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A Promising Approach for the Treatment of Experimental Alzheimer's disease: Impact of Cardamom Essential Oil

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Abstract

Alzheimer's disease is the most commonly seen progressive neurodegenerative disorders in elderly populations that represent a major factor for the prevalence of dementia in the aged population worldwide. We aimed in this study to investigate the promising effect of crude cardamom oil, as a neuroprotective agent in rats suffering from Alzheimer's disease. Cardamom essential oil (CEO) was extracted; analysis was carried out using a Hewlett-Packard coupled gas chromatography / mass spectrometry. Phenolic and flavonoid contents were determined. Forty albino male rats are randomized divided into four groups including normal control, Alzheimer's disease group and treated groups. Inflammatory and oxidative stress markers were estimated after the experimental period and also brain neurotransmitters were estimated by high performance liquid chromatography (HPLC) using ultraviolet (UV) detector that set at 270 nm.

The current results indicated that the mean value of tumour necrosis factor α (TNF-α), amyloid precursor protein (APP) and amyloid beta (Aβ) were significantly increase due to the harmful effect of aluminum chloride (AlCl3) ,however these values were attenuated by cardamom essential oil and these effect was attributed to the high contents of alpha-terpinyl acetate (50.24 %) and eucalyptol (39%); in addition to a high value of flavonoids (4.52 g of catechins/100 g of oil). Conclusion: cardamom essential oil offers a new strategy for the treatment of experimental Alzheimer's disease due to its high contents of anti-oxidants and anti-inflammatory compounds.

Keywords: Alzheimer's disease, norepinephrine, dopamine, serotonin, cardamom oil.

1. Introduction

Alzheimer's disease (AD) is considered the most frequently seen progressive neurodegenerative disease in elderly populations, and it is a major cause of dementia in the old population globally [1] .Numerous studies have revealed that risk factors, including family history, depression, aging, head injury, oxidative stress, environmental metals exposure, gut microbiota imbalance, neuroinflammation, and cognitive activity, are link to AD [2].

Several hypotheses have been planned to clarify this complicated disease. The first hypothesis depends on the oxidative stress, which is generally associated with Aβ42 oligomers, which promote tau hyperphosphorylation, leading to toxification of the synapses and mitochondria and also rigidity and damage to the cell membranes [3]. The second hypothesis is attributed to the amyloid cascade demonstrated that the main cause of AD is the irregular accumulation of Aβ in the brain[4]. In addition to the important player which is the neuroinflammation where amyloid β 42(Aβ42) plaques initiate microglia that in turn motivate the releasing of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β) that sequentially promotes the production of Aβ42 oligomers[5] . Cholinergic hypothesis indicated that, the main cause of AD is the reduction in the synthesis of acetylcholine (ACh) [6]. Acetylcholinesterase (AChE) may play a role in β-amyloid fibrillogenes that impaired cholinergic functions [7]. TNF- α is one of the most well-defined cytokines during AD pathogenesis[4,8] .Dopamine (DO) and **norepinephrine** (NE) are important neuromodulators that regulate brain states, vigilance, action, reward,

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learning, and memory[9] .Alzheimer's disease is characterized by neurotransmitter' disturbances. However, norepinephrinergic system abnormalities are also included. It was reported that AlCl3-induced AD in rats with a decline in the serum level of DO in comparison with their control [10].
Accordingly, there is an important and urgent need for improvement of novel agents for management this huge problem. Natural products are popular because herbs are safer than other synthetic drugs[11,12] . Cardamom, Elettaria cardamomum L. (Zingiberaceae) was indicated in different diseases ; in addition , the main chemical constituents of cardamom oil are 1,8 cineole and -terpinyl acetate that have an inhibiting effect on the acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activities [7]. So, the target here was to determine the role of crude cardamom oil, as a neuroprotective agent in rats suffering from Alzheimer's disease.

2. Materials and methods

2.1. -Extraction and phytochemical analysis of cardamom oil

Fresh cardamom oil was imported from authenticated SRI VENKATISH AROMS (SVA), India, Lot No. 5314-SVA-2019, Website: www.svananaturals.com/ www.srivenkatesharomas.com (Sri Venkatesh Aromas T-2/202, Mangolpuri Industrial Area, Phase - 1, Delhi - 110 083 GSTIN: - 07ABTFS4416Q1ZA PAN: ABTFS4416Q IEC: 0512070806) by importing department of National Research Centre (NRC) (INVOICE #9968).

