Evaluation of Dorema Ammoniacum and Acupuncture's Therapeutic Effects in Patients With Ischemic Stroke: A Randomized Controlled Clinical Trial

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Abstract

Aim: Stroke is the third prevalent cause of disability worldwide. This study aimed to evaluate the role of *Dorema ammoniacum* and acupuncture in the management of patients with stroke.

Methods: In this randomized controlled clinical trial, patients with a recent ischemic stroke (within the first month of stroke) were investigated. The patients were divided into three groups. The first group was managed by acupuncture, while the second group received 1 g of *Dorema ammoniacum* (two 500 mg capsules per day) from ammoniacum gum. The two intervention groups also received standard treatment with routine medical therapy and physiotherapy. The final group was the control, which only received conventional treatment and physiotherapy. The patients were evaluated immediately before the interventions, and one month after the interventions, using the Modified Rankin Scale (mRS) and Modified National Institutes of Health Stroke Scale (mNIHSS).

Results: There was a significant difference in the mean score of mNIHSS at the beginning and end of the study in all of the three studied groups ($P < 0.001$). There were significant pre-treatment/post-treatment differences between the groups ($P < 0.001$). After controlling for the effect of mNIHSS score at the beginning of the study and the follow-up visit, a significant difference was observed between the three groups regarding the mean mNIHSS score post-intervention ($P < 0.001$). The results of the post-hoc test indicated a significant difference between the acupuncture and control groups, *Dorema ammoniacum* and control groups ($P < 0.001$), acupuncture, and *Dorema ammoniacum* groups ($P < 0.001$); the extent of reduction was greater in the acupuncture group. The mean mNIHSS scores of the acupuncture and *Dorema ammoniacum* groups were 1.82 and 1.04 lower than the control group's mean score, respectively. There was a significant difference in the mean mRS score at the beginning and end of the study in all three groups ($P < 0.001$). However, the extent of reduction was greater in the acupuncture group.

Conclusion: Acupuncture and *Dorema ammoniacum* may be beneficial if started within the first month of stroke incidence. However, acupuncture can cause a greater reduction in the mNIHSS score of stroke patients.

Trial registration: Iranian Registry of Clinical Trials (IRCT20170227032797N2). Registered 5 March 2018 - Retrospectively registered, <https://www.irct.ir/trial/25469>

Introduction:

Stroke is considered the second cause of mortality after ischemic heart disease and the most common cause of adult disability [1, 2]. In mainstream medicine, there is no definite treatment for motor disorders caused by stroke. On the other hand, conventional physiotherapeutic methods have not been successful in the management of these disorders.

In recent years, the use of complementary therapies, such as acupuncture and herbal medicine, has increased to treat ischemic strokes. The discovery and synthesis of medications from natural compounds

and herbs have attracted a great deal of attention [3, 4]. In Persian traditional medicine, many natural compounds and plant sources have been suggested, which can be used alongside modern medicine to treat stroke and its associated disabilities. One of the suggested plants for this condition is *Dorema ammoniacum* or “Ushaq” [5–7]. Medicinal gum resin is extracted from this plant, commonly known as ammoniacum gum with therapeutic and industrial applications [8, 9].

Dorema ammoniacum exhibits different pharmacological effects, including anxiolytic, anti-inflammatory, anti-coagulation, and vasodilatory effects according to multiple studies [4, 10, 11]. In Persian traditional medicine textbooks, one of the materia medica, frequently mentioned for stroke and paralysis, is *Dorema ammoniacum*. One of the functions of this species is to open the blood vessels. It has also been commonly described as a thrombolytic agent. In traditional medicine, its use, both as a materia medica and in combination with other drugs, seems to be beneficial for stroke and paralysis [5–7].

On the other hand, acupuncture is a healthy and accessible method with minimum side effects. This method can contribute to an increase in the blood flow, regulation of gene and protein expression, reduction of oxidative stress damage, inhibition of inflammatory reactions, prevention of apoptosis, improvement of neurovascular regeneration, reduction of cerebral edema, and mitigation of spasms. It also leads to diminished ischemic damage and improved motor functioning [12].

