Journal of Neuroimmunology 326 (2019) 79–83

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Gelatin hydrogel containing cerium oxide nanoparticles covered by interleukin-17 aptamar as an anti- inflammatory agent for brain inflammation

Seyedhossein Hekmatimoghaddam[a], Maryam Iman[b,*], Hossein Shahdadi Sardo[b], Ali Jebali[a,c,**]

[a] Department of Laboratory Sciences, School of Paramedicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[b] Chemical Injuries Research Center, Systems biology and poisonings institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[c] Medical biotechnology Research Center, Ashkezar Branch, Islamic Azad University, Ashkezar, Yazd, Iran

ARTICLE INFO

Keywords:
Cerium oxide
Nanoparticles
Aptamer
Brain inflammation

ABSTRACT

The purpose of this study was to evaluate the anti-inflammatory property of gelatin hydrogel containing cerium oxide nanoparticles coated with interleukin-17 Aptemer ([CeON@IL-17]). Here, the brain inflammation model was induced by both proteolipid protein (PLP) and parathion. Then, the expression of some inflammatory genes and the serum level of related interleukins were evaluated. This study showed that the expression of *IL-17, IL-10,* and *IL-6* genes and their serum levels were significantly decreased ($P < .05$) by administration of gelatin hydrogel containing [CeON@IL-17].

1. Introduction

Brain inflammation can be due to diseases such as Multiple sclerosis (MS) or chemicals such as nerve toxins. In both of them, some interleukins (ILs) are secreted, e.g., IL-17. IL-17 is an important cytokine not only for protective immunity against intracellular and extracellular pathogens, but also for the pathogenesis of various autoimmune inflammatory diseases of Brain and central nervous system (Kuwabara et al., 2017).

Interestingly, the increase of some ILs may be shown in brain inflammation due to chemicals. Parathion is an example of organophosphate pesticides that induce brain inflammation (Kazemi et al., 2012). Extreme usage of pesticides increases the pesticide residues in drinking water or in wastewater. The pesticide transmission in soil and water depends on different physical, chemical and biological processes, including adsorption, uptake, degradation, run off and leaching. It is highly toxic not only for insects but also for non-target organisms, such as human. The usual concentrations which used are 0.05 to 0.1%. Parathion can inactive acetylcholinesterase indirectly. After ingesting, an oxidase replaces the double bonded sulfur with oxygen to give paraoxon. The phosphate ester is more reactive than the phosphorothiolate ester. These reactive chemicals can leads to human brain damage. Brain inflammation induced by organophosphate toxins (BIIOTs) is an acute cerebrovascular disorder that causes physical disability. The cause of the disease is still unclear, but its main mechanism is damaged by the immune system or disruption of the cells producing myelin (Li et al., 2015; Yadav et al., 2016). Inflammation is present in all stages of the disease, but in the acute phase of inflammation, it is more noticeable than the chronic stage. Primary lesions indicate that immune cells attack the central nervous system and pass through a blood-brain barrier. These cells have a greater percentage of macrophages and TCD + 8 cells, while TCD + 4 cells and B cells are less filtered into the central nervous system. IL-17, IL-10, IL-6, and IL-23 are the main cytokines involved in the disease (De Felice et al., 2016; Delaney & Environmental Exposures, 2018). The person with BIIOTs has all the signs or symptoms of the neurology. The most common symptoms are the autonomic, visual, motor and sensory nervous system problems. Specific symptoms are identified through the sites of the ulcer in the nervous system, including low odor or loss of appetite such as molestation, spasm Muscle weakness, involuntary reactions, muscle cramps or inability to move, inability to coordinate and balance muscle imbalance, difficulty speaking or dysphagia, visual problems (ocular movement, vision loss, or double vision), feeling tired, severe pain or chronic pain And the problem is in urine and stool. However, in some cases, this worsening of the disease follows common symptoms and occurs more often in the spring and summer. Similarly, viral infections such as common colds, influenza or inflammation can increase their likelihood. Stress may also cause an attack (Monnet-

* Corresponding author at: Chemical Injuries Research Center, Systems biology and poisonings institute, Baqiyatallah University of Medical Sciences, Tehran, Iran.
** Co-corresponding author at: Department of Laboratory Sciences, School of Paramedicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
E-mail addresses: maryamiman2008@gmail.com, iman1359@yahoo.com (M. Iman), alijebal2011@gmail.com (A. Jebali).

https://doi.org/10.1016/j.jneuroim.2018.11.011
Received 2 August 2018; Received in revised form 28 August 2018; Accepted 21 November 2018

Tschudi et al., 2007; Rauh et al., 2012).

