International Journal of Advanced Biotechnology and Research (IJBR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-8, Issue-3, 2017, pp1939-1946
http://www.bipublication.com

Research Article

Cognitive Function Enhancement and Glucocorticoid Receptor Resistance Decrement after *Rosa Damascena* (L.) and *Lavandula Officinalis* (L.)Essential Oil Aromatherapy in Hemodialysis Patients

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Short Title: Aromatherapy and GCR in Hemodialysis Patients
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ABSTRACT
Previous studies have revealed that chronic diseases, such as kidney dysfunction, can affect the stress system and cognitive function. On the other hand, plant essential oil aromatherapy may affect cognitive function. In the present study, attempts were made to clarify the effects of *Rosa damascena* (L.) and *Lavandulaofficinalis* (L.) essential oil aromatherapy on stress system activity by means of glucocorticoid receptor resistance and cognitive function in 90 hemodialysis patients (n = 30/group). The patients were either exposed to one of the aromas [*R. damascena* (R) or*L. officinal is*(L)] during their hemodialysis sessions or received no aroma (control group –C). Before and after the completion of experiments, patients' cognitive functions were evaluated by using Paced Auditory Serial Addition Test (PASAT) software. In addition, blood samples were collected from the patients for cortisol and leukocyte evaluations. These data were used for possible glucocorticoid receptor resistance. Results obtained from the PASAT software revealed a comprehensive improvement in the general mental health, mental fatigue, sustained attention, and reaction time in the R and L groups. In addition, neutrophil/lymphocyte ratio and blood cortisol levels were decreased in R and L groups after aromatherapy, which indicated a decrease in GCR in these groups as compared with the control group. It is concluded that *R.damascene* and *L.officinalis* essential oil aromatherapy in hemodialysis patients improves their cognition function, which may be due to a decrease in GCR in these patients.

KeyWords: Aromatherapy; Glucocorticoid Receptor Resistance; Hemodialysis Patients;LavandulaOfficinalis;Paced Auditory Serial Addition Test; RosaDamascena

INTRODUCTION:

Stress is considered as the state of mind in which, internal homeostasis is endangered by different internal and/or external factors and during which, the activity of the body's stressaxes, that is, the sympathoadrenal and hypothalamus-pituitary-adrenal (HPA) axes, increases[1].This activity increase eventually leads to an increase in plasma levels of catecholamineand glucocorticoid hormones[2-3]. This increase in plasma levels of cortisolhormone can be caused as a symptom of stress and also of mental and physical diseases related to stress[4-6]. Previous studies suggested that chronic stress not only disrupts memory but also causes additional disorders in mental procedures related to memory such as decision making, reaction, and theability to integrate

sensory inputs[1]. One of the adverse chronic consequences of stress is systemic inflammation, which is demonstrated as glucocorticoid receptor resistance (GCR) [7]. GCR is believed to be related to a malfunction of the HPA axis and points to reduced immune system sensitivity due to glucocorticoid over-activity[8-10]. It has been reported in the parents of children with cancer [11]as well as in patients with brain cancer[12]. Considering these facts, it is not surprising that patients with chronic kidney disease (CKD) may also suffer from cognitive dysfunction. In this regard, Murray et al., have shown that these patients suffer from several cognitive deficits[13]. On the otherhand, a study by Tholen et al., indicated that plasma β-amyloid concentration was reducedafter hemodialysis, and patients' cognitive function as assessed by the Montreal CognitiveAssessment test improved[14]. Another investigation revealed that cognitive deficit is common in CKD[15]. However, none of these researchers investigated the possibleinvolvement of GCR in the results they obtained.Today, different methods are used as complementary medicine to reduce stress and anxiety.Among the interesting methods usedin this regard is aromatherapy. Aromatherapy denotes the use of aromatic compounds extracted from different parts of plants to help in the treatment of different diseases[16]. Some studies have demonstrated that aromatherapy decreases blood cortisol levels by reducing stress and anxiety[17-18]. However, there is still doubt about the usefulness of aromatherapy, and its useful effects have not been decisively proved[19]. One ofthe communities suffering from high stress and anxiety due to the chronic and progressive nature of their disease are patients with chronic renal disease undergoing treatment with hemodialysis[20]. As mentioned above, these patients suffer from chronic stress-induced side-effects thatmaybe the result or part of the etiology of CKD, as well as cognitive dysfunction. The purpose of thisstudy was to determine whether *Rosa damascena* (L.) and *Lavandulaofficinalis* (L.) essential oilaromatherapy have a positive effect on cognitive function improvement in CKD patients who are treated with hemodialysis. The second research aimwas to determine whether aromatherapy-induced cognitive function improvement is associated with a reduction in systemic inflammation and GCR.

