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Role of 3-Acetyl-11-Keto-Beta-Boswellic Acid in Counteracting LPS-Induced Neuroinflammation via Modulation of miRNA-155

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Abstract Neuroinflammation is one of the most important mechanisms underlying neurodegeneration. Lipopolysaccharide (LPS) is a potent inflammogen which causes cognitive dysfunction. *Boswellia serrata* is known since many years as a powerful anti-inflammatory herbal drug. Its beneficial effect mainly arises from inhibition of 5-lipoxygenase (5-LO) enzyme. 3-acetyl-11-keto-β-boswellic acid (AKBA) is the most potent 5-LO inhibitor extracted from the oleo-gum-resin of *Boswellia serrata*. The aim of the present work is to study the molecular mechanisms underlying the anti-inflammatory and neuroprotective effects of AKBA and dexamethasone (DEX) in LPS-induced neuroinflammatