Original Article

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

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.[3] 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]

Ebrahim Esfandiary, Zahra Abdolali¹, Victoria Omranifard¹, Mustafa Ghanadian², Reza Bagherian - Sararoud³, Mohammad Karimipour³, Behzad Mahaki⁴, Shahrir Dabiri⁵

Departments of Anatomical Sciences and Molecular Biology Isfahan University of Medical Sciences, Isfahan, Islamic Republic of Iran, ¹Department of Pharmacognosy, The School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Islamic Republic of Iran, ²Department of Biostatistics, The school of Health, Isfahan University of Medical Sciences, Isfahan, Islamic Republic of Iran, ³Department of Pathology, School of Medicine, Kerman University of Medical Sciences, Islamic Republic of Iran


Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.IJPVM_199_17

Quick Response Code:
These drugs are used widely in AD, cerebrovascular, and Lewy body dementia.\(^4\) 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.\(^1,14\) 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 Alzheimer’s Disease” was conducted in Isfahan University of Medical Sciences in 2012–2015. The results showed that Rose extract affects refining amyloid 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.
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. 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.

**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%.

**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 Gutmann 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.

### 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).

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

<p>| 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 |
|------------------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>ACE-R variables</th>
<th>Group</th>
<th>Time (mean±SD)</th>
<th>Time effect</th>
<th>Interaction</th>
<th>Group effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Intervention</td>
<td>7.38±4.28</td>
<td>8.19±4.42</td>
<td>8.57±4.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>6.57±4.07</td>
<td>4.29±6.57</td>
<td>6.42±4</td>
<td>0.272</td>
</tr>
<tr>
<td>Memory</td>
<td>Intervention</td>
<td>2.66±3.27</td>
<td>3.71±3.46</td>
<td>4±3.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>2.63±2.77</td>
<td>3.42±4.41</td>
<td>3±4.34</td>
<td>0.330</td>
</tr>
<tr>
<td>Fluency</td>
<td>Intervention</td>
<td>0.52±1.99</td>
<td>0.42±1.02</td>
<td>0.38±1.02</td>
<td>0.800</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>0.47±0.90</td>
<td>0.68±1.63</td>
<td>0.57±1.53</td>
<td>0.561</td>
</tr>
<tr>
<td>Language</td>
<td>Intervention</td>
<td>9.71±6.92</td>
<td>10.66±6.35</td>
<td>11.57±6.21</td>
<td>0.004</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>8.94±7.35</td>
<td>8.63±7.66</td>
<td>7.89±7.43</td>
<td>0.09</td>
</tr>
<tr>
<td>Visual</td>
<td>Intervention</td>
<td>4.90±4.20</td>
<td>5.33±4.13</td>
<td>5.66±4.21</td>
<td>0.024</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>4.05±4.18</td>
<td>4.21±3.90</td>
<td>4.21±3.98</td>
<td>0.765</td>
</tr>
<tr>
<td>Total</td>
<td>Intervention</td>
<td>25.80±17.35</td>
<td>27.71±17.31</td>
<td>30.19±17.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>22.68±17.43</td>
<td>24±20.17</td>
<td>22.42±19.80</td>
<td>0.900</td>
</tr>
</tbody>
</table>

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

<p>| 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 |
|------------------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>ACE-R variables</th>
<th>Group</th>
<th>Time (mean±SD)</th>
<th>Time effect</th>
<th>Interaction</th>
<th>Group effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>Intervention</td>
<td>11.04 (7.09)</td>
<td>13.28 (7.46)</td>
<td>14.09 (7.34)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>10.89 (7.03)</td>
<td>10.68 (7.64)</td>
<td>10.26 (7.57)</td>
<td>0.254</td>
</tr>
</tbody>
</table>

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

<p>| 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 |
|------------------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>ACE-R variables</th>
<th>Group</th>
<th>Time (mean±SD)</th>
<th>Time effect</th>
<th>Interaction</th>
<th>Group effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS</td>
<td>Intervention</td>
<td>15.28 (7.96)</td>
<td>13.95 (7.58)</td>
<td>13.47 (7.54)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>15.15 (7.32)</td>
<td>15.26 (6.73)</td>
<td>13.47 (7.54)</td>
<td>0.765</td>
</tr>
</tbody>
</table>

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

<p>| 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 |
|------------------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>ACE-R variables</th>
<th>Group</th>
<th>Time (mean±SD)</th>
<th>Time effect</th>
<th>Interaction</th>
<th>Group effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral problem</td>
<td>Intervention</td>
<td>102.52 (54.67)</td>
<td>99.42 (53.86)</td>
<td>96.61 (54.53)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>103.21 (46.06)</td>
<td>102.78 (46.64)</td>
<td>103 (47)</td>
<td>0.530</td>
</tr>
<tr>
<td>Daily activity</td>
<td>Intervention</td>
<td>17.52 (6.86)</td>
<td>16.57 (6.51)</td>
<td>15.85 (6.44)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>18.36 (6.17)</td>
<td>18.84 (6.05)</td>
<td>18.73 (6.45)</td>
<td>0.081</td>
</tr>
</tbody>
</table>

*Statistically significant at *P*<0.01, MPBC=Memory and behavioral problems checklist
**R. damascena** had a neurogenesis effect on rat model of AD. 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. 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. Other reports have presented acetylcholinesterase inhibitor effect of **R. damascena**.

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. 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. In another study, ethanol extract of **R. damascena** did not have antidepressant effect. 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. 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. damascena** 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.

**Acknowledgments**

This work was done on the patients referred to Psycho-Geriatrics Research Center of Isfahan University of Medical Sciences, and financially supported by research deputy of this university. None of the authors have any conflict of interest. The authors would like to thank Dr. Mitra Molaei Nejad for her help in writing this paper. We also thank Dr. Omid Iravani for his role in literary editing this article.

**Financial support and sponsorship**

This work was done on the patients referred to Psychosomatic Research Center of Isfahan University of Medical Sciences, and financially supported by research deputy of this university.

**Conflicts of interest**

There are no conflicts of interest.

**Received:** 03 May 17  **Accepted:** 17 Jun 17  **Published:** 29 Jun 18

**References**

8. Terry AV Jr., Buccafusco JJ. The cholinergic hypothesis of...


