Review Article

ANTI-NEUROINFLAMMATORY POTENTIAL OF HERBAL FORMULATIONS IN ATTENUATION OF NEURODEGENERATIVE DISEASES

ABSTRACT:

The reaction characterized by inflammation in the brain or the spinal column is known medically as "neuroinflammation." The central nervous system is impacted by neurodegeneration, which is epitomized by the loss of neural functioning and structure. Neurodegeneration occurs as a result of viral infection. It is mostly observed in a range of conditions referred to as "neurodegenerative diseases," which primarily affect the elderly and hurt mental as well as physical performance. These illnesses include amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, and Alzheimer's disease. Neurodegeneration's fundamental causes continue to remain a mystery. Nevertheless, new research indicates that several neurodegenerative mechanisms that are related to depression a side effect of neurodegenerative disease are intimately associated with the inflammatory process. Cytokines that promote inflammatory processes are crucial to understanding the pathophysiology of depression and dementia. Activated microglial cells are believed to play a major role in the inflammatory and immune responses that occur in neurological conditions and neurodegenerative conditions. Signaling chemicals are produced throughout neuroinflammation and these molecules regulate multiple pro-apoptotic mechanisms. Treatment strategies for neurological conditions with an inflammatory component involve grasping neurological inflammation pathways, controlling the generation of cytokines, and managing the microglial inflammatory reaction.

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Keywords: neuroinflammation, neurodegenerative diseases, Parkinson's disease, Alzheimer's disease.

1. INTRODUCTION

1.1 Neuroinflammation and Neurodegeneration

The reaction called neuroinflammation involves every type of cell that inhabits the central nervous system (CNS), including macroglia, microglia, and neurons. Several factors, such as initial insult, family history, surroundings, age, in/or past experiences, combine to stimulate microglia and a complex neuroinflammatory process [1]

For example, lipopolysaccharide (LPS), an endotoxin present in a Gram-negative bacterial outermost membrane, triggers systemic inflammatory reaction through tolling-like receptor (TLR) signaling. Once LPS interacts with TLR4 on the outer layer of microglia, 2 pathways for signaling are triggered, including phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) and mitogen-activated protein kinase (MAPK), which in turn activates NF-B. The stimulation of NF-B then mediates the generation of cytokines that are pro-inflammatory, chemokines that, and stimulated enzymes, like COX-2 and nitric oxide synthase (iNOS), leading to neurological inflammation. Understanding how the body's immune system processes information and uses NF-B to identify pathogens is vital [2,3]

1.2 Role of Microglia in Neuroinflammation

Microglia, which are natural cerebral macrophages, are crucial for both repair of tissues and the organism's defense. They play a critical part in inflammatory neurodegenerative brain diseases. The initial indication of neurological inflammation is the rise in the activity of microglia [4]. Microglia when triggered in response to infectious agents, damage to tissues, abnormal stimulation, neurotoxins, infection, or trauma and activating a multitude of protein and gene products, such as iNOS, cytokines that are pro-inflammatory such as Interleukin 1 beta (IL-1), tumor necrosis factor-alpha (TNF-), COX-1, COX-2, reactive oxygen species (ROS), and potentially neurotoxic chemicals that cause neural problems, microglia gather, expand, move around, phagocytose, provide antigens to T-cells, discharge an array of oxidants, and cell death [5].

The long-term neurotoxicity is facilitated by the released mediators along with additional neurotoxic substances from these cells that are stimulated in recurrent neurological inflammation. Activated microglia exhibit a neurodegenerative function. But they might additionally have an anti-infective effect (neuroprotective role) [6,7]

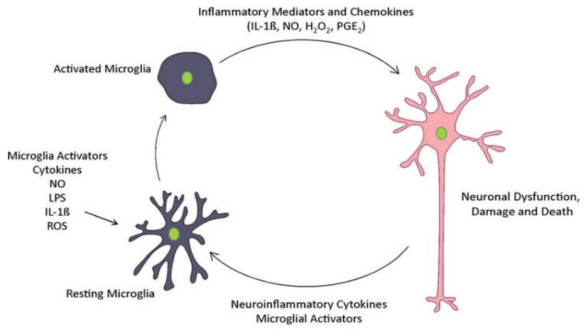

Figure 1: Injury to neurons and the activation of microglia. The infection, stress caused by oxidation, and neurotoxins, all activate microglia. Neuronal decline and malfunction are brought about by chemical mediators released by microglia that are stimulated.

2. VARIOUS PATHWAYS OF NEUROINFLAMMATION

2.1 Neuroinflammatory pathway including cytokines

A cytokine produced within a single cell may have contradictory impacts, leading to the cell's demise, growth, and survival, relying on the physiological environment in which it functions [8].

Microglia activities linked to the inbuilt immune response are connected to TNF- signaling & the regulation of both inflammation and death. Given the established correlation between TNF-mRNA concentrations and hippocampal cell death, it seems plausible that a specific TNF concentration is required to initiate apoptotic mechanisms. Rises in TNF- and IL-1 were observed before the death of neurons. Beginning with the release of proinflammatory cytokines like TNF- and IL-1 as well as adhesion molecules, inflammation is typically defined and controlled [9].

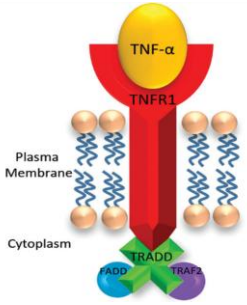

Figure 2: TNFR1 signalling pathway. TNF-α binds to its receptor (TNFR1), and following tumor necrosis factor receptor 1-associated death domain protein (TRADD), binding, neuroinflammation and apoptosis pathways can be initiated

Both accelerated progression of illness and pathogenic inflammation depend on TNF-α and IL-1. They are believed to have the ability to disrupt the blood-brain barrier (BBB) [10], and allow the passage of dangerous substances such as nitric oxide (NO). Both long-term neurological conditions like AD and PD and sudden neuroinflammatory disorders like strokes, ischemia, & brain damage depend on IL-1 for their progression. TNF is a potent cytokine of inflammation that triggers death by activating sensors that have a similar cytoplasm pattern that indicates an internal death domain.

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The key mediator of the effects of IL-1 is the interleukin 1 receptor (IL-1R1). Via a caspase 3-mediated pathway, TNFR1 stimulation provides a biochemical pathway that facilitates the quick demise of cells [11].

2.1.1 Neuroinflammation pathway and ROS

Because of inflammation-induced cellular oxidative stress & harm to DNA, macrophages and microglia overproduce reactive oxygen species (ROS) [12]. The body is continually producing free radicals and oxidative stress, which can damage the brain and are possible causes or effects of many disorders.

ROS is a multi-potent, diffusible biochemical atomic or molecular type with an unattached electron that reacts with stimuli from the environment [13]. ROS is capable of performing transmitting signals tasks. ROS may trigger disease by directly harming macromolecules in biology as well as by triggering several genes that regulate the signaling processes that lead to inflammation. Acute and chronic inflammation illnesses, heredity, and aging represent a few of the primary reasons for increased ROS formation.

Mitochondria are an important conduit of ROS generated by the chain of electron transport because they're susceptible to oxidative harm, which can cause dysfunction in the mitochondria & harm to tissues. Redox-sensitive factor NF-B cascade activation can be brought about by oxidative stress, which is the condition resulting from malfunctioning mitochondria. While the etiology of a number of these types of neurological conditions varies, mitochondrial dysfunction is commonly observed in a variety of neurodegenerative conditions, including brain ischemia-reperfusion damage, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and memory loss caused by alcohol [14,15]

2.1.2 Nitric oxide and neuroinflammation pathway

NO is an unbound gas signaling agent that regulates the neurological & immune systems. Several simulations, including LPS, TNF- α, IL-1 or IFN-gamma, may contribute to the

formation of iNOS. By the manufacture of NO via the induced isoform of iNOS, which catalyzes the transformation of l-arginine to l-citrulline & NO, neuroinflammation may also result in the demise of neurons [16]. Higher concentrations of NO have been shown to cause the nitrification of many proteins in the brain tissues of patients suffering from neurodegenerative diseases such as AD, PD, HD, and amyotrophic lateral sclerosis (ALS). Nitroxidative stress in the brain can result from being exposed to cytotoxic chemicals or from neurological disorders that cause increased amounts of superoxide anions and NO. Superoxide anion and NO together can generate other cytotoxic compounds that may be connected to the demise of neural cells. However, in high concentrations, they can be significant cytotoxic substances leading to neurodegeneration [17].

