Clinical Imaging and Case Reports (ISSN 2770-9205)

EFFECTIVENESS OF THYMOKINO IN ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW IN RAT MODELS

Dr. Gökhan Doğukan AKARSU[a], Assoc. Prof. Rukiye HÖBEK AKARSU[b]

a Yozgat Bozok Üniversity, Vocational School of Health Services, Yozgat/Turkey, g.dogukan.akarsu@yobu.edu.tr, +905012741044

b Yozgat Bozok Üniversity, Faculty of Health Sciences, Yozgat/Turkey, rukiye-hobek@hotmail.com, +905069016738

Corresponding author

Assoc. Prof. Rukiye HÖBEK AKARSU[b]
b Yozgat Bozok Üniversity, Faculty of Health Sciences, Yozgat/Turkey,
Email : rukiye-hobek@hotmail.com,
Phone : +905069016738

Received Date: June 10 2022
Accepted Date: June 12 2022
Published Date: July 10 2022

Abstract

This study is a systematic review and was prepared according to the PRISMA checklist and Cochrane guide. Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Pubmed, Cochrane Library, using the Proquest database "Alzheimer Disease", "Alzheimer", "A.D"., "Thymoquinone" , "TQ", "Nigella Sativa", "NS" etc. Search was made using keywords. The abstracts of 251 theses, which were scanned between March and April 2022 and constitute the universe, were systematically examined and 18 articles suitable for the purpose of the research formed the sample of the research.

INTRODUCTION

Alzheimer's disease is a disease that starts with wandering disorders at first, occurs in the brain and is characterized by progressive memory decline with the effect of gradually increasing neurofibrillary tangles and amyloid plaques, eventually resulting in death. The main problem is neurotransmitter imbalance. Therefore, the main goal in Alzheimer's treatment is to improve neurotransmitter imbalance. Chemical preparations containing various molecules are used to assist treatment. However, in the meantime, a method to completely cure the disease has not been found yet. Because the amyloid plaques and neurofibrillary tangles to be formed must be prevented, and the formed ones must be disintegrated. In recent years, many studies have been conducted to determine the effect of thymoquinone on neurotransmitter imbalance.

Thymoquinone has been used to prevent and treat various diseases in recent years (Vuorela et al. 2004). It has been reported to have anti-inflammatory, antioxidant and anti-neoplastic effects both in vitro and in vivo (Pagola et al. 2004).

In various studies, it has been stated that thymoquinone has an anti-neoplastic effect in some carcinomas, while its effect on normal cells is limited. In Alzheimer's disease, the effectiveness of thymoquinone on oxidative stress parameters, amyloid plaques, and neurofibrillary tangles was mostly evaluated in rat experiments (Worthen et al 1998).

It is stated that the use of thymoquinone in the treatment of Alzheimer's will contribute to the prevention of the disease in the pre-disease period and the treatment of the disease during the disease. For this reason, giving different results of the studies in the literature together and collecting the studies on this field in the same article will be an important source for the literature. The aim of this systematic review is to examine the studies evaluating the efficacy of thymoquinone in the treatment from the experimental Alzheimer's model created in rats. According to many different studies, thymoquinone has various properties, including antioxidant, anti-inflammatory, memory and learning ability enhancement, antianxiety, antidepressant, antipsychotic and analgesic effects. The aim of this article is to summarize several rat studies to understand the neuropharmacological role of thymoquinone.

Materials and Methods

Type of Research

This study is a systematic review prepared according to the PRISMA checklist and Cochrane guideline (Higgins et al. 2019; Moher et al. 2009).

Research Strategy: The thymoquinone molecule found in the black cumin plant, which is used in the treatment of Alzheimer's disease, has been examined. The research was searched using the database of Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Pubmed, Cochrane Library. Search "Alzheimer Disease", "Alzheimer", "A.D"., "Thymoquinone" , "TQ", "Nigella Sativa", "NS" etc. words are used. The databases were searched between March-April 2022 and articles published in English since 2017 were searched.