Isolation of essential oil

Clevenger's equipment was used in a hydro-distillation process to extract the essential oil from cardamom. The amount of volatile oil produced was determined and calculated in 100 g dry plant[8] .

Essential oils analysis

The examination was achieved using a Hewlett-Packard model (5890) coupled gas chromatography / mass spectrometry [13].

2.2. Assessment of Antioxidant Activity

a) ABTS and FRAP assay

2,2-azinobis (3- ethyl-benzothiazoline - 6- sulfonic acid) (ABTS) assay and ferric reducing antioxidant power (FRAP) were estimated respectively as described previously [14,15].

2.3. phenolic assessments:

Phenolic amount was measured [14] using a calibration curve created with Gallic acid and the results were represented as mg of Gallic acid equivalent (GAE) per ml of sample.

2.4. flavonoid content was determined according to the methods described previously[14].

2.5. Lethal dose (LD50):

It is carried out on five separate groups of rats (n=5) ; groups1,2,3,4,5 received 4, 6, 8, 10, and 12 g extract /kg b.w.) orally [15] .

2.6. Animals and ethical approval

Animals were housed in a light/dark cycle at suitable temperature and 40-60% humidity prior to the experimentation; the animals were acclimatized for one week. All animals were fed a standard pellet diet and water. 40 rats were distributed into four groups after a week of acclimatization (each containing ten animals). The National Research Centre's Ethics Committee approved all experimental protocols (ethical approved number is 19 229)
Induction of Alzheimer's disease
Aluminum chloride solution was prepared and injected intraperitoneal into rats with a concentration of 100 mg/kg. b.w./ day for 42 days [15].

2.7. *Experimental design*

Rats were randomized divided into four groups / 10 animals each.
Group I : control rats received a vehicle, group II : AD group, group III: AD+ donepezil hydrochloride (DP) group in which rats injected intraperitoneal with aluminum chloride solution, then treated with donepezil hydrochloride (commercial name; Arecipt) (1 mg/kgb.w./ day) orally for 42 days, one hour after administration of aluminum chloride, group IV : AD +CEO in which rats were injected intraperitoneal with aluminum chloride solution and treated with crude form of CEO 400 mg/ k.g. b.w. / day (1/10 LD50) orally for 42 days, 1 h after aluminum chloride administration.
Collection of samples
Following an overnight fast, all animals were euthanized with 2% ether anesthesia, blood was withdrawn, and the serum was kept at - 20 °c. Isolated rat brains (hippocampi) were homogenized in PBS (pH

7.4) and centrifuged for 10 minutes. The supernatants were kept at - 20 °C until the biochemical analysis could be performed.

2.8. Biochemical measurements

Tumour Necrosis Factor alpha (TNF α), acetylcholine (ACh), amyloid beta (Aβ) and amyloid precursor protein (APP) were measured by ELISA kits for rats, Avi-Bion ELISA Kit (Orgenium Laboratories, Finland).

2.8.1. Estimation of neurotransmitters:
Dopamine, norepinephrine, and serotonin levels in the brain were measured using high performance liquid chromatography (HPLC), Agilent technologies 1100 series as described previously [11,16].

2.9. Statistical analysis

SPSS version 25 was used to analyses all data (IBM corporation, Armonk, NY, USA). A p value of ≤0.05 was considered significant. The data was presented as the mean standard deviation (SD). If the p value in one-way analysis of variance was 0.05, Tukey's post hoc test was used (ANOVA).

3. Results

Data in table (1) showed that crude form of cardamom oil having high content of alpha -Terpinyl acetate (50.24 %) and Eucalyptol (39%) when analyzed by gas chromatography-mass spectrometry analysis.
Table (2) appeared that the total contents of flavonoids in the cardamom oil were 1.77 g GAE/100 g oil. Also it contained 4.52 gm of catechins/100 g of oil.
Table (3) showed a significant elevation in the serum levels of Aβ , TNF-α ,APP concomitant with a significant reduction in ACh in rats with AD as compared to their control; However the treatment with CEO attenuated these parameters to become more or less near the control group.

