Introduction

Epileptic seizures affect the life of noticeable number of people in all over the world. In epileptic seizures the sudden discharge of neurons are associated with muscle contraction and cognitive behaviors dysfunction. Oxidative stress, inflammation, programmed cell death and heat shock proteins have been suggested as important causes in epileptic seizures pathogenesis. Dysfunction of membrane proteins including neurotransmitter receptors and ion channels followed by brain oxidative and nitrosative stress has been also demonstrated to involve in neuronal hyper-excitability. In addition, the elevated level of inflammatory cytokines such as interleukin (IL) 1β in the brain has been reported to promote seizure activities. Electrical and chemical kindling are employed for induction of epileptic seizures in experimental models. Kainic acid and pentylenetetrazole (PTZ) are two well-known chemical substances which are applied for seizure outspread in laboratory animals. PTZ as a GABA receptor blockers has been shown to decrease the level of antioxidant indexes such as glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) in cells of CA1 and CA3 areas of hippocampus in rats. Researchers also reported that the activation of glucagon like peptide 1 receptor (GLP1R) associated with inhibition of oxidative

Effects of Hydro-ethanolic Extract of Tanacetum parthenium and its N-Butanol and Aqueous Fractions on Brain Oxidative Damage in Pentylenetetrazole-Induced Seizures in Mice

Fereshteh Asgharzadeh, Mahmoud Hosseini, Rahimeh Bargi, Farimah Beheshti, Hassan Rakhshandeh, Somaye Mansouri, Azita Aghaei, Hamid Reza Sadeghnia, Akbar Anaeigoudari

1Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran. 
2Division of Neurocognitive Sciences, Psychiatry and Behavioral Sciences Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
3Neurogenic Inflammation Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
4Neuroscience Research Center, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran.
5Department of Physiology, School of Paramedical Sciences, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran.
6Department of Anatomy, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
7Department of Physiology, School of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran.

Abstract

Background: Epileptic seizures affect the life of noticeable number of people in all over the world. Tanacetum parthenium (TP) is used in traditional medicine. We studied the effects of hydro-ethanolic extract of TP and its n-butanol and aqueous fractions on brain oxidative damage in pentylenetetrazole (PTZ)-induced seizures in mice.

Methods: Male mice were divided into: (1) Control; (2) PTZ (100 mg/kg, i.p.); (3-5) hydro-ethanolic extract of TP (50, 100 and 200 mg/kg); (6) n-butanol (NBut) (100 mg/kg) and (7) aqueous (Aq) (100 mg/kg) fractions. Extracts were injected (i.p.) for 3 days and 30 min before PTZ. Latencies in onset of Minimal Clonic Seizures (MCS) and Generalized Tonic-Clonic Seizures (GTCS) as well as biochemical indicators were evaluated.

Results: Medium dose of TP extract and NBut fraction prolonged the MSC and GTCS latencies. Biochemical data confirmed that administration of hydro-ethanolic extract of TP significantly reduced MDA and enhanced total thiol content and the activity of SOD and CAT in brain tissues. Comparison the effect of NBut and Aq fractions with medium dose indicated a higher level of MDA and lower amount of total thiol content and the activity of SOD and CAT in brain tissues of PTZ-Aq100 and PTZ-NBut100 groups than PTZ-TP100 group.

Conclusion: Results demonstrated that the medium dose of TP extract had the most protective effect against brain oxidative damage in PTZ-induced seizure model. N-butanol and aqueous fractions of TP could not exert stronger effect than medium dose on reduction PTZ-induced brain oxidative stress.
stress and up-regulation of heat shock protein70 (Hsp70) in hippocampus of rats could exert the protective effects against PTZ-stimulated seizures.\textsuperscript{16} In addition, increased level of pro-inflammatory mediators such as IL-1\(\beta\), IL-6, IL-18 and tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) was reported in rats kindled by PTZ.\textsuperscript{17}

*Tanacetum parthenium* (TP), named feverfew, is a member from Asteraceae family which grows in different areas of the world such as Iran.\textsuperscript{18} Therapeutic effects including anti-inflammatory,\textsuperscript{19} anti-asthma,\textsuperscript{18} anti-fever,\textsuperscript{20} anti-migraine and anti-arthritis\textsuperscript{21} are attributed to this plant. Antioxidant ingredients such as sesquiterpene lactones, parthenolide, flavonoids and luteolin have been also identified in extract of TP.\textsuperscript{22,23} It has been documented that pre and post treatment with TP extract ameliorated hepatotoxicity followed by CCl\(_4\) injection via reduction of free radicals, modulation of antioxidant enzymes activity such as superoxide dismutase (SOD) and catalase (CAT) and suppression of lipid peroxidation in rats.\textsuperscript{24} Researchers showed that the quercetin present in TP extract has considerable protective effect on central nervous system.\textsuperscript{25} This substance derived from TP extract also could enhance slow waves sleep in rats.\textsuperscript{26} TP extract and its constituents have been also suggested to alleviate the headaches resulted from migraine through inhibition of nitric oxide production, suppression of serotonin release and reduction of Calcitonin Gene-Related Peptide (CGRP) secretion.\textsuperscript{27} Despite these lucrative properties, the anticonvulsant effect of TP has been not understood. Therefore, we designed this study to assess the effect of TP extract and its N- butanol and aqueous fractions on brain oxidative damage in PTZ-induced seizures in mice.

**Materials and Methods**

**Drugs and chemicals**

PTZ and biochemical reagents were used. PTZ was prepared from Sigma Aldrich Company [St. Louis, USA]. Reagents were bought from Merck Company.

**Preparation of the plant extract and the fractions**

Using a blender, the plant material was ground to fine powder. To prepare the hydro- ethanolic extract of TP, 50 g of the provided powder was extracted during 48 h with 300 ml ethanol-water (70/30 v/v) using a Soxhlet apparatus. The solvent was removed using vacuum distillation method. The yielded of this extract was 10% (w/w). To prepare the fractions, each 10 g of dried hydro- ethanolic extract was suspended in 300 ml distilled water, transferred to a separator funnel, and partitioned with n-butanol (300 mL × 6). The N- butanol fraction was separated and the lower water-soluble layer was considered as water fraction.\textsuperscript{14,28} The resulting fractions were dried on a water bath. Water fraction dissolves polar compounds and water-soluble plant constituents. N- butanol fraction has non-polar agents.\textsuperscript{29}

**Animals and groups**

Male mice were randomly distributed into 7 groups (n=10 mice/group): (1) Control group, received saline instead of PTZ and extract, (2) PTZ group, received 100 mg/kg of PTZ, (3-5) groups, given 3 doses (50, 100 and 200 mg/kg)\textsuperscript{26} of hydro-ethanolic extract of TP (6) n-butanol (NBut) group, treated with 100 mg/kg of n-butanol fraction of TP and (7) Aqueous (Aq) group, injected with 100 mg/kg of aqueous fraction of TP. In 3-7 groups, the extract and the fractions were intraperitoneally administered for 3 days and 30 minutes before PTZ injection.

**PTZ- induced seizures**

Induction of seizure in mice was carried out by PTZ. For this purpose, after administration of PTZ (100 mg/kg) the animals were located in a plexiglass chamber (30× 30× 30 cm) and their behavior was monitored for 60 min. The latency time in onset of Minimal Clonic seizure (MCS) and Generalized Tonic-Clonic seizure (GTCS) were considered as indexes of seizures intensity.

**Biochemical measurement**

After behavioral tests, the animals were euthanized and their brains were collected for biochemical measurements.

**Assessment of malondialdehyde concentration**

The assessment of malondialdehyde (MDA) concentration was done using relevant reagents as it has been previously declared.\textsuperscript{30}

**Determination of total thiol content**

The total thiol content (SH) was evaluated using appropriate reagents as we have already described.\textsuperscript{30}

**Estimation of SOD activity**

The activity of SOD was estimated based on the method of Madesh and Balasubramanian as we have depicted it in our previous works.\textsuperscript{31}

**Measurement of CAT activity**

The activity of CAT was measured using the method of Aebi as it has been previously explained.\textsuperscript{32}

**Statistical analysis**

The findings were analyzed using the SPSS 20 software. The groups were compared with each other by one way ANOVA test followed by LSD as the post hoc test. P <0.05 was considered to be statistically significant.

**Results**

**Effect of hydro-ethanolic extract of TP on PTZ-induced seizures**

Administration of PTZ triggered the MCS and GTCS in all groups. The medium dose (100 mg/kg) of hydro-ethanolic extract of TP lengthened the onset of seizure attacks (MCS and GTCS) in PTZ-TP100 group than PTZ group (P<0.001). Based on results, the latency time in onset of MCS...
Effects of Tanacetum parthenium on PTZ-Induced Seizures

Pharmaceutical Sciences, 2020, 26(3), 252-260  | 254

and GTCS in PTZ-TP100 group was more than PTZ-TP50 group (P<0.001). The delay in onset of MCS and GTCS in PTZ-TP200 group was also lesser than PTZ-TP100 group (P<0.001). Data did not exhibit any significant difference in onset of MCS and GTCS between PTZ-TP50 and PTZ-TP200 groups with PTZ group (Figures 1A and 1B).

Comparison the effect of the most effective dose (100 mg/kg) of TP extract with its aqueous and N-butanol fractions on PTZ-induced seizures

Pretreatment with n-butanol fraction of TP postponed the onset of MCS and GTCS in PTZ-NBut100 group compared with PTZ group (P<0.001). We did not perceive any significant difference in onset of MCS and GTCS in PTZ-NBut100 group with respect to PTZ-TP100 group. According to the results of current study, the effect of aqueous fraction of TP on latency time of seizure parameters was lesser than that of PTZ-TP100 group (P<0.01). Data also denoted that the beginning of MCS and GTCS in PTZ-NBut100 group was longer than PTZ-Aq100 group (Figures 2A and 2B).

Effect hydro-ethanolic extract of TP on oxidative stress indicators in cortical and hippocampal tissues

We observed an increased accumulation of MDA in cortical and hippocampal tissues of PTZ group than control group (P<0.001). All three doses of TP extract remarkably lowered the concentration of MDA in brain tissues compared with PTZ group (P<0.001). MDA level of injected mice with 100 mg/kg of TP extract was noticeably lower than those treated with 50 mg/kg of TP extract (P<0.01). Data did not indicate any significant difference between PTZ-TP100 and PTZ-TP200 groups in this parameter (Figures 3A and 4A).

The total thiol content was also assessed in all experimental groups. We figured out a significant reduction in concentration of this antioxidant indicator in brain tissues of treated mice with PTZ in comparison with control group (P<0.001). The hippocampal tissue results demonstrated that all three doses of TP extract raised the total thiol level of PTZ-TP groups than PTZ group (P<0.01 and P<0.001). According to the cortical tissue data, only the dose of 100 mg/kg of TP extract could significantly enhance the total thiol content in comparison with PTZ group (P<0.001) (Figures 3B and 4B). As clarified in Figures 3B and 4B, the medium dose of TP extract (100 mg/kg) significantly increased the total thiol level of mice brain tissues than dose 50 mg/kg (P<0.01 and P<0.001). Findings also showed that the total thiol content in brain tissues in PTZ-TP200 group was lower than PTZ-TP100 group (P<0.05 and P<0.001) (Figures 3B and 4B). We also checked the activity of SOD and CAT in brain tissues of mice. The results demonstrated that the activity of these antioxidant enzymes in cortical and hippocampal tissues of mice was lower in PTZ group than control group (P<0.001). All three doses of TP extract elevated the SOD activity in hippocampal and cortical tissues of PTZ-TP groups than PTZ group. The activity of CAT in
Figure 3. Comparison of MDA concentration (A), total thiol level (B) and activity of SOD (C) and CAT (D) in hippocampus tissue in treated groups. Data were declared as the mean ± SEM (n=10). ***P<0.001 versus control group, **P<0.01 and +++P<0.001 versus PTZ group, +++P<0.001 and +++P<0.001 versus PTZ-TP50 group and +++P<0.001 and +++P<0.001 versus PTZ-TP100.

Figure 4. Comparison of MDA concentration (A), total thiol level (B) and activity of SOD (C) and CAT (D) in cortical tissue in treated groups. Data were declared as the mean ± SEM (n=10). ***P<0.001 versus control group, **P<0.01 and +++P<0.001 versus PTZ group, **P<0.01 and +++P<0.001 versus PTZ-TP50 group and **P<0.01 and +++P<0.001 versus PTZ-TP100.
Effects of Tanacetum parthenium on PTZ-Induced Seizures

PTZ-TP50 and PTZ-TP100 groups also was higher than PTZ group (P<0.01 and P<0.001). The results confirmed that the activity of SOD and CAT in hippocampal and cortical tissues of PTZ-TP100 group was more than PTZ-TP50 (P<0.05 and P<0.001). The activity of SOD and CAT in mice brain tissues in PTZ-TP200 group was lesser than PTZ-TP100 group (P<0.05, P<0.01 and P<.001) (Figures 3C, 3D, 4C and 4D).

Comparison the effect of the most effective dose (100 mg/kg) of TP extracts with its aqueous and N- butanol fractions on oxidative stress indexes

Biochemical results displayed that the MDA level of hippocampal and cortical tissues of PTZ-Aq100 and PTZ-NBut100 groups was higher than PTZ-TP100 group (P<0.001) (Figures 5A and 6A). The total thiol level of brain tissues of PTZ-Aq100 group was lesser than PTZ-TP100 group (P<0.01). The content of total thiol of hippocampal tissue of PTZ-NBut100 group was more than PTZ-Aq100 group (P<0.01). There was not any significant difference in total thiol level of brain tissues of PTZ-NBut100 group with PTZ-TP100 group (Figures 5B and 6B).

Data indicated that the activity of SOD and CAT in hippocampal and cortical tissues of PTZ-Aq100 and PTZ-NBut100 groups was lower than PTZ-TP100 group (P<0.01 and P<0.001) (Figures 5C, 5D, 6C and 6D).

Discussion

Neuronal hyper-excitability resulted from repeated seizures can terminate to neuro-degeneration and brain oxidative damage. PTZ is a GABA<sub>A</sub> receptors inhibitor which can irritate frequent neuronal discharges resulting in convulsion and neuronal death. In present work, intraperitoneal injection of PTZ led to severe neuronal discharges associated with fast MCS and GTCS in mice. Oxidative stress, inflammatory responses and apoptosis have been proposed to have an important contribution in brain seizures pathogenesis. Down-regulation of antioxidant agents such as total SOD, α- tocopherol and glutathione disulfide (GSSG) in cerebral cortex of PTZ-kindled animals has been also documented. Electron paramagnetic resonance (EPR) imaging from brain of mice kindled by PTZ indicated a strong imbalance in oxidative state in susceptible brain areas to oxidative damage including cortex and hippocampus. Moreover, uncontrolled generation of free radicals such as nitric oxide (NO) and mitochondrial damage in epileptic brain has been revealed. In agreement with these reports, we observed an imbalance in oxidative state of cortex and hippocampus tissues of PTZ-kindled mice. Higher level of MDA, lower content of thotal thiol groups and lesser activity of antioxidant enzymes, SOD and CAT, in cortex and hippocampus tissues of PTZ-injected mice than those

![Figure 5](attachment:image.png)

**Figure 5.** Comparison the effect of aqueous and N-butanol fractions of TP with medium dose on MDA concentration (A), total thiol level (B) and activity of SOD (C) and CAT (D) in hippocampus tissue in treated groups. Data were showed as the mean ± SEM (n= 10). ***P<0.001 versus control group, **P<0.01 and *P<0.05 versus PTZ group, +P<0.05, ++P<0.01 and +++P<0.001 versus PTZ group, $P<0.01 and $$P<0.001 versus PTZ-TP100 group and &&P<0.01 versus PTZ-Aq100.
of control group support this scientific finding.

TP is a medicinal herb which has an abroad spectrum of therapeutic properties including anti-inflammatory, anti-asthma, anti-pyrogenic, anti-migraine, anti-arthritis, anti-parasitic and anti-diabetic. In this study, to determine the most effective dose we examined the effect of three doses of hydro-ethanolic extract of this plant on PTZ-promoted seizures in mice. Retardation in inception of MCS and GTCS is considered as an index to evaluate the violence of seizures in experimental models. According to behavioral results; the moderate dose of TP extract (100 mg/kg) acted as the best dose and prolonged the beginning of MCS and GTCS in animals of PTZ-TP100 group compared with PTZ group. Our results indicated that the lowest and highest doses of extract did not affect the delay in onset of seizures caused by PTZ injection. Therefore, it is deduced that the effect of TP extract on PTZ-induced seizures was applied in dose-independent manner in rats. In traditional medicine, there are a large massive of evidence that emphasize that the plant extracts and their ingredients can improve brain oxidative stress. Parthenolide, luteolin and flavonoids found in TP extract has been introduced to be as antioxidant compounds. Mitigation of free radicals accumulation and augmentation of SOD and CAT by TP extract in CCl\textsubscript{4}-caused hepatotoxicity in rats has been illustrated. In another study, researchers suggested that methanolic extract of TP improved renal dysfunction induced by CCl\textsubscript{4} in rats. This ameliorative effect was attributed to decline in lipid peroxidation and enhancement of SOD and GPx activity in renal tissues of rats. In current study, the moderate dose of TP normalized oxidative stress state in cortical and hippocampal tissues of mice. Decrement in accumulation of MDA, increscent in total thiol level and amplification in SOD and CAT activity were perceived in cortical and hippocampal tissues of PTZ-TP100 group than the animals of PTZ group. Thus it seems that a part of anticonvulsant effects of TP that perceived in current investigation was carried out via modulation of oxidative damage resulted from PTZ administration. Furthermore, parthenolide present in TP extract has been suggested to attenuate inducible nitric oxide synthase (iNOS) expression, to reduce the activity of transcriptional causes involved in inflammatory pathways such as nuclear factor–Kappa B and to inhibit IκB kinase complex β as one of the principal player in inflammation caused by cytokines. Based on these findings, modulation of inflammatory responses by anti-inflammatory causes of TP extract can be considered as another possible mechanism for anticonvulsant effects of this herb. However; this needs to more detailed investigation to elucidate.