The abstracts of 251 studies that constituted the universe published between March-April 2022 were systematically

examined, and then 18 studies related to the use of thymoquinone in the experimental Alzheimer's model in rats, which were suitable for the purpose of the study, formed the sample of the study (Figure 1). Although all searches were performed by a single reviewer, full-text review and data abstraction were done in duplicate. Studies using thymoquinone in the treatment of Alzheimer's disease in rats were included when scanning the articles. The effect of thymoquinone in other disease models or the therapeutic modalities applied to Alzheimer's disease other than thymoquinone are not included.

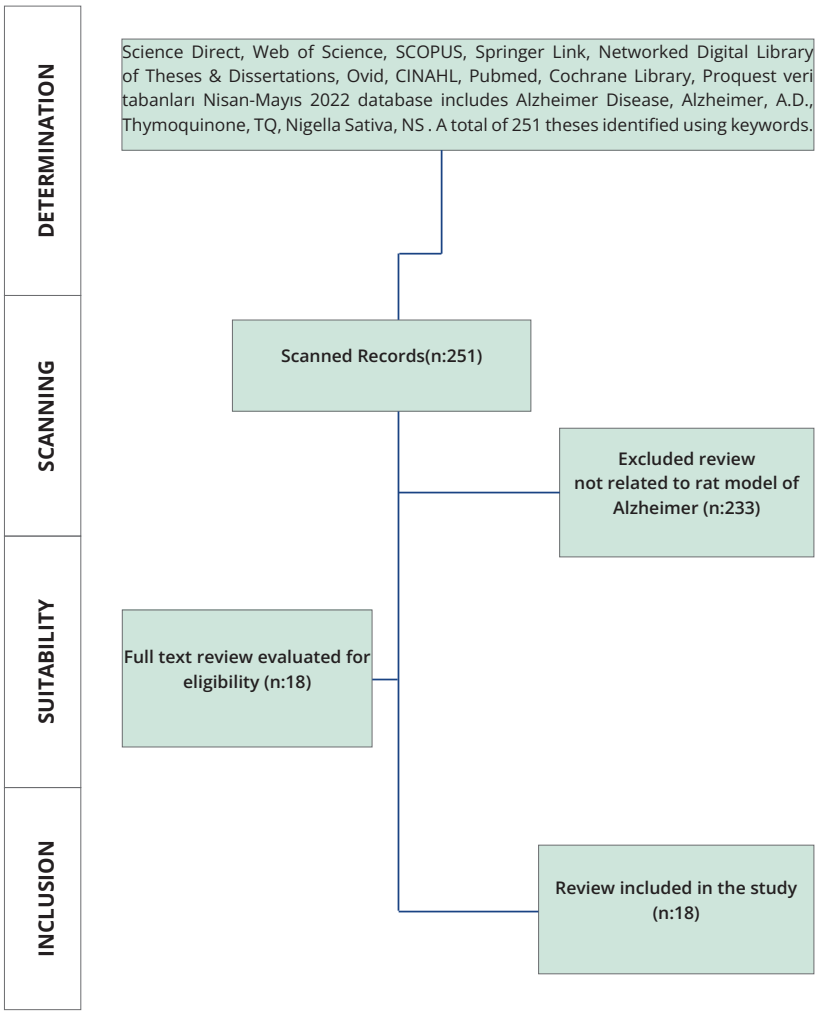
Inclusion criteria

- Full text accessible,
- In the field of Alzheimer, Norodegenerative disease
- About experimental Alzheimer rat model,
- Studies published in the Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Pubmed, Cochrane Library database between 2017-2022 were included.

In this study, PICOS;

* (P: Patient): Alzheimer disease, and norodegenerative disease
* (I: Intervention): Experimental Alzheimer Rat Model
* (C: Comparison): Thymoquinone dose and process
* (O: Outcomes): Alzheimer treatment using terapotic agent thymoquinone .
* (S: Study design): Treatment of experimental Alzheimer disease model

Figure 1. PRISMA Flow Chart



Limitation of the study

Reviews that were not included in the Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Pubmed, Cochrane Library, Proquest database and were not registered in the system could not be reached. The limitations of the study are that the search was only in the field of experimental Alzheimer and norodegenerative disease rat model for teratment of thymoquinone, the same reviews were reached with different keywords, and the number of reviews reached was low. Cell line studies were not included in our study.

