Original Article

Novel Effects of *Rosa damascena* Extract on Patients with Neurocognitive Disorder and Depression: A Clinical Trial Study

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Abstract

Background: Dementia as a major cognitive neurological disorder is defined as impairment in one or more cognitive territories compared with the former level of performance. This disorder disrupts patient's independence, and the patient would need others aid in order of doing daily and complex activities. The aim of this study was to evaluate the efficacy of Rosa damascena extract in the improvement of cognitive function in patients with dementia. **Methods:** This study is a randomized double-blind, placebo-controlled clinical trial on 40 patients older than 55 years with dementia referred to Specialized Elderly Patients Clinic in 2015–2016. Patients were divided randomly into two groups (control and intervention). The intervention group used donepezil and *R. damascena* capsules, and in control group, placebo capsule instead of *R. damascena* added on donepezil. Four test was filled three times at the study initiation, after month one and also after month three: Mini–Mental State Examination (MMSE) and Addenbrooke's Cognitive Examination Revised (ACE-R) were used for cognition evaluation, for depression assessment, Geriatric Depression Scale was administered, and checklist of memory and behavioral disorders were filled. **Results:** The results showed add-on donepezil and *R. damascena* versus placebo improved cognitive impairment based on MMSE with $P = 0.002$, ACE-R with total $P = 0.001$, depression ($P = 0.012$), behavioral disorders ($P < 0.001$), and daily activity ($P < 0.001$). **Conclusions:** The *R. damascena* extract affected cognitive impairment of dementia patients significantly and also have significant effects on improving depression and behavioral problems.

Keywords: *Dementia, neurocognitive disorders, Rosa damascena*

Introduction

Dementia is defined as progressive cognitive function disorder that occurs in the absence of delirium. Based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, dementia is known as major neurocognitive disorder, in which a patient would have remarkable impairment in one/more cognitive domains.[1] In the other hand, behavioral and psychological symptoms of dementia such as anxiety, aggression, frequent questioning, and wandering can be detected in up to 90% of these patients.[2] Dementia also affects both basal and instrumental daily living activities negatively.[3]

The most frequent type of dementia is Alzheimer disease (AD) which includes 60% of all dementia and the second prevalent is vascular dementia that forms 20% of them.[4] The third frequent is coincidence of AD and vascular dementia.[5] While there is less prevalent type of diseases such as Lewy body and frontotemporal dementia.[4]

AD has slow onset and gradual progress. Due to communities' aging, as one of the main risk factors of AD, the prevalence of this disorder is dramatically increasing.[6] In this disease, extracellular deposition of β-amyloid in senile plaques, formation of intracellular neurofibrillary tangles, and loss of neural and pyramidal neurons synapses may be detected in microscopic fields.[7] One hypothesis about AD is "Cholinergic Hypothesis" that cholinergic dysfunction leads to toxic neurotic plaque deposition.[8] Other hypothesis is oxidative stress induced by beta-amyloid peptides.[9]

Due to mentioned hypothesizes, the first approved drug for AD by the Food and Drug Administration was cholinesterase inhibitor drugs including; tacrine, donepezil, rivastigmine, and galantamine.[4]

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These drugs are used widely in AD, cerebrovascular, and Lewy body dementia.[10] Other drug used for AD is memantine.[4]

Nonetheless, it must be admitted that finding a decisive treatment to treat dementia is still an important clinical challenge. The WHO estimates that 80% of world people will bring on traditional medicines.[11] Among herbal medicines experimented, *Ginkgo biloba*, *Melissa officinalis* extract, and *Salvia officinalis* extract, has been found useful in the treatment of Alzheimer's.[12]

