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ORIGINAL ARTICLE

Apamin administration impact on miR-219 and miR-155-3p expression in cuprizone induced multiple sclerosis model

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Abstract

Multiple sclerosis (MS) is a chronic debilitating disease that attacks the central nervous system. This study aims to investigate miR-219 and miR-155-3p expression levels involved in the myelination process following the administration of apamin peptide in the model of multiple sclerosis disease. Forty-four 8 week C57BL/6 male mice (22 ± 5 g) randomly divided into six groups. Apamin (100 µg/kg/BW) was administered intraperitoneally as a co-treatment during phase I (demyelination) or post-treatment phase II (remyelination) twice a week in cuprizone induced MS model. At the end of study myelin content and microRNA expression levels were measured with LFB staining and quantitative Real-Time PCR method, respectively. It was observed that the intended microRNAs were dysregulated during the different phases of disease induction. After 6 weeks of cuprizone exposure, miR-219 downregulated in phase I in comparison with the negative control. On the other hand, the apamin co-treatment significantly inhibit the miR-155-3p upregulation during the phase I as compared with the cuprizone group ($p < 0.0001$). Apamin has more impact on the miR155-3p reduction in phase I than miR-219 elevation in phase II. It could be considered as a therapeutic option for decreasing plaque formation during the exacerbation phase of the MS disease. Apamin has more impact on the miR155-3p reduction in phase I than miR-219 elevation in phase II. It could be considered as a therapeutic option for decreasing plaque formation during the exacerbation phase of the MS disease.

Keywords miR-155-3p · miR-219 · Apamin · Multiple sclerosis · Myelination · Cuprizone

Introduction

Multiple sclerosis (MS) is one of the most prevalent neurological diseases in young adults characterized by numerous demyelinated plaques scattered in the central nervous system (CNS) [1]. It is reported that around 2.1 million people are challenged with MS Worldwide and its incidence rate increased regardless of the living region [2]. Recent studies reported that clinical symptoms in MS may be resolved by inducing the remyelination process. However, spontaneous remyelination is limited because of the difficulties differentiation or maturation of the oligodendrocyte precursors (OPCs), recruiting them to injured areas and finally a failure in the production of myelin sheaths [3–5].

Apitherapy is the use of bee products such as honey, pollen, propolis, royal jelly, bee venom, wax, and apilarnil to prevent or treat illness and promote the healing process. Bee venom is a colorless, bitter and acidic product (pH of 4.5–5.5) that easily dissolves in water and compromised a complex mixture of proteins, peptides, and low molecular weight components [6]. Recently it was reported that apamin, the second most common peptide in bee venom, could cross the blood–brain barrier [7].

Apamin is a polypeptide of 18 amino acids having a molecular weight of 2039 Da, containing two disulfide bridges connecting position 1 with 11, and position 3 with 15 [8]. It selectively inhibits the small-conductance

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Ca2+ -activated K+ channels (SK-channels, KCNN2) and potassium voltage-gated channels (Kv 1.3) [9, 10]. Furthermore, it has been reported that apamin reduced the activity of inflammatory cytokines and adhesion molecules, such as VCAM-1 and ICAM-1, significantly in THP-1 derived macrophages [11].

Recently, the potential role of Kv 1.3 channel, mainly expressed on the membrane of the immune cells such as T cells, macrophages, dendritic and especially microglia cells, has gained much attention in neuroinflammation and neurodegenerative disease [12, 13]. It has been shown that the activation of these channels is essential for inducing programmed cell death, and an increase in the potassium ions output from the neuronal cell causes neuronal apoptosis [14, 15]. It should be noted that oligodendrocytes which are supportive cells in the central nervous system and are responsible for producing myelin also express this type of channel at their surface. Interestingly the inhibition of potassium efflux in these cells induces the maturation process which is an essential event in the myelin synthesis process [16].

MicroRNAs (miRs), are a class of single strand small non-coding RNAs with around 22 nucleotides, considered as a master regulator of post transcriptional gene expression and protein translation [17]. Several studies suggested that specific miRNAs play a key role in MS pathogenesis and responses to treatment. It has been demonstrated that miR-219 promotes oligodendrocyte formation in the normal chick neural tube and mouse cortex development also acts as a critical regulator in OPC differentiation [18–20]. miR155-3p is another involved important modulator in microglia activation which is significantly upregulated in active white matter lesions [21].

Considering the discussed documents in this research we examined the effects of apamin administration on the expression of miR-219 and miR155-3p in cuprizone induced multiple sclerosis model.

Material and methods

Multiple sclerosis model

Eight-week-old (22 ± 5 g) C57BL/6 male mice were obtained from Royan institute (Isfahan, Iran) and kept under standard conditions of 12/12-h light/dark cycles with controlled humidity and ad libitum access to food and water. All procedures were approved by the Iran National Committee for Ethics in Biomedical Research (ethical approval ID: IR.MUI.RESEARCH.REC.1397.387) which was performed following the Guidelines for the Care and Use of Laboratory Animals. Possible efforts were made to decrease animal numbers and distress.

Based on the approved protocol mice were fed cuprizone (Sigma-Aldrich, USA) pellets (0.2% w/w) for 6 weeks for myelin degeneration after that fed with normal diet for 2 weeks to restore the myelin loss. So our model had two-phase: disease induction with cuprizone exposure (phase I) and disease improvement after cuprizone withdrawal (phase II).

As it is shown in Fig. 1 mice were randomly divided into 6 groups. Group 1 (negative control, n = 6) received the regular food pellets during the study and served as a negative control group. Group 2 composed of two subgroups of 6 animals each (n = 2 × 6) was recruited to evaluate the effect of cuprizone administration on demyelination after 6 weeks (the first group sacrificed at this point) and remyelination (other groups) after 2 weeks without any particular treatment. Group 3 (co-treatment group) composed of two subgroups of 6 animals each (n = 2 × 6). Both subgroups received apamin (100 µg/kg) intraperitoneally twice a week for 6 weeks. The first subgroup terminated at the end of phase I and the rest of them were sacrificed at the end of phase II. Group 4 (post-treatment, n = 6) received an apamin (100 µg/kg) intraperitoneally twice a week for 2 weeks during phase II. Groups 5 and 6 (vehicle, n = 6 in each group) received phosphate-buffered saline as the vehicle of apamin during both phases. At the end of each phase, mice were deeply anesthetized.

Brain sampling

The thoracic chamber of anesthetized mice was opened and 5 ml PBS was injected into the left ventricle. At the same time, the right atrium was cut and the next syringe containing 5 ml 4% neutral formalin was injected after PBS. At the end of perfusion, the brain was removed cut into two parts at midbrain based on the Allen Mouse Brain Atlas [22].

Samples were kept in − 20 °C for further microRNA expression evaluation. The other part was processed with the Sakura tissue processor (Sakura Tissue Tek VIP E150, Sakura, Japan) then serial coronal Sects. (5 µm) were obtained and the best one was used for corpus callosum myelin staining.

Myelin quantification

Slices were stained with luxol fast blue staining (Sigma, USA). Samples were placed in luxol fast blue overnight at 56 °C and washed with 95% alcohol followed by distilled water to remove the excess blue stain. The blue color was trapped in myelinated white matter after lithium carbonate exposure step (20 s). Slides were washed three times with 75% alcohol and the background was stained with Cresyl violet for 1 min. After myelin staining, the image of each slide was captured using Nikon Eclipse 55i light

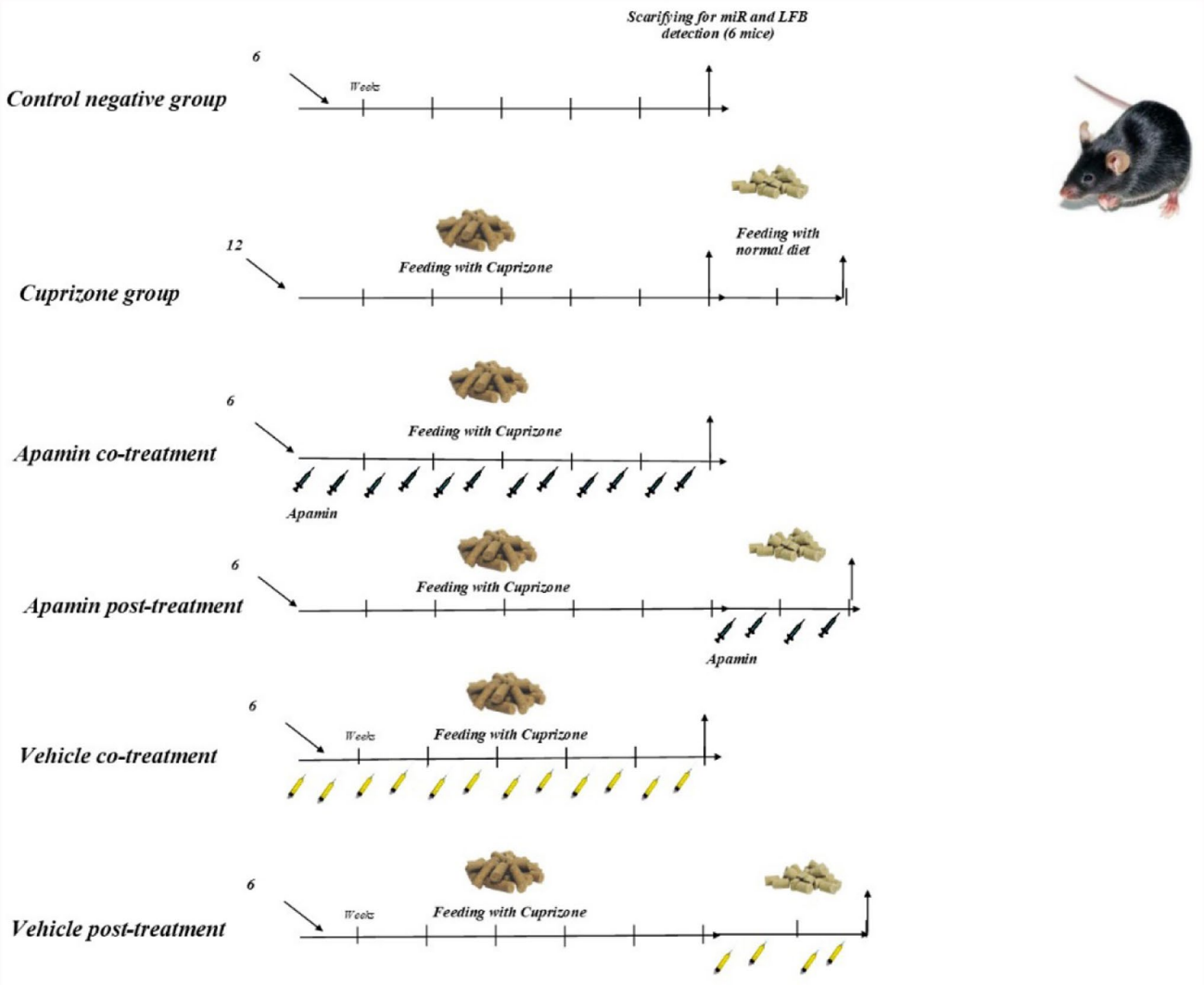

Fig. 1 Forty-two mice were randomly divided into 6 groups. Negative control (n = 6) was fed regular food pellets cuprizone group (n = 12) fed with 0.2% cuprizone containing food pellets for 6 weeks for demyelination followed by 2 weeks remyelination. Group 3 and 4 received apamin (100 µg/kg) intraperitoneally twice a week during the phase I or phase II. Groups 5 and 6 (vehicle, n = 6 in each group) received phosphate-buffered saline as the vehicle of apamin during both phases

microscope (Nikon, Japanese) with a 4 × objective magnification and the corpus callusom area was processed with NIH Fiji software via deconvolution plugin (National Institute of Health, Bethesda, Maryland, USA).

The density of all samples median corpus callusom was quantified three times with the equation below:

$$\text{Myelin percent} = 1 - \frac{(X1 - Xs)}{\text{X1}} \times 100$$

where X_1 is the mean of measured integrity density of normal control and X_s is the same region of interest integrated density of each sample.

RNA extraction

Snap-frozen brain tissues were homogenized in cold buffer and total RNA were extracted using RNX plus kit (Sinaclone, Iran) according to the manufacturer's protocol. During the extraction process, samples were treated with RNase-free DNase based on the manufacturer's instruction. Finally, the extracted RNA quality and quantity were measured with a 260/280 nm absorbance ratio using a nanodrop spectrophotometer (Nanodrop 1000; Thermo Scientific).

Reverse transcriptase and quantitative real-time PCR

Biomir cDNA synthesis kit (Biomir, Iran) was applied for complementary DNA (cDNA) synthesis from purified total RNA. Briefly, RNA (2 µg) was heated up to 70 °C for 5 min and mixed dNTP mix, reverse transcriptase Enzyme, random hexamers within buffered media. All of the samples were amplified in the thermocycler (BioRad, USA) at 37 °C for 60 min and 70 °C for 5 min.

The sample's miR expression level was quantified using a step one Real-Time PCR System and the corresponding software (Applied Biosystems) for all groups according to the Biomir recommended protocol. The QPCR was done with the following steps including one cycle containing denaturation at 95 °C for 10 min, followed by 40 cycles at 95 °C for 15 s, annealing and development for 40 s at 60 °C. All reactions were performed twice and the efficiency of reactions was assumed 100%. The relative expression of miRs was normalized with the housekeeping gene and quantified based on the Livak comparative CT method ($2^{-\Delta\Delta Ct}$).

Statistical analysis

Statistical differences between various groups were analyzed by analysis of variance (ANOVA) followed by Bonferroni Multiple Comparison post hoc test using GraphPad Prism software (San Diego, CA). Values of $P \leq 0.05$ were defined as statistically significant.

Results

Myelination was evaluated during the study through corpus callusom LFB staining. As it is shown in Fig. 2c average density of white matter fibers in the control group was assumed 100% and the other groups calculated values were compared at the end of the demyelination or remyelination phase. All of the groups had significant lower myelin content