In the present study, there is a significant decrease in the level of NE in brain tissues of rats with AD (GI) as compared to their control. Also, AD rats treated with DP showed an increase in NE comparing with (GII). Furthermore, AD rats when treated with crude oil (GIV) showed a significant increment in the brain levels of noradrenergic (NE) and dopaminergic (DO) while no change in serotoninergic systems as compared to rats with AD in GII (table 4).

Table (1) Chemical components of cardamom essential oil

Peak	RT	Term	Formulation	Area	Area %
1	11.545	.alpha.-Pinene	C10H16	7150622.1	0.84
2	12.997	Sabinene	C10H16	8500688.2	1
3	15.346	Eucalyptol	C10H18O	330336110	39
4	17.7	1,6-Octadien-3-ol, 3,7-dimethyl-	C10H18O	15360998	1.81
5	20.504	Terpinen-4-ol	C10H18O	6649294.6	0.78
6	21.034	.alpha.-Terpineol	C10H18O	16839489	1.99
7	23.104	Linalyl acetate	C12H20O2	27256136	3.22
8	25.709	.BETA.-TERPINYL ACETATE	C12H22O2	4769894.4	0.56
9	26.583	.alpha.-Terpinyl acetate	C12H20O2	425610688	50.24

Table (2): Total phenolic and flavonoids contents of cardamom essential oil

Types of extraction	Total phenolic (g GAE/100g oil)	Total flavonoids (g catechin / 100g oil)
Cardamom oil extract	1.77±0.05	4.52±0.81

Table (3) : Cytokines levels and acetylcholine in studied groups

	Amyloid precursor protein (Pg/ml)	Amyloid beta (Pg/ml)	Tumour necrosis factor α (ng/L)	Acetylcholine (U/ml)
Group I	168.0 ± 6.2 [a]	34.0± 2.9 [a]	62.96 ± 10.0 [a]	8.21 ± 1.0 [a]
Group II	631.1 ± 43.87 [b]	76.0 ± 3.9 [b]	96.8 ± 8.0 [b]	3.01 ± 0.55[b]
Group III	383.0 ± 37.22 [c]	47.7 ± 4.1 [c]	60.0 ± 4.37 [c]	5.71 ±0.81 [a]
Group IV	464 ± 17.5 [d]	42.0 ± 3.6 [c]	78.8 ± 6.1 [b]	3.8 ± 0.75 [c]

Data sharing the same superscript= not significant (N.S); sharing different superscript = significant where p< 0.05 or p <0.001

Table (4) levels of dopamine, norepinephrine and serotonin different groups

	Brain		
	Norepinephrine μg/ g. tissue	Dopamine μg/ g. tissue	Serotonin μg/ g. tissue
GI	4.4 ± 0.9 [a]	5.2± 1.2 [a]	3.37± 1.0 [a]
GII	3.16 ±0.03[b]	3.4 ± 0.04[b]	2.83± 0.13[b]
GIII	3.7± 0.32[b]	4.5± 0.28[c]	3.0± 0.14[a]
GIV	6.1 ± 0.8[c]	4.7 ±0.9[c]	2.8 ± 0.4[b]

Data sharing the same superscript= not significant (N.S); sharing different superscript = significant where p< 0.05 or p <0.001.

4. Discussion

AD is an uncharacteristic neurodegenerative disease initiated by neurons losing, generally in the hippocampus and cerebral cortex. This condition is characterized by mental impairment, behavioral abnormalities and loss of memory. A number of potential underlying mechanisms have been proposed to explain the pathogenesis of Alzheimer's disease; there is substantial evidence that memory impairment in Alzheimer's disease is caused by synapse failure and loss. As a result, therapies aimed at restoring or preserving synapse function and cognition are urgently needed [17,18] .

Disruption in cholinergic neurotransmission strongly correlates with the severity of neuropathological changes associated with Alzheimer's disease[19] . It was reported that aluminum disturbs the cholinergic neurotransmission, where it induces the activity of AChE and thus increase ACh breakdown in the brain [20,21].

It was found that the accumulation of senile plaques in the brain is considered one of the hypotheses in the AD development. Aβ, which is the main constituent of the senile plaques, is produced from β-plated sheet fibrils and neuritis of destructed synapses and dendrites and attacking astrocytes as well as inflammatory. Additionally, it was recognized that Aβ is the first point for AD pathophysiology. The difference between Aβ production and Aβ clearance favors the elevation of toxic Aβ oligomers with subsequent improvement of ACh deprivation[22] .