Rosa damascena is a plant of the rose family used as ornamental plants that many studies have shown that it is a rich source of flavonoids source including glycosides, quercetin, kampferol and their derivatives, which may have multiple therapeutic effects on psychiatric disorders. The physiological effects of these flowers may be associated with an abundance of polyphenols.[13,14] According to Esfandiary *et al.,*[16] R. *damascena* purified the brain tissues from beta amyloid quickly, after a few weeks of drug administration. While this drug can also induce neurogenesis, in the time later. [16] In this regard, the study of "Novel effects of *R. damascena* extract on memory and neurogenesis in a rat model of Azheimer`s Disease " was conducted in Isfahan University of Medical Sciences in 2012–2015. The results showed that Rose extract affects refining amyloidal deposits in brain tissue positively and caused complete elimination of symptoms of cognitive dysfunctions.[16]

According to population age pyramid of Iran, dementia will be a serious issue while a limited number of medications are available. In the other hand, for patients with bradyarrhythmia, there are limitations in the administration of cholinesterase inhibitors.[17]

Due to the study of *R. damascena* on improving cognitive dysfunctions in rat and based on acceptable position of herbal medicine, particularly *R. damascena* in Iran, we decided to conduct a study on new cases of dementia in the human sample, who these not take any chemical and herbal drugs, before their reception.

Methods

Patients

This study is a randomized double-blind, placebo-controlled clinical trial conducted on patients more than 55 years old with dementia referred to Specialized Elderly Patients Clinic of Isfahan University of Medical Sciences in 2015–2016. Random allocation in our study was conducted using permuted block randomization of size two: both patients and investigators were double-blinded and unaware about the intervention content.

Therefore, 43 patients were chosen based on diagnosis of dementia whom all were informed about the process of study and one of their relatives, signed the consent form. They were divided into two groups of 22 patients as intervention and 21 patients as control, in a way that cases with odd numbers were put in group of intervention and even numbers in group of control.

Among all 137 referred patients, 61 were not accepted, as they did not have inclusion criteria, 15 because of lack of interest to use *R. damascena* capsule and 17 because of not having compliance of attending in follow-ups. Thus, 43 patients remained for this study. During the study, an intervention and one control were eliminated because their family did not bring them for doing cognitive-behavioral test. Furthermore, a patient of control group left the study because of his bradycardia during the study [Figure 1].

Inclusion criteria were as following; (1) diagnosis of dementia by a psychiatrist based on criteria of DSMIV-TR, (2) mild-to-moderate cognitive decline, (3) age of 55 years and above, (4) lack of schizophrenia diagnosis, (5) no diagnosis of epilepsy and other severe neurological diseases such as multiple sclerosis and Parkinson in patient's history, and (6) not having any contraindication for donepezil consumption.

Exclusion criteria for this study were; (1) no cooperation, (2) concomitant use of any other drug that can lead to cognition decline or incidence of significant side effects, and (3) low compliance for drug administration.

Treatment Method

Both cases and controls received donepezil. Intervention group treatment was added on with *R. damascena* extract but control group with placebo.

Rosa damascena extract preparation

Rosa damascena extract was preprepared in the capsule form, by Dr. Mustafa Ghanadian in Department of Pharmacognosy, School of Pharmacy, Isfahan University of Medical Sciences.

Drug administration

The way of drug administration was as following in control group; they used 5 mg of donepezil daily for the first 2 weeks and in order of not having any side effect, they used 10 mg until end of the 1st month and the dose increased to 15 mg in the 2nd month. A placebo capsule, similar to *R. damascena* capsules, was added on for daily consumption in the 1st week, then 2 capsules for the 2nd week and 3 capsules in the 3rd week until the end of the study. In intervention group, *R. damascena* capsules were added on, instead of placebo.

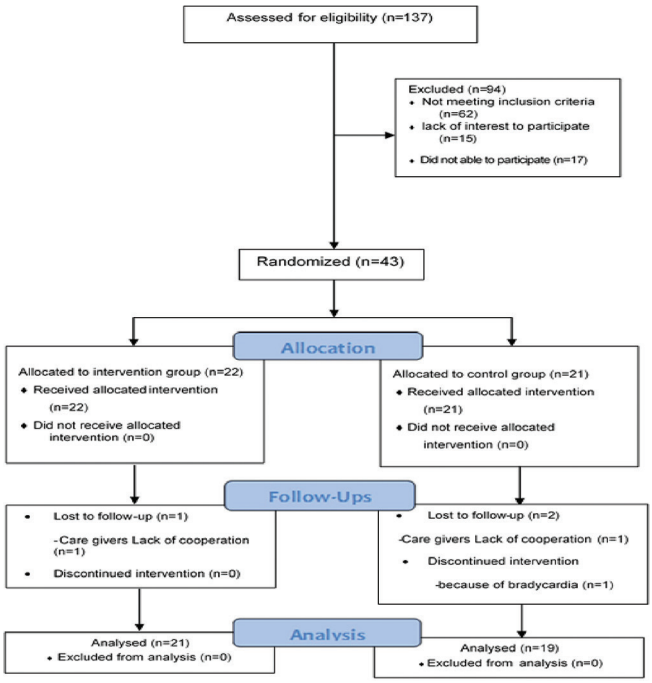

Figure 1: Consort flow diagram of patient recruitment and follow-up

The duration of treatment for our study was 3 months. The only reported adverse effect of *R. damascena* was diarrhea. Thus, we started this regimen with low dose of (a capsule daily), in intervention group of not complaining from any side effect, the dose was increased weekly. If the patient could not tolerate the drug, he/she had to be excluded, but actually none of our patient got diarrhea in the study. Placebo consisted of Calcium-Phosphate capsule.

For initiation of treatment, routine assessments including, taking the history of physical complaints, especially cardiovascular diseases evaluation were done for all patients. We advise patients with a history of cardiovascular and complaints to take a justification letter from their specialist for using donepezil. Patient's follow-ups for assessing mental status changing was done by a trained clinical psychologist, as the following: four test forms were filled three times at study: initiation, after month one and also after month three: Addenbrooke's Cognitive Examination Revised (ACE-R), Geriatric Depression Scale (GDS), and Memory and Behavioral Problems Checklist (MBPC), were done for all patients.

Data collection tools

Addenbrooke's Cognitive Examination-Revised

ACE-R is a neuropsychological test for the assessment of cognitive function of patients, which is a developed model of Mini–Mental State Examination (MMSE) (indeed MMSE score is derived from shaded squares on the left of ACE-R test). ACE-R test consists of 5 subtypes that assessed various aspects of cognitive functions. Maximal score is 100 as following; attention (18 scores), memory (26 scores), fluency (14 scores), language (26 scores), visual-spatial (16 scores). Its cutoff, sensitivity, and specificity are of above 0.80, 82, and 88, respectively.[18] In 2009, Pouretemad *et al*. assessed the validity of this test. The results showed that reliability of current test with Cronbach's alpha was 0.84. Correlation of ACE-R test in patients with moderate cognitive disorder and dementia was 0.88. Sensitivity and specificity of Persian format of this test was 91% and 93%, respectively, with the cutoff of 78.[19]

Geriatric Depression Scale

This scale was provided by Yesavage and Brink for elderly depression assessment in 1983. It contains 30 Yes/No items. GDS was evaluated in Iran ten years ago, and the results showed cut-off of 16.5 with sensitivity of 88% and specificity of 87%.[20]

Memory and Behavior Problems Checklist

Memory and Behavior Problems Checklist (MBPC) has 41 questions about evaluation of AD affected patients in terms of behavioral problems (frequent asking, roaming, and object lost) and daily activities (food and drugs use, dressing, and personal hygiene). This checklist includes a list of 32 options about behavioral problems and a 9-option list about daily activity. The responders to questions are family members. MPBC with Guttman split-half reliability of 0.65 for problem checklist and 0.66 for caregivers' distress has acceptable reliability. Furthermore, test-retest reliability of 0.80 for problem checklist and 0.56 for caregivers' distress has notable stability.[21]

Statistical analysis

Quantitative and qualitative data were presented as mean ± standard deviation and frequency percentage, respectively. Independent *t*-test and Chi-square test were used for between groups comparisons based on quantitative and qualitative added, respectively.

Nonnormal data were subjected to logarithmic transformation repeated measures ANOVA was used as the main statistical method for evaluating the time in intervention and time × intervention effects. Statistical analysis was conducted by using SPSS 20 (SPSS Inc., Chicago, Illinois).

Results

This study was conducted on 40 patients (20 male and 20 female) more than 55 years old with dementia referred to Specialized Elderly Patients Clinic of Isfahan University of Medical Sciences in 2015–2016. Based on Tables 1 and 2, two groups are compared in regard of demographic and medical variables that may affect the brain function and variables of cognition and other study variables (e.g., diabetes, hypertension, and …). No significant difference was found between groups.

Addenbrooke's Cognitive Examination-Revised test

Table 3 is about the analysis of variance of ACE-R variables. "Attention" changes was significantly different at the time of initiation, in a month, and 3 months after the study in intervention group ($P \leq 0.001$) but not in control group ($P = 0.272$). Comparing attention changes in intervention with control group showed significant difference ($P = 0.030$).

Regarding "memory" variable, these changes were significant during assessment in intervention group ($P \leq 0.001$) but not in control group ($P = 0.330$). Comparing two groups showed no significant difference ($P = 0.06$) that was marginally significant ($P < 0.1$).

Among all assessments, only "fluency" was not significantly changed in intervention group ($P = 0.800$) and also in control group ($P = 0.561$). Groups were not different with each other ($P = 0.338$).

The next variable is "language." During this assessment, intervention group changes ($P = 0.004$) were significant, control group ($P = 0.09$) were not, and comparing the groups ($P = 0.001$) was as well.

Another assessment was "visual-spatial," it was significant among intervention group ($P = 0.024$), not significant among control group ($P = 0.765$) and also comparing of cases and controls ($P = 0.203$).

In general, "total" comparing of these five factors shows significant change in intervention group ($P \leq 0.001$), no changes in control group ($P = 0.900$). Comparison of these two groups showed significant change ($P = 0.001$).

Mini–Mental State Examination

As seen in Table 4, MMSE changing trend was significantly different in two groups ($P = 0.002$). Comparison within groups showed significant changes in intervention group ($P = 0.001$) but not in control group ($P = 0.254$).

Geriatric Depression Scale

According to Table 5, GDS changes was significant in cases ($P \leq 0.001$), not significant in controls ($P = 0.765$), and again significant in comparing of two groups ($P = 0.012$).

Memory and Behavioral Problems Checklist

Finally, in Table 6, about PMBC test – Behavioral problem cases showed significant changes ($P \leq 0.001$), controls did not ($P = 0.530$), and comparison of two groups was significant ($P \leq 0.001$).

The last assessment was about daily activity that was similar to behavioral problems ($P \leq 0.001$ for cases, $P = 0.810$ for controls and $P \leq 0.001$ for comparing).

Table 1: The demographic characteristics in two intervention and control groups

Demographic and medical characteristics	Intervention	Control	*P*
Sex			
Male	10 (47.6)	10 (52.6)	>0.999
Female	11 (52.4)	9 (47.4)	
Job			
Retired	7 (33.3)	6 (31.6)	>0.999
Self-employed	4 (19.0)	3 (15.8)	
Homemaker	10 (47.6)	10 (52.6)	
None	7 (33.3)	7 (36.8)	
Education			
Primary	8 (38.1)	5 (26.3)	0.872
Guidance	1 (4.8)	3 (15.8)	
Diploma	3 (14.3)	3 (15.8)	
Associate degree	1 (4.8)	0	
Bachelor and more	1 (4.8)	1 (5.3)	
Age (mean±SD)	76 (10.98)	77 (8.68)	0.753