MATERIALS AND METHODS

Subjects: This research was down in three groups during sixteen days between April and June, 2014 attended by patients suffering from end stage renal disease (ESRD) undergoing treatment with maintenance hemodialysis. The population under study included 90 patients undergoing hemodialysis treatment having entered the study from two dialysis centers in two hospitals in Tehran (Baqiyatallah and ShahidChamran Hospitals). The sampling method was of the continuous type, and the random allocation manner was of the cluster block randomization type. Here, the research environment of the two hospitals was divided based on even and odd days, and then each day and hospital was assigned to one of the groups under study based on simple random drawing. And on that basis, the patients were divided into three groups of 30, test 1 (*L.Officinalis*), test 2 (*R. damascena*), and control groups. The inclusion criteria of the study included all ESRD patients who were dialyzed three times a week on a regular basis, had been undergoing hemodialysis treatment for more than three months, and were literate. The exclusion criteria of the study included having had allergy to aromatics, having a proven problem with the sense of smell, having experienced a stressful event during the past three months, having missed more than three consecutive sessions during the intervention period, and having been undergoing treatment by a psychiatrist due to a mental disorder.

Ethical considerations: The research followed the tenets of the Declaration of Helsinki. The purpose of the research was told to the patients and Informed consents were obtained. All patients took part in this study voluntary. The research was approved by ethical committee of Baqiyatallah University of Medical Sciences, Tehran. Iran (Number: 340-169). In addition, this study was

registered in Iranian Registry of Clinical Trials (IRCT) and achieved the code ofIRCT2013101314998N1. The patients were assured that their information remained confidential and that they were free to stop cooperation at any time.

Measurement Tools and Method: Personal information including age, gender, weight, marital status, previous dialysis, and education, was collected using demographic questionnaires. The essential oils used: The standard *L. Officinalis* essential oil was provided from Barij Essence Pharmaceutical Company (Kashan, Iran). The Rose wax was offered by Ali Mohammadi-Mofrad from Rose Water Arghavan-Qum, Iran (May 2013). To assess plasma cortisol, the ELISA KIT (Cortisol ELISA KIT, Diagnostics Biochem Canada Inc, dbc) was used. For this purpose, 5 ml blood samples were collected from the patients in each group (n=17/group) before beginning the PASAT (Paced Auditory Serial Addition Test) in tubes with volumes of 10 milliliters and were centrifuged at 3000 RMP for 5 min at 4°C.The supernatant was collected and kept in a freezer at -20°C until the ELISA reading.

Calculating of GCR: GCR calculation was performed as described earlier. Briefly, blood samples for cortisol evaluations were collected from the participants (n=17/group). Percent of the neutrophils and lymphocytes were obtained and the neutrophil to lymphocytes ratio (N/L %) calculated. The GCR was then calculated by plotting Log_{10} this ratio against Log_{10} cortisol concentration. Lack of correlation was considered as a marker of GCR.

PASAT software performance: To assess cognitive functioning improvement, the PASAT software was used. PASAT software is performed by presenting 60 pairs of single-digit numbers where the last two digits should be added up. For example, if numbers 3, 4, 2, 6, and 1 are respectively presented, the subject should express numbers 7, 6, 8, and 7. It has been demonstrated in reports that the PASAT software test is a difficult test, where the individual may not even be willing to continue due to the test's difficulty. In this study, the PASAT software was used to examine effects of aromatherapy on general mental health (the total number of correct responses), sustained attention (the longest sequence of consecutive correct responses), reaction time (average reaction time), and mental fatigue (the longest sequence of consecutive incorrect responses). The reliability and validity of the PASAT software have been confirmed in different studies and societies also in Iran.

Interventions: After the collection of the initial information, the interventions begin. Here, once the patient was connected to the dialysis machine, a piece of cloth smeared with three drops (200 micro-liters) of essential oil (*L. officinalis* for experimental group 1 and *R. damascena* for experimental group 2) with a constant, equal density in all sessions. The piece was attached to the patient's right collar 20 centimeters away from the nose, and the patient was asked to breathe normally. The intervention lasted up to the end of the dialysis session (240 minutes in average). In the control group, the piece with drops of distilled water was attached to their clothes. For all groups the usual cares also was given. At the end of the fourth week, the blood samples were collected again, and then the PASAT software was performed. To avoid and reduce probable errors due to physiologic changes in cortisol during the day, blood collection was performed at the same time.

