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Antiepileptic and Antidepressant Activity of Majoon Najah (A Traditional Unani Formulation) in Experimental Animals

Mohd Urooj[1,*], Gulam Mohammed Husain[1], Mohd. Nadeem[1], Mohammed Abdul Rasheed Naikodi[2], Mahe Alam[3], Munawwar Husain Kazmi[1]

[1]Pharmacology Research Laboratory, National Research Institute of Unani Medicine for Skin Disorders, Hyderabad, Telangana, INDIA.
[2]Drug Standardization Research Unit, National Research Institute of Unani Medicine for Skin Disorders, Hyderabad, Telangana, INDIA.
[3]Central Council for Research in Unani Medicine, New Delhi, INDIA.

ABSTRACT

Background: Majoon Najah is a polyherbal traditional Unani formulation recommended for the treatment of neurological disorders. To evaluate antiepileptic and antidepressant activity of majoon najah and majoon najah extract in experimental animals. **Methods:** Anticonvulsant activity was tested using maximal electroshock induced convulsion in male sprague dawley rats using diazepam 3 mg/kg, p.o. as positive control. Pentylenetetrazole induced convulsion in swiss male albino mice was performed using phenytoin 25 mg/kg i.p. as positive control. The antidepressant activity of MN was evaluated using forced swim test model in male using Imipramine 20 mg/kg, p.o. as positive control. **Results:** Antiepileptic study data showed reduction of all parameters like, tonic hind limb extension, clonic convulsion and stupor; however the values were not found statistically significant at all tested dose levels. The results of forced swim test model indicated that majoon najah effectively showed significant (P<0.001) reduction in immobility duration in animals treated with majoon najah classical at dose 500 mg/kg bw and 1000 mg/kg bw as compared to control rats. **Conclusion:** Based on above findings, it may be concluded that majoon najah did not showed effectiveness in epilepsy however, the results evident that majoon najah is a potential Unani formulation having antidepressant activity which may be preferred as an alternative therapy over modern medicine to treat depression.

Key words: Majoon Najah, Antiepileptic, Antidepressant, Polyherbal, Traditional medicine.

Correspondence

Dr. Mohd. Urooj
Research Officer (Pharmacology), Pharmacology Research Laboratory, National Research Institute of Unani Medicine for skin Disorders, Hyderabad 500038, Telangana, INDIA.
Phone no: +91-7088889991
Email: qaziurooj@gmail.com

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INTRODUCTION

Majoon Najah (MN) is a traditional semisolid polyherbal Unani formulation. It is a multicomponent Pharmacopoeial formulation mentioned in the National Formulary of Unani Medicine (NFUM), Part-I and other classical text of Unani system of medicine. It is recommended for the treatment of neurological disorders like, *malikhuliya* (Depression), *Ikhtenaqurraham* (hysteria), *sara* (Epilesy), Kutrib (*psychosis*), Junoon (schizophrenia), Juzam (leprosy), Dual-kulb (*mania*) and waja-ul-mafasil (arthritis) .The key ingredient of MN is Triphala or Itrifal consisting of Post-e-Halela kabli (*Terminalia chebula*), Post-e-Balela (*Terminalia bellerica*) and Amla (*Emblica officinalis*).[1]Today, millions of people globally are affected with neurological disorders such as epilepsy and depression.[2] Around 80 % people suffering from epilepsy in developing world do not get adequate treatment. *Terminalia chebula and Terminalia bellerica* has been traditionally used in Ayurvedic and Unani system of medicine primarily for gastrointestinal disorders. However, recently several studies were carried out on these ingredients to evaluate the protective effect against seizure and antidepressant activity in animals using classical form as well as extract.[3, 4] The third ingredient Amla (*Emblica officinalis*) has superior place in entire indigenous system including Ayurveda due to multifaceted clinical use. It is considered as one of the best source of Vitamin C and possesses antioxidant properties. Amla has been widely used as a nutraceutical in several diseases since it is known to boost immunity and offers numerous health benefits. Amla is one among all ingredients in Unani formulation used to treat mental disorders.[5]Despite the advancement in pharmacotherapy of epilepsy and depression these disorders still do not have complete cure. The efficacy and safety of available therapy is questionable hence, there is an immense need for developing newer effective and safe alternative antiepileptic and antidepressant medications. Therefore, the current study was planned to confirm the antiepileptic and antidepressant activity of MN and MN extract using different animal models.

