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Original Article

Effects of exposure to Sericin during gestation on brain growth factor and antioxidant levels following parturition in mice

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ABSTRACT

This paper aimed to determine effects of exposure to Sericin during gestation on brain growth factor and antioxidant levels following parturition in mice. Pregnant mice were randomly assigned to four groups. Pregnant mice in the control group were provided with water as a fake treatment, while pregnant female mice in groups 2-4 were given sericin orally (112.5, 225, and 450 mg/kg) on various days of pregnancy (5, 8, 11, 14, and 17). Following parturition, the animals were euthanized by decapitation, the skulls were dissected to obtain brain samples from mothers to measure the levels of the Brain-derived neurotrophic factor (BDNF), myelin/oligodendrocyte glycoprotein (MOG), myelin-associated glycoprotein (MAG), myelin Basic Protein (MBP), as well as cortical and sub-cortical malondialdehyde (MDA), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) levels were determined. Based on findings, exposure to sericin during gestation in a dose dependent manner and significantly increased levels of the BDNF, MAG, MBP in postpartum mice compared to control group ($p< 0.05$). Also, sericin exposure during pregnancy in a dose dependent manner significantly decreased MOG levels in postpartum mice compared to control group ($p< 0.05$). Exposure to sericin in a dose dependent manner decreased cortical and sub-cortical MDA and increased SOD, GPx and CAT levels compared to control group ($p< 0.05$). Findings of this study show that sericin can play an important protective and regulatory role in the brain function following parturition in mice.

اثرات تجویز سریسین طی دوران آبستنی بر مقادیر فاکتور رشد مغز و آنتی اکسیدان متعاقب زایمان در موش کوچک آزمایشگاهی

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چکیده

این مقاله به بررسی تأثیرات قرارگیری در معرض سرسین در دوران بارداری بر سطوح فاکتور رشد مغز و آنتی‌اکسیدان‌ها پس از زایمان در موش‌ها پرداخته است. موش‌های باردار به‌طور تصادفی به چهار گروه تقسیم شدند. موش‌های باردار در گروه کنترل نرمال سالین (آب مقطر) دریافت کردند، در حالی که موش‌های ماده باردار در گروه‌های ۲-۴ به صورت خوراکی سرسین (۱۱۲.۵، ۲۲۵ و ۴۵۰ میلی‌گرم بر کیلوگرم) در روزهای مختلف بارداری دریافت کردند. (۵، ۸، ۱۱، ۱۴ و ۱۷). پس از زایمان، حیوانات کشته شدند، جمجمه‌ها برای تهیه نمونه‌های مغزی از مادران برای اندازه‌گیری سطوح فاکتور نوروتروفیک مشتق از مغز (BDNF)، گلیکوپروتئین میلین/الیگودندروسیت (MOG)، گلیکوپروتئین مرتبط با میلین (MAG)، پروتئین پایه میلین (MBP)، و همچنین سطوح مالون‌دی‌آلدئید (MDA)، گلوتاتیون پراکسیداز (GPx)، سوپراکسید دیسموتاز (SOD)، و کاتالاز (CAT) قشر و زیرقشر اندازه‌گیری شدند. بر اساس یافته‌ها، قرار گرفتن در معرض سرسین در طول بارداری به صورت وابسته به دوز و به طور قابل توجهی سطح BDNF، MAG و MBP را در موش‌های پس از زایمان نسبت به گروه کنترل افزایش داد ($p< 0.05$). همچنین، قرارگیری در معرض سریسین در طول بارداری به صورت وابسته به دوز به طور قابل توجهی سطح MOG را در موش‌ها پس از زایمان نسبت به گروه کنترل کاهش داد ($p< 0.05$). قرار گرفتن در معرض سریسین به صورت وابسته به دوز، MDA قشری و زیرقشری را کاهش و سطوح SOD، GPx و CAT را نسبت به گروه کنترل افزایش داد ($p< 0.05$). یافته‌های این مطالعه نشان می‌دهد که سرسین می‌تواند نقش محافظتی و تنظیمی مهمی در عملکرد مغز پس از زایمان در موش‌ها ایفا کند.