SD=Standard deviation

Table 2: The medical characteristics in two intervention and control groups

Medical characteristics	Intervention	Control	*P*
Hypertension			
Yes	10 (47.6)	9 (47.4)	>0.999
No	11 (52.4)	10 (52.6)	
Myocardial infarction			
Yes	2 (9.5)	3 (15.8)	0.654
No	19 (90.5)	16 (84.2)	
Diabetes			
Yes	3 (14.3)	5 (26.3)	0.442
No	18 (85.7)	14 (73.7)	
CVA			
Yes	1 (4.8)	0	>0.999
No	20 (95.2)	19 (100.0)	
Neurosurgery			
Yes	0	0	-
NO	21 (100.0)	19 (100.0)	
CPR			
Yes	4 (19.0)	1 (5.3)	0.345
No	17 (81.0)	18 (94.7)	
Schizophrenia			
Yes	0	21 (100.0)	-
No	0	19 (100.0)	
Bipolar			
Yes	1 (4.8)	0	>0.999
No	20 (95.2)	19 (100.0)	
MDD			
Yes	1 (4.8)	4 (21.1)	0.172
No	20 (95.2)	15 (78.9)	

CVA=Cerebrovascular accident, CPR=Cardiopulmonary resuscitation, MDD=Major depressive disorder

Discussion

This study was conducted on patients above 55 years old with dementia. Assessment of 5 variables of ACE-R about attention, memory, fluency, language, and visual-spatial were analyzed separately. The results of the current study

showed that comparison of changes trend for attention, memory, and language in two groups was significantly different, whereas it was not statistically different about other two assessments. Eventually, comparing of all five aspects in two groups (total score) had significantly changes.

Another evaluation based on MMSE showed that cases cognition status had significantly changed during our study too. According to these findings, we found that *R. damascena* add-on therapy improved cognition functions of dementia patients. This finding is in accordance with what was reported by Esfandiary *et al.*, who reported that

Table 3: Analysis of variance of Addenbrooke's cognitive examination-revised at three evaluation sessions: Before the intervention, the 1st month and 3rd month of the intervention in two intervention and control groups

ACE-R variables	Group	Time (mean±SD)			Time effect	Interaction	Group effects
		Prior to study	Prior to study	Within 3 months			
Attention	Intervention	7.38±4.28	8.19±4.42	8.57±4.36	<0.001	0.015	0.030*
	Control	6.574±4.07	4.29±6.57	6.42±4	0.272		
Memory	Intervention	2.66±3.27	3.71±3.46	4±3.71	<0.001	0.253	0.06
	Control	2.63±2.77	3.42±4.41	3±4.34	0.330		
Fluency	Intervention	0.52±1.99	0.42±1.02	0.38±1.02	0.800	0.478	0.338
	Control	0.47±0.90	0.68±1.63	0.57±1.53	0.561		
Language	Intervention	9.71±6.92	10.66±6.35	11.57±6.21	0.004	<0.001	0.001*
	Control	8.94±7.35	8.63±7.66	7.89±7.43	0.09		
Visual	Intervention	4.90±4.20	5.33±4.13	5.66±4.21	0.024	0.185	0.203
	Control	4.05±4.18	4.21±3.90	4.21±3.98	0.765		
Total	Intervention	25.80±17.35	27.71±17.31	30.19±17.24	<0.001	0.001	0.001*
	Control	22.68±17.43	24±20.17	22.42±19.80	0.900		

*Statistically significant at $P<0.01$, SD=Standard deviation, ACE-R=Addenbrooke's cognitive examination-revised

Table 4: Analysis of mini–mental state examination at three evaluation sessions: Before the intervention, the 1st month, and 3rd month of the intervention in two intervention and control groups

ACE-R variables	Group	Time (mean±SD)			Time effect	Interaction	Group effects
		Prior to study	Within 1 month	Within 3 months			
MMSE	Intervention	11.04 (7.09)	13.28 (7.46)	14.09 (7.34)	0.002*	<0.001*	0.001*
	Control	10.89 (7.03)	10.68 (7.64)	10.26 (7.57)	0.254		

*Statistically significant at $P<0.01$, MMSE=Mini–mental state examination

Table 5: Analysis of Geriatric Depression Scale at three evaluation sessions: Before the intervention, the 1st month, and 3rd month of the intervention in two intervention and control groups