To the best of our knowledge, very few clinical trials have evaluated *Dorema ammoniacum*'s effect on stroke. This suggestion of Persian traditional medicine has not been compared with the conventional treatment of stroke or other traditional approaches, such as acupuncture. Considering the great importance, high prevalence, and progressive trend of cerebral ischemic stroke, besides the deficiencies of available treatments, in the present study, we aimed to evaluate the role of *Dorema ammoniacum* and acupuncture in improving some clinical complications of patients with stroke.

Methods:

Study design:

This randomized controlled clinical trial was conducted on patients with a recent stroke in the Acupuncture Clinic of Imam Reza Hospital, affiliated to Mashhad University of Medical Sciences, Mashhad, Iran, from July 2017 to September 2018. Data were collected via [convenience sampling](#).

Sample size calculation method:

Randomization and blinding:

The neurologist and statistician were blind to the study groups. The randomization process was performed through permuted block randomization with varying block sizes of 3, 6, and 9.

Data collection:

The participants were selected via convenience sampling among patients admitted to the Emergency Neurology Department of Ghaem Hospital, Mashhad, Iran. Ischemic stroke was diagnosed based on clinical examinations and brain computed tomography (CT) scans. Patients were screened for the eligibility criteria, and written informed consent were obtained from the patients and their relatives under the neurologist's supervision. Patients who met the inclusion criteria were interviewed. The interventions were explained to the patients and their families, and those who were willing to participate were included.

Inclusion and exclusion criteria:

The patients were randomly assigned to three groups (A, B, and C). All of the groups received the conventional standard treatment (325 mg of aspirin, 20 mg of atorvastatin, and medications for hypertension and diabetes) plus physiotherapy. The patients in group A receive acupuncture in addition to standard therapy, while patients in group B received *Dorema ammoniacum*. Group C, as the control group, only received the conventional treatment and physiotherapy.

Interventions and comparisons:

Acupuncture group:

The selection of points was selected based on acupuncture reference books and acupuncture therapist experience. Acupuncture performed by an acupuncturist clinician with a Ph. D. in Acupuncture from Beijing Chinese Medical University follows this method:

1. After a random selection of the acupuncture group, according to the research method's standards, patients were introduced to the acupuncture clinic of Imam Reza Hospital in Mashhad, affiliated to Mashhad University of Medical Sciences.
2. The therapist first explained the method of acupuncture for patients.
3. The therapist used the reducing method in the corresponding points entered the body bilaterally to reach the sense of de qi. The exception points were CV6-GV23-GV24, Which are in the center of the body.

4. needles were kept in the patient's body for 30 minutes and then removed from the patient's body. Participants in the acupuncture group (group A) received acupuncture in addition to standard therapy. Acupuncture was performed every other day for 12 sessions (three times per week for four weeks), each session lasting 30 minutes. An acupuncturist performed acupuncture on GV20, GB20, GV24, GV23, CV6, LI15, TW5, SP10, ST36, ST40, LV3, and KI1 points (Table 1). Table 2 showed Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).

Dorema ammoniacum group:

The participants in group B received 1 g of *Dorema ammoniacum* (two 500 mg capsules per day) from ammoniacum gum, in addition to standard therapy. It should be noted that all patients in the three groups

received standard therapy for stroke. The treatment duration was one month. By monitoring all possible aspects, drugs were provided for the intervention group receiving *Dorema ammoniacum*.

Outcome measurements:

The patients in the three groups did not have any contact with each other. The symptoms were recorded at the beginning and end of treatment in a questionnaire, regardless of the patient's group. The extent of improvement in motor functioning and mitigation of motor disability were evaluated in patients with ischemic stroke immediately before the intervention and at the end of the intervention (one month after the intervention), based on the Modified Rankin Scale (mRS) and mNIHSS. During the study, the patients had access to their physician, either in person or through phone calls, and their drug consumption was monitored. If any possible side effects occurred during the intervention, they were recorded, and the patient was excluded from the study and treated based on the medical ethics principles.