MATERIALS AND METHODS

Composition of Formulation

The following ingredients were presents in MN as per NFUM part I

Preparation of Majoon Najah

MN used in present study was prepared as per the standard Pharmacopoeial procedure in the GMP certified pharmacy of NRIUMSD Hyderabad. The *Halailajat* myrobalan fruits (Tirphala) from S.No 1 to 3 (Table 1) were dried to evaporate moisture content and minced into coarse powder and then passed through appropriate sieve. The powder obtained undergo the process of detoxification of *Triphala* known as rubbing (*Tad'heen or Charb*) using *Raughan Zard* (Cow Ghee). Remaining ingredients from S.No 4-8 (Table 1) were separately dried, powdered and sieved.

Formulation base called as *Qiwam* was prepared by adding 600 g sugar in 225 ml of water. Then it is heated on low flame with continuous stirring until boiling of solution. Afterward, it is removed from heat

and all the powdered ingredients (300 g) were mixed with it along with 2-3 g of benzoic acid as preservative. MN was ready to store in air tight container.[1,6]

HPTLC Fingerprinting of Majoon Najah

HPTLC of make Desaga Sarstedt Gruppe (Germany) was employed, pre coated silica gel 60 F_{254} Aluminium TLC plates (Merck, KgaA, Germany) was used. All the solvents used in the study were of HPLC grade. The MN formulation in different forms i.e. classical form and powdered ingredients of classical form without sugar were subjected to develop HPTLC fingerprinting.

Majoon Najah Hydro-alcoholic extract

5g of Majoon sample (Classical form) was taken and refluxed with 200 ml of alcohol: water (1:1) using soxhlet apparatus over heating mantle till the complete extraction was carried out. The content of extract was filtered and evaporated to concentrate up to 5 ml and resultant was used as a sample for HPTLC analysis.

Powdered ingredients of Majoon Najah(Classical) without sugar Hydro-alcoholic extract

5 g of sample powdered ingredients of MN was taken and refluxed with 200 ml of alcohol: water (1:1) using soxhlet apparatus over heating mantle till the complete extraction was carried out. The content of extract was filtered and evaporated to concentrate up to 5 ml and resultant was used as a sample for HPTLC analysis.

Chromatographic Conditions

HPTLC of make Desaga Sarstedt Gruppe (Germany) was employed in developing the fingerprinting profile of MN. The development Twin-trough chamber was used 20 X10 cm, Stationary phase was pre coated silica gel 60 F_{254} Aluminum plates (Merck, KgaA, Germany), Plate thickness was 0.2 mm, Plate size was 200 x 100 mm, Sample applied keeping distance 20 mm from starting edge and distance from bottom was kept as 10 mm, Volume applied was 5 µl, band length kept as 10 mm, distance between the tracks as 20 mm and TLC plate was developed up to the distance of 80 mm. Mobile phase selected for the development of TLC plate was Toluene: Ethyl acetate: Methanol (7: 2: 1, v/v/v).

Animals

SD Rats (150-250 gm) and swiss albino mice (25-30 gm) were used for different animal models. The animals were procured from Edara Research Foundation, Hyderabad, India. All animals were housed in polycarbonate cages in the air conditioned room maintained at the temperature of 22°C ± 3°C and relative humidity of 30-70%, with a 12:12 h light/dark illumination cycle.[7] Purpose of Control and Supervision of Experiments on Animals guidelines of laboratory animal care was followed throughout the experiment.[8] Protocol of the study was approved by the Institutional Animals Ethics Committee vide protocol no. CRIUM/IAEC/2018/01/P05 dated 21.07.2018. Animals were provided unlimited supply of water and feed pellets (Amrut Laboratory Animal Diet, Krishna Valley Agrotech LLP, Pune, India). Animals were acclimatized to the laboratory conditions for one week before using them for experiment.

Dose Selection

The clinical dose of MN as mentioned in literature NFUM part-1 is 5-10 g per day. Human dose of 5 g was used for dose translation (back calculation on the basis of body surface area) for study animals.[9] Anticonvulsant activity was tested using maximal electroshock induced convulsion (MES) at the dose of 500 and 1000 mg/kg bw of classical MN and 170 and 340 mg/kg bw of 50% hydro alcoholic extract using diazepam 3 mg/kg, p.o. as positive control. Pentylenetetrazole (PTZ) induced convulsion model was performed in at the dose levels of 1000 and 2000 mg/kg bw of classical MN and 340 and 680 mg/kg bw of 50% hydro alcoholic extract using phenytoin 25 mg/kg i.p. was used as positive control.