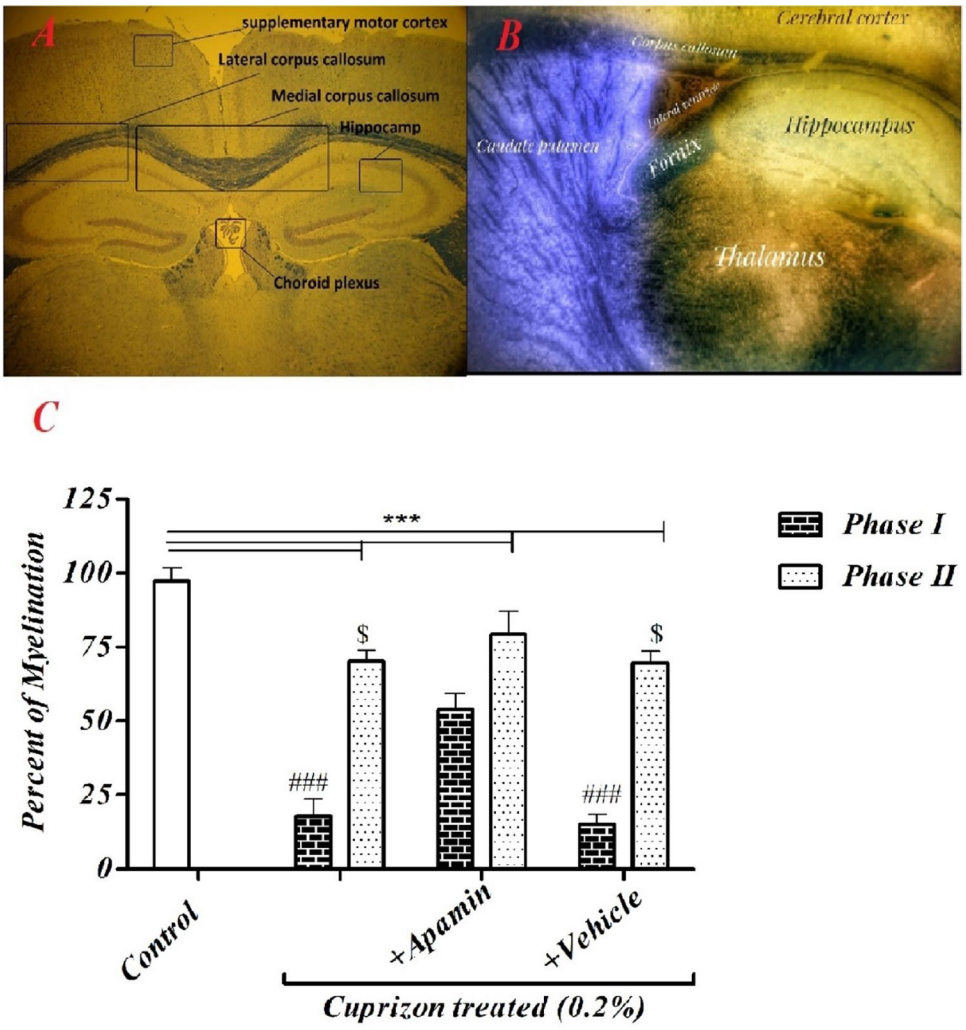

Fig. 2 Part **a** (coronal) and **b** (sagittal) are shown in different parts of stained brain sections. Part **c** has reported the effect of apamin (100 µg/kg, ip) or phosphate-buffered saline as vehicle treatment on cuprizone-induced demyelination after 6 weeks' demyelination (phase I) or 2 weeks of remyelination (phase II). Data represented as mean ± SD (n = 6). ***Significant differences in comparison with the control group, $P \leq 0.001$. $^{\#\#\#}P < 0.001$ and $^{\$}P \leq 0.05$ show significant differences in comparison with the apamin-treated group during phases I and II respectively

as compared to the control group even after 2 weeks of remyelination ($p < 0.001$). At the end of phase I it was observed that myelin content decreased to 17.83 ± 5.91 in cuprizone and 53.83 ± 5.49 in apamin exposed groups. Interestingly, after 2 weeks of cuprizone withdrawal myelin content was increased to 70.17 ± 3.71 in group 2 and 79.33 ± 7.76 in apamin post-treated group ($p < 0.05$).

The amount of miR-219 expression in each group is shown in Fig. 3. As it is demonstrated miR-219 expression did not statistically change during phase I and phase II of cuprizone exposure. However, it was observed that apamin post-treatment has significantly increased the relative expression level after phase II in comparison to the control group (p value < 0.001).

As it is shown in Fig. 4. the relative expression of miR-155-3p was multiplied more than two times during the cuprizone exposure in phase I and decreased at the end of phase II to the lower level than the negative control. Interestingly, the apamin co-treatment significantly inhibit the miR-155-3p upregulation during the phase I as compared with the cuprizone or vehicle group ($p < 0.0001$). The results of the miRs expression change following apamin administration showed that miR-219 and miR-155-3p respectively had better efficacy in phase II and phase I.

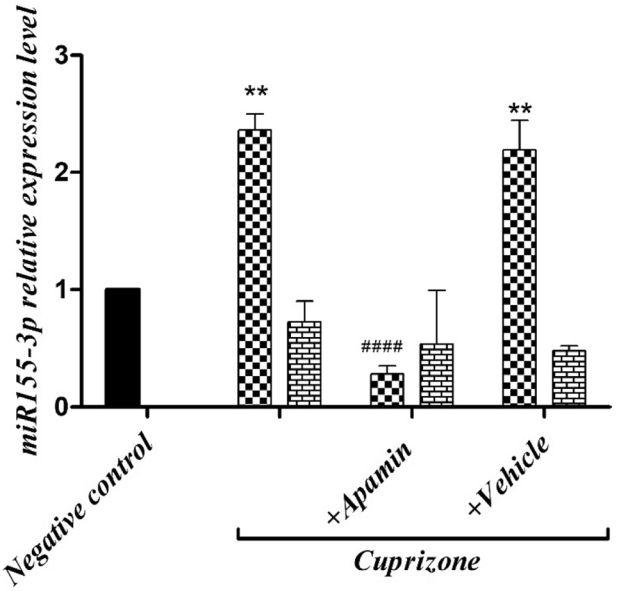

Fig. 4 Analysis of qPCR data for miR-155-3p expression at the end of phase I (demyelination) and phase II (remyelination) after apamin treatment (100 µg/kg. ip) in cuprizone induced multiple sclerosis mice brain. Data are presented as relative expression levels as compared with normal controls. Data are presented as mean ± SD which analyzed by two-way ANOVA followed with multiple comparisons using the Bonferroni post hoc test. **$p < 0.01$ in comparison with negative control and $^{\#\#\#\#}p < 0.0001$ compared with the cuprizone phase I

Discussion

Here, we applied the CPZ mouse model to mimic the demyelination process which occurs during MS disease. Recent studies suggested the critical role of miRNAs as a potential regulator in MS pathogenesis [23, 24]. Also, various studies were confirmed this condition in CPZ induced model [25, 26]. MicroRNAs are important regulators of the oligodendrocytes differentiation, microglia activity and finally in myelination. Several microRNAs have been identified that promote the oligodendrocytes differentiation include miR-388, miR-219, miR-29, miR138, miR-23 [27]. On the other hand, some microRNAs participate in microglia activation such as miR-221 and miR-155-3p [27, 28]. In the present study, we assessed the expression change in microRNA-219 and microRNA-155-3p during apamin administration to evaluate the impact of potassium channel inhibition effect on microglia and oligodendrocyte activity.

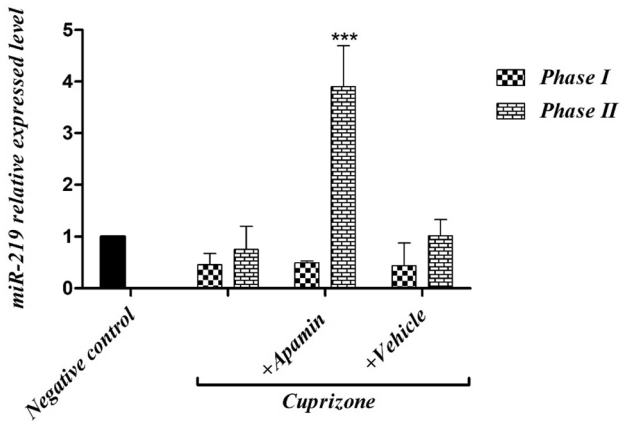

Fig. 3 Analysis of qPCR data for miR-219 expression at the end of phase I (demyelination) and phase II (remyelination) after apamin treatment (100 µg/kg. ip) in cuprizone induced multiple sclerosis mice brain. Data are presented as relative expression levels as compared with normal controls. Data are presented as mean ± SD which analyzed by two-way ANOVA followed with multiple comparisons using the Bonferroni post hoc test. ***$p < 0.001$ in comparison with the negative control

Dutta et al., investigated the expression of miR-124 in hippocampal demyelination using dietary CPZ combined with an intraperitoneal injection of rapamycin and their results showed overexpression of miR-124 could elevate hippocampal demyelination and memory dysfunction [29]. In another study, the injection of miR-146a increased the demyelinated corpus callosum remyelination process [25]. MiR-219 was found to be upregulated in adult oligodendrocytes meanwhile, miR-155-3p was upregulated in active MS lesions [23, 30]. Previous studies have confirmed that miR-219 induces differentiation of oligodendrocytes in vitro and improves myelination in vivo [18, 31]. miR-219

recombinant retrovirus injection into the corpus callosum attenuated demyelination in the CPZ model [32].