واژه های کلیدی: سرسین، فاکتور رشد مغز، آنتی اکسیدان، زایمان، موش

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INTRODUCTION

The antioxidant activity of silk sericin is a significant feature that contributes to its partial biological activities; however, the precise processes of its action are still not fully understood [1]. Sericin has been shown to enhance liver detoxification by increasing the expression of genes encoding detoxification enzymes and urea cycle enzymes, which play a role in metabolizing lipid and alcohol toxins as well as ammonia [2]. Despite having a variety of presentations, inflammation is a common characteristic of many neuropathological processes and has been identified as a key mechanism driving the development of the neurodegenerative diseases such as multiple sclerosis, Parkinson's disease, Alzheimer's disease, traumatic brain injury, and stroke. Neuro-inflammation is viewed as a two-edged sword that can protect or harm the neurological system, particularly when it comes to healing and restoration [3]. Sericin can generally control insulin secretion, lipid and insulin metabolism, and the suppression of inflammation in addition to maintaining appropriate glucose levels. Thus, sericin protein has the potential to be transformed into a unique functional meal that has a markedly hypoglycemic impact [4]. Demonstrated its hypoglycemic effects in type 2 diabetic mice, also through its antioxidant and anti-inflammatory properties [5]. It is showed that sericin can ameliorate dystrophic phenotypes in dystrophin-deficient mice, potentially through its ability to reduce oxidative stress and inflammation. Lastly [6] found that sericin can suppress skin tumorigenesis in mice by reducing oxidative stress, inflammatory responses, and the expression of the tumor promoter TNF-α. These studies collectively suggest that sericin's ability to decrease MDA tissue levels in mice mothers compared with the control group mothers may be due to its antioxidant and anti-inflammatory properties. One of the critical and unique properties of Sericin is its anti-inflammatory property, other uses for the drug include anti-diabetic, anti-cholesterol, metabolic modulator, anti-tumor, heart protection, antioxidant, antibacterial, wound healing, cell proliferation, UV protection, freezing, and skin moisturizing [7]. Furthermore, Sericin normalized Sleep deprivation induced reduction in the hippocampus activity of the SOD and GPx, increased TAC, and decreased MDA levels. Sleep deprivation induced memory impairment and pretreatment with sericin improved memory via its antioxidant, anti-inflammation, and up-regulation of synaptic proteins in the hippocampus [8]. Brain-derived neurotrophic factor is involved in the pathophysiology of PD and L-DOPA-induced dyskinesias. These effects have been attributed to changes in BDNF levels in the substantia nigra and cerebral cortex. Moreover, sericin treatments decreased TNF-α and IL-6 concentration levels and enhanced the levels of the BDNF [9]. Sericin, a component of silk protein, has been shown to increase the levels of the SOD in various tissues. In a study on atopic dermatitis in mice, sericin supplementation increased the levels of sphingoid bases and phosphates, which are involved in skin barrier function [10]. Moreover, sericin treatments decreased oxygen species (ROS) and lipid peroxidation levels, restored MMP, and enhanced total antioxidant capacity and enzyme activity of the GPx and SOD in both brain regions [11]. Also, reported that sericin decreased MDA levels in mice mothers, suggesting a potential antioxidant effect [8]. immunological basis for the very potent encephalitogenicity of the MOG, a minor component of myelin in the CNS that is widely used to induce experimental autoimmune encephalomyelitis (EAE) [12]. This is significant as noradrenergic activity has been linked to the regulation of mood, arousal, and stress response. Furthermore, the administration

of sericin has been shown to increase the levels of the BDNF in the hippocampus, a region of the brain associated with memory and learning [13]. Myelin-associated glycoprotein thus appears to play a crucial role in the long-term maintenance of the integrity of both myelin and axons. It has recently been shown that mice deficient in the gene for myelin associated glycoprotein develop normal myelin sheaths in the peripheral nervous system [14]. Chronic stress reduces glucocorticoid receptor expression in rats' prefrontal cortex. Glutamate release after BDNF application is attenuated in chronically stressed rats. Parallel changes in behaviors and BDNF-dependent neural function are observed [15]. The compact myelin sheath functions as an insulator for efficient conduction of nerve impulses. The formation of myelin sheaths around the axons of the most actively functioning neurons continues not only at the stage of brain development, but also in the process of learning and acquiring certain skills. Pathological or age-related disruption in myelin results in nerve conduction failure and neurodegeneration. Myelin Basic Protein is the main constituent of the myelin sheath, representing about 30 % of the total myelin proteins in the central nervous system [16]. Based on the literature, this study aimed to determine effects of exposure to Sericin during gestation on brain growth factor and antioxidant levels following parturition in mice.