The antidepressant activity of MN was evaluated using FST (forced swim test) model at dose of 500 and 1000 mg/kg bw of classical MN and 170 and 340 mg/kg bw of 50% hydro alcoholic extract using Imipramine 20 mg/kg, p.o. as positive control

Drug Administration

The test formulation MN and Positive control (Standard Drug) were administered by oral (gavage) for whole study duration as per study protocol schedule.

Study Design and Procedure

Maximal Electroshock Seizure - Induced Convulsion in Rats: Animals were divided into six groups of eight (8) rats each. Group I served as control and orally administered 0.3 % CMC as vehicle. Group II was positive control which received Diazepam (3 mg/kg, p.o.) continuously for seven days. Group III and IV were test dose groups for classical form of MN which were administered 500 and 1000 mg/kg bw per day respectively consecutively for seven days. Group V and VI were hydro alcoholic extract treated groups administered with 170 and 340 mg/kg bw per day, respectively, consecutively for seven days.

The electroshock was delivered to rats via ear-clip electrodes using digital electro-convulsiometer (Ugo Basile; Italy). The stimulus duration was 0.2 sec and the current intensity was 150 mAmp, 50 hertz. Test was performed on 7th day, 60 min after oral administration of MN or standard drug Diazepam. The animals were observed for the occurrence and duration of Tonic Hind Limb Extension (THLE) (sec), Duration of clonic convulsion (sec), Stupor (sec) and % mortality for duration of 15 min.[10]

Pentylenetetrazole induced convulsion in mice: Animals were divided into six groups of eight (8) animals each. Group I served as control orally treated with 0.3 % CMC. Group II served as positive control and was treated with Phenytoin (25 mg/kg i.p.) continuously for seven days. Group III and IV were test dose groups for classical form of MN which were administered 1000 mg/kg bw per day and 2000 mg/kg bw per day respectively consecutively for seven days till the experiment day. Group V and VI were hydro alcoholic extract treated groups administered with 340 and 680 mg/kg bw per day respectively consecutively for seven days.

Test was performed on 7th day, PTZ 65 mg/kg bw was administered intraperitoneally 45 min after oral administration of vehicle or test formulation (MN) and 30 min after administration of standard drug Phenytoin. Animal's epileptic behavior was observed for 30 min after PTZ administration and classified based on following scoring system.[11]

0: Normal behavior, no abnormality.

1: Immobilization, lying on belly.

2: Head nodding, facial, forelimb, or hind limb myoclonus.

3: Continuous whole-body myoclonus, Myoclonic jerks, tail held up stiffly.

4: Rearing, tonic seizure, falling down on its side.

5: Tonic-clonic seizure, falling down on its back, wild rushing and jumping.

6: Death.

Antidepressant activity using forced swim test in rats: Animals were divided into six groups of six animals each. Group I served as control and

orally treated with 0.3 % CMC as vehicle. Group II was positive control which received Imipramine (20 mg/kg bw p.o.). Group III and IV were test dose groups for classical form of MN which were administered at the doses of 500 and 1000 mg/kg bw of MN per day consecutively for two weeks. Group V and VI were 50% hydro-alcoholic extract treated groups administered with 170 and 340 mg/kg bw per day, respectively, for two weeks.

The test was carried out according to the method described in the literature[11]the forced swim (also termed behavioral despair with slight modifications. Rats were forced to swim in a vessel (20 cm diameter × 40 cm high) filled with water at 24–26°C. The total duration of immobility (seconds) was recorded in the test session. Rats were considered immobile when they made no attempts to escape except the movements necessary to keep their heads above the water (for floating). This method consisted of two sessions, the pretest and the test session, whereas in old method, the animals were subjected to direct immersion after administration of drugs, 40 min before test session.[12]

Pre-Test Session: On Day-1, 25 hr prior to test session, the animals were placed in the experimental room at least 60 min before the beginning of the pretest session. In the pretest session, conducted on Day-1, the animals were allowed to swim individually for 15 min in vessel filled with water, after which the animals were removed, dried and returned to home cages.

Test Session: On the 2nd day, test session was performed and each rat forced to swim for 5 min and duration of immobility was recorded (i.e., the time at which animal halts swimming, except for those movements which keep its head above water) through stop watch.

Two, pretest administrations of test substance/ vehicle at 24 hr (i.e., after pretest session) and 60 min prior to the test session (i.e., Day-2) were used in the present study. Control animals were receiving the same frequency of vehicle administrations. Treatment was continued for two weeks and again another test session (5 min duration) was performed on 14th day to observe the effect of test substance following repeated administration.[13]

Statistical analysis

The data obtained for various parameters were statistically evaluated by one way analysis of variance (ANOVA) followed by Tukey's multiple comparison as *post hoc* test. The mean values ± SEM was calculated for each parameter. Level of significance was kept at $p < 0.05$.

RESULTS

HPTLC Fingerprinting

In the MN sample extracts which are applied on TLC plate was developed in Toluene: Ethyl acetate: Methanol (7:2:1) for MN as shown in Figure 1. HPTLC densitogram the corresponding R_f values for the spots obtained were as shown in Table 2, Figure 2 and Figure 3. HPTLC revealed the presence of phytoconstituents having different R_f values and in TLC showed separated bands under UV 366 nm. Upon detection under UV 366 nm the MN hydro-alcoholic extract shows three major spots at Rf values 0.61 (dark blue), 0.70 (blue), 0.77 (blue) and Powdered ingredients of MN (without sugar) hydro-alcoholic extract under UV 366 nm shows six spots at R_f values 0.06 (blue), 0.31 (pale yellow), 0.52 (blue) 0.61 (dark blue), 0.70 (blue), 0.77 (blue).

Effect of (Majoon Najah Classical and Majoon Najah Extract) on electroshock induced convulsion in Rats

The average duration of all measured parameters for all groups is presented in Figure 4. The results showed that there was a decrease in duration of THLE, clonic convulsion and stupor phase in MN treated group as compared to control group. However, there were no statistically significant reduction in both classical and extract treated animals at both dose levels as compared to animals of control group. The statistical significant reduction ($P<0.05$ or $P<0.01$) were observed in positive control animals treated with diazepam as compared to control animals for all measured parameters.

Effect of (Majoon Najah Classical and Majoon Najah Extract) on pentylenetetrazole induced convulsion in Mice

The seizure score of epileptic behavior measured 30 min after PTZ administration showed reduction in all MN treated groups compared to control as shown in (Table 3). However, statistically significant reduction was observed only in phenytoin treated group as compared to control ($P < 0.01$). Percent mortality in different treatment groups is mentioned in Table 3.

Effect of (Majoon Najah Classical and Majoon Najah Extract) on forced swim test in rats

Swimming behavior was recorded following acute dose on 2nd Day and after repeated drug administration on 14th day. The results showed reduction in immobility duration and increase in swimming behavior in all treatment groups at all dose levels after administration of acute dose on 2nd day. However, the decreased values were not found statistically significant as compared to control group (Figure 5). In contrast, there was statistically highly significant ($P<0.001$) decrease in immobility duration in positive control (Imipramine 20 mg/kg bw) group and MN classical group at both dose level 500 mg/kg bw and 1000 mg/kg bw,

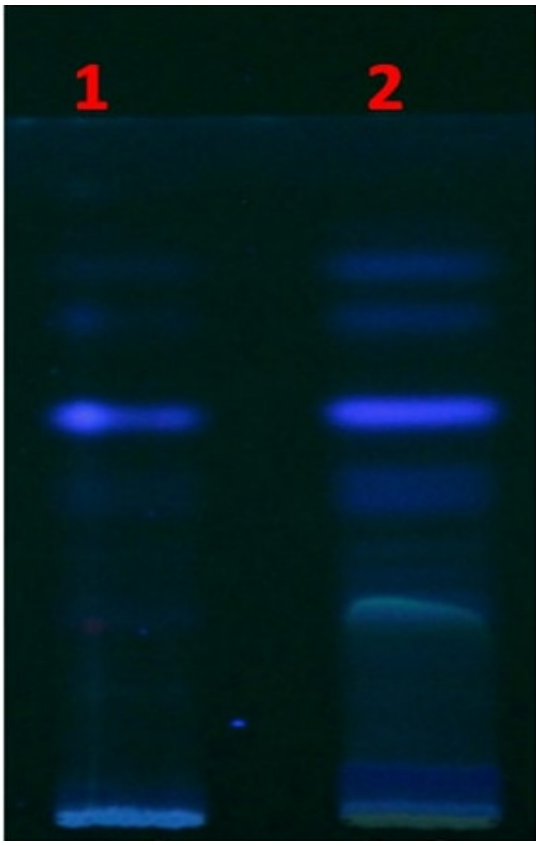


Figure 1: Chromatogram of MN Extracts.
1. MN Classical Hydro alcoholic extract
2. MN powdered ingredients (without sugar) Hydro alcoholic extracts

Table 1: Ingredients of MN.

S.No	Unani Name	Botanical Name	Part Used	Quantity (g)
1	Post-e-halelakabli	*Terminalia chebula* Retz	Fruit	50
2	Post-e-Balela	*Terminalia bellerica* Roxb	Fruit	50
3	Aamla	*Emblica officinalis* Gaertn.	Fruit	50
4	Halela Siyah	*Terminalia chebula* Retz	Fruit	50
5	Turbud	*Operculina turpethum* Linn	Root	25
6	Bisfayej	*Polypodium vulgare* Linn	Root	25
7	Aftimoon	*Cuscuta reflexa* Roxb	Whole Plant	25
8	Ustukhuddus	*Lavandula stoechas* Mill	Flowers	25
9	Qandsafaid (Sugar)			600

Table 2: Rf values for the spots found in MN Extracts.

Type of extract	MN hydro-alcoholic extract	Powdered ingredients of MN (without sugar) Hydro-alcoholic extract
No. of spots	4	6
Peak no	R_f values	R_f values
1	0.02	0.02
2	0.57	0.08
3	0.65	0.31
4	0.96	0.58
5	--	0.72
6	--	0.94

Table 3: Effect of (MN Classical and MN Extract) on PTZ induced convulsion.

Treatment Group (*n*=8)	Seizure Score	% Mortality
Control	5.38±0.26	50
Phenytoin 25 mg/kg	2.13±0.58**	12.50
MN Classical 1000 mg/kg	3.75±0.65	25
MN Classical 2000 mg/kg	3.50±0.66	25
MN Extract 340 mg/kg	3.63±0.53	12.5
MN Extract 680 mg/kg	3.38±0.73	25

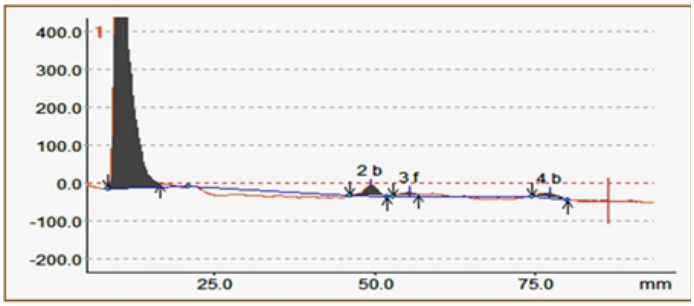
measured after repeated administration on 14th day. The immobility duration was significantly reduced in extract high dose (340 mg/kg bw) group (Mean ± SEM: 31.33 ± 1.667), while no significant difference was observed in extract low dose (170 mg/kg bw) group as compared to animals of control group.

DISCUSSION

MN is a traditional Unani formulation reported to be more effective for mental diseases which are caused due to excess of Sauda (black bile).[14] In the present study we have tested the anticonvulsant and antidepressant activity in rodents. Data of antiepileptic study showed that in spite of reduction of THLE, clonic convulsion and stupor phase in rats, the values obtained were not found significantly different at any tested dose level for classical MN or MN extract[15] reported significant reduction in THLE and seizure threshold in Increased Current Electroshock Seizure (ICES) method in Swiss albino mice at 1700 mg/kg bw of MN and 260 mg/kg bw of hydro ethanolic extract (ethanol and distilled water ratio 80:20) of MN following one week treatment. The observed difference in activity in our study may be attributable to variables like species difference (SD rats versus Swiss albino mice) and methodology adopted (MES at 150 mAmp in our study versus ICES upto 30mAmp current).In PTZ model, although mortality was reduced in all treated mice compared to vehicle treatment group, the seizures score in MN treated group animals was not statistically different as compared to control (though score was reduced). Phenytoin significantly reduced the seizures score compared to control group. Findings of our study are contrary to the reported antiepileptic effect of MN in mice.[15]

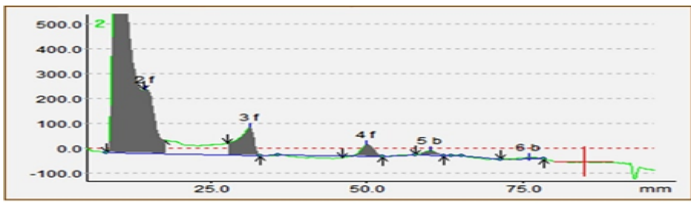
The antidepressant activity of MN was evaluated using FST model in rats. The results indicated that MN effectively showed significant (P<0.001) reduction in immobility duration in animals treated with MN classical at dose 500 mg/kg bw and 1000 mg/kg bw as compared to control rats. The MN extract showed significant (P<0.001) reduction in immobility duration only at higher dose level (340mg/kg bw). These findings are in concurrence with the report of anti-depressant activity in tetrabenazine antagonism test and yohimbine toxicity enhancement test in mice following single dose of hydroethanolic extract of 260 and 520 mg/kg bw.[16] The findings of yohimbine toxicity enhancement test suggested that yohimbine occupies central α2 receptors and prevents noradrenaline from binding to α2 receptors, thus allowing an increase in noradrenaline release and concentration.[16]

There are several reports of antidepressant activity of various ingredients of MN with possible molecular mechanism. A study on aqueous extract of *Emblica officinalis* Gaertn (Amla) showed anti-depressant activity comparable to imipramine and fluoxetine in mice. Aqueous extract at the dose of 200 and 400 mg/kg bw for 14-days significantly reduced the immobility period in FST and tail suspension test in mice.[17] The antidepressant effect of *E. officinalis* extract was significantly reversed by pretreatment of animals with prazosin (α1-adrenoceptor antagonist), sulpiride (dopamine D2-receptor antagonist), p CPA (a serotonin synthesis inhibitor). Anti-depressant effect was attributed to inhibition of MAO-A and GABA.[18] Aqueous extract (50, 100 and 200 mg/kg) and ethanolic extract (100 mg/kg) of *Terminalia bellirica* Roxb., which is one of the chief ingredient of MN significantly reduced the immobility time of mice in FST and tail suspension test (TST) following 10-days oral administration. Both extracts reversed reserpine-induced extension of immobility period of mice in FST and TST. Prazosin (62.5 microg/kg, ip; an alpha1-adrenoceptor antagonist), sulpiride (50 mg/kg, ip; a selective D2 receptor antagonist) and p-chlorophenylalanine (100 mg/kg, ip; an



Peak no	Y-Pos	Area	Area %	Height	Rf value
1	10.6	1982.53	93.31	769.98	0.02
2	49.4	71.97	3.39	28.36	0.57
3	55.3	26.70	1.26	10.64	0.65
4	77.2	43.47	2.05	12.77	0.96

Figure 2: Densitogram of MN hydro alcoholic extract and peak listed at UV 366nm.



Peak no	Y-Pos	Area	Area %	Height	Rf value
1	10.1	3407.89	77.34	1552.64	0.02
2	14.5	490.78	11.14	251.83	0.08
3	31.1	324.31	7.36	110.35	0.31
4	50.0	110.25	2.50	48.37	0.58
5	60.1	43.28	0.98	17.98	0.72
6	75.9	29.63	0.67	8.35	0.94

Figure 3: Densitogram of Powdered ingredients of MN (without sugar) hydro alcoholic extract and Peak listed at UV 366nm.

inhibitor of serotonin synthesis) significantly attenuated the aqueous and ethanolic extract-induced antidepressant-like effect in TST. Thus, both the aqueous and ethanolic extracts of *T. bellirica* elicited a significant antidepressant-like effect in mice by interaction with adrenergic, dopaminergic and serotonergic systems (Dhingra and Valecha, 2007). Another study reported that aqueous extracts of *T. chebulaat* 780 and 1560 mg/kg and *Phyllanthus emblica* at 1560 and 3120 mg/kg reduced immobility time in FST while in TST, 1560 mg/kg of *T. chebula* and 3120mg/kg of *P. emblica* decreased immobility in mice.[19]