The mRS and mNIHSS were completed for the evaluation of patients. At baseline, the patients were examined by mRS and mNIHSS. In almost all acute stroke trials, mRS and mNIHSS are used as primary outcome scales in acute stroke [14-16]. The mRS is rated from 0 to 6, running from "perfect health without symptoms" to "death" [16]. On the other hand, the mNIHSS contains eight items, including the level of consciousness, best gaze, visual field, motor arm, motor leg, sensory abilities, best language, and neglect. This scale has been widely used as a standard part of the assessment in clinical trials. Its scores range from 0 to 31, with scores above 20 indicating severe neurological impairment, 4-20 suggesting moderate impairment, and scores below 4 indicating mild impairment [17]. In this study, the mRS and mNIHSS were completed at baseline and the end of treatments. The primary and secondary outcomes and their differences (pre-treatment and post-treatment differences), based on mNIHSS and mRS, were compared in the study groups.

Hemoglobin A1c (HBA1c), fasting blood sugar (FBS), triglyceride (TG), cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), plasma creatinine concentration (Cr), and blood urea nitrogen (BUN) levels were measured before the intervention and after 30 days (end of the intervention) for the primary assessment of patients and investigating the possible side effects.

Statistical method:

The baseline characteristics are expressed as mean $\pm$ standard deviation for continuous variables or percentages for categorical variables. A Chi-square test was used for the comparison of categorical data. Between-group differences in primary and secondary outcomes are expressed as mean $\pm$ standard deviation and examined by the Kruskal-Wallis test. For within-group comparisons, Wilcoxon signed-rank test was used. In order to control for the confounding factors, analysis of covariance was used, and the Bonferroni test was performed for multiple comparisons. A P-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out in SPSS for Windows Version 19.

Results:

Seventy-one out of 137 examined patients did not meet the eligibility criteria. A total of 66 patients were included in the study and randomly allocated to three groups. During the intervention, some patients were excluded due to different reasons (Fig. 1). Finally, 61 patients were included in our analysis. The study flowchart is presented in Fig. 1.

Out of 61 patients, 31 (50.8%) and 30 (49.2%) were male and female. The mean age of the subjects was 64.69 ± 6.46 years. The interval between the incidence of stroke and the onset of treatment was 13.61 ± 7.27 days. In terms of education, 47.5% of the participants were illiterate. Other information of the participants is presented in Table 3. According to the chi-square test results, the three groups were homogeneous in terms of primary and demographic information, including gender, BMI, education, smoking, marital status, and history of cardiovascular diseases.

Table 1. Selected acupoints for the treatment of stroke disability symptoms

Point	location
GV20(Baihui)	7 cun above the midpoint of the posterior hairline, 5 cun above midpoint of anterior hairline, midway on a line connecting the apex of both ears.
GV24(Shenting)	0.5 cun above the midpoint of the anterior hairline.
GB20(Fengchi)	In the depression created between the origins of the Sternocleidomastoid and Trapezius muscles, at the junction of the occipital and nuchal regions. Lateral and level with GV16.
CV6(Qihai)	On the midline, 1.5 cun inferior to the umbilicus
CV23 (Lianquan)	On the midline, in the depression superior to the hyoid bone
LI15(Jianyu)	Anterior and inferior to the acromion, on the upper portion of the deltoid muscle, in a depression formed when the arm is in full abduction.
TW5(Waiguan)	On the dorsum of the forearm, 2 cun above the wrist crease in the depression between the radius and the ulna.
SP10(Xuehai)	With the knee in flexion, 2 cun superior to the superior border of the patella, on the bulge of the medial portion of the quadriceps femoris muscle
ST36(Zusanli)	3 cun below the lower border of the patella (the depression just lateral to the patellar tendon), one finger width lateral from the anterior crest of the tibia, in the tibialis anterior muscle
ST40(Fenglung)	On the anterior aspect of the lower leg, 8 cun superior to the tip of the external malleolus, two finger width lateral to the anterior crest of the tibia.
LV3(Taichong)	On dorsum of the foot in a depression distal to the junction of the 1st and 2nd metatarsal bones
KI1(Yongquan)	On the sole of the foot, in a depression when the foot is in plantar flexion at the junction of the anterior 1/3 and posterior 2/3 of line connecting base of 2nd and 3rd toes and the heel