Exposure to AlCl3 amplified the formation of Aβ and the reduction of its degradation[23,24] as observed in this study.

In AD, Aβ42 plaques play an important role by motivating the microglia, these stimulated microglia motivate the production of pro-inflammatory cytokines, such as TNF-α and interleukin 1β (IL-1β) which sequentially encourage additional production of Aβ42 oligomers[25]. This inflammatory and oxidative stress responses cascade lead to alteration of neuronal ionic homeostasis. Henceforward, neuronal & synaptic dysfunction and the selective harm of ACh neurons occur, with subsequent ACh shortfalls, producing dementia[26] .

The elevation of TNF-α level in AD group was in agreement with previous studies [27,28] which reported that AlCl3 induced neuroinflammation through enhancement of inflammatory cytokine production such as IL-1β, IL-6, and TNF-α; this was related to the stimulation of microglia in a feed forward circuit during a process called reactive microgliosis [29] . Whereas CEO ameliorated this effect in treated group due to its high contents of active compounds as was appeared in table (1,2) that recognized by their anti-inflammatory properties .In These study, the anti-inflammatory properties of CEO was appeared by reducing TNF-γ, APP , and Aβ levels in treated group.

It was discovered that TNF-γ increased the expression of APP in astrocytes and neurons; these results demonstrate the potential involvement of neuroinflammation with the amyloid precursor system in the development of AD[30] as was appeared in the current study. A lot of research is being done on neurotransmitters because they play a big part in learning and memory; in addition to cognitive decline, about half of Alzheimer's disease patients also exhibit dysfunctions of the noradrenergic , dopaminergic , and serotoninergic systems. [31,32] .

It was postulated that NE and DO may work in concert to promote learning and preserve the conditions necessary for typical cognitive processes[9]. In the cortex and hippocampus, dopamine and noradrenaline in particular seem to cross-talk quite a bit.

Dopamine pathway alterations and neuronal loss have been reported in Alzheimer's disease, resulting in a decrease in DO content, implying that DO is clearly involved in the pathophysiology of cognitive decline and non-cognitive symptoms found in this disease[33].

A reduction in serotonin level was seen in this study. It's interesting to note that the serotonin system and the dopamine (DO) system interact strongly. Indeed, it has been reported that serotonin receptor (5HT2AR) is expressed by DO neurons[34] . Also, DO release is influenced by the 5HT2AR activity[35].

On the other hand, treatment with DP revealing a slight increase in 5-(HT) level; .Cineole was found to improve cognition and has anti-inflammatory effect in neurodegenerative disorder including AD. According to the analysis of the using oil, it was found that crude form of cardamom oil having high content of alpha - Terpinyl acetate (50.24 %) and Eucalyptol (39%) as well as flavonoids and total phenolic compounds which is characterized by their antioxidant and anti-inflammatory properties[36]. Thus, treatment with cardamom is considered a promising approach in pharmacotherapy of AD

5. Conclusion

The present study showed a neuroprotective effect of crude cardamom oil on the cholinergic system by up-regulation of ACh and have anti-inflammatory action by reducing inflammatory cytokines in rats with aluminum chloride-induced cognitive impairment. Hence it can be a promising, economic, safe and therapeutic alternative to current Alzheimer's disease treatments.

Declarations:

Ethics approval and consent to participate:
The National Research Centre's Ethics Committee approved all experimental protocols (ethical approved number is 19 229).

Consent for publication:
All authors are agree for publication

Availability of data and materials:
Availability of data and materials all of the material is owned by the authors

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Conflicts of interest
Authors declared that there are no conflicts of interest.

6. References

[1] P. Sandupama, D. Munasinghe, M. Jayasinghe, Coconut oil as a therapeutic treatment for alzheimer's disease: a review, Journal of Future Foods 2 (2022) 49-60.