MATERIALS AND METHODS

Animals

Sixteen NMRI mice, male, and 40 female mice who were virgins, all weighing between 28-30 g and aged 8-10 weeks, were obtained and housed in a lab setting with a temperature of 22 ± 2°C and a 12-hour light/dark cycle, with unlimited standard chow pellet and fresh water available. Following that, the female mice were placed in cages with fertile male mice. Each morning, the female mice were examined to determine their pregnancy status by checking for the presence of sperm or a vaginal plug.

Study protocol

The pregnant mice were randomly assigned to four groups. Pregnant mice in the control group were provided with water as a fake treatment, while pregnant female mice in groups 2-4 were given sericin orally (112.5, 225, and 450 mg/kg) on various days of pregnancy (5, 8, 11, 14 and 17) [17]. All experimental procedures were approved by the Animal Ethics Committee of the Science and Research Branch of Islamic Azad University in Tehran, Iran. The experimental pain in animals was investigated following the guidelines of the Guide for the Care and Use of Laboratory Animals [18].

Biochemical analysis

Following parturition, the animals were euthanized by decapitation, the skulls were dissected to obtain brain samples from mothers to measure the levels of the BDNF, MOG, MAG, MBP, as well as cortical and sub-cortical MDA, GPx, SOD, MDA, and CAT levels (2, 3). The brain tissues, both cortical and subcortical, were mixed together in a solution with 0.32 mol/L sucrose, 1 mmol/L EDTA, and 10 nmol/L Tris-HCl at a pH of 7.4. Next, the tissues were spun in a centrifuge at a rate of 13,600 g for 30 minutes. The liquids on top were gathered and frozen at -80 ◦C for future investigation. Bradford's method from 1976 was used to measure protein concentrations in the different samples, using bovine serum albumin as a reference. Assay kits from Zell Bio GmbH (Germany) were used to evaluate cortical and sub-cortical tissue MDA, SOD, GPx, and CAT [1]. Brain samples were assayed for BDNF levels we used a commercially available sandwich ELISA kit (KA0331 Abnova, Walnut,

CA, USA) according to the manufacturer's instructions [5]. Brain tissue MAG was determined using Abcam ELISA Kit (ab289652) according to the manufacturer's instructions. Myelin basic protein (MBP) ELISA Kit (Novus biologicals, NBP2-81166) was used to determine brain tissue MBP levels according to the manufacturer's instructions. Mouse myelin MOG was determined using Abcam, ELISA Kit (ab282304).

Statistical Analysis

Data were analyzed using one-way ANOVA and were presented as mean ± SE (standard error) using SPSS version 22.0. For treatments showing significant differences by ANOVA, between-group evaluations were performed using the Tukey post hoc test ($p< 0.05$).

RESULTS

As seen in Figure 1, exposure to sericin during gestation in a dose dependent manner and significantly increased levels of the BDNF in postpartum mice compared to control group ($p< 0.05$). Also, sericin exposure during pregnancy in a dose dependent manner significantly decreased MOG levels in postpartum mice compared to control group ($p< 0.05$) (Figure 1). According to Figure 2, sericin in a dose dependent manner increased levels of the MAG in postpartum mice compared to control group ($p< 0.05$), however, no significant difference observed between dosage of the 112.5 and 225 mg/kg ($p> 0.05$). Based on Figure 2, exposure to sericin during gestation in a dose dependent manner significantly increased levels of the MBP in comparison to control group ($p> 0.05$). As observed in Figure 2, exposure to sericin in a dose dependent manner decreased cortical MDA levels compared to control group ($p< 0.05$). In this study, exposure to sericin during gestation significantly increased cortical SOD levels in postpartum mice in comparison to control group ($p< 0.05$) (Figure 2). Based on our findings, exposure to sericin during gestation in a dose dependent manner and significantly increased cortical levels of the GPx in postpartum mice compared to control group ($p< 0.05$) (Figure 3). As observed, exposure to sericin during gestation significantly increased cortical levels

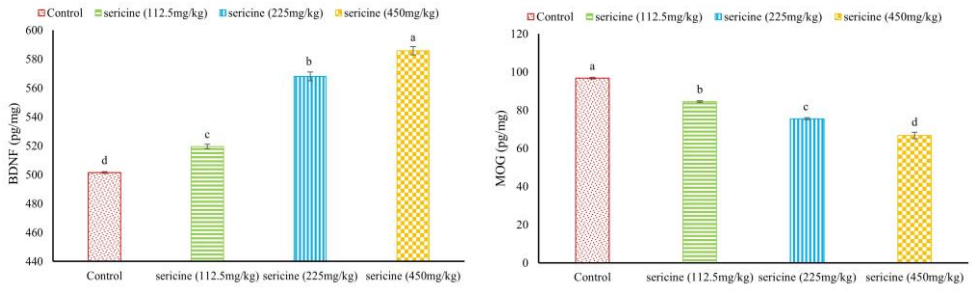

Figure 1: (Left chart): effects of the exposure to sericin during gestation on postpartum levels of BDNF in mice. The non-equivalent letters (a-c) represent significant differences between the. (Right chart): Effects of the exposure to sericin during gestation on postpartum levels of MOG in mice. The non-equivalent letters (a-d) represent significant differences between the experimental groups ($p < 0.05$).

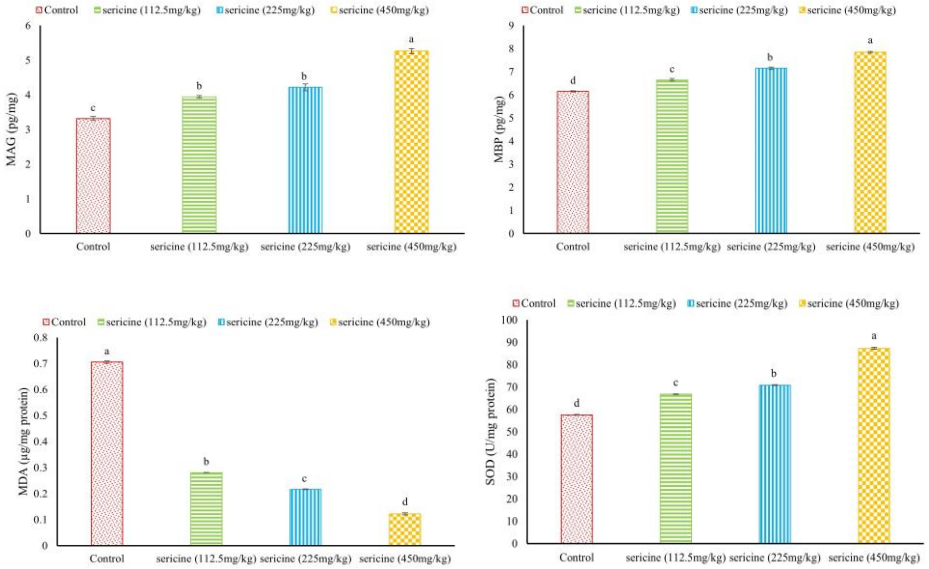

Figure 2: (Top left chart): Effects of the exposure to sericin during gestation on postpartum levels of MAG in mice. The non-equivalent letters (a-c) represent significant differences between the experimental groups (p< 0.05). (Top right chart): Effects of the exposure to sericin during gestation on postpartum levels of MBP in mice. The non-equivalent letters (a-c) represent significant differences between the experimental groups (p< 0.05). (Bottom left chart): Effects of the exposure to sericin during gestation on cortical MDA levels following parturition in mice. The non-equivalent letters (a-d) represent significant differences between the experimental groups (p< 0.05). (Bottom right chart): Effects of the exposure to sericin during gestation on cortical SOD levels following parturition in mice. The non-equivalent letters (a-d) represent significant differences between the experimental groups (p< 0.05).