Recently, hypnotic poetries of hydro-alcoholic extract and ethyl acetate fraction of TP have been confirmed in rats.
Effects of Tanacetum parthenium on PTZ-Induced Seizures

Scientific studies also showed that ethyl acetate fraction which possesses ingredients with partial polarity such as flavonoids not only shortened latency of sleep but also lengthened the time of sleep in rats. Hydro-ethanolic fraction of TP has been also reported to have antiviral effects. This antimicrobial effect is due to parthenolide and chlorogenic present in this fraction. In current study we also compared the effect of n-butanol and aqueous fractions of TP with its moderate dose of TP extract on seizure parameters and biochemical dial. Based on behavioral results, the effect of n-butanol fraction in putting off the latency time of MCS and GTCS irritated by PTZ was similar to that of moderate dose. As shown in Figures 2A and 2B the administration of aqueous fraction of TP did not affect the latency time of MCS and GTCS in PTZ-Aq100 group compared with PTZ group. Biochemical findings also demonstrated that neither n-butanol fraction nor aqueous fraction could exert a better effect on brain oxidative damage followed by PTZ infusion than moderate dose of TP. Therefore, it was deduced that effective ingredients of TP extract are likely not purified by n-butanol and aqueous solvents. We also compared the effect of n-butanol fraction of TP with its aqueous fraction on PTZ-induced seizures. Findings showed that n-butanol fraction of TP with respect to aqueous fraction considerably could attenuate the severity of seizures. Considering the extraction of polar ingredients by water fraction and dissociation of non-polar agents by n-butanol fraction, it is possible that non-polar compounds contribute in reduction of seizures in our study. Unlike the behavioral results we did not find any significant difference in concentration of biochemical indexes in brain tissues of mice between these two fractions. Therefore, it was concluded that likely other mechanisms are responsible in reduction seizures by TP fractions. But it needs to be examined more precisely in future.

Conclusion

In final, the results showed that the moderate dose of hydro-ethanolic extract of TP acted as the most effective dose and diminished the severity of seizures triggered by PTZ in mice. These effects can be attributed to probable antioxidant properties this extract. In addition, it was detected that n-butanol and aqueous fractions of TP could not restore brain oxidative stress caused by PTZ when they compared with moderate dose.

Ethical Issues

All processes of this project were confirmed by the research ethics committee of Mashhad University of Medical Sciences with IR.MUMS.fm.REC.1397.134 ethic code.

Acknowledgments

The authors appreciate the Vice Chancellor for Research and Technology of Mashhad University of Medical Sciences for their financial support (961201).

Conflict of Interests

The authors claim that there is no conflict of interest.

References

1. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069-77. doi:10.1111/j.1528-1167.2009.02397.x
2. Conradsen I, Wolf P, Sams T, Sorensen HB, Beniczky S. Patterns of muscle activation during generalized tonic and tonic-clonic epileptic seizures. Epilepsia. 2011;52(11):2125-32. doi:10.1111/j.1528-1167.2011.03286.x
3. Kundap UP, Paudel YN, Kumari Y, Othman I, Shaikh MF. Embelin Prevents Seizure and Associated Cognitive Impairments in a Pentylenetetrazole-Induced Kindling Zebrafish Model. Front Pharmacol. 2019;10:315. doi:10.3389/fphar.2019.00315
4. Sudha K, Rao AV, Rao A. Oxidative stress and antioxidants in epilepsy. Clin Chim Acta. 2001;303(1-2):19-24. doi:10.1016/s0009-8981(00)00337-5
5. Galic MA, Riazi K, Heida JG, Mouhate A, Fournier NM, Spencer SJ, et al. Postnatal inflammation increases seizure susceptibility in adult rats. Version 2. J Neurosci. 2008;28(27):6904-13. doi:10.1523/JNEUROSCI.1901-08.2008
6. Lee JM, Ji ES, Kim TW, Kim CJ, Shin MS, Lim BV, et al. Treadmill exercise improves memory function by inhibiting hippocampal apoptosis in pilocarpine-induced epileptic rats. J Exerc Rehabil. 2018;14(5):713-23. doi:10.12965/jer.36394.197
7. Hussein AM, Abbas KM, Abulseoud OA, El-Hussainy EMA. Effects of ferulic acid on oxidative stress, heat shock protein 70, connexin 43, and monoamines in the hippocampus of pentylenetetrazole-kindled rats. Can J Physiol Pharmacol. 2017;95(6):732-42. doi:10.1139/cjp-2016-0219
8. Pearson-Smith JN, Patel M. Metabolic Dysfunction and Oxidative Stress in Epilepsy. Int J Mol Sci. 2017;18(11):2365. doi:10.3390/ijms18112365
9. Islas-Espinoza AM, Campos-Rodriguez C, San Juan ER, Thalidomide protects against acute pentylenetetrazol and pilocarpine-induced seizures in mice. J Toxicol Sci. 2018;43(11):671-84. doi:10.2131/jts.43.671
10. Sun Y, Ma J, Li D, Li P, Zhou X, Li Y, et al. Interleukin-10 inhibits interleukin-1β production and inflammasome activation of microglia in epileptic seizures. J Neuroinflammation. 2019;16(1):66. doi:10.1186/s12974-019-1452-1
11. Möller C, Wolf F, van Dijk RM, Di Liberto V, Russmann V, Keck M, et al. Toward evidence-based severity assessment in rat models with repeated seizures: I. Electrical kindling. Epilepsia. 2018;59(4):765-77. doi:10.1111/epi.14028
12. Chen Y, He X, Sun Q, Fang Z, Zhou L. Effect
of lamotrigine on seizure development in a rat pentylenetetrazole kindling model. Brain Behav. 2017;7(7):e00727. doi: 10.1002/brb3.727

13. Yang H, Zhang R, Jia C, Chen M, Yin W, Wei L, et al. Neuronal protective effect of Songling Xuemaikang capsules alone and in combination with carbamazepine on epilepsy in kainic acid-kindled rats. Pharm Biol. 2019;57(1):22-8. doi: 10.1080/13880290.2018.1563619

14. Anaiegoudari A, Hosseini M, Karami R, Vafaee F, Mohammadpour T, Ghorbani A, et al. The effects of different fractions of Coriandrum sativum on pentylenetetrazole-induced seizures and brain tissues oxidative damage in rats. Avicenna J Phytomed. 2016;6(2):223-35.

15. Munguía-Martínez MF, Nava-Ruiz C, Ruiz-Díaz A, Díaz-Ruíz A, Yescas-Gómez P, Méndez-Armenta M. Immunohistochemical Study of Antioxidant Enzymes Regulated by Nrf2 in the Models of Epileptic Seizures (KA and PTZ). Oxid Med Cell Longev. 2019;2019:1327986. doi: 10.1155/2019/1327986

16. Hussein AM, Eldosoky M, El-Shafey M, El-Mesery M, Abbas KM, Ali AN, Helal GM, Abulseoud OA. Effects of GLP-1 Receptor Activation on a Pentylenetetrazole-Kindling Rat Model. Brain Sci. 2019;9(5):108. doi: 10.3390/brainsci9050108

17. Gao B, Wu Y, Yang YJ, Li WZ, Dong K, Zhou J, Yin YY, Huang DK, Wu WN. Sinomine exerts anticonvulsant profile and neuroprotective activity in pentylenetetrazole kindled rats: involvement of inhibition of NLRP1 inflammasome. J Neuroinflammation. 2018;15(1):152. doi: 10.1186/s12974-018-1199-0

18. Sharopov FS, Setzer WN, Isupov SJ, Wink M. Composition and bioactivity of the essential oil of Tanacetum parthenium from a wild population growing in Tajikistan. Am J Essent Oil. 2015;2(4):32-4.

19. Tiuman TS, Ueda-Nakamura T, Garcia Cortez DA, Dias Filho BP, Morgado-Díaz JA, de Souza W, et al. Antileishmanial activity of parthenolide, a sesquiterpene lactone isolated from Tanacetum parthenium. Antimicrob Agents Chemother. 2005;49(1):176-82. doi: 10.1128/AAC.49.1.176-182.2005

20. Polatoglu K, Demirci F, Demirci B, Gören N, Başer KH. Antibacterial activity and the variation of Tanacetum parthenium (L.) Schultz Bip. essential oils from Turkey. J Oleo Sci. 2010;59(4):177-84. doi: 10.5650/jos.59.177

21. Pareek A, Suthar M, Rathore GS, Bansal V. Feverfew (Tanacetum parthenium L.): A systematic review. Pharmacogn Rev. 2011;5(9):103-10. doi: 10.4103/0973-7847.79105

22. Patel NM, Nozaki S, Shortle NH, Bhat-Nakshatri P, Newton TR, Rice S, Gelfanos V, Boswell SH, Goulet RJ Jr, Sledge GW Jr, Nakshatri H. Paclitaxel sensitivity of breast cancer cells with constitutively active NF-kappaB is enhanced by IkappaBalpha super-repressor and parthenolide. Oncogene. 2000;19(36):4159-69. doi: 10.1038/sj.onc.1203768

23. Williams CA, Harborne JB, Geiger H, Houlit JR. The flavonoids of Tanacetum parthenium and T. vulgare and their anti-inflammatory properties. Phytochemistry. 1999;51(3):417-23. doi: 10.1016/s0031-9422(99)00021-7

24. Mahmoodzadeh Y, Mazani M, Rezagholizadeh L. Hepatoprotective effect of methanolic Tanacetum parthenium extract on CCl4-induced liver damage in rats. Toxicol Rep. 2017;4:455-62. doi: 10.1016/j.toxrep.2017.08.003

25. Youdim KA, Qaiser MZ, Begley DJ, Rice-Evans CA, Abbott NJ. Flavonoid permeability across an in situ model of the blood-brain barrier. Free Radic Biol Med. 2004;36(5):592-604. doi: 10.1016/j.freeradbiomed.2003.11.023

26. Kambe D, Kotani M, Yoshimoto M, Kaku S, Chaki S, Honda K. Effects of quercetin on the sleep-wake cycle in rats: involvement of gamma-aminobutyric acid receptor type A in regulation of rapid eye movement sleep. Brain Res. 2010;1330:83-8. doi: 10.1016/j.brainres.2010.03.033

27. Moscano F, Guiducci M, Maltoni L, Striano P, Ledda MG, Zoroddu F, et al. An observational study of fixed-dose Tanacetum parthenium nutraceutical preparation for prophylaxis of pediatric headache. Ital J Pediatr. 2019;45(1):36. doi: 10.1186/s13052-019-0624-z

28. Ghorbani A, Sadeghnia HR, Asadpour E. Mechanism of protective effect of lettuce against glucose/serum deprivation-induced neurotoxicity. Nutr Neurosci. 2015;18(3):103-9. doi: 10.1179/1476830513Y.00000000107

29. Ghorbani A, Javadi Yousofabad N, Rakhshandeh H. Effect of Viola tricolor on pentobarbital-induced sleep in mice. Afr J Pharm Pharmacol. 2012;6(35):2600-6.

30. Baghcheghi Y, Beheshti F, Shafei MN, Salmani H, Sadeghnia HR, Soukhtanloo M, et al. The effects of vitamin E on brain derived neurotrophic factor, tissues oxidative damage and learning and memory of juvenile hypothryoid rats. Metab Brain Dis. 2018 Jun;33(3):713-24. doi: 10.1007/s11011-017-0176-0

31. Hosseini M, Anaiegoudari A, Beheshti F, Soukhtanloo M, Nosratabadi R. Protective effect against brain tissues oxidative damage as a possible mechanism for beneficial effects of L-arginine on lipopolysaccharide induced memory impairment in rats. Drug Chem Toxicol. 2018;41(2):175-81. doi: 10.1080/01480545.2017.1336173

32. Beheshti F, Hosseini M, Taheri Sarvtnin M, Kamali A, Anaiegoudari A. Protective effect of aminoguanidine against lipopolysaccharide-induced hepatotoxicity and liver dysfunction in rat. Drug Chem Toxicol. 2019;42(7):713-24. doi: 10.1080/01480545.2018.1561712