Table 2: Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).

Item	Item criteria	Descriptions
1- Acupuncture	1a) Style of Acupuncture	Chinese Medicine therapy
Rationale	1b) reasoning of treatment provided- Based on Reliable references, Practitioners experiences	1) Chinese Medicine Department attending of MUMS agreement 2) Textbook of Acupuncture 3) Relevant articles (4) 4) Practitioners experience on Iranian Patients
	1c) Extent to which treatment varied	Standardized treatment
2- Details of Needling	2a) Number of needle inserted	20
	2b) Names of Acupoints	GV20 (Bai Hui), GB20 (Feng Chi). GV23 (Shang Xing), GV24 (Shen Ting), CV6 (Chi Hai), LI15 (Jian YU), TW5 (Wai Zhong), SP10 (Xue Hai), ST36 (Zu Sanli), ST40 (Feng Long), LV3 (Tai Chong), KI 1 (Yong Quan)
	2c)Dept of needle insertion	In Scalp 2-3 mm, In Nape 10–15mm, In Abdomen 15 -20 mm, in arm 10-15 mm, In thigh 15-20 mm, In leg 15 -30 mm, In foot 10-15 mm
	2d) Response sought	Inserting till feeling De qi or arrival qi
	2e) Needle Stimulating	Manually by Reducing method
	2f) Needle retention time	30 minute
	Needle type	Sterile, disposable acupuncture needles (size 0.25 × 40mm); SMC , Inc., Geumcheon-Gu Seoul, Korea;
3- Therapeutic protocol	3a) Number of treatment session	12
	3b) Frequency and duration of treatment sessions	Three times per week/ for 4 weeks
4- Other treatment components	Nothing	

5-Practitioner background	Description of practitioner background	MD base, and Clinical PhD of Acupuncture and Massage from Beijing University of Chinese Medicine (BUCM, Associate Professor of MUMS
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Table 3
Demographic characteristics of the study groups.

characteristic		Acupuncture	Dorema ammoniacum	Control	P-value
Gender No. (%)	Male	11 (55.0)	10 (50.0)	10 (47.6)	0.89
	Female	9 (45.0)	10 (50.0)	11 (52.4)	
Age, Mean (SD)		63.45 ± 7.40	63.20 ± 6.44	67.29 ± 6.40	0.08
Body mass index (BMI) No. (%)	18.4>	4(20.0)	2(10.0)	4(19.0)	0.91
	18.5–24.9	7(35.0)	8(40.0)	9(42.9)	
	25-29.9	7(35.0)	6(30.0)	6(28.6)	
	30-34.9	2(10.0)	4(20.0)	2(9.5)	
Marital status No. (%)	Single	0(0)	0(0)	0(0)	0.89
	Married	12(60.0)	11(55.0)	13(61.9)	
	Divorce or spouse death	8(40.0)	9(45.0)	8(38.1)	
Education No. (%)	Illiterate	9(45.0)	9(45.0)	11(52.4)	0.86
	Diploma	11(55.0)	11(55.0)	10(47.6)	
Smoking No. (%)	Yes	7(35.0)	9(45.0)	10(47.6)	0.69
	No	13(65.0)	11(55.0)	11(52.4)	
History of hypertension	Yes	16(80.0)	15(75.0)	15(71.4)	0.81
	No	4(20.0)	5(25.0)	6(28.6)	
History of diabetes	Yes	10(50.0)	10(50.0)	10(47.6)	0.98
	No	10(50.0)	10(50.0)	11(52.4)	
History of hyperlipidemia	Yes	12(60.0)	9(45.0)	13(61.9)	0.49
	No	8(40.0)	11(55.0)	8(38.1)	
Side of paresis or plegias	Right	12(60.0)	11(55.0)	12(57.1)	0.95
	Left	8(40.0)	9(45.0)	8(42.9)	