ACE-R variables	Group	Time (mean±SD)			Time effect	Interaction	Group effects
		Prior to study	Within 1 month	Within 3 months			
GDS	Intervention	15.28 (7.96)	13.95 (7.58)	13.47 (7.54)	<0.001*	0.015*	0.012*
	Control	15.15 (7.32)	15.26 (6.73)	13.47 (7.54)	0.765		

*Statistically significant at $P<0.01$, GDS=Geriatric Depression Scale

Table 6: Analysis of variance of memory and behavioral problems checklist at three evaluation sessions: Before the intervention, the 1st month, and 3rd month of the intervention in two intervention and control groups

ACE-R variables	Group	Time (mean±SD)			Time effect	Interaction	Group effects
		Prior to study	Within 1 month	Within 3 months			
Behavioral problem	Intervention	102.52 (54.67)	99.42 (53.86)	96.61 (54.53)	<0.001*	<0.001*	<0.001*
	Control	103.21 (46.06)	102.78 (46.64)	103 (47)	0.530		
Daily activity	Intervention	17.52 (6.86)	16.57 (6.51)	15.85 (6.44)	<0.001*	<0.001*	0.001*
	Control	18.36 (6.17)	18.84 (6.05)	18.73 (6.45)	0.081		

*Statistically significant at $P<0.01$, MPBC=Memory and behavioral problems checklist

R. damascena had a neurogenesis effect on rat model of AD.[16] In 2009, Awale *et al*. found that *R. damascena* extract had protective effects on beta-amyloid formation and also apoptosis induced by this substance. Thus, *R. damascena* extract caused suppression of neural atrophy in animal models and improvement of brain function.[15] These findings are similar to results of Mohammadpour *et al*. that found extract of *R. damascena* caused improvement of cognition disorder and reduction of lipid peroxidation (oxidative stress protection) in rats.[22] Other reports have presented acetylcholinesterase inhibitor effect of *R. damascena*.[23]

Other assessed scale was GDS, during the period of treatment had significant change in status of intervention group. Trend of changes in this group was similar to the findings of Naziroğlu *et al*. has flavonoids as antioxidant. As oxidative stress has important role in mental stress like depression, therefore *R. damascena* extract can be useful for the treatment of depression.[24] Other study has presented following hypothesis that flavonoids of *R. damascena* extract have affinity to central benzodiazepine receptors thus it has hypnotic, antianxiety, and antidepressant effect.[25] In another study, ethanol extract of *R. damascena* did not have antidepressant effect.[26] Mohebitabar *et al*., in their study found that the origin of antidepressant effects of *R. damascena* take origin its antagonist effect of this extract on stimulation of postsynaptic 5-HT3 and 5-HT2 receptor can be mentioned.[27] Due to the important side effects of selective serotonin reuptake inhibitors and tricyclic antidepressants, *R. damascena* extract can be useful for depression treatment.

Other two remained variables, behavioral problem and daily activity, were parts of MBPC test. Two groups had significant difference based on MBPC. To the best of our knowledge, there is no other study in which effect of *R. damascena* extract on AD based on MBPC has been evaluated. It can be concluded that the effect of this extract on behavior and activity of patients may be because of the direct effect of *R. damascena* on cognition and its indirect effect on depression.

Conclusions

This study has been the first human study about the effects of Roses on cognitive problems of patients with dementia. Furthermore, it is the first assessment of this extract effect on depression, behavioral problems, and daily activities of dementia-affected patients. Considering high position of *R. damscena* in herbal medicine in Iran, as well as, significant results in our study, this drug could be considered as a choice treatment of patients with dementia. That is because depression was detected widely in our study patients and administration of this drug was accompanied with much better daily activity and less behavioral problems; therefore, *R. damascena* prescription can affect life of dementia patients and their caregivers, positively. At the end, *R. damascena* flower actually is not a drug but is a spice food; therefore, we advise middle-aged people to use wildly this flower as a dried powder or as a drug, for dementia prevention.

Limitations

As this study was conducted on patients who were not diagnosed with dementia previously and had not received any treatment, we could not include larger population in our study, so to generalize results of this study to all communities, further studies with larger population are recommended.

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Conflicts of interest

There are no conflicts of interest.

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