2.1.3 MAPK pathway in neuroinflammation

Microglia when stimulated induces the MAPK cascade. A variety of external stimuli & cytokines associated with inflammation can stimulate the MAPK-related genes SAPK and JNK. It is shown that activated SAPK/JNK phosphorylates the c-jun and regulates the function of multiple transcription factors after translocating into the nucleus. Upon stimulation, SAPK/JNK links onto the trans-activation region of the c-Jun amino acid and increases the production of the AP-1-dependent gene. AP-1 regulates the production of several mediators of inflammation, including COX-2 and the iNOS. In conclusion, it has been shown that LPS-induced stimulation of microglia throughout neuroinflammation depends critically upon the p38 MAPK, AKT, and mTOR pathways [18,19]

3. NEURODEGENERATION-INDUCED NEUROINFLAMMATION

Microglia are first activated after an offence, and this causes the production of pro-inflammatory mediators that encourage the permeabilization of the BBB after a systemic neuroinflammation [20]. As a result, there is a chance that peripheral macrophages could play a significant role in how neuroinflammation turns out as a result of increased BBB permeability. Accordingly, altered CD4+ and CD8+ T cells have been seen in the peripheral blood of individuals with neurodegenerative disorders, indicating a persistent antigenic assault and the possibility that T cells may be involved in neurodegenerative diseases [21].

While T cells invade the CNS, astrocytes and neurons, the most prevalent glial cell population of the CNS that also takes part in the innate immune response, which is triggered as a result of constant insult during inflammation or infection, cell factors that affect microglial fate invade the epithelial cells of the BBB. HIV-1 if stored in astrocytes, which contributes significantly to the neurodegenerative effects of the virus. Accordingly, the

pathogenesis of neurodegenerative illness places a strong emphasis on chronic neuroinflammation and microglia activation [22,23].

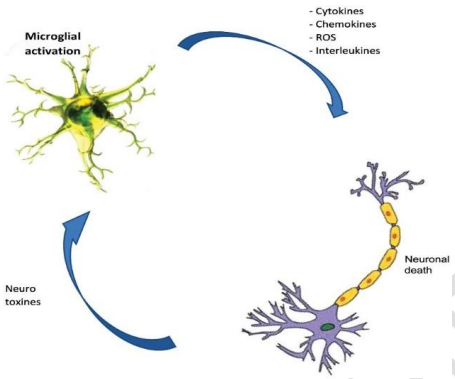

Figure 3: Relationship between neuronal death and microglial activation. Release of neurotoxic or protective compounds may occur as a result of microglial activation. When neurotoxic chemicals are released, they favour neuroinflammation or neuronal death, which results in neurodegeneration. Reactive oxygen species (ROS)

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Reactive oxygen and nitrogen species, tumor necrosis, and glutamate are primarily produced by microglial cells and are all neurotoxic when released in high doses following microglial activation, which is most likely brought on by the stimulation of TLRs via aggregated proteins, as is the case in AD, MS, PD, and ALS patients [24].

4. TREATMENT:

4.1 Various formulations for treating neuroinflammation induced neurodegeneration

4.1.1 *Curcumin Longvida*

Due to curcumin's poor bioavailability and BBB permeability, which have been recognised as possible limitations in the majority of CNS illnesses, regulated formulation of curcumin is necessary for efficient treatment results. Another noteworthy example is Longvida Optimised

Curcumin, which has about 80 mg of curcumin in a solid lipid formulation. It can traverse the blood-brain barrier because of its lipid layers, according to studies in mice. The bioavailability of Longvida is said to be four times higher than that of unformulated curcumin. According to behavioural findings, this modest dose of Longvida curcumin enhanced cognitive abilities. This biodegradable curcumin formulation can improve neuroinflammation and the ensuring neurological impairment by achieving the desired bioavailability in the brain [25].