Data related to the mNIHSS score, mRS score, and creatinine level had abnormal distributions, while other variables showed a normal distribution. At the beginning of the study, the three groups were

homogeneous in terms of the mean mNIHSS score ($P = 0.77$). After the interventions, the mean mNIHSS score was not significantly different between the three groups, whereas the mean pre-/post-treatment differences were significant in the three groups ($P < 0.001$)(Table 4). Figure 2 demonstrates the pre- and post-treatment mNIHSS scores and their differences.

Table 4
Primary and secondary mNIHSS and mRS in the study groups

Variable	Group	Before	After	Post-pretreatment differences	Significance
mNIHSS	Acupuncture	8.65 ± 3.40	3.50 ± 1.58	5.15 ± 0.98	¹ $p < 0.001$
	dorema ammoniacum	8.55 ± 3.88	4.10 ± 3.27	4.45 ± 1.39	² $p < 0.001$
	Control	8.38 ± 3.78	4.90 ± 4.23	3.47 ± 0.92	³ $p < 0.001$
mRS	Acupuncture	3.75 ± 0.85	2.40 ± 1.23	1.35 ± 0.58	¹ $p = 0.1$
	dorema ammoniacum	3.50 ± 1.19	2.35 ± 1.42	1.15 ± 0.58	² $p = 0.6$
	Control	3.67 ± 0.98	2.81 ± 1.43	0.95 ± 0.66	³ $p = 0.6$
1 = significant change from baseline to second evaluation between the Acupuncture and Control					
2 = significant change from baseline to second evaluation between the dorema ammoniacum and Control					
3 = significant change from baseline to second evaluation between the Acupuncture and dorema ammoniacum					
mNIHSS: modified National Institutes of Health Stroke Scale					
mRS: modified Rankin Scale					

Analysis of covariance test indicated that by controlling for the effect of mNIHSS at baseline and after the intervention, the mean mNIHSS score was significantly different between the three groups after the intervention ($P < 0.05$). A Bonferroni test was also carried out for the three groups. Robust evidence suggested a significant difference between the acupuncture and control groups ($P < 0.001$), *Dorema ammoniacum* and control groups ($P < 0.001$), and acupuncture and *Dorema ammoniacum* groups after the treatment ($P < 0.001$); however, the extent of reduction was greater in the acupuncture group. The mean mNIHSS scores of the acupuncture and *Dorema ammoniacum* groups were 1.82 and 1.04 lower than the control group's mean score, respectively (Table 5).

Table 5

The results of the analysis of covariance of the mNIHSS index at the beginning and end of the study in all three groups.

Name of variable	Estimation	Standard deviation	T	P-value
Group				
Acupuncture	-1.82	0.25	7.28	< 0.0001
Dorema ammoniacum	-1.04	0.24	4.18	< 0.0001
Control (reference)	-	-	-	-
mNIHSS at the beginning of the study	0.94	0.03	33.01	< 0.0001
Day of visit	0.1	0.01	7.30	< 0.0001

At the beginning of the study, the three groups were homogeneous in terms of the mean mRS score ($P = 0.75$). Also, after the interventions, there was no significant difference between the groups ($P = 0.13$). Based on Wilcoxon signed-rank test, paired comparison of the groups indicated a significant decline in the mean mRS score from the beginning to the end of the study in all of the three groups ($P < 0.001$); nevertheless, the extent of reduction was greater in the acupuncture group. Finally, there was no significant difference between the intervention groups and the control group from the beginning to the end of the study regarding the mean levels of HDL, cholesterol, creatinine, BUN, FBS, ALT, AST, triglyceride, and LDL ($P > 0.05$) (Table 6).

Table 6
Primary and secondary laboratory findings in the study groups.

Variable	Group	Before	After	Post-pre treatment differences	Significance	¹ Significance
FBS	Acupuncture	108.90 ± 15.69	105.26 ± 14.31	4.42 ± 16.15	0.24	P = 0.98
	dorema ammoniacum	111.57 ± 19.41	106.47 ± 18.41	5.11 ± 23.24	0.35	
	Control	110.75 ± 18.09	106.36 ± 18.94	4.15 ± 18.70	0.35	
BUN	Acupuncture	19.67 ± 3.48	19.44 ± 5.03	0.36 ± 2.75	0.56	P = 0.19
	dorema ammoniacum	18.35 ± 5.18	16.15 ± 4.28	2.05 ± 3.84	0.03	
	Control	19.47 ± 5.43	19.73 ± 5.07	0.42 ± 2.70	0.52	
Creatinine	Acupuncture	1.16 ± 0.18	1.16 ± 0.23	0.0016 ± 0.28	0.29	P = 0.26
	dorema ammoniacum	1.11 ± 0.22	1.02 ± 0.18	0.09 ± 0.28	0.006	
	Control	1.16 ± 0.21	1.16 ± 0.19	0.005 ± 0.16	0.65	
Cholesterol	Acupuncture	162.60 ± 42.59	152.15 ± 28.20	4.26 ± 30.15	0.55	P = 0.97
	dorema ammoniacum	170.65 ± 28.20	167.36 ± 26.65	2.15 ± 23.20	0.69	
	Control	166.85 ± 21.83	162.0 ± 37.12	3.0 ± 21.70	0.55	
HDL	Acupuncture	43.0 ± 7.25	46.58 ± 10.45	3.94 ± 8.07	0.047	P = 0.1
	dorema ammoniacum	49.45 ± 12.14	52.47 ± 9.55	2.73 ± 7.77	0.69	
	Control	42.40 ± 6.66	44.26 ± 13.24	2.36 ± 12.91	0.43	

¹ = significant change from baseline to second evaluation between the groups

FBS: Fasting blood glucose, BUN: Blood urea nitrogen, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HbA1C: Glycosylated hemoglobin

Variable	Group	Before	After	Post-pre treatment differences	Significance	¹ Significance
LDL	Acupuncture	95.30 ± 33.25	82.52 ± 20.65	7.78 ± 19.33	0.09	P = 0.62
	dorema ammoniacum	90.45 ± 25.29	89.21 ± 34.90	1.21 ± 26.33	0.84	
	Control	101.65 ± 18.25	97.21 ± 25.22	3.05 ± 16.61	0.43	
TG	Acupuncture	116.95 ± 43.76	113.11 ± 38.77	0.53 ± 26.40	0.93	P = 0.98
	dorema ammoniacum	109.45 ± 37.93	109.42 ± 30.67	0.47 ± 26.30	0.94	
	Control	127.05 ± 96.62	141.21 ± 148.24	13.21 ± 23.52	0.85	
AST	Acupuncture	22.84 ± 9.90	20.42 ± 5.69	2.42 ± 5.48	0.07	P = 0.58
	dorema ammoniacum	26.36 ± 9.14	23.63 ± 9.95	2.74 ± 5.65	0.049	
	Control	24.73 ± 6.97	23.63 ± 7.05	1.11 ± 4.09	0.25	
ALT	Acupuncture	22.68 ± 12.67	19.78 ± 8.20	2.89 ± 8.28	0.14	P = 0.55
	dorema ammoniacum	26.63 ± 10.84	22.63 ± 11.57	4.0 ± 8.19	0.048	
	Control	21.94 ± 7.37	20.57 ± 7.95	1.36 ± 5.20	0.26	
HbA1C	Acupuncture	6.12 ± 0.46	5.90 ± 0.37	0.22 ± 0.26	0.001	P = 0.31
	dorema ammoniacum	5.95 ± 0.73	5.87 ± 0.80	0.03 ± 0.57	0.81	
	Control	6.01 ± 0.56	5.95 ± 0.49	0.06 ± 0.32	0.4	
¹ = significant change from baseline to second evaluation between the groups						
FBS: Fasting blood glucose, BUN: Blood urea nitrogen, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HbA1C: Glycosylated hemoglobin						

Discussion:

Stroke-related disabilities are among the most critical health issues worldwide. For reperfusion in acute ischemic stroke, the only Food and Drug Administration (FDA)-approved medical therapy involves the use of rtPA [18]. However, considering the short therapeutic window of intravenous thrombolysis, most ischemic stroke patients cannot benefit from this intervention. Because of these obstacles, complementary therapies, such as herbal treatments and acupuncture, have recently attracted more attention [18].

Acupuncture is a form of alternative treatment in traditional Chinese medicine, which has been used for stroke and post-stroke rehabilitation for thousands of years [19]. This treatment has valuable effects on ischemic stroke rehabilitation [20]. In the present study, the mean mNIHSS score significantly reduced in the acupuncture group compared to the control group. The suggested mechanism for the efficacy of acupuncture in stroke patients includes cerebral blood flow regulation, modulation of gene and protein expression, promotion of cell proliferation in the CNS and several ischemic tissues, regulation of important neurochemicals (such as antioxidants, inflammation-related substances, neurotransmitters, metabolic substrates, and neurotrophic factors), decrease brain edema and ultimately potentiation, learning, and hippocampal memory recovery [21].

From the perspective of Persian traditional medicine, blockage, as the cause of stroke, does not denote physical obstruction, but may imply slow or static movements [22–25]. According to Persian medicine resources, each plant has a unique temperament (traditionally called “Mizaj”) [22, 23]. This temperament can be assessed with respect to the plant's effects on the body [26–27].

Dorema ammoniacum has a warm temperament. There are some correlations between the organoleptic properties of plants and some aspects of diseases and anthropometric indices. According to the Persian medicine literature, *Dorema ammoniacum* may improve blood circulation and is therefore considered an “opener” of obstructive diseases (“Mofatteh” in the Persian medicine terminology) [28–29]. Traditional medicine specialists have mentioned natural remedies, such as *Dorema ammoniacum*, for the treatment of obstructive diseases, especially stroke [5].

In traditional medicine, the effects of *Dorema ammoniacum* on stroke and plegia treatment have been reported. The present study showed that *Dorema ammoniacum* could significantly reduce the mNIHSS and mRS scores after the occurrence of stroke. This plant's beneficial effects on other CNS disorders, such as epilepsy, and joint pain reduction have been discussed. Previous studies have also indicated the antimicrobial, cytotoxic, and acetylcholinesterase inhibitory activities of *Dorema ammoniacum*. However, the exact mechanism of this plant's effects on stroke treatment is not clearly understood, although it may be related to its anti-inflammatory, antioxidant, and vasodilatory effects and inhibition of acetylcholinesterase properties [30].

Different studies have shown the effects of acetylcholinesterase inhibitors on improving blood flow in the cerebral ischemia cortex of patients with stroke [31, 32]. It is well-documented that oxidative stress and

inflammation are involved in stroke's pathological process [33]. Importantly, *Dorema ammoniacum* has considerable anti-inflammatory and antioxidant effects [34, 35], which may account for this plant's positive role in alleviating stroke consequences. Moreover, *Dorema ammoniacum* exerts neuroprotective effects by modifying the GABAergic and glutamate systems; these properties may also help decrease stroke's adverse outcomes [10].

