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Effect of Nepeta menthoides on cognitive disorders in Alzheimer's disease: a clinical trial

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Abstract

Nowadays, given the outbreak of Alzheimer disease (AD) as a global phenomenon, it is absolutely essential to take efficacious measures against it. Heating up the brain is a recommended approach to decrease the symptoms of AD. Furthermore, using hot herb is an effective method to enhance the temperature of the brain. One of the hot herbs is *Nepeta menthoides* which is known as Ostokhodus and has neuroprotective effects. In the present paper, the effect of Nepeta on the treatment of Alzheimer was studied. A trial was carried out on two groups of AD patients. While the first group was prescribed the capsules of Nepeta extraction, the second group was given the placebo capsules. The results of the taken MMSE inventories from both of the tested groups as the comparison criteria revealed that Nepeta had positive influence on the treatment of AD.

Keywords: *Nepeta menthoides,* Alzheimer's disease, cognitive disorder

Introduction

As the age of the population augments all over the world, the need for extra resources to care for individuals afflicted with Alzheimer Disease (AD) is felt more than ever. In 2006, the global pervasiveness of AD was 26.6 million. It will break out approximately 4 times by 2050; 1 in 85 persons will be affected by Alzheimer's(Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). Alzheimer's is a progressive neurodegenerative disorder which causes cognitive impairment, neuropsychiatric symptoms, disability, dependency, caregiver burden, substantial healthcare, expenditure and premature death(Brookmeyer et al., 2011). Objectively, AD attacks recent memories, the executive functions and verbal fluency. Progression in the disease culminates in changes in emotions, intensification of the psychotic symptoms, depression and changes in personality. Early damage in the brain structure happens in hippocampus and the interconnected cortical zones which perform a role in the memory function(Scheff et al., 2015). In AD, the major pathological changes that occur in the brain are (i) extracellular amyloid plaques, containing mainly amyloid-β (Aβ) peptide, (ii) intraneuronal neurofibrillary tangles (NFTs), made of hyperphosphorylated and misfolded tau; other pathological changes linked with this neurodegenerative illness are (iii) oxidative stress, (iv) gliosis, (v) inflammation, (vi) dystrophy of neurons, (vii) neuronal death, (viii) synapse death, and (ix) altered levels of neurotransmitters(Amtul, 2015).

Alzheimer as a neurological disorder is related to the cold intemperament of the brain. In other words, it means that the brain's texture has lower temperature than its normal, healthy form. One strategy or approach known as the Iranian Traditional Medicine (ITM) recommends increasing the temperature of the brain by either physical methods or medical "hot" herbs. One of these "hot" herbs is *Nepeta menthoides* Boiss and Buhse (Ostokhodus in Persian language)(Ahmadian-Attar, Ahmadiani, Kamalinejad, Dargahi, & Mosaddegh, 2014).

Genus Nepeta of the Lamiaceae family consists of about 300 herbaceous species. Nepeta has delightful flowers. The greatest diversity of this genus species is distributed in Himalayas and the Southwestern Asia particularly Iran, Turkey and Hindu Kush. Iran, especially, is one of the centers of the birthplace of the Nepeta. There are sixty-seven species of this genus in Iran about 53% of which are endemics(Asgarpanah, Sarabian, & Ziarati, 2014).