STATISTICAL ANALYSIS:

Data are shown as mean±SEM of % of change in variable for PASAT software factors. These data were statistically analyzed using Un-paired t-Test. Demographic data were analyzed using chi-square. The GCR was calculated based on the associations of blood cortisol concentration [log_{10}] with the ratio of neutrophils to lymphocytes (N/L%) [Log_{10}]. The statistical calculations were performed using the SPSS software version 20. $P<0.05$ considered as statistical difference.

RESULTS

Demographic Analysis

Three patients from the L. Officinalis group (due to death, transfer to another center, and missing

more than three sessions) and two patients from the R. damascena group (due to transfer to another center and missing more than three sessions) were excluded from the study, and 85 patients participated in the study up to the end. 52 (61.2%) participants were men, and 81 (95.3%) were married. The mean age of the control group was 57.9 ± 12.5 y, that of the L. Officinalis group was 58.2 ± 15.4 y, and that of the R. damascena group was 58.8 ± 13.4 y, which were not statistically different. The chi-square test demonstrated that the distribution of the demographic variables in the two groups was homogeneous.

PASAT software data analysis

Forty-three participants (9 in the control group, 17 in the *L. officinalis* group, and 17 in the *R.damascena* group) completed the PASAT software test. The PASAT software results demonstrated that in the control group, none of the cognitive variables including general mental health, sustained attention, reaction time, and mental fatigue has been significantly different before and after intervention, while all of the variables were improved h in the *L. officinalis* and *R. damascena* groups after intervention (Fig 1).

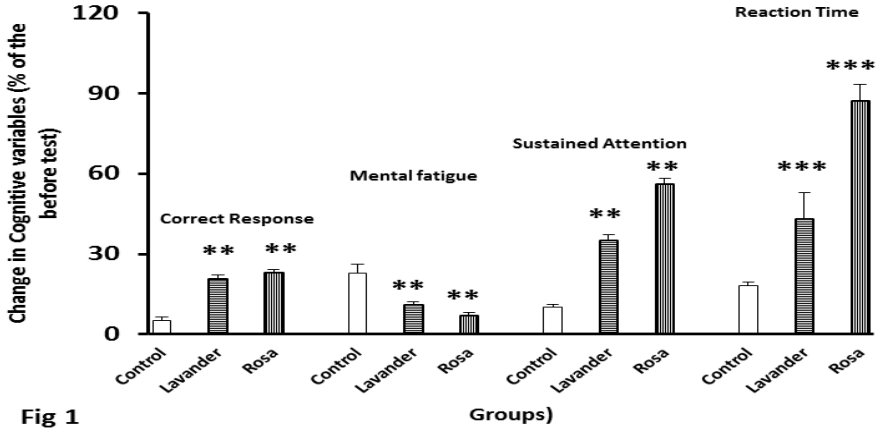

Figure 1: Changes in the General Mental Health, Reaction Time, Sustained Attention, and Mental Fatigue in the patients before and after the intervention. As it is shown in the figure, all the factors were improved in the R. damascena and L. Officinalis essential oil treated patients compared to the control group (n=9 in the control group, 17 in the L. Officinalis group, and 17 in the RD Damascena group). **P<0.01 and ***P<0.001 difference between the before and after tests.

Reduction of GCR after aromatherapy

Results of our experiment showed that before intervention, there is no correlation between the plasma cortisol concentration and N/L%. Interestingly, after aromatherapy, both *R. damascena*and *L. officinalis* treated groups showed a correlation between the variables mentioned above. Defining that aromatherapy reduces GCR in these groups (Figs 2, 3, 4).

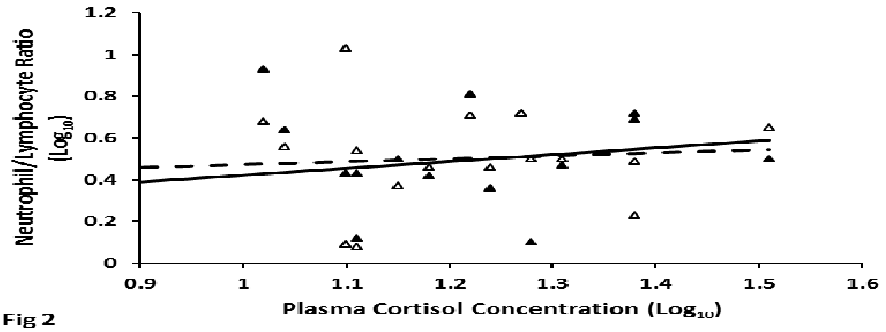

Figure 2: Association between blood cortisol and neutrophils/lymphocytes ratios for patients in the control group before and after the experiments. Lack of correlation is a marker of GCR. Filled triangles/solid line, before the experiments; open triangles/dashed line, after the experiments.