33. Yu JT, Liu Y, Dong P, Cheng RE, Ke SX, Chen KQ, et al. Up-regulation of antioxidative proteins TRX1, TXNL1 and TXNRD1 in the cortex of PTZ kindling seizure model mice. PLoS One. 2019;14(1):e0210670. doi: 10.1371/journal.pone.0210670
34. Hao F, Jia LH, Li XW, Zhang YR, Liu XW. Garcinol upregulates GABAA and GAD65 expression, modulates BDNF-TrkB pathway to reduce seizures in pentylenetetrazole (PTZ)-induced epilepsy. Med Sci Monit. 2016;22:4415-25. doi:10.12659/msm.897579

35. Bibi F, Ullah I, Naseer MI. Metformin attenuate PTZ-induced apoptotic neurodegeneration in human cortical neuronal cells. Pak J Med Sci. 2017;33(3):581-5. doi:10.12669/pjms.333.11996

36. Rauca C, Wiswedel I, Keilhoff G, Krug M. The role of superoxide dismutase and alphatocopherol in the development of seizures and kindling induced by pentylenetetrazol - influence of the radical scavenger alpha-phenyl-N-tert-butyl nitron. Brain Res. 2004;1009(1-2):203-12. doi:10.1016/j.brainres.2004.01.082

37. Emoto MC, Yamato M, Sato-Akaba H, Yamada K, Fujii HG. Brain redox imaging in the pentylenetetrazole (PTZ)-induced kindling model of epilepsy by using in vivo electron paramagnetic resonance and a nitroxide imaging probe. Neurosci Lett. 2015;608:40-4. doi:10.1016/j.neulet.2015.10.008

38. Zhu X, Dong J, Han B, Huang R, Zhang A, Xia Z, et al. Neuronal Nitric Oxide Synthase Contributes to PTZ Kindling Epilepsy-Induced Hippocampal Endoplasmic Reticulum Stress and Oxidative Damage. Front Cell Neurosci. 2017;11:377. doi:10.3389/fncel.2017.00377

39. Johnson ES, Kadam NP, Hylands DM, Hylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. Br Med J (Clin Res Ed). 1985;291(6495):569-73. doi:10.1136/bmj.291.6495.569

40. Pattrick M, Heptinstall S, Doherty M. Feverfew in rheumatoid arthritis: a double blind, placebo controlled study. Ann Rheum Dis. 1989;48(7):547-49. doi:10.1136/ard.48.7.547

41. Jain NK, Kulkarni SK. Antinociceptive and anti-inflammatory effects of Tanacetum parthenium L. extract in mice and rats. J Ethnopharmacol. 1999;68(1-3):251-9. doi:10.1016/s0378-8741(99)00115-4

42. Baghchechi Y, Hosseini M, Beheshti F, Salmani H, Anaegoudari A. Thymoquinone reverses learning and memory impairments and brain tissue oxidative damage in hypothyroid juvenile rats. Arq Neuropsiquiatr. 2018;76(1):32-40. doi:10.1590/0004-282X20170182

43. Goodla L, Manubolu M, Pathakoti K, Jayakumar T, Sheu JR, Fraker M, et al. Protective Effects of Ammannia baccifera Against CCl4-Induced Oxidative Stress in Rats. Int J Environ Res Public Health. 2019;16(8):1440. doi:10.3390/ijerph16081440

44. Mazani M, Mahmoodzadeh Y, Chinifroush Asl MM, Banaei S, Rezagholizadeh L, Mohammadnia A. Renoprotective effects of the methanolic extract of Tanacetum parthenium against carbon tetrachloride-induced renal injury in rats. Avicenna J Phytomed. 2018;8(4):370-9.

45. Forouzanfar F, Ghazavi H, Yahedi MM, Tarrah K, Yavari Z, Hosseini A, Aghae A, Rakhshandeh H. Tanacetum parthenium enhances pentobarbital-induced sleeping behaviors. Avicenna J Phytomed. 2020;10(1):70-7.

46. Benassi-Zanqueta É, Marques CF, Valone LM, Pellegrini BL, Bauermeister A, Ferreira ICP, et al. Evaluation of anti-HSV-1 activity and toxicity of hydroethanolic extract of Tanacetum parthenium (L.) Sch.Bip. (Asteraceae). Phytomedicine. 2019;55:249-54. doi:10.1016/j.phymed.2018.06.040