4.1.2 Curcumin as Meriva formulation

Another formulation regarded as one of the most blood-brain barrier disruption. As liposome nanocarriers that have been developed for the available sources of curcumin is Meriva®. It is an Indena formulation of curcumin that has a patent. A total of 20% of the product's weight is made up of curcumin, which is combined with soy lecithin in a 1:2 weight ratio during formulation. Meriva curcumin was found in several clinical studies to have a greater bioavailability than regular curcumin. Human volunteers underwent simultaneous examinations of Meriva and curcuminoid absorption and final bioavailability [26]

4.1.3 Quercetin

There was a suggestion that there is a molecular relationship between AD and a few of the risk indicators associated with this neurodegenerative disease; oxysterols appear to be the missing piece due to their neurotoxic characteristics. The anti-inflammatory flavonoid quercetin had been pretreated on the cells to bolster these results. Remarkably, flavonoids' anti-inflammatory effects in SH-SY5Y cells were enhanced when it was incorporated into cyclodextrin-dodecyl carbonate nanoparticles compared to flavonoid in their free form. Scientists incorporated quercetin into nanoparticles to improve the antioxidant's ability to cross the blood-brain barrier and enter target cells. The findings suggest that this mode of drug administration might offer a novel therapeutic strategy for halting or delaying the progression of AD [27].

4.1.4 Methyl prednisolone liposomes

GSH-PEG liposomal methylprednisolone in this trial showed an extended plasma circulation over the free drug, according to the pharmacokinetics. GSH-PEG liposomes increase methylprednisolone's medicinal availability, enabling the achievement of a successful brain level at a lower dose and frequency of administration. GSH-PEG liposomal drug treatment resulted in a notably higher eight-hour brain absorption of the medication than the free medication (6.5). Lastly, the notion that enhanced medication delivery to the central nervous

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system is beneficial for managing the neuroinflammation associated with EAE, as well as MS, is supported by glutathione pegylated liposomal methylprednisolone's greater effectiveness over free the medication and non-targeted pegylated liposomal methylprednisolone [28,29].

4.1.5 TNF-α siRNA nanoemulsions

Neuroinflammation is a hallmark of both acute and chronic neurological disorders. The main goal of this research was to evaluate if an intranasal cationic nanoemulsion carrying an anti-TNF siRNA may have any anti-inflammatory properties. Nanoemulsion significantly lowered TNF-α concentrations in LPS-stimulated cells [30]. In the animal's brain, charged nanoemulsions were absorbed almost five times faster being injected by i.v, versus non-encapsulated siRNA. Additionally, in an LPS-induced experiment involving neuroinflammation, TNF siRNA nanoemulsions administered intravenously dramatically reduced the unregulated levels of TNF-α. These results showed that intranasal administration of cationic nanoemulsions carrying TNF siRNA was a successful method to knock down the gene, and this approach has great promise for averting neurological inflammation [31].

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4.1.6 Rutin

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This investigation looks into the potential benefits of rutin in protecting rats administered intracerebroventricular streptozotocin (ICV-STZ) infusions against oxidative harm and cognitive impairments. The animals received bilateral injections of ICV-STZ (3 mg/kg), while the untreated rats received the same dosage of a vehicle. In the hippocampus of ICV-STZ rats, rutin pretreatment in order (25 mg/kg, oral, every day for three weeks) substantially lowered the levels of thiobarbituric acid (TBA) reacting substances, poly ADP-ribosyl polymerase action, nitrite, lowered glutathione (GSH), and the function of its relying enzymes, glutathione peroxidase [GPx] and glutathione reductase [GR], as well as catalase [32]. Supplementing with rutin substantially mitigated cognitive abnormalities noticed in ICV-STZ rats. As a result, this research suggests that rutin might be useful in managing neuroinflammation and sporadic Alzheimer-type dementia in addition to being useful for minimizing cognitive impairment [33].

5. CONCLUSION

These investigations concluded that the formulations effectively protected against neurodegeneration in models of animals. Conditions known as neuroinflammatory disorders impact the parts of the brain where the body's immune response is compromised. Glial cells

in general, but especially microglia, and inflammation effectors from both the acquired and innate immune systems serve as detectors for disrupted neural tissue equilibrium in the central nervous system and regionally respond to injury to nerve cells or the introduction of foreign materials through the brain. The primary mechanism governing neuroinflammation is the differential activation of microglial cells, which may give rise to either toxicity resulting in neurodegeneration or neurological protection. Consequently, reliant upon surroundings, neurons may degenerate or become preserved.