There is currently no definitive treatment for brain inflammation, but in recent years, there has been a dramatic improvement. The basis of therapeutic medicines is immune suppression and immunization. These drugs reduce the number of attacks and delay the progression of the disease and only affect the inflammatory parts of the disease. These suppressing inflammatory agents have little or no effect on the patient's healing (Chen, 2012; Kim et al., 2012). The purpose of this study was to evaluate the anti-inflammatory property of gelatin hydrogel containing cerium oxide nanoparticles covered with interleukin-17 Aptemer ([CeON@IL-17]).

2. Materials and methods

2.1. Materials

Cerium chloride ($CeCl_2$), NaOH, gelatin, and Parathion were purchased from Sigma Company, Germany. All primers and aptamer were provided from TakapoZyzt Company, Iran. RiboX buffer was sourced from GeneAll company, South Korea. SYBR® Green Real-Time Master Mix, cDNA Mastermix, and gelatin hydrogel were purchased from Invitrogen, UK. ELISA kits for IL-17, IL-10, and IL-6 detection were provided from Abcam, UK.

2.2. Preparation of [CeON@IL-17]

Depend on the solubility of $CeCl_2$, 50 g of it was dissolved in 50 mL of distilled deionized water. According to its molecular weight, the concentration of the solution was about 4 M. Also, 8 g of NaOH was dissolved in 50 mL of distilled water, and a solution at a concentration of 4 M was prepared. Serial concentrations (4, 2, 1, 0.1, 0.01, 0.001 M) of both $CeCl_2$ and NaOH were prepared, and mixed in a matrix. After 5 min incubation at room temperature, all tubes were centrifuged. After washing, the tube was chosen which had the most sediment. Then, 25 μg of prepared nanoparticle was mixed with 500 μL of interleukin-17 aptamer at concentration of 100 pM, and then incubated for 3 h at 37 °C. To further dissolve of coated nanoparticles and to allow injection into mice, 200 μL of dextran solution at concentration of 100 mg/mL was added to coated nanoparticles, and it was again washed three times with PBS. In order to characterize final nanoparticles, a scanning electron microscope was used. The concentration of 5 μg/ml was used for mice injection. To prepare final formulation, 5 mL of [CeON@IL-17] at 50 μg/mL was mixed with 5 mL of gelatin 1%, and incubated for 1 h at 37 °C, and then stored at 4 °C.

2.3. Characterization of [CeON@IL-17]

SEM was used to find the shape and size of nanoparticles. The sample was coated with gold by a metalizer. Moreover, both size distribution and zeta potentials were measured on a Malvern ZEN2600 Zetasizer Nano Z. Also, FTIR spectra were carried out on broker FTIR spectrometer to estimate the binding of aptamer on the surface of CeO nanoparticles.

2.4. Preparation of animal model for brain inflammation

To prepare brain inflammation, two models were used, including toxin model and experimental autoimmune encephalomyelitis (EAE) model. For toxin model, 100 μL of Parathion 10%*v*/v was separately injected intra-peritoneal to C57BL/6 female mice, weight 25 g sourced from Institute pastur, Iran. After this, injection was done. The injection was intravenous into the rat's tail region. The injection volume was 100 μL for 3 days, and the injection time was after secondary immunization. For EAE model, C57BL/6 female mice were immunized with proteolipid protein (PLP), and then sensitized with pertussis toxin (Brocke et al., 1994). All experiments were in accordance with the guidelines of the National Institute of Health, and ethics committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran and Baqiyatallah University of Medical Sciences, Tehran. Iran.

2.5. Study groups

1) C57BL/6 female mice that received neither parathion or gelatin hydrogel containing [CeON@IL-17], 2) C57BL/6 female mice that only received parathion, 3) C57BL/6 female mice that received both parathion and gelatin hydrogel containing [CeON@IL-17], 4) C57BL /6 female mice that only exposed to PLP, 5) C57BL/6 female mice that exposed to PLP and treated with gelatin hydrogel containing [CeON@IL-17].

2.6. Real-time PCR

RiboX buffer was used for extraction of total RNA. To synthesis of cDNA, 10 μL of cDNA Mastermix was added to 10 μL of total RNA and incubated at 50 °C for 60 min. After synthesis, quantitative PCR was done. For this purpose, 2 μL of cDNA, 2 μL of forward primer, and 2 μL of reverse primer of each gene were added to 10 μL of SYBR® Green Real-Time Master Mix. After running of Real-time PCR machine (ABI 1 plus, USA), CT of each gene was recorded, and the expression of *IL-17, IL-10,* and *IL-6* was calculated by ΔΔCT formula.

2.7. ELISA

After each week, blood samples were collected from the mice to analyze the level of IL-17, IL-10, and IL-6 by ELISA assay according to the manufacturer's protocol. The concentration of each cytokine was calculated based on the plotted standard curve.

2.8. Statistical analysis

All tests were done three times and reported as the mean ± standard deviation (SD). To find significant differences between groups, one-way ANOVA method was applied. *P*-value < .05 was considered as statistically significant.

3. Results

3.1. Characterization

Fig. 1a and b shows SEM image and DLS graph of [CeON@IL-17], respectively. The synthesized nanoparticles were circular and had a size of 25–80 nm with zeta potential of –50 mV. It was found that the binding process did not significantly lead to agglomeration. FTIR spectra of [CeON@IL-17] showed five main characteristic peaks at 1544 cm^{-1} (amide II) and 1645 cm^{-1} (amide I), 1250 cm^{-1}, 756 cm^{-1}, and 1347 cm^{-1} which indicated correct coating.

3.2. Gene expression

Table 1 shows the expression of *IL-17, IL-10,* and *IL-6* gene when C57BL/6 female mice exposed to Parathion alone and then treated with gelatin hydrogel containing [CeON@IL-17]. Table 2 demonstrates the expression of *IL-17, IL-10,* and *IL-6* gene when C57BL/6 female mice exposed to PLP and then treated with gelatin hydrogel containing [CeON@IL-17]. As seen in both tables, the expression of *IL-17, IL-10,* and *IL-6* genes was increased during 5 weeks when exposed to Parathion. Importantly, from week 3, the expression of these interleukins was significantly decreased ($P < .05$). This pattern was seen for treated groups.

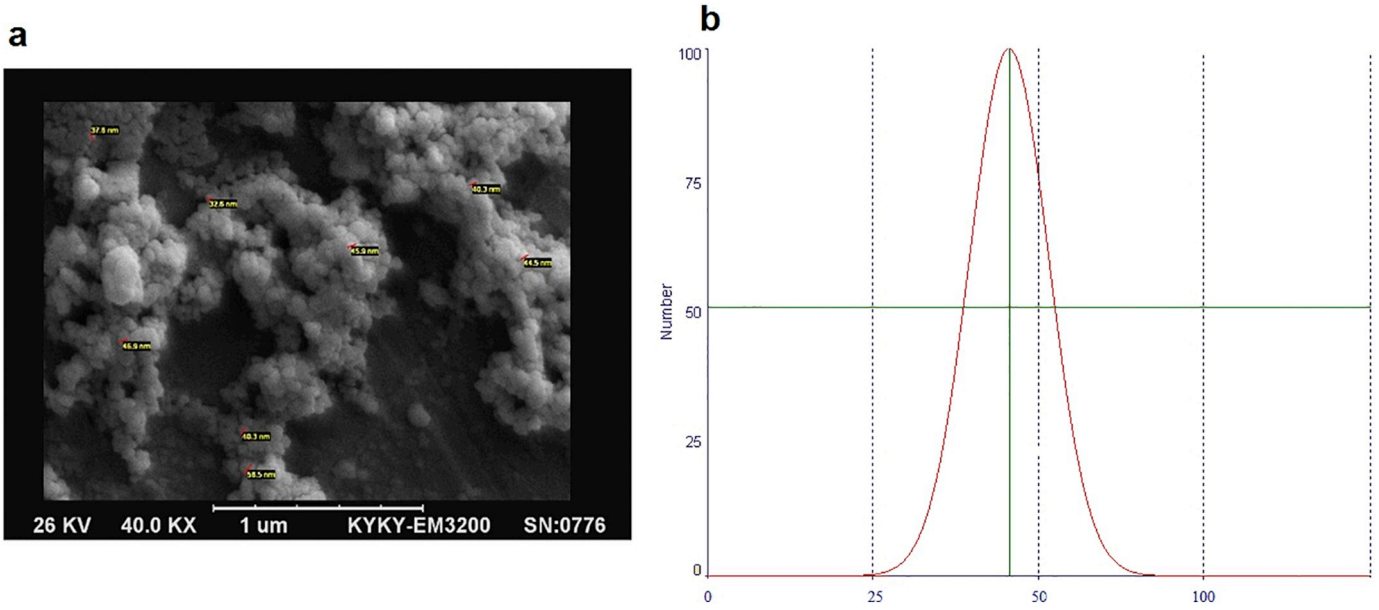

Fig. 1. Characterization data of [CeON@IL-17]. SEM image (a) and DLS graph (b).

Table 1
The expression of *IL-17, IL-10,* and *IL-6* gene when C57BL/6 female mice exposed to Parathion alone and [CeON@IL-17] + Parathion.

	Week 1	Week 2	Week 3	Week 4	Week 5
	IL-17				
Parathion and [CeON@IL-17]	1	11	2.2*	1.8*	1*
Parathion control	1.1	10	12	12.5	15
	IL-10				
Parathion and [CeON@IL-17]	1	8.1	3.2*	2*	2.1*
Parathion control	1	8	9	12	14.5
	IL-6				
Parathion and [CeON@IL-17]	1.1	13	5.3*	2.1*	2.1*
Parathion control	1.1	12	13	15	17

* $P < .05$ compared to control, $n = 5$.

Table 2
The expression of *IL-17, IL-10,* and *IL-6* gene when C57BL/6 female mice exposed to PLP alone and PLP + [CeON@IL-17].

	Week 1	Week 2	Week 3	Week 4	Week 5
	IL-17				
PLP and [CeON@IL-17]	1.2	10	2.3*	1.6*	1.1*
PLP[a]	1.1	11	11.8	12.2	15.6
	IL-10				
PLP and [CeON@IL-17]	1.2	8.2	3*	2.2*	2.4*
PLP	1.2	8.1	9.5	12.3	14
	IL-6				
PLP and [CeON@IL-17]	1	13.7	5*	2.7*	2.6*
PLP	1.1	12.3	13.6	15.1	17.9

* $P < .05$ compared to control, n = 5.
[a] PLP induces EAE model.

3.3. ELISA

Table 3 demonstrates the serum level of IL-17, IL-10, and IL-6 when C57BL/6 female mice exposed to PLP alone and then treated with gelatin hydrogel containing [CeON@IL-17]. Table 4 shows the serum level of IL-17, IL-10, and IL-6 when C57BL/6 female mice exposed to Parathion alone and then treated with gelatin hydrogel containing [CeON@IL-17]. As seen in both tables, the concentration of IL-17, IL-10, and IL-6 was increased during 5 weeks when exposed to Parathion. Same as gene expression, from week 3, the level of all interleukins was sharply decreased ($P < .05$). Here, this pattern was seen for treated groups.

Table 3
The serum level of IL-17, IL-10, and IL-6 when C57BL/6 female mice exposed to PLP alone and PLP + [CeON@IL-17].