Methanolic extract of *Cuscuta reflexa*, another ingredients of MN has been reported to possess antidepressant activity in TST (EC 50 ~ 50 mg/kg) and this effect was attributed to quercetin mediated rise in neuronal serotonin and noradrenaline levels possibly via MAO inhibition.[20] In another study, antidepressant-like effects of metabolites extracted (methanol) from the leaves of *C. reflexa* (200 and 400 mg/kg) has been attributed either due to the inhibition of monoamine reuptake or significant suppression of HPA axis activation.[21] Pre-treatment for 12 days with hydro alcoholic extract of aerial parts of *Lavandula officinalis* reduced immobility period in rats in a dose-dependent manner.[22] Further, in a clinical study, subjects were given 2 cups of the infusion of 5 g dried *Lavandula angustifilia* (another species of Lavender) in addition to Citalopram 20 mg twice a day. Lavandula angustifilia infusion has revealed positive therapeutic effects on depressed patients and decreased mean depression score.[23]

In light of reported studies, it may be concluded that multiple constituents present in ingredients of MN might interact with

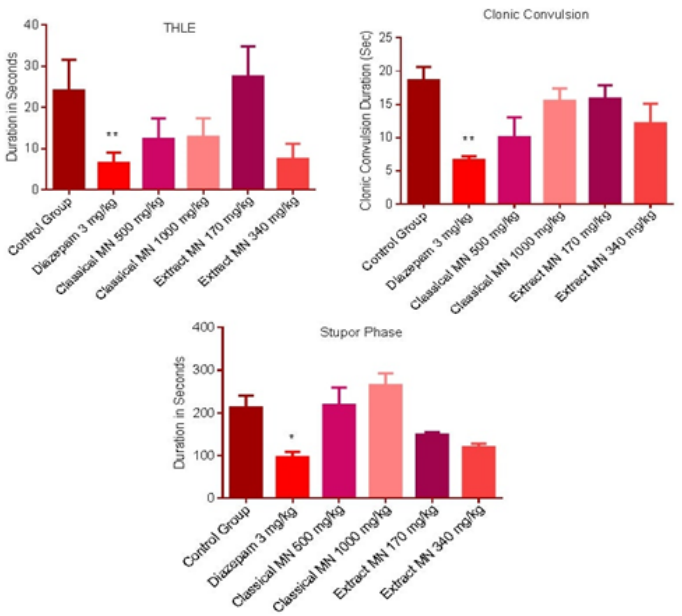


Figure 4: Parameters observed in MES model. Values were Mean±SEM (n=8). Statistical significance was determined by ANOVA, followed by Tukey's multiple comparison-test, $^{**}P<0.01$ vs. control.

adrenergic, dopaminergic and serotonergic receptors and resulted in increase in level of nor epinephrine, dopamine and serotonin; and reduction in the levels of GABA in brains of animals.[3] Hence it may be concluded that MN is a potential Unani formulation having antidepressant activity which may be preferred as an alternative therapy over modern medicine to treat depression.

The developed fingerprint profile of MN hydro alcoholic extracts showed that a spot at R_f value 0.31 is only observed in the hydro alcoholic extract of powdered ingredients of MN without sugar which is not seen in MN hydro-alcoholic extract representing a slight difference in the composition of sample extract.

CONCLUSION

HPTLC fingerprinting revealed active constituents at different R_f value for MN extract and MN dried powder without sugar. These results could be utilized as reference for future studies. Data obtained in antiepileptic activity test showed that the values obtained were not found significantly different at any tested dose level for classical MN or MN extract as compared to control. Further, the MN evident promising antidepressant effect in FST model at both tested dose level of MN and high dose level of MN extract. Therefore it may be concluded that MN did not possess antiepileptic effect while MN could be uses as potential Unani formulation having antidepressant activity which may be preferred as an alternative therapy over modern medicine to treat depression.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

ABBREVIATIONS

MN: Majoon Najah; **NFUM:** National Formulary of Unani Medicine; **SD:** Sprague Dawley; **MES:** Maximal Electroshock; **PTZ:** Pentylenetetrazol; **FST:** Forced Swim Test; **TST:** Tail Suspension Test; **THLE:** Tonic hind limb extension.

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