REFERENCES

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1. Carson MJ, Doose JM, Melchior B, Schmid CD, Ploix CC. CNS immune privilege: hiding in plain sight. Immunological reviews. 2006;213(1):48-65. https://doi.org/10.1111/j.1600-065x.2006.00441.x
2. Lyman M, Lloyd DG, Ji X, Vizcaychipi MP, Ma D. Neuroinflammation: the role and consequences. Neuroscience research. 2014;79: 1-2. Available from: http://dx.doi.org/10.1016/j.neures.2013.10.004
3. Park SE, Sapkota K, Kim S, Kim H, Kim SJ. Kaempferol acts through mitogen- activated protein kinases and protein kinase B/AKT to elicit protection in a model of neuroinflammation in BV2 microglial cells. British journal of pharmacology. 2011;164(3):1008-25.https://doi.org/10.1111/j.1476-5381.2011.01389.x
4. Giatti S, Boraso M, Melcangi RC, Viviani B. Neuroactive steroids, their metabolites, and neuroinflammation. Journal of molecular endocrinology. 2012;49(3): R125-34.
5. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. 2010;140(6):918-34.
6. Harry GJ, Kraft AD. Neuroinflammation and microglia: considerations and approaches for neurotoxicity assessment. Expert opinion on drug metabolism & toxicology. 2008;4(10):1265-77.
7. Bradl M, Hohlfeld R. Molecular pathogenesis of neuroinflammation. Journal of Neurology, Neurosurgery & Psychiatry. 2003;74(10):1364-70.
8. Allan SM, Rothwell NJ. Inflammation in central nervous system injury. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences. 2003;358(1438):1669-77. Available from: https://doi.org/10.1098/rstb.2003.1358

9. Nitsch R, Bechmann I, Deisz RA, Haas D, Lehmann TN, Wendling U, Zipp F. Human brain-cell death induced by tumour-necrosis-factor-related apoptosis-inducing ligand (TRAIL). The Lancet. 2000;356(9232):827-8. Available from: http://dx.doi.org/10.1016/S0140-6736(00)02659-3
10. Blamire AM, Anthony DC, Rajagopalan B, Sibson NR, Perry VH, Styles P. Interleukin-1β-induced changes in blood–brain barrier permeability, apparent diffusion coefficient, and cerebral blood volume in the rat brain: a magnetic resonance study. Journal of Neuroscience. 2000;20(21):8153-9.
11. Swaroop S, Sengupta N, Suryawanshi AR, Adlakha YK, Basu A. HSP60 plays a regulatory role in IL-1β-induced microglial inflammation via TLR4-p38 MAPK axis. Journal of neuroinflammation.2016;13:1-9.
12. Noh H, Jeon J, Seo H. Systemic injection of LPS induces region-specific neuroinflammation and mitochondrial dysfunction in normal mouse brain. Neurochemistry international. 2014; 69:35-40.https://doi.org/10.1016/j.neuint.2014.02.008
13. Naik E, Dixit VM. Mitochondrial reactive oxygen species drive proinflammatory cytokine production. Journal of Experimental Medicine. 2011 Mar 14;208(3):417-20.https://doi.org/10.1084/jem.20110367
14. Roy S, Packer L. Redox regulation of cell functions by\alpha- lipoate: biochemical and molecular aspects. Biofactors. 1998 Jan 1;7(3):263-7.https://doi.org/10.1002/biof.5520080104
15. Mohammed Akbar, Musthafa Mohamed Essa, Ghazi Daradkeh, Mohamed A. Abdelme geed, Youngshim Choi, Lubna Mahmood, Byoung-Joon Song. Mitochondrial dysfunction and cell death in neurodegenerative diseases through nitroxidative stress. Brain Research. 2016; 1637, 34–55. https://doi.org/10.1016/j.brainres.2016.02.016
16. Peng YL, Liu YN, Liu L, Wang X, Jiang CL, Wang YX. Inducible nitric oxide synthase is involved in the modulation of depressive behaviors induced by unpredictable chronic mild stress. Journal of neuroinflammation. 2012;9:1-2.
17. Terazawa R, Akimoto N, Kato T, Itoh T, Fujita Y, Hamada N, Deguchi T, Iinuma M, Noda M, Nozawa Y, Ito M. A kavalactone derivative inhibits lipopolysaccharide-stimulated iNOS induction and NO production through activation of Nrf2 signaling in BV2 microglial cells. Pharmacological Research. 2013;71:34-43.https://doi.org/10.1016/j.phrs.2013.02.002