	Week 1	Week 2	Week 3	Week 4	Week 5
	IL-17(ng/mL)				
PLP[a] and [CeON@IL-17]	2	10	12*	13*	17*
PLP	2.1	16	17	21	25
	IL-10(ng/mL)				
PLP and [CeON@IL-17]	2	10*	14*	15*	17*
PLP	2.4	21	25	27	31
	IL-6(ng/mL)				
PLP and [CeON@IL-17]	2	12*	13*	15*	15*
PLP	2.1	20	25	27	34

* $P < .05$ compared to control, n = 5.
[a] PLP induces EAE model.

Table 4
The serum level of IL-17, IL-10, and IL-6 when C57BL/6 female mice exposed to Parathion alone and [CeON@IL-17] + Parathion.

	Week 1	Week 2	Week 3	Week 4	Week 5
	IL-17(ng/mL)				
Parathion and [CeON@IL-17]	2.2	11	13*	13.3*	17.3*
Parathion control	2.1	16.2	17.3	21.5	26
	IL-10(ng/mL)				
Parathion and [CeON@IL-17]	2.3	10.3*	14.1*	15.8*	17.3*
Parathion control	2.4	22	25.2	28	31.9
	IL-6(ng/mL)				
Parathion and [CeON@IL-17]	2.3	12.2*	14*	13.2*	15.3*
Parathion control	2.1	21	25.3	27.9	34.1

* $P < .05$ compared to control, n = 5.

4. Discussion

In brain inflammation, nerve cells in the brain and spinal cord are damaged. This damage can interfere with the ability of the parts of the

nervous system that is responsible for communication, resulting in many signs and symptoms. Brain inflammation appear in several forms, including acute and chronic. In relapses, the symptoms of the disease may disappear completely. However, permanent neurological problems occur continuously in the next stages. Although the cause of the disease is organophosphate toxins, the related mechanisms are not known. The main mechanism is damaging of nerve cells by the immune system or disruption of glial cells. Usually, brain inflammation is detected based on the symptoms and some medical tests. Although medications that are prescribed to treat brain inflammation are slightly effective, they have side effects and are difficult to tolerate. So, many researchers are seeking new therapies (Li et al., 2015; Tuler & Bowen, 1989; Iyer et al., 2015).

In this study, gelatin hydrogel containing [CeON@IL-17] was studied to reduce brain inflammation in mice suffering BIIOT. Parathion was used for this project, because these toxins are now widely used in agriculture and industry. The reason for the use of cerium oxide was its anti-inflammatory and anti-oxidant property. Our hypothesis was that cerium oxide nanoparticles could decrease brain inflammation. Of course, the entry of cerium oxide nanoparticles into the brain is an important challenge that should be further explored. Designing specialized carriers to actively or passively passage into the brain is important. The coating of nanoparticles with aptamer was also done in this direction. Since this interleukin is abundant in the inflammatory regions of the brain, it can be a good target for nanoparticle delivery. In this study, we aimed to target brain inflammation by anti-Interleukin aptamer which covered on cerium oxide nanoparticles. It should be noted, however, that there are several barriers to act this structure properly. Firstly, since aptamers are highly dependent on its structure, it is possible that its conformation changes by inflammatory cytokines or other brain chemicals. Secondly, different enzymes which presented in the blood may break down aptamer. Coating nanoparticles with polymers, such as PEG, dextran, starch, etc. can protect aptamer from blood Dnase. Also, enzyme resistance aptamer can be achieved by a slight change in the structure of oligonucleotides. It is a novel way to rejuvenate aptamers.

At the moment, there is still no proper animal model that illustrates all of the molecular aspects of BIIOTs. Although EAE model is the defined model which researchers have been used, it also has own problems. The incomplete brain inflammation and structural changes in myelin are among the disadvantages of EAE models. However, in this research, we tried to prepare two animal model by EAE and parathion toxin. Both sensory evaluations showed that could induce stronger animal model than parathion. This study showed that the expression of *IL-17, IL-10,* and *IL-6* genes was increased during 5 weeks when exposed to Parathion and PLP. Importantly, from week 3, the expression of these interleukins was significantly decreased ($P < .05$). Moreover, the level of IL-17, IL-10, and IL-6 was increased during 5 weeks when exposed to Parathion and PLP. Same as gene expression, from week 3, the level of all interleukins was sharply decreased ($P < .05$). In this study, only one dose of gelatin hydrogel containing [CeON@IL-17] was used, and other doses were not studied. In another study, the tolerable dosage of gelatin hydrogel containing [CeON@IL-17] should be determined and pharmacokinetic of this new drug should be determined. The ability to pass this engineered nanoparticle into the brain should also be studied. In this study, brain reaction was evaluated only 5 weeks after injection of nanoparticles, which was better that it was investigated more long time. It may be less time to give brain inflammation and improve sensory evaluation.

