinorum*: A case report. J. Clin. Psychopharmacol. 2001;21:634-5. PMID: 11763023.
33. Yu V, Nesterova TN, Povetieva NI, Suslov AA, Pushkarskiy SV. Antidepressant activity of diterpene alkaloids of *Aconitum baicalense* Turcz. Bull. Exp. Biol. Med. 2011;151(4):425-8.
34. Rocha FF, Lima-Landman MT, Souccar C, Tanae MM, De Lima TC, Lapa AJ. Antidepressant-like effect of *Cecropia glazioui* Sneth and its constituents - *in vivo* and *in vitro* characterization of the underlying mechanism. Phytomedicine. 2007;14(6):396-402. Doi:10.1016/j.phymed.2007.03.011.
35. Pirl WF, Roth AJ. Diagnosis and Treatment of Depression in Cancer Patients. In: Licino J, Wang ML, editors. Biology of Depression, From Novel Insights to Therapeutic Strategies. 1999;1:378.

© 2014 Chahardehi et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=486&id=32&aid=4288