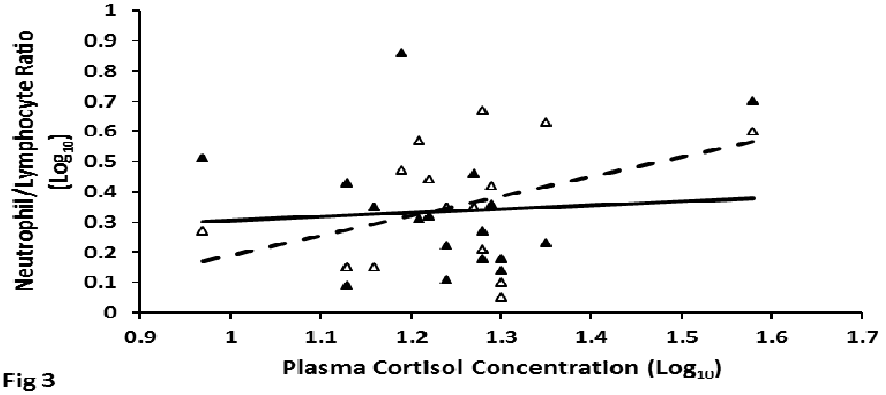

Figure 3: Association between blood cortisol and neutrophils/lymphocytes ratios for patients in the R. damascena essential oil treated group before and after the experiments. Lack of correlation is a marker of GCR. Filled triangles/solid line, before the experiments; open triangles/dashed line, after the experiments.

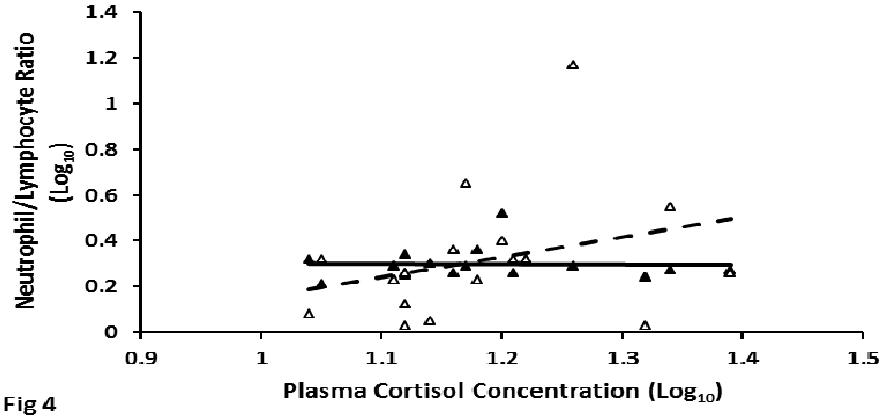

Figure 4: Association between blood cortisol and neutrophils/lymphocytes ratios for patients in the L. Officinalis essential oil treated group before and after the experiments. Lack of correlation is a marker of GCR. Filled triangles/solid line, before the experiments; open triangles/dashed line, after the experiments.

DISCUSSION

The purpose of this study was to examine the effects of inhalation aromatherapy using *R. damascena* and *L. officinalis* essential oils on the improvement of cognitive function and reduction in GCR in hemodialysis patients. In the present study, positive effects of aromatherapy on the reduction in GCR markers wereobserved in hemodialysis patients.The results obtained from the PASAT system also revealed that both *R. damascena*and *L. officinalis* essential oils improved all cognitive features that could be measured by the software including general mental health, reaction time, sustained attention, and mental fatigue[23]. At first, our dataindicated that both essential oils could improve general mental health. General mental health denotes the brain's ability to coordinate sensory inputs and the communication function of the cortex and executive areas of the frontal cortex[23]. It is shown that different diseases can chronically activate the stress system; in turn, due to sustained plasmaglucocorticoid hormone concentration elevations, the functions of these areas and the communication between them are usually disrupted[6]. Thus, scores obtained from the PASATsoftware for general mental health may decrease dramatically. In other words, a low PASAT software score means a decrease in the potential for coordinate functioning between the above-mentioned parts of the brain[23]. Our results showedthat the *R. damascena* was able to improve general mental health. *L. officinalis* ranked nextwith weaker functioning. Inthe control

group, however, no statistically significant difference was observed between the pre-and post-intervention time points. These differences suggest that the *R. damascena* essential oil may have (a) factor(s) that can helpto improve communication between different brain parts in regard to a specific mental activity. It is uncertain whether improvement of this functioning is due to improvement of stress system activity or to direct effects of the essential oil components on the brain cortex.Nonetheless, our research demonstrated that the stress system was greatly affected by the essential oil and thus it is highly probable that the oil directly affected this system.The PASAT was also used to calculate reaction time. Regarding reaction time, it was found that *R. damascena* essential oil has a greater ability to reduce reaction time than *L.officinalis*essential oil. Reaction time suggests the rate at which, correct communication is established between different brain parts that are involved in memory, sensing, decision making, and execution[23]. The greater the reaction time decrement, the more the potentialfor establishment of correct communication increases. In our research, *R. damascena* essential oil demonstrated the most pronounced effect, which suggests the important factthat *R. damascena* essential oil is associated with improved cognitive activity. Again as discussed above, it is uncertain which partof the brain was directly affected. Neuroimagingstudies with MRI and fMRI may reveal more features of the action of the *R. damascena* in the brain.Our research also demonstrated that the values of mental fatigue and sustainedattention in the *R. damascene*-treated group improved as compared with those in the *L.officinalis* and control groups. Mental fatigue occurs when due to several factors, such as the presence of oxidative stress or a decrease in neurotrophic factors in the brain, the brain fails to establish a correct memory because of fatigue occurring in neurons. This status occurs in the brain when the brain isfaced with a decrease in oxygen or nutrient input. This occurs much faster in patients than in healthy individuals, and patients gradually lose theirbrain performance due to a decrease in oxygen supply, nutrient supply or both[8]. In our research, the sustained attention increase and mental fatigue decrease in patients treated with the *R. damascena* essential oil demonstrate improvement in brain status in this regard, and hold implications for whether or not the essential oil can be used to improve mental functioning, even in healthy people. In another part of our study, it was demonstrated that *R. damascena*aromatherapy significantly reduces GCR in patients. It was interesting that patients showed significant improvement in their cognitive function. *R. damascena* is an ornamental plant with a pleasant aroma, for which, medicinal properties have been reportedincluding antibacterial, anti-cough, relaxant, and soporific effects[18]. Previous research inanimal models has also shown that the *R. damascena*extract was able to inhibit depression induced by the forced swimming test in rats[24], and flavonoids in the rose oil have stimulatory effects on the D_2 dopamine receptors in the brain,which may be the cause ofdepression reduction[25]. A similar mechanism may be involved inthe results obtained from the present study. In previous research, no mention has been made of the effects of the*R. damascena* essential oil or extract on reduction of GCR which was observed in the present research.Similar effects of L. officinalis essential oil were observed. Different studies have reported anxiolytic and relaxation effects of *L. officinalis*[26-28]. *L. officinalis* aromatherapy may produce its anxiolytic effect via serotonin (5HT) turnover increment in the striatum and hippocampus. In addition, *L. officinalis* can also mask stressinhibition of fast nerve growth factor receptor (NGFR) mRNA, and the activity-regulated cytoskeletal-associated protein (Arc) gene in stressed animals[29]. However, in normal animals, *L. officinalis* essential oil may act as a stressor[29]. The researchers mentioned that the effect of *L. officinalis* essential oil inhalationmay be that of either a stress inhibitor or a stressor, depending on the subject's state[29]. These findings all are in accordance with our results indicating that *L. officinalis* essential oil aromatherapy for 1 month during dialysis causes a significant improvement in GCR in the subjects.

These results may alsoindirectly indicate that the patient's stress system activity is heading toward the normal state. Further research in this area can answer the question of whether or not the stress system is alsodirectly affected by *R. damascena*and *L. officinalis* essential oils. We propose that this study bebroadened in future research, in terms of both the study periodand the sample size. Moreover, more detailed cellular and molecular investigations, such as investigation of antioxidant systems as well as investigation of cytokines like interleukin 6, TNF-α, and other chemokine that possibly interfere in this regard, like ghrelin and leptin, can enhance to some extent our biological understanding of how these essential oils function to improve patients' conditions.In conclusion, the present study demonstrated that aromatherapy using the *R. damascena* and *L.officinalis* essential oils decreased GCR and succeeded at improving cognitive functioning inhemodialysis patients, which may be due to dampening of stress system activity. However, morestudies are needed in this area for a detailed elucidation of essential oils' actions in the body.

ACKNOWLEDGEMENTS:

This article was extracted from a master's thesis at Baqiyatallah NurseryCollege. We hereby thank and appreciate the Nephrology Research Center and NeuroscienceResearch Center of Baqiyatallah University of Medical Sciences, and all of the dear patients whoparticipated in this research. The Rose wax was offered by Ali Mohammadi-Mofrad from Rose Water Arghavan-Qum, Iran.

Financial Disclosure: There was no conflict of interest.

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