For the first time, this study showed anti-inflammatory property of gelatin hydrogel containing [CeON@IL-17]. In this section, some related studies have been linked. Mohajeri et al. (2010) argued that polymerized nano curcumin reduces neuronal symptoms in the EAE model and it can be improved by adjusting the inflammation, enhancing nerve protection and improving the myelin membrane. They confirmed a significant reduction in the level of demyelination and inflammation and failure of the blood-brain barrier. Gene expression and ELISA data indicated a decrease in inflammation and improve myelination (Mohajeri et al., 2015). In 2011, Mahmoudi and his colleagues claimed that superparamagnetic iron oxide nanoparticles can be used to diagnose and treat brain inflammation. With these nanoparticles, various medical techniques (e.g., positron emission tomography and magnetic resonance) can be improved. These nanoparticles also reduce inflammation and demyelination (Laurent & Mahmoudi, 2011). In 2016, Pires et al. introduced both nano- and micro-based systems for induction of immune tolerance in brain inflammation. They claim that the use of nano and micromaterials is an emerging and innovative solution for the reduction of brain inflammation. In addition, they proposed the use of a new method called microneedle patches, as a new therapeutic route to deliver specific antigens and drugs (Pires et al., 2016). Huiz et al. declared the potential of engineered nanoparticles for treatment of brain inflammation. They noted in their article that many anti-inflammatory drugs have been used in the clinic with several side effects. Meanwhile, nanoparticles are able to overcome such side effects and allow for more accurate delivery of drugs. In addition, nanoparticles can be used to decrease brain inflammation (In't Veld et al., 2017). Yekta et al. showed NaY/Mn0.5Zn0.5Fe2O4 as a new synthesized nanocomposite could adsorb and degrade methyl parathion (Yekta & Sadeghi, 2018). Poupot et al. demonstrated that engineered nanoparticles are good candidates to deliver drugs for brain inflammation to the CNS (Poupot et al., 2018). Gonzalez et al. found that silver nanoparticles (AgNPs) could penetrate into the brain and cause neuronal death. Moreover, AgNPs showed significant anti-inflammatory effects, reducing lipopolysaccharide (LPS)-stimulated ROS, nitric oxide and TNFα production (Gonzalez-Carter et al., 2017).

5. Conclusion

It can be concluded that the expression of *IL-17, IL-10,* and *IL-6* genes and their serum levels were significantly decreased ($P < .05$) by administration of gelatin hydrogel containing [CeON@IL-17]. We think that this can be used for reduction of inflammation due to organophosphate toxins or other brain inflammation diseases.

Acknowledgments

This article was financially supported by Shahid Sadoughi University of Medical Sciences, Yazd, Iran (grant code: 4624) and Baqiyatallah University of Medical Sciences, Tehran. Iran (grant code: 97-02-002252). All experiments were in accordance with the guidelines of the National Institute of Health, and ethics committee codes of above mentioned universities.

Conflict of interest

There was no conflict of interest.

References

Brocke, S., Gijbels, K., Steinman, L., 1994. Experimental autoimmune encephalomyelitis in the mouse. In: Autoimmune Disease Models. Elsevier, pp. 1–14.

Chen, Y., 2012. Organophosphate-induced brain damage: mechanisms, neuropsychiatric and neurological consequences, and potential therapeutic strategies. Neurotoxicology 33 (3), 391–400.

De Felice, A., Greco, A., Calamandrei, G., Minghetti, L., 2016. Prenatal exposure to the organophosphate insecticide chlorpyrifos enhances brain oxidative stress and prostaglandin E 2 synthesis in a mouse model of idiopathic autism. J. Neuroinflammation 13 (1), 149–160.