Ethical aspect of research

Ethical permission was not obtained because reviews were open to access were used in this systematic review. Reviews were selected by the researchers considering the PRISMA checklist.

Analysis of data

The data were evaluated using the data summary form prepared by the researchers. The data summary form includes the author, the thymoquinone administration time, and the results of the studies. Data summary forms were evaluated independently by the researcher and filled in by himself.

Results

Alzheimer's Disease, Alzheimer's, A.D., Thymoquinone, TQ, Nigella Sativa, NS. etc. which included the keywords, studies published between 2017-2022, in which experimental Alzheimer's disease was created on rats and treated with thymoquinone were compiled. It was determined that 78% of the studies were applied on male rats, 45% of the dose times were in the range of 15-28 days, 61% were administered intraperitoneally, and 66% of the daily dose was 1-10 mg/kg (Table 1).

Table 1: Distribution of studies according to some characteristics (n=18)

Gender	**n**	**Percentage**
Male	14	78%
Female	2	11%
transgenic	1	5%
Unspecified	1	5%
Dose Duration (Days/Number of Applications)		
1-7	2	11%
8-14	4	22%
15-28	8	45%
29-42	2	11%
43 and above	2	11%
Application Method		
intraperitoneal	11	61%
gavage	6	33%
Oral	1	6%
Administration dose		
1-10 mg/kg/day	25	66%
20-40 mg/kg/day	10	26%
40 And Above mg/kg/day	3	8%

Table 2. Distribution of the examined articles according to some characteristics (n=18)

Author and Year	Animal model/ experimental Alzheimer's model	Thymoquinone Administration dose	Results
Elibol et. al. (2020)	Female Sprague Dawley Rats	10 and 20 mg/kg/day by gavage for 15 days.	Thymoquinone administration improved memory performance of Aβ 1-42 vaccinated rats and also improved neuronal loss in CA1 (cornu ammonis) but did not change the DG (dentate gyrus), Thymoquinone treatment reduced accumulation and fibril deposition in Aβ 1-42 vaccinated animals, Aβ Expressed that the expression profiles of mir29c and Bax, which were significantly up-regulated in 1-42 vaccinated animals, were attenuated by Thymoquinone, administration of Thymoquinone reduced the expressions of Aβ, phosphorylated-tau and BACE-1 proteins.
Abulfadl et. al. (2018)	Sprague Dawley Albino Rats	20 mg/kg/day intraperitoneally for 14 days.	Thymoquinone significantly decreased AChE activity, increased ACh immunoreactivity, TAC and SOD activities and Bcl-2 and BDNF levels, decreased MDA and NO levels in rat brains, Thymoquinone treatment succeeded in restoring the balance between ROS or RNS production and removal by the endogenous antioxidant system, It has been stated that it reduces the oxidative/nitrosative state, reduces neuronal apoptosis, and significantly reduces TNF-α immunoreactivity.
Abulfadl et. al. (2018)	Sprague-Dawley Male Albino Rats	10, 20 and 40 mg/kg/day by gavage for 14 days	It has been stated that thymoquinone increases cholinergic function and synaptic plasticity and reduces oxidative damage, neuronal apoptosis and neuroinflammation.
Dalli et. al. (2018)	Female Sprague Dawley Rats	20 mg/kg/day by gavage for 15 days.	It has been stated that thymoquinone provides activation of JNK protein, decreases the upregulation of mir-124, ERK1/2, NOS (nitric oxide synthase) enzymes and phosphorylated Tau protein.
Ismail et. al. (2017)	Male Sprague Dawley Rats	20–500 mg/kg/day by gavage for 3 months.	Thymoquinone-rich fraction nanoemulsion (TQRFNE) Aβ40 and Aβ42 by upregulating IDE (insulin degrading enzyme) and LRP1 (ipoprotein receptor related protein 1) and downregulating BACE1 and RAGE (advanced glycation end product receptor) levels have been reported.
Poorgholam et. al. (2018)	Male Wistar Rats	5 and 10 mg/kg/day intraperitoneally for 4 weeks.	He stated that thymoquinone administration caused a decrease in plaque formation in the CA1 region of the hippocampus and an increase in the number of surviving neurons in the hippocampus
Ardah et. al. (2019)	C57BL/6c Rats	10 mg/kg/day intraperitoneally for 1 week.	It has been stated that thymoquinone pretreatment can induce a neuroprotective effect by increasing antioxidant capacity and inhibiting neuroinflammation, preventing cellular toxicity in an in vitro cellular model.
Abbas et. al. (2022)	Male Wistar Albino Rats	10 mg/kg/day intraperitoneally for 6 weeks.	Thymoquinone exhibits potent antioxidant activity as well as anti-inflammatory effects in models of chemically induced toxicity, improves TAS, and simultaneously measures numerous measures of normal brain function, including ACh and monoamine neurotransmitter levels, motor coordination, anxiety-like behavior, and depression-like behavior. has been reported to improve.
Ustunova et. al. (2022)	Male Wistar Albino Rats	10 mg/kg/day by gavage for 15 days.	It has been reported that thymoquinone increases BDNF levels, NMDA receptor expression and antioxidant markers in the CA1 region of the hippocampus.