[2] M.-H. Weng, S.-Y. Chen, Z.-Y. Li, G.-C. Yen, Camellia oil alleviates the progression of Alzheimer's disease in aluminum chloride-treated rats, Free Radical Biology and Medicine 152 (2020) 411-421.
[3] A. Kurz, R. Perneczky, Novel insights for the treatment of Alzheimer's disease, Progress in Neuro-Psychopharmacology and Biological Psychiatry 35 (2011) 373-379.
[4] O.F. Shallie, E. Dalle, M.V. Mabandla, Memory decline correlates with increased plasma cytokines in amyloid-beta (1–42) rat model of Alzheimer's disease, Neurobiology of learning and memory 169 (2020) 107187.
[5] M.A. Rather, A.J. Thenmozhi, T. Manivasagam, M.D. Bharathi, M.M. Essa, G.J. Guillemin, Neuroprotective role of Asiatic acid in aluminium chloride induced rat model of Alzheimer's disease, Frontiers in Bioscience-Scholar 10 (2018) 262-275.
[6] R.T. Bartus, R.L. Dean III, B. Beer, A.S. Lippa, The cholinergic hypothesis of geriatric memory dysfunction, Science 217 (1982) 408-414.
[7] S.T. Auti, Y.A. Kulkarni, Neuroprotective effect of cardamom oil against aluminum induced neurotoxicity in rats, Frontiers in Neurology 10 (2019) 399.
[8] G. Lamaty, C. Menut, J. Bessiere, P.A. Zoilo, Aromatic plants of tropical central Africa. I. Volatile components of two annonaceae from cameroon: Xylopia aethiopica (dunal) A. Richard and Monodora myristica (Gaertn.) Dunal, Flavour and Fragrance Journal 2 (1987) 91-94.
[9] Y. Ranjbar-Slamloo, Z. Fazlali, Dopamine and noradrenaline in the brain; overlapping or dissociate functions?, Frontiers in molecular neuroscience 12 (2020) 334.
[10] H.A. Elreedy, A. Elfiky, A. Mahmoud, K. Salaheldin Ebrahim, M. Ghazy, Effect of quercetin as therapeutic and protective agent in Aluminum Chloride-induced Alzheimer's disease rats, Egyptian Journal of Chemistry 65 (2022) 633-641.
[11] E. Badawy, W. Rasheed, T. Elias, J. Hussein, M. Harvi, S. Morsy, Y.E.-L. Mahmoud, Flaxseed oil reduces oxidative stress and enhances brain monoamines release in streptozotocin-induced diabetic rats, Human & Experimental Toxicology 34 (2015) 1133-1138.
[12] Z. El-Khayat, W. Rasheed, T. Ramzy, J. Hussein, M. Agaiby, S. Morsy, F. Morsy, N. Shaffie, Protective effect of garlic oil against liver injury in experimental animals, Journal of Medicinal Plants Research 4 (2010) 2359-2369.
[13] M. Moore, A. Adams, Calcification resistance, biostability, and low immunogenic potential of porcine heart valves modified by dye-mediated photooxidation, Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 56 (2001) 24-30.
[14] K. Thaipong, U. Boonprakob, K. Crosby, L. Cisneros-Zevallos, D.H. Byrne, Comparison of ABTS, DPPH, FRAP, and ORAC assays for estimating antioxidant activity from guava fruit extracts, Journal of food composition and analysis 19 (2006) 669-675.
[15] A.A. Gomaa, R.M. Makboul, M.A. El-Mokhtar, E.A. Abdel-Rahman, I.A. Ahmed, M.A. Nicola, Terpenoid-rich Elettaria cardamomum extract prevents Alzheimer-like alterations induced in diabetic rats via inhibition of GSK3β activity, oxidative stress and pro-inflammatory cytokines, Cytokine 113 (2019) 405-416.
[16] J. Hussein, D.A. El-matty, Z. El-Khayat, Y. Abdel-Latif, Therapeutic role of coenzyme Q10 in brain injury during experimental diabetes, Journal of Applied Pharmaceutical Science 3 (2013) 213-217.
[17] I. Gutiérrez Cañas, C. Dello Russo, F. Novellino, J.R. Caso Fernández, B. García Bueno, J.C. Leza Cerro, J.L. Muñoz Madrigal, Noradrenaline in Alzheimer's Disease: A New Potential Therapeutic Target, (2022).
[18] S.C. Lourenço, M. Moldão-Martins, V.D. Alves, Antioxidants of natural plant origins: From sources to food industry applications, Molecules 24 (2019) 4132.
[19] S. Haider, L. Liaquat, S. Ahmad, Z. Batool, R.A. Siddiqui, S. Tabassum, S. Shahzad, S. Rafiq, N. Naz, Naringenin protects AlCl3/D-galactose induced neurotoxicity in rat model of AD via attenuation of acetylcholinesterase levels and inhibition of oxidative stress, Plos one 15 (2020) e0227631.
[20] S.-S. Xie, X. Wang, N. Jiang, W. Yu, K.D. Wang, J.-S. Lan, Z.-R. Li, L.-Y. Kong, Multi-target tacrine-coumarin hybrids: cholinesterase and monoamine oxidase B inhibition properties against Alzheimer's disease, European Journal of Medicinal Chemistry 95 (2015) 153-165.
[21] A. Justin Thenmozhi, T.R. William Raja, T. Manivasagam, U. Janakiraman, M.M. Essa,