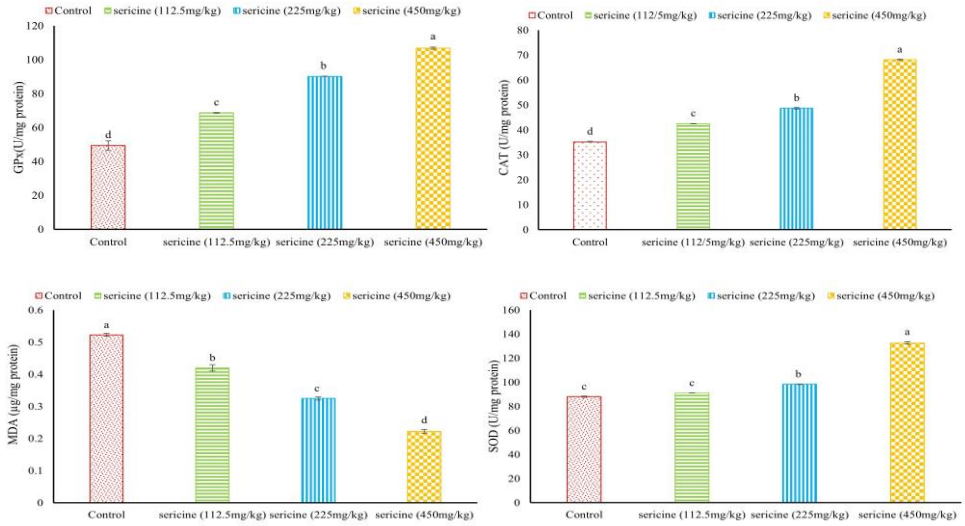

Figure 3: (Top left chart): effects of the exposure to sericin during gestation on cortical GPx levels following parturition in mice. The non-equivalent letters (a-d) represent significant differences between the experimental groups (p< 0.05). (Top right chart): effects of the exposure to sericin during gestation on cortical CAT levels following parturition in mice. The non-equivalent letters (a-d) represent significant differences between the experimental groups (p< 0.05). (Bottom left chart): effects of the exposure to sericin during gestation on sub-cortical MDA levels following parturition in mice. The non-equivalent letters (a-d) represent significant differences between the experimental groups (p< 0.05). (Bottom right chart): effects of the exposure to sericin during gestation on sub-cortical SOD levels following parturition in mice. The non-equivalent letters (a-d) represent significant differences between the experimental groups (p< 0.05).

of the CAT compared to control group (p<0.05) (Figure 3). As observed in Figure 3, in a dose dependent manner decreased sub-cortical MDA levels compared to control group (p< 0.05). In this study, exposure to sericin during gestation significantly increased sub-cortical SOD levels in postpartum mice in comparison to control group (p< 0.05) (Figure 3). Based on our findings, exposure to sericin during gestation in a dose dependent manner and significantly

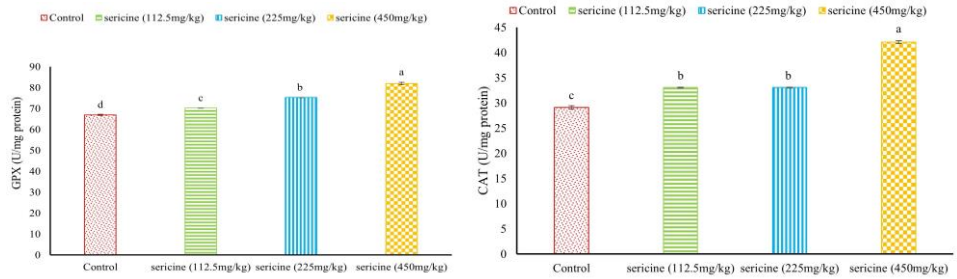

Figure 4: (Left chart): effects of the exposure to sericin during gestation on sub-cortical GPx levels following parturition in mice. The non-equivalent letters (a-d) represent significant differences between the experimental groups ($p< 0.05$). (Right chart): effects of the exposure to sericin during gestation on sub-cortical CAT levels following parturition in mice. The non-equivalent letters (a-c) represent significant differences between the experimental groups ($p< 0.05$).

increased sub-cortical levels of the GPx in postpartum mice compared to control group ($p< 0.05$) (Figure 4). As observed, exposure to sericin during gestation significantly increased sub-cortical levels of the CAT compared to control group ($p< 0.05$) (Figure 4).

DISCUSSION

Examining the effect of sericin on the tissue levels of the MDA, SOD, GPx, and CAT in the mothers of the NMRI laboratory mice provides a picture of metabolic and defense changes in response to oxidative stress. Detailed analysis of these data shows the reduction of oxidative damage and strengthening of antioxidant defense. The reduction of the MDA tissue values indicates the reduction of lipid peroxidation and cell damage. MDA is the final product of the oxidative production of lipids, and its reduction can indicate a reduction in oxidative processes that damage cell membranes, and help maintain the structure and function of cell membranes and prevent apoptosis or cell death caused by oxidative damage [19]. This reduction may be due to the increase in antioxidant activity, which effectively neutralizes free radicals and prevents lipid peroxidation. An increase in SOD tissue levels indicates an improvement in the cell's ability to convert destructive superoxide radicals into hydrogen peroxide and oxygen, two relatively less dangerous products. The stimulation of SOD activity can be considered as a defense mechanism against the increased oxidative stress caused by sericin. This increase can also help reduce superoxide levels in cells and help maintain redox balance. Increase in tissue amounts of GPx and CAT enzymes play an important role in neutralizing hydrogen peroxide, GPx converts hydrogen peroxide to water and oxygen, and CAT performs a similar reaction. Increasing the activity of these enzymes leads to a significant decrease in the level of hydrogen peroxide, which itself helps to reduce oxidative stress and prevent cell damage. This increase may have occurred as a defensive reaction to the increase of free radicals as a result of exposure to sericin and indicates an improvement in the ability of cells to manage oxidative stress and protect vital cellular components. The decrease in MDA may indicate changes in the lipid composition of membranes that help them become more resistant to peroxidation. These changes can happen in the form of an increase in membrane lipids with more saturation or a decrease in unsaturated lipids that are more prone to peroxidation. Activation of the Nrf2 pathway is a transcription factor that is activated in response to oxidative stress and promotes the expression of antioxidant genes including SOD, GPx, and CAT. The activation of this pathway can explain the observed increase in the activity of these enzymes, which is caused by the activation of cellular signaling pathways that are specifically activated in response to oxidative

stress. For example, the mitogen-activated protein kinase (MAPK) pathway and the transcription factor NF-κB may be involved in this process, both of which can enhance antioxidant responses and lead to the expression of genes related to antioxidant enzymes [11, 20]. Overall, the findings of this study show that sericin plays an important protective and regulatory role in subcortical function by affecting oxidative stress, regulation of neurotransmitters, synaptic plasticity, neurogenesis and inflammation. This information can be used in various fields of neurological and neuropharmacological research. Considering the effects of sericin on the regulation of neurotransmitters, synaptic plasticity and the survival of neurons in the subcortical region, it can be expected that this compound has an effect on the cognitive functions related to these areas [21]. BDNF is a key neurotrophic factor that plays an important role in the survival, growth and differentiation of neurons in the brain. The increase in BDNF levels under the influence of sericin can help to improve the function of neurons and synaptic plasticity in the brain of mothers. This effect of sericin on BDNF can be useful in the prevention and treatment of cognitive and neurodegenerative disorders related to pregnancy [22, 23]. MOG is an oligodendrocyte-specific protein that plays a role in myelination and central nervous system function. The reduction of MOG levels under the influence of sericin may be related to the improvement of myelination and central nervous system function in mothers. This effect of sericin on MOG can be useful in the prevention and treatment of myelination and neurological disorders related to pregnancy [24, 25]. MAG is an important factor in myelin damage and degeneration, which is associated with inflammation and oxidative stress. The increase in MAG levels under the influence of sericin can indicate the reduction of myelin damage and the improvement of the state of myelination in the brain of mothers. This effect of sericin on MAG can be useful in the prevention and treatment of myelination disorders related to pregnancy [26, 27]. MBP is a major myelin protein that plays a key role in the formation and maintenance of the myelin sheath in the central nervous system. The increase in MBP levels under the influence of sericin can indicate the improvement of myelination and central nervous system function in mothers. This effect of sericin on MBP can be useful in the prevention and treatment of myelination and neurological disorders related to pregnancy [28-30].The possible mechanisms of the effects of sericin on brain factors by increasing BDNF can be caused by the induction of the BDNF gene expression or the activation of signaling pathways related to this neurotrophic factor. The decrease of the MOG and the increase of the MAG and MBP may be related to the positive regulation of signaling pathways related to myelination and the reduction of myelin damage. These effects probably take place through reducing oxidative stress and inflammation, regulating the activity of neurotransmitters and improving blood supply in the brain of mothers [31-33]. Improving myelination by sericin by increasing MAG and MBP and decreasing MOG can be effective in preventing and treating myelination and neurological disorders related to pregnancy. These effects of sericin on brain factors can be used in the design of new drugs and therapeutic interventions to improve brain function during pregnancy [34]. Overall, the findings of this study show that sericin can play an important protective and regulatory role in the brain function of mothers by affecting important brain factors such as BDNF, MOG, MAG and MBP [35]. following parturition in mice which might have protective role for both mother and dam.

CONCLUSION

In conclusion this findings suggested that sericin can play an important protective and regulatory role in the brain function following parturition in mice.

ETHICS

Approved.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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