Delaney, S., Hornig, M., 2018. Environmental exposures and neuropsychiatric disorders: what Role does the Gut–immune–brain axis play? Current Environ. Health Rep 5 (1), 158–169.

Gonzalez-Carter, D.A., Leo, B.F., Ruenraroengsak, P., Chen, S., Goode, A.E., Theodorou, I.G., et al., 2017. Silver nanoparticles reduce brain inflammation and related neurotoxicity through induction of H 2 S-synthesizing enzymes. Sci. Rep. 7, 42871–42879.

In't Veld, R. Huis, Da Silva, C.G., Kaijzel, E.L., Chan, A.B., Cruz, L.J., 2017. The potential of nano-vehicle mediated therapy in vasculitis and multiple sclerosis. Curr. Pharm. Des. 23 (13), 1985–1992.
Iyer, R., Iken, B., Leon, A., 2015. Developments in alternative treatments for organophosphate poisoning. Toxicol. Lett. 233 (2), 200–206.
Kazemi, M., Tahmasbi, A.M., Valizadeh, R., Naserian, A.A., Soni, A., 2012. Organophosphate pesticides: a general review. Agric Sci Res J. 2 (9), 512–522.
Kim, S.Y., Buckwalter, M., Soreq, H., Vezzani, A., Kaufer, D., 2012. Blood–brain barrier dysfunction–induced inflammatory signaling in brain pathology and epileptogenesis. Epilepsia 53 (s6), 37–44.
Kuwabara, T., Ishikawa, F., Kondo, M., Kakiuchi, T., 2017. The role of IL-17 and related cytokines in inflammatory autoimmune diseases. Mediat. Inflamm. 2017, 102–108.
Laurent, S., Mahmoudi, M., 2011. Superparamagnetic iron oxide nanoparticles: promises for diagnosis and treatment of cancer. Int. J. Mol. Epidemiol. Gen. 2 (4), 367–370.
Li, Y., Lein, P.J., Ford, G.D., Liu, C., Stovall, K.C., White, T.E., et al., 2015. Neuregulin-1 inhibits neuroinflammatory responses in a rat model of organophosphate-nerve agent-induced delayed neuronal injury. J. Neuroinflammation 12 (1), 64–69.
Mohajeri, M., Sadeghizadeh, M., Najafi, F., Javan, M., 2015. Polymerized nano-curcumin attenuates neurological symptoms in EAE model of multiple sclerosis through down regulation of inflammatory and oxidative processes and enhancing neuroprotection and myelin repair. Neuropharmacology 99, 156–167.
Monnet-Tschudi, F., Zurich, M., Honegger, P., 2007. Neurotoxicant-induced inflammatory response in three-dimensional brain cell cultures. Human Exp. Toxicol 26 (4), 339–346.
Pires, L.R., Marques, F., Sousa, J.C., Cerqueira, J., Pinto, I.M., 2016. Nano-and micro-based systems for immunotolerance induction in multiple sclerosis. Human Vaccines Immunotherap 12 (7), 1886–1890.
Poupot, R., Bergozza, D., Fruchon, S., 2018. Nanoparticle-based strategies to treat neuroinflammation. Materials. 11 (2), 270–280.
Rauh, V.A., Perera, F.P., Horton, M.K., Whyatt, R.M., Bansal, R., Hao, X., et al., 2012. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. Proc. Natl. Acad. Sci. 109 (20), 7871–7876.
Tuler, S.M., Bowen, J.M., 1989. Toxic effects of organophosphates on nerve cell growth and ultrastructure in culture. J. Toxicol. Environ. Health, Part A Current Issues. 27 (2), 209–223.
Yadav, S.S., Singh, M.K., Yadav, R.S., 2016. Organophosphates induced Alzheimer's disease: an epigenetic aspect. J. Clin. Epigen 2 (1), 10–15.
Yekta, S., Sadeghi, M., 2018. Adsorption and degradation of methyl parathion (MP), a toxic organophosphorus pesticide, using NaY/Mn 0.5 Zn 0.5 Fe_2O_4 nanocomposite. Res. Chem. Intermed. 44 (3), 1865–1887.