Hesperidin ameliorates cognitive dysfunction, oxidative stress and apoptosis against aluminium chloride induced rat model of Alzheimer's disease, Nutritional Neuroscience 20 (2017) 360-368.
[22] K. Sharma, Cholinesterase inhibitors as Alzheimer's therapeutics, Molecular medicine reports 20 (2019) 1479-1487.
[23] D. Praticò, K. Uryu, S. Sung, S. Tang, J.Q. Trojanowski, V.M.Y. Lee, Aluminum modulates brain amyloidosis through oxidative stress in APP transgenic mice, The FASEB Journal 16 (2002) 1138-1140.
[24] D. Medhat, H.A. El-Mezayen, M.E. El-Naggar, A.R. Farrag, M.E. Abdelgawad, J. Hussein, M.H. Kamal, Evaluation of urinary 8-hydroxy-2-deoxyguanosine level in experimental Alzheimer's disease: Impact of carvacrol nanoparticles, Molecular biology reports 46 (2019) 4517-4527.
[25] F. Brosseron, M. Krauthausen, M. Kummer, M.T. Heneka, Body fluid cytokine levels in mild cognitive impairment and Alzheimer's disease: a comparative overview, Molecular neurobiology 50 (2014) 534-544.
[26] A. Prema, A. Justin Thenmozhi, T. Manivasagam, M. Mohamed Essa, G.J. Guillemin, Fenugreek seed powder attenuated aluminum chloride-induced tau pathology, oxidative stress, and inflammation in a rat model of Alzheimer's disease, Journal of Alzheimer's Disease 60 (2017) S209-S220.
[27] B. Decourt, D. K Lahiri, M. N Sabbagh, Targeting tumor necrosis factor alpha for Alzheimer's disease, Current Alzheimer Research 14 (2017) 412-425.
[28] A. Shata, W. Elkashef, M.A. Hamouda, H. Eissa, Effect of artesunate vs memantine in aluminum chloride induced model of neurotoxicity in rats, Advances in Alzheimer's Disease 9 (2020) 1-19.
[29] S. Gauthier, P. Scheltens, J. Cummings, Alzheimer's Disease and Related Disorders, CRC Press, 2005.
[30] J. Chen, X. Liu, Y. Zhong, Interleukin-17A: the key cytokine in neurodegenerative diseases, Frontiers in aging neuroscience 12 (2020) 566922.
[31] K. Ceyzériat, Y. Gloria, S. Tsartsalis, C. Fossey, T. Cailly, F. Fabis, P. Millet, B.B. Tournier, Alterations in dopamine system and in its connectivity with serotonin in a rat model of Alzheimer's disease, Brain Communications 3 (2021) fcab029.
[32] D. Svob Strac, D. Muck-Seler, N. Pivac, Neurotransmitter measures in the cerebrospinal fluid of patients with Alzheimer's disease: a review, Psychiatria Danubina 27 (2015) 0-24.
[33] M.K. Burns, A.M. VanDerHeyden, Using response to intervention to assess learning disabilities: Introduction to the special series, Assessment for Effective Intervention 32 (2006) 3-5.
[34] C. Nocjar, B. Roth, E. Pehek, Localization of 5-HT2A receptors on dopamine cells in subnuclei of the midbrain A10 cell group, Neuroscience 111 (2002) 163-176.
[35] L. Albizu, T. Holloway, J. González-Maeso, S.C. Sealfon, Functional crosstalk and heteromerization of serotonin 5-HT2A and dopamine D2 receptors, Neuropharmacology 61 (2011) 770-777.
[36] M.R. Morshedloo, H. Mumivand, L.E. Craker, F. Maggi, Chemical composition and antioxidant activity of essential oils in Origanum vulgare subsp. gracile at different phenological stages and plant parts, Journal of Food Processing and Preservation 42 (2018) e13516.