Yusuf et. al. (2021)	Male Albino Mice	5 and 20 mg/kg/day and Thymoquinone nanoparticle 5 mg/kg/day	It has been stated that thymoquinone nanoparticle increases SOD by crossing the blood brain barrier, reduces the accumulation of Aβ and hyperphosphorylated tau protein tangles by acting directly on the antioxidant cascade, thus reducing oxidative stress.
		intraperitoneally for 28 days.	
Lotfi et. al. (2021)	Male Wistar Rats	2.5, 5 and 10 mg/kg/day intraperitoneally for 21 days.	Thymoquinone inhibited the accumulation of alpha-synuclein protein in the axon terminal of neurons.
El-Far et. al. (2021)	Male Wistar Rats	10 and 20 mg/kg/day orally for 42 days.	It has been stated that thymoquinone overcomes oxidative changes in the brain and heart, and provides brain and heart protection.
Oskouei et. al. (2021)	Male Wistar Rats	2.5, 5, 10 mg/kg/day intraperitoneally for 56 days.	It has been stated that thymoquinone helps prevent oxidative damage and inflammation in the hippocampus.
Samad et. al. (2021)	Albino Male Mouse	2, 10 and 20 mg/kg/day intraperitoneally for 28 days.	It has been stated that thymoquinone prevents oxidative deterioration, prevents behavioral and cognitive deficiencies, and improves psychological functions by increasing the activity of antioxidant enzymes, decreasing lipid peroxide and inflammatory markers, and stimulating cholinergic transmission by decreasing AChE activity.
Mohamed et. al. (2020)	Male Sprague Dawley Albino Rats	10 mg/kg/day by gavage for 28 days.	It has been stated that thymoquinone has an antioxidant role and has the ability to increase antioxidant capacity.
Fanoudi et. al. (2019)	Male Wistar Rats	10, 20, 40 mg/kg/day intraperitoneally for 10 days.	It has been stated that thymoquinone treatment improves learning and memory processes by reducing hippocampal oxidative stress and AChE activity, and will be beneficial in cases of cerebrovascular insufficiency.
Fouad et. al. (2018)	Albino Male Rat	2.5 and 10 mg/kg/day intraperitoneally for 7 days.	It was stated that thymoquinone treatment caused a decrease in the levels of Cyto-C, Casp-3, LDH and Aβ-42 in brain homogenates and had the ability to prevent apoptotic cell death.
Bargi et. al. (2017)	Male Wistar Rats	2, 5, 10 mg/kg/day intraperitoneally for 14 days.	It has been stated that thymoquinone improves learning and memory disorders.

*All studies were performed on rats using different agents that induce Alzheimer's disease.