The *Nepeta menthoides* Boiss and Buhse, usually referred to as Ostokhodus-e Khorasani or in brief Ostokhodus, is used as a medicine to cure neurological diseases like epilepsy and melancholia(Naghibi, Mosaddegh, Mohammadi Motamed, & Ghorbani, 2010). Moreover, this species has been claimed to have neuroprotective influences on the axotomized spinal motoneurons(Azizzadeh Delshad & Farzan, 2013; Delshad, Naseri, Parvizi, Fattah, & Sharayeli, 2011). For their antiasmathic, antiseptic, antispasmodic, antitussive, diuretic and febrifuge effects, diverse species of Nepeta have widespread use in the traditional medicine(Miceli et al., 2005). The experts in the traditional medicine take pride in stating that Ostokhodus wards off the production of the infection inside the body and also reinforces the heart and the urinary system. Ostokhodus, moreover, is useful for the chest (lung) and kidney ailments and is suitable for the health condition of the elders(Avicenna., 2005; Biruni, 2004; Nafis., 2008). In ITM, the organs of the body comprise an amalgam of quadruple humors named akhlat, safra (with warm and dry qualities), sauda (with cold and dry qualities), balgham (with cold and wet qualities) and dam (with warm and wet qualities); these are the mixture of four basic elements viz. water, air, fire and soil(Abdolahadi Azam & Esmaeili Somayeh, 2016). This herb removes the black bile or sauda from the heart, head and balgham or phlegm of the body. The black bile and phlegm are two types of humor (in Persian named khelt). Sauda has cold and dry qualities and phlegm has cold and wet qualities(Aghili-Shirazi, 1773; SI, 1976).

. The therapeutic impacts of the Nepeta genus are mainly due to the high contents of the flavonoids and essential oils in their leaves' textures(Jamzad et al., 2003). Because of their potentiality to function as antioxidant and scavenger of free radicals, these components are applicable in medicine(Soobrattee, Neergheen, Luximon-Ramma, Aruoma, & Bahorun, 2005). Also there is no need to resort to other remedies to compensate for the probable side effects of consuming Ostokhodus(El-Bitar, 1877). As of yet, however, the probable therapeutic effects of *Nepeta menthoides* Boiss and Buhse on the AD have not been studied. Hence, in line with this desideratum for research in this uncharted territory and due to the widespread applications of *Nepeta menthoides* in Iran, the present study was performed as an attempt to scrutinize the possible therapeutic capacities of this genus for the treatment of Alzheimer's disease.

Materials and Methods

The oral capsule (500 mg) of Nepeta menthoides, elicited from its hydro alcoholic extraction ,after the microbial and qualitative control of the Nepeta sample, was prepared. Also the placebo capsules were prepared by inserting 500 mg of starch into every capsule. A placebo is an artificial or clinically ineffectual treatment for an ailment or other medical condition with the purpose of deceiving the recipient (https://en.oxforddictionaries.com/definition/placebo, 2017).

Patients and design of the study

The study was conducted in 2015 at Shahid Beheshti University of Medical Sciences, Tehran, Iran. Both Nepeta and placeboes capsules were 500 mg. The entrance criteria adopted by the researchers for selecting the AD patients as participants in the trial were as follows:

The age of the population being between 65 and 85, the scores being below 20 in the MMSE inventories at the onset of the trial, being literate at least up to fifth grade, taking consent from patient or the executer of the patient, underlying no other psychological disease such as depression, having no severe disease except psychiatric and neurological disorders based upon the assessment of an specialist, consuming no drugs except nicotine and caffeine, having no allergic history to the cholinesterase enzyme restrainers, and having no heart disease, hysteria, asthma, peptic trauma and urinary blockade history.

A total of 78 sick individuals as a statistical society (39 people in every group) were selected under the supervision of a psychiatrist. In case the patients felt the tendency to quit the trial or some side effects pertinent to the prescribed capsules were observed on the patients, the affected people were excluded from the trial and the additional or required medications were performed on them. After providing the needed explanations and having the informed consent forms signed by the patients, the history and the results of the MMSE inventories were determined before the trial. The two groups didn't have any meaningful differences in factors of age (p-value=0.496), sex (p-value=1.000), education (p-value=0.644), physical activity (p-value=1.000) and body mass index (p-value=0.792). All the patients were randomly assigned to two groups. The prepared capsules were distributed randomly amongst the patients based upon the codes assigned to them and, the researcher was kept unaware of the coding process. The patients in the first group were prescribed 3 capsules daily with 500 mg content of Nepeta L. The second group was given the same amount of placeboes. At the first step, the duration of the treatment was one month. At the end of the due time the history and new scores of the MMSE inventories were surveyed again. At the second phase, the clinical trial was carried out for another three months and the new elicited results were gauged. Since Alzheimer's could be a serious and life-threatening disease, both group members were prescribed the conventional Alzheimer medications as the primary drugs. The analysis of the patients' data, including the scores of the MMSE inventories, was done utilizing T-test through the SPSS software.