In addition, the vasodilatory properties of *Dorema ammoniacum* have been reported in the literature [36, 37]. Vasodilators have been used to treat stroke for many years [38, 39], without any apparent reasons. However, since oxidative stress is more prominent in the early weeks and the acute phase, brain stroke can initiate several pathophysiological events, deteriorating the patient's condition, such as inflammation, sub-acute phase of cell death, and acute phase of oxidative stress [40]. Excessive production of reactive oxygen species (ROS) leads to oxidative stress, and their weakened degradation following cerebral ischemia causes cell death [41, 42].

It seems that the antioxidant and anti-inflammatory effects of herbs, such as *Dorema ammoniacum*, may decrease the inflammatory process and consequently reduce brain injury induced by stroke. Recently, animal studies have shown that the opioid receptors' level increases early on following a stroke and then decreases [43]. Kao et al. showed that opioidergic agents might have a significant therapeutic potential against stroke [44]. A study by Motevalian et al. [15] found that *Dorema ammoniacum* activates opiate receptors in the brain. Therefore, the effects of *Dorema ammoniacum* on these receptors decrease the adverse effects of stroke. Our study showed that both *Dorema ammoniacum* and acupuncture had minimal effects on laboratory findings than the control group. However, very few studies have evaluated the effects of *Dorema ammoniacum* on hematological parameters. Consequently, more studies with a larger sample size must be performed to address these effects.

One of the strengths of this study was the matching of the groups. We tried to consider most of the factors that affected patients' prognosis with acute strokes, such as BMI and involved arteries, and matched the groups as much as possible. Besides, we evaluated cofounders' role, such as age and mNIHSS at baseline and after the intervention, to reach more reliable results. This is the first study comparing the efficacy of Persian medicine and Chinese medicine approaches alongside conventional therapies to the best of our knowledge. Finally, we used objective and subjective parameters as primary and secondary outcomes. We used stroke scales and performed laboratory exams to evaluate the effects of this plant on these parameters.

Limitations:

One limitation of this study was the inclusion of patients with moderate symptoms rather than severe symptoms. Therefore, it is impossible to determine the effects of this herb on patients with severe stroke. On the other hand, there are very few studies evaluating the toxicity of *Dorema ammoniacum* in humans. In this study, we used the minimum dose of the herb based on traditional medicine textbooks. Consequently, the effect of a higher dose of *Dorema ammoniacum* needs to be evaluated in future

studies. Besides, lack of a long-term follow-up is another limitation of this study; therefore, longer follow-ups are required to ensure the therapeutic outcomes. It should be noted that patients with diabetes or hypercholesterolemia may use different medications with various doses. Accordingly, the results regarding the effects of interventions on laboratory findings should be interpreted with caution. Further studies are also recommended to evaluate the effects of these interventions on laboratory parameters.

Conclusion:

Both acupuncture and *Dorema ammoniacum* are beneficial within the first month of stroke incidence. However acupuncture can induce a more significant decline in the mNIHSS and mRS scores. A combination of these two approaches is suggested in future studies.

Declarations

Ethics approval and consent to participate:

Informed consent forms were obtained from both patients and their companions. The Ethics Committee approved this study of Mashhad University of Medical Sciences (12/2016; ethics code: IR.MUMS.REC.1395.518). It was also registered in the Iranian Registry of Clinical Trials (IRCT20170227032797N2).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on request.

Consent for publication:

Not applicable.

Competing interests:

The authors declared no potential conflicts of interest.

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Author contributions

HB, KG, MY, MM, MA, HA, HR contributed to conception, design of the study. OM and MM conducted literature search. MM made data extraction. MM, AH, MA and OM contributed to acquisition, analysis, and

interpretation. MM, MY, MA, OM, HB, KG made substantial contributions in drafting the manuscript and revising it critically for important intellectual content. All authors have read and approved the final version of manuscript.

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Figures

Figure 1

Disposition of Participants based on consort diagram

Figure 2

The effect of accupuntre and dorema ammoniacum on primay , secondary mNIHSS and their Post-pre treatment differences in cases of stroke

Supplementary Files

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