*The doses, duration and application methods of thymoquinone in the studies are given in the table.

*A summary of studies on the effects of thymoquinone in various conditions.

Results

Elibol et al. (2020), amyloid beta 1-42 (Aβ 1-42) peptide was administered to the hippocampus of female sprague dawley rats and its effects were tried to be determined by giving thymoquinone at doses of 10 mg/kg/day and 20 mg/kg/day to the rats by gavage for 15 days in the alzheimer disease model. According to the results of the study, thymoquinone administration increased the memory performance of Aβ 1-42 vaccinated rats and also improved the neuronal loss in CA1 (cornu ammonis) but did not change the DG (dentate gyrus), and thymoquinone treatment was effective in reducing amyloid plaque and fibrillary fibrillation in Aβ 1-42 vaccinated animals. They stated that the expression profiles of mir29c and Bax, which were significantly up-regulated in animals vaccinated with Aβ 1-42, were attenuated by thymoquinone, and thymoquinone administration decreased the expressions of Aβ, phosphorylated-tau and BACE-1 proteins. Again, Poorgholam et al. (2018) stated that thymoquinone treatment after Aβ 1-42 injection into the hippocampus caused both a decrease in plaque formation in the CA1 region of the hippocampus and an increase in the number of surviving neurons in the hippocampus.Ustunova et al. (2022) reported that thymoquinone given to rats exposed to 900 MHz electromagnetic field increased BDNF levels, NMDA receptor expression and antioxidant markers in the CA1 region of the hippocampus. Abulfadl et al. (2018), in an experimental Alzheimer's model created with AlCl3 and D-Gal, sprague dawley rats were given 20 mg/kg/day doses of thymoquinone for 14 days, and it significantly reduced AChE activity, decreased ACh immunoreactivity, TAC and SOD activities in the experimental groups. Thymoquinone increased Bcl-2 and BDNF levels, decreased MDA and NO levels in rat brains, thymoquinone treatment managed to restore the balance between ROS or RNS production and their removal by the endogenous antioxidant system, reduced oxidative/nitrosative status, reduced neuronal apoptosis, TNF-α immunoreactivity. has been reported to be significantly reduced. In addition to Abulfadl et al. (2018), in the Alzheimer's model induced by AlCl3 and D-Gal, 10, 20 and 40 mg/kg/day thymoquinone was given by gavage for 14 days, the effective dose was 20 mg/kg/day, and thymoquinone improved cholinergic function and synaptic plasticity. It has been reported to increase the decrease oxidative damage, neuronal apoptosis and neuroinflammation. El-Far et al. (2021), it was stated that thymoquinone defeated oxidative changes in the brain and heart, and provided brain and heart protection. Abbas et al. (2022), thymoquinone showed strong antioxidant activity as well as anti-inflammatory effects in models of chemically induced toxicity, improving TAS and simultaneously including ACh and monoamine neurotransmitter levels, motor coordination, anxiety-like behavior, and depression-like behavior. It has been reported to improve numerous measures of normal brain function. Dalli et al. (2018), female sprague dawley rats were given thymoquinone at a dose of 20 mg/kg/day by gavage for 15 days in an experimental Alzheimer's model induced by streptozotocin, and thymoquinone provided activation of JNK protein, upregulation of mir-124, ERK1/2, it has been expressed to reduce NOS (nitric oxide synthase) enzymes and phosphorylated Tau protein.

Ismail et al. (2017) and Yusuf et al. (2021), thymoquinone nanoparticles upregulate IDE (insulin degrading enzyme) and LRP1 (ipoprotein receptor related protein 1) and downregulate BACE1 and RAGE (advanced glycation end product receptor) Aβ40-42. It has been stated that it reduces the levels of Aβ and hyperphosphorylated tau protein tangles by acting directly on the antioxidant cascade, thereby reducing oxidative stress.