It was observed that miR-219 expression decreased during the demyelination phase in all groups as compared to the normal control without any significant differences between apamin treatment or vehicle administration. Meanwhile, after the cuprizone withdrawal, the apamin group showed a fourfold increase in miR-219 expression. miR-219 enhances oligodendrocytes differentiation/maturation by targeting the regulators of the PDGFRα, SOX6 and, Hes5 [19, 33]. Each of these regulators will help to promote OPC proliferation. Zhao et al. multiplied the oligodendrocytes number by stimulating them with miR219 and miR-388 administration [19]. Also, it was assumed that miR-219 could improve the differentiation of oligodendrocytes and reduce myelin degradation in the cuprizone induced model by altering the expression of monocarboxylate transporter 1 [31].

For the first time, Meinl and his partners reported the miR-155 changes in isolated white matter lesions from samples of multiple sclerosis patients' brains [28]. On one hand, it was reported that miR-155 significantly upregulated (11.9 times) in active white matter lesions relative to normal white matter [34]. On the other hand, it was observed that miR-155 was increased in white brain tissue compared to the collected lesions from several patients with relapsing–remitting, primary progressive, and secondary progressive [21].

As it is shown we observed that miR-155-3p relative expression level significantly decreased during phase I while the cuprizone or vehicle exposed group expressed more than twofold miR-155-3p in comparison to the negative control group. The expression changes in phase II has the same manner between groups without obvious differences. This observation means that apamin administration has more impact on inhibiting the elevation of miR-155-3p expression triggering through cuprizone exposure. This finding is confirmed with myelin content staining during both phases which are shown apamin extremely inhibit demyelination than stimulating the remyelination process.

miR-155 is required to polarize astrocytes to activated A1 astrocytes which can cause neuronal and oligodendrocytes cell death, and it is highly active in brain tissue of neurodegenerative conditions such as Multiple sclerosis, Alzheimer 's, Huntington's and Parkinson's disease [28]. In animal model proved that miR-155 removal using antagomiR could improve the ischemic stroke condition because of alteration in neuroinflammation [35]. miR-155-5p and miR-155-3p are two different forms of miR-155 which miR-155-3p is strongly related to the T helper cells upregulation and infiltration them to the brain by regulating Dnaja2/Dnajb1 genes [36].

Microglia cells are one of the immune system components such as macrophages and dendritic cells, where is activated upon miR-155 up-regulation. This overexpression enhanced the neural inflammation and degeneration while its reduction had protective effects on the glial cells. IL-1 and IFNγ can remarkably elevate the miR155-3p and miR155-5p expression in astrocytes. Also, it was reported that inhibition of the miR-155 significantly decreased the IL-6, IL-8, TNFα, and nitric oxide production [37]. So, hindering the miR155-3p expression could suppress the microglia activation. The capacity of miR155 to create a transcriptome of activated myeloid cells to promote the inflammatory response is well recognized. Also, it is important in posttranscriptional gene regulation of the immune system [38].

Taken together, our findings illustrated that apamin, as a special component of bee venom which can easily cross the BBB, has more impact on the miR155-3p reduction in phase I than miR-219 elevation in phase II. So, it could be inferred that blocking the potassium channels play a crucial role in inhibiting the microglia activation than stimulating the oligodendrocytes progenitor cell differentiation to mature oligodendrocyte cells. However, future studies will, therefore, be necessary to further evaluate the exact mechanism of apamin action on microglia suppression or OPC migration should be evaluated with specific markers such as Olig2, NG2, PDGFRα and so on with immunohistochemistry in each phase.

In conclusion, an apamin could be considered as a therapeutic option for decreasing plaque formation during the exacerbation phase of the disease to improve the Multiple sclerosis patient's quality of life.

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Author contributions SG and MAO conceived of the presented idea, SG and MM carried out the experiment, SME and MAO helped supervise the project, all authors provided critical feedback and helped shape the research, analysis and manuscript.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval All procedures were approved by the Iran National Committee for Ethics in Biomedical Research (IR.MUI.RESEARCH.REC.1397.387) which was performed in accordance with the Guidelines for the Care and Use of Laboratory Animals.

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