Results

Among the 78 individuals who were registered in this research, 48.7% were male and 51.3% were female. 52.6% of the patients had the age range of 65 to 75. In addition, 47.4% of them were between 75 and 85 years old. 93.6 % of the patients were educated up to high school and 6.4 % had bachelor's degree. Body mass index distribution for 75.6 % of the patients was lower than 25 and for 24.4% was higher than 25. Two groups didn't have statistically meaningful differences based upon the physical activity. In both of the groups 74.4% of members had mild physical activity. The scores and standard deviations of the MMSE inventory before the treatment are displayed in Table 2. The juxtaposition of the results indicates that there is no significant difference between the two groups before launching the trial (p-value=0.488). The differences between the garnered scores of the MMSE inventory are depicted in diagram 1. It has been revealed that the differences between MMSE scores prior to the consumption (MMSE1) and after one month of consumption (MMSE2) are more significant for group 2 relative to group 1 (p-value=0.000). This shows that Nepeta is effective in improving MMSE scores. In addition, the diagram displays that the difference between MMSE2 and the MMSE3 score- the score of MMSE after three months and after the discontinuation of the consumption- is also more for the Nepeta consuming group (Group 2) in comparison with the placebo consuming group (Group 1)(p-value=0.000). This reveals that MMSE3 score in group 2 has

decreased more sharply compared to group 1. The difference between MMSE1 and MMSE3 scores in the two groups is not statistically meaningful (p-value=0.716). Based upon the data in table 2, three months after stopping the trial, patients' minimental scores dropped down and exhibited meaningful differences *visa a vise* the scores obtained in the the second step. These scores, nevertheless, did not reveal meaningful and considerable differences with the primary scores of the patients. Sex, age, education, body mass index and physical activity seemed to have no significant effects on the test results of the MMSE inventory

Table 1. Distribution of gender, age, education, BMI, physical activity and their p-values in both groups under study

	Sex		Age		Education		BMI		Physical-Activity	
	Male	Female	65-75	75-85	Illiterate	Literate	<25	>25	Mild	Moderate
Group 1	19	20	19	20	37	2	30	9	29	10
Group 2	19	20	22	17	36	3	29	10	29	10
P-Value	1.000		0.496		0.644		0.792		1.000	

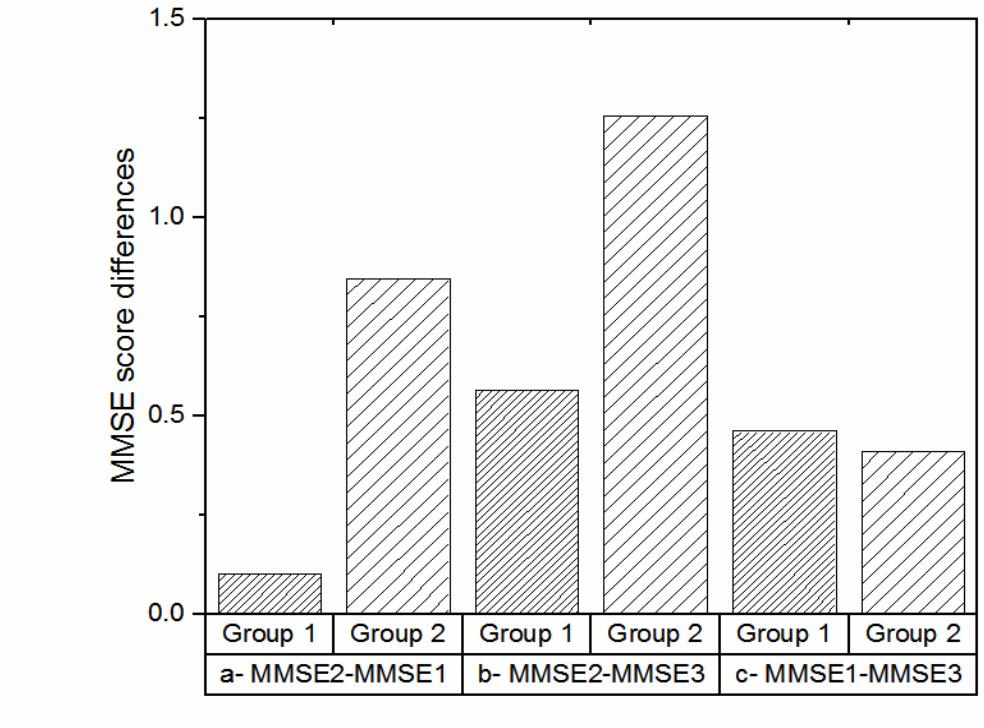

Diagram 1 -The differences of MMSE scores: (a) MMSE 2 - MMSE1, (b) MMSE2 - MMSE3 and (c) MMSE1 – MMSE3 between the placebo consuming group (Group 1) and Nepeta consuming group (Group 2)

Table 2. Average Minimental Scores and their differences with p-value for both groups under study

	Mini1	Mini2	Mini3	Mini2 - Mini1	Min2 – Mini3	Mini1 – Mini3
Group 1	13.33	13.44	12.87	0.1026	0.5641	0.4615
Group 2	13.79	14.64	13.38	0.8462	1.2564	0.4103
p- value	0.488	0.075	0.432	0.000	0.000	0.716

Discussion

The present research scrutinized the efficacy of one herbal product as a helper for the treatment of the Alzheimer disease. Today, using herbal medicines are prevalent as a way to treat the neurodegenerative diseases(Kahkeshani, Khanavi, & Hadjiakhoondi, 2014). The achieved data unveiled that Nepeta menthoides might be an effective remedy for the patients who have succumbed to Alzheimer. This study revealed further the efficacies of Nepeta menthoides accompanied by the conventional medications for diminishing the impairing impacts of AD. Diagram 1-(a) shows that consuming Nepeta can be highly effective but Diagram 1-(b) shows that discontinuation of the consumption of Nepeta can adversely affect the cognitive abilities of the patients to the point that there would be no meaningful difference between the two groups after 3 months (Diagram1- (c)). *Nepeta menthoides* is referred to as Ostokhodus Khorasani in the Iranian traditional medicine(Amin, 1991). It is normally used as medicine to treat high blood pressure, rheumatic pains and nervous ailments(Amin, 1991; Ghahreman & Okhovvat, 2010; Hiroyukimoteki, Yamada, Hirotakakatsuzaki, & Komiya, 2002; Joharchi & Amiri, 2012). The presence of some of the components such as terpineol, terpinolene, 1,8-cineole and limonene in the essential oil of Nepeta menthoides have the antitumor activity(Hassan, Gali-Muhtasib, Göransson, & Larsson, 2010), reducing the protein expression of AKT1 and inhibiting cell proliferation(Okumura, Yoshida, Nishimura, Kitagishi, & Matsuda, 2012), antimicrobial activity(Sivropoulou et al., 1997), Inhibition of acetylcholinesterase (Gould, 1997) and anticancer activity(Miyazawa & Yamafuji, 2005). Based on previous researches 1,8-cineol, ⟨-pinene, limonene, ⟨-terpineol and ©-terpinene are shown to play preventive role of acetyl cholinesterase activity. Acetyl cholinesterase had the key role in Alzheimer involution(Aazza, Lyoussi, & Miguel, 2011). 1,8-cineol, which includes the major composition of Nepeta menthoides, plays a substantial role as the inhibitor of the enzyme(Aazza et al., 2011; Ciftci, Ozdemir, Tanyildizi, Yildiz, & Oguzturk, 2011; Dohi, Terasaki, & Makino, 2009; Perry, Houghton, Theobald, Jenner, & Perry, 2000). The existence of myrcene, 1,8- cineole, limonene, ⟨-terpinene and ⟨-terpinolene in the composition of Nepeta menthoides makes it a powerful antioxidant(Kim et al., 2004). The antioxidant activity can proffer protection cells from the oxidation and following growth cycle malfunction (which leads to cancer and neurodegenerative problems)(Kim et al., 2004; Roberto, Micucci, Sebastian, Graciela, & Anesini, 2010; Ruela de Sousa et al., 2007).

Flavonids, as the most significant pigments for flower coloration in various Nepeta species, have anti-allergic, anti- inflammatory, antimicrobial, anti- cancer(Tereschuk, Riera, Castro, & Abdala, 1997), anti- infective(Al-Saleh, Gamal El-Din, Abbas, & Saeed, 1997; Aladesanmi, Sofowora, & Leary, 1986; Asadi Balsin Sharif Abadi, Nasri, Amin, & Bidaran, 2013; Bourrel, Perineau, Michel, & Bessiere, 1993; Mahmoud, Jawad, Hussain, Al-Omari, & Al-Naib, 1989; Quarenghi, Tereschuk, Baigori, & Abdala, 2000; Rauha et al., 2000; Singh & Nath, 1999; Tarle &

Dvorzak, 1990; Torrenegra, Ricardo, Pedrozo, & Fuentes, 1989), antibacterical and anti-fungal effects(Daulatzai, 2010; Holtzman & Simon, 2000). One of the factors influential in the progression of AD is hypothermia. The molecular changes demonstrated that a 14-day Cold Water Hypothermia induced tau hyperphosphorylation, apoptosis and the formation of beta-amyloid plaques(A Whittington, Papon, Chouinard-Decorte, & Planel, 2010; Aid, Langenbach, & Bosetti, 2008; Aid et al., 2010; Planel et al., 2004).

Moreover, some neuroinflammatory features of the AD demonstrated that the COX-II has some influence on neuroinflammation(Blais, Turrin, & Rivest, 2005). Some research has reported that the inhibition or genetic removal of the COX-II would exacerbate the neuroinflammation(Choi, Aid, Choi, & Bosetti, 2010) . The amount of the COXII protein is considerable in the early stages of AD; it, however, decreases with the progression of the disease . Hypothermia increases COX-II. Surprisingly however, along with memory impairment, the expression of COX-II decreased after 14-day Cold Water Hypothermi(Ahmadian-Attari et al., 2015; Delshad & Parvizi, 2014; Tuo, Tuaillon, Shen, & Chan, 2004). Nepeta, as a hot herb, has the therapeutic potential for the treatment of the AD occurred by hypothermia effects. One study signaled that the impaired memory due to hypothermia at rats coerced to swim in cold water could be neutralized by prescribing the Nepeta menthoides decoction. 100 mg/Kg of NM reversed memory impairment as well as tau hyperphosphorylation(Ahmadian-Attari et al., 2015). Other studies have surveyed the effects of the *N.menthoides* essential oil on mice regaining their memories and also its neuroprotective impacts on rats(Kiyani et al., 2012; Sarahroodi et al., 2012). Previously, different researches have been performed on the influences of Nepeta through the biological samples such as rats(Ahmadian-Attar et al., 2014; Ahmadian-Attari et al., 2015; Delshad & Parvizi, 2014) bacteria [58] and fungi(Ezzatzadeh, Sofla, Pourghasem, Rustaiyan, & Zarezadeh, 2014). In the present paper, the curing effect of Nepeta on AD with human samples was done for the first time.

Conclusion

To sum up, the present study revealed that using *Nepeta menthoides* as a herbal remedy accompanied by the conventional medications for the treatment of the neurodegenerative diseases such as Alzheimer's seems to be an efficacious, economical and safe therapeutic approach. Performing a trial on a group of AD patients that were prescribed oral capsules containing extraction of Nepeta along with normal AD medications unveiled that this herb could be effective in decreasing the AD symptoms. Further studies, nonetheless, are warranted to proffer a more vivid picture and to generalize the results of the present study.

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