As seen in the studies, thymoquinone (Lotfi et al. 2021) prevents the accumulation of alpha-synuclein protein in the axon terminal of neurons, helps to prevent oxidative damage and inflammation in the hippocampus (Oskouei et al. 2021), increases the activity of antioxidant enzymes, lipid peroxide and inflammatory markers and AChE. It has been shown to prevent oxidative deterioration, prevent behavioral and cognitive deficits, and improve psychological functions by stimulating cholinergic transmission by decreasing its activity (Samad et al. 2021; Fanoudi et al. 2019). Fanoudi et al. (2018), it was stated that thymoquinone treatment caused a decrease in the levels of Cyto-C, Casp-3, LDH and Aβ-42 in brain homogenates and had the ability to prevent apoptotic cell death.

Discussion

Aβ plaques and neurofibrillary tangles are shown among the causes of Alzheimer's disease. These structures reduce the communication between neurons and create an imbalance. This neuro degeneration manifests itself with wandering disorders and the first signs of disease effects are observed. Fouad et al. (2018) study, Aβ1-42 formation induced by glutamate was evaluated with negative control groups. In the experimental model induced by glutamate, in the comparison of 2.5 and 10 mg/kg/day dose of thymoquinone, thymoquinone reduced the effect of glutamate, Cytoc and Casp-3, in the group by aplication of 10 mg/kg/day. In addition to It has been stated that there is a decrease in LDH and Aβ levels.

Ebrahimi et al. (2017) and Sedaghat et al. (2014) stated that thymoquinone can improve motor neuron defects in parkinson-like disease models, protect neurons against rotenone toxicity through its antioxidant effect, reduce apomorphine-induced rotations in rats with 6-OHDA lesions,

reduce the loss of substantia nigra pars compacta neurons, and reduce midbrain MDA levels.

In Alzheimer's disease, an increase in the levels of MDA (malonyldialdehyde), which is one of the biomarkers, is observed. It is also stated that the increase in the levels of these biomarkers in the patients indicates the rate of progression of the disease. Bagri et al. (2017) showed that MDA levels increased in the model performed with LPS, and thymoquinone administered at doses of 5 and 10 mg/kg/day caused a decrease in hippocampal MDA levels. It has been stated that the effect of thymoquinone on SOD and CAT enzymes was also observed. Bagri et al. In their study in (2017), thymoquinone was given at doses of 2, 5 and 10 mg/kg/day before LPS application in the experimental model induced by LPS, and it was investigated to what extent it could eliminate the learning and memory deficiencies that occurred as a result of LPS application. As a result of the experiment, the hippocampal content of IL6 in the experimental group was found to be higher than the control group, and thymoquinone at 5 and 10 mg/kg/day reduced the LPS-induced hippocampal IL6 levels. Thymoquinone 10 mg/kg/day dose also caused a decrease in TNF-α levels compared to the LPS group. In addition, thymoquinone has been shown to reduce NO levels in all administration groups. Oxidative stress increases in Alzheimer's disease, and with this increase, the progressive memory deterioration of the disease accelerates (Abdulfadl et al. 2018). It shows that thymoquinone improves learning and memory processes by reducing hippocampal oxidative stress and AChE activity (Fanoudi et al. 2019). All these effects show that thymoquinone can be used as a therapeutic agent, especially in the progression of neurodegenerative diseases. Ustunova et al. (2022) reported that rats exposed to 900 MHz electromagnetic field increased BDNF levels, NMDA receptor expression and antioxidant markers in the CA1 region of the hippocampus. These results show that thymoquinone will be beneficial not only in neurodegenerative diseases, but also in reducing the effects of devices such as wifi, microwave oven, radio transmitters and base stations, which are especially in our lives, on the living body. Collet et al. (2022) stated in their study that exposure of rats to radio frequency electromagnetic field (RF-EMF) was associated with a lower WBC count, a lower total lymphocyte count, and a higher rate of neutrophils in peripheral blood. Mohamed et al. (2020) and Bargi et al. (2017) also stated that thymoquinone has an antioxidant role and has the ability to increase antioxidant capacity and improves learning and memory disorders.