18. Kyriakis JM, Avruch J. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiological reviews. 2001;81(2):807-69. https://doi.org/10.1152/physrev.2001.81.2.807
19. Cowan KJ, Storey KB. Mitogen-activated protein kinases: new signaling pathways functioning in cellular responses to environmental stress. Journal of Experimental Biology. 2003;206(7):1107-15.
20. Crutcher KA, Gendelman HE, Kipnis J, Perez-Polo JR, Perry VH, Popovich PG, Weaver LC. Debate:“is increasing neuroinflammation beneficial for neural repair?”. Journal of Neuroimmune Pharmacology. 2006;195-211.
21. Ostanin DV, Bao J, Koboziev I, Gray L, Robinson-Jackson SA, Kosloski-Davidson M, Price VH, Grisham MB. T cell transfer model of chronic colitis: concepts, considerations, and tricks of the trade. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2009;296(2): G135-46.
22. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000prime reports. 2014;6.
23. González H, Elgueta D, Montoya A, Pacheco R. Neuroimmune regulation of microglial activity involved in neuroinflammation and neurodegenerative diseases. Journal of neuroimmunology.2014;274(1-2):1-3.
24. Henkel JS, Engelhardt JI, Siklós L, Simpson EP, Kim SH, Pan T, Goodman JC, Siddique T, Beers DR, Appel SH. Presence of dendritic cells, MCP- 1, and activated microglia/macrophages in amyotrophic lateral sclerosis spinal cord tissue. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2004;55(2):221-35.
25. Rock RB, Gekker G, Hu S, Sheng WS, Cheeran M, Lokensgard JR, Peterson PK. Role of microglia in central nervous system infections. Clinical microbiology reviews. 2004;17(4):942-64.
26. Querfurth HW, LaFerla FM. Alzheimer's disease. New England Journal of Medicine. 2010 Jan 28;362(4):329-44.
27. Pawar YB, Munjal B, Arora S, Karwa M, Kohli G, Paliwal JK, Bansal AK. Bioavailability of a lipidic formulation of curcumin in healthy human volunteers. Pharmaceutics. 2012;4(4):517-30.

28. Parada E, Buendia I, Navarro E, Avendaño C, Egea J, López MG. Microglial HO- 1 induction by curcumin provides antioxidant, antineuroinflammatory, and glioprotective effects. Molecular nutrition & food research. 2015;59(9):1690-700.
29. Priprem A, Watanatorn J, Sutthiparinyanont S, Phachonpai W, Muchimapura S. Anxiety and cognitive effects of quercetin liposomes in rats. Nanomedicine: nanotechnology, biology and medicine. 2008;4(1):70-8.https://doi.org/10.1016/j.nano.2007.12.001
30. Gaillard PJ, Appeldoorn CC, Rip J, Dorland R, van der Pol SM, Kooij G, de Vries HE, Reijerkerk A. Enhanced brain delivery of liposomal methylprednisolone improved therapeutic efficacy in a model of neuroinflammation. Journal of controlled release. 2012;164(3):364-9. https://doi.org/10.1016/j.jconrel.2012.06.022
31. Brasnjevic I, Steinbusch HW, Schmitz C, Martinez-Martinez P, European NanoBioPharmaceutics Research Initiative. Delivery of peptide and protein drugs over the blood–brain barrier. Progress in neurobiology. 2009;87(4):212-51.https://doi.org/10.1016/j.pneurobio.2008.12.002
32. Yadav S, Gandham SK, Panicucci R, Amiji MM. Intranasal brain delivery of cationic nanoemulsion-encapsulated TNFα siRNA in prevention of experimental neuroinflammation. Nanomedicine: Nanotechnology, Biology and Medicine. 2016;12(4):987-1002.https://doi.org/10.1016/j.nano.2015.12.374
33. Javed H, Khan MM, Ahmad A, Vaibhav K, Ahmad ME, Khan A, Ashafaq M, Islam F, Siddiqui MS, Safhi MM. Rutin prevents cognitive impairments by ameliorating oxidative stress and neuroinflammation in rat model of sporadic dementia of Alzheimer type. Neuroscience. 2012;210:340-52.