Conclusion

The available evidence indicates that thymoquinone helps to prevent the formation of amyloid plaques and fibrillary tangles and to break down existing aggregates by various mechanisms. For this purpose, thymoquinone is a promising candidate for treatment in cognitive dysfunction diseases. For this reason, there is a need to observe the effects on humans in clinical studies as soon as possible.

References

1. Abbas, F., Eladl, M. A., El-Sherbiny, M., Abozied, N., Nabil, A., Mahmoud, S. M., ... & Ibrahim, D. (2022). Celastrol and thymoquinone alleviate aluminum chloride-induced neurotoxicity: Behavioral psychomotor performance, neurotransmitter level, oxidative-inflammatory markers, and BDNF expression in rat brain. Biomedicine & Pharmacotherapy, 151, 113072.

2. Abulfadl, Y. S., El-Maraghy, N. N., Ahmed, A. A. E., Nofal, S., & Badary, O. A. (2018). Protective effects of thymoquinone on D-galactose and aluminum chloride induced neurotoxicity in rats: biochemical, histological and behavioral changes. Neurological research, 40(4), 324-333.

3. Abulfadl, Y. S., El-Maraghy, N. N., Ahmed, A. E., Nofal, S., Abdel-Mottaleb, Y., & Badary, O. A. (2018). Thymoquinone alleviates the experimentally induced Alzheimer's disease inflammation by modulation of TLRs signaling. Human & experimental toxicology, 37(10), 1092-1104.

4. Ardah, M. T., Merghani, M. M., & Haque, M. E. (2019). Thymoquinone prevents neurodegeneration against MPTP in vivo and modulates α-synuclein aggregation in vitro. Neurochemistry International, 128, 115-126.

5. Bargi, R., Asgharzadeh, F., Beheshti, F., Hosseini, M., Sadeghnia, H. R., & Khazaei, M. (2017). The effects of thymoquinone on hippocampal cytokine level, brain oxidative stress status and memory deficits induced by lipopolysaccharide in rats. Cytokine, 96, 173-184.

6. Collet, L., Jenlis, A. B., Khorsi-Cauet, H., Naudot, M., Djekkoun, N., Ghamlouch, H., ... & Marolleau, J. P. (2022). 900 MHz Electromagnetic Fields Induce Microbiota Dysbiosis and Adaptive Immune System Disorders in Juvenile Rats.

7. Dalli, T., Beker, M., Terzioglu-Usak, S., Akbas, F., & Elibol, B. (2018). Thymoquinone activates MAPK pathway in hippocampus of streptozotocin-treated rat model. Biomedicine & Pharmacotherapy, 99, 391-401.

8. Ebrahimi, S. S., Oryan, S., Izadpanah, E., & Hassanzadeh, K. (2017). Thymoquinone exerts neuroprotective effect in animal model of Parkinson's disease. Toxicology letters, 276, 108-114.

9. Elibol, B., Beker, M., Terzioglu-Usak, S., Dalli, T., & Kilic, U. (2020). Thymoquinone administration ameliorates Alzheimer's disease-like phenotype by promoting cell survival in the hippocampus of amyloid beta1–42 infused rat model. Phytomedicine, 79, 153324.

10. El-Far, A. H., Elewa, Y. H., Abdelfattah, E. Z. A., Alsenosy, A. W. A., Atta, M. S., Abou-Zeid, K. M., ... & Noreldin, A. E. (2021). Thymoquinone and Curcumin Defeat Aging-Associated Oxidative Alterations Induced by D-Galactose in Rats' Brain and Heart. International journal of molecular sciences, 22(13), 6839.

11. Fanoudi, S., Alavi, M. S., Hosseini, M., & Sadeghnia, H. R. (2019). Nigella sativa and thymoquinone attenuate oxidative stress and cognitive impairment following cerebral hypoperfusion in rats. Metabolic Brain Disease, 34(4), 1001-1010.

12. Fouad, I. A., Sharaf, N. M., Abdelghany, R. M., & El Sayed, N. S. E. D. (2018). Neuromodulatory effect of thymoquinone in attenuating glutamate-mediated neurotoxicity targeting the amyloidogenic and apoptotic pathways. Frontiers in Neurology, 9, 236.

13. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. Cochrane, 2019. [Erişim Tarihi 22 Aralık 2021]. Erişim adresi: https://training.cochrane.org/handbook.

14. Ismail, N., Ismail, M., Azmi, N. H., Bakar, M. F. A., Yida, Z., Abdullah, M. A., & Basri, H. (2017). Thymoquinone-rich fraction nanoemulsion (TQRFNE) decreases Aβ40 and Aβ42 levels by modulating APP processing, up-regulating IDE and LRP1, and down-regulating BACE1 and RAGE in response to high fat/cholesterol diet-induced rats. Biomedicine & Pharmacotherapy, 95, 780-788.

15. Lotfi, M., Kazemi, S., Ebrahimpour, A., Pourabdolhossein, F., Satarian, L., Eghbali, A., & Moghadamnia, A. A. (2021). Thymoquinone Improved Nonylphenol-Induced Memory Deficit and Neurotoxicity Through its Antioxidant and Neuroprotective Effects.

16. Mohamed, A. B., Mohamed, A. Z., & Aly, S. (2020). Effect of Thymoquinone against Aluminum Chloride-Induced Alzheimer-Like Model in Rats: A Neurophysiological and Behavioral Study. The Medical Journal of Cairo University, 88(March), 355-365.

17. Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009; 6(7):1–6.

18. Oskouei, Z., Mehri, S., Kalalinia, F., & Hosseinzadeh, H. (2021). Evaluation of the effect of thymoquinone in d galactose induced memory impairments in rats: Role of MAPK, oxidative stress, and neuroinflammation pathways and telomere length. Phytotherapy Research, 35(4), 2252-2266.

19. Pagola, S., Benavente, A., Raschi, A., Romano, E., Molina, M. A. A., & Stephens, P. W. (2004). Crystal structure determination of thymoquinone by high-resolution X-ray powder diffraction. Aaps Pharmscitech, 5(2), 24-31.

20. Poorgholam, P., Yaghmaei, P., & Hajebrahimi, Z. (2018). Thymoquinone recovers learning function in a rat model of Alzheimer's disease. Avicenna journal of phytomedicine, 8(3), 188.

21. Samad, N., Manzoor, N., Muneer, Z., Bhatti, S. A., & Imran, I. (2021). Reserpine-induced altered neuro-behavioral, biochemical and histopathological assessments prevent by enhanced antioxidant defence system of thymoquinone in mice. Metabolic Brain Disease, 36(8), 2535-2552.

22. Sedaghat, R., Roghani, M., & Khalili, M. (2014). Neuroprotective effect of thymoquinone, the nigella sativa bioactive compound, in 6-hydroxydopamine-induced hemi-parkinsonian rat model. Iranian journal of pharmaceutical research: IJPR, 13(1), 227.

23. Ustunova, S., Kilic, A., Bulut, H., Gurel-Gurevin, E., Eris, A. H., & Meral, I. (2022). Impaired memory by hippocampal oxidative stress in rats exposed to 900 MHz electromagnetic fields is ameliorated by thymoquinone. Toxicological & Environmental Chemistry, 1-18.

24. Vuorela, P., Leinonen, M., Saikku, P., Tammela, P., Rauha, J. P., Wennberg, T., & Vuorela, H. (2004). Natural products in the process of finding new drug candidates. Current medicinal chemistry, 11(11), 1375-1389.

25. Worthen, D. R., Ghosheh, O. A., & Crooks, P. A. (1998). The in vitro anti-tumor activity of some crude and purified components of blackseed, Nigella sativa L. Anticancer research, 18(3A), 1527-1532.

26. Yusuf, M., Khan, M., Alrobaian, M. M., Alghamdi, S. A., Warsi, M. H., Sultana, S., & Khan, R. A. (2021). Brain targeted Polysorbate-80 coated PLGA thymoquinone nanoparticles for the treatment of Alzheimer's disease, with biomechanistic insights. Journal of Drug Delivery Science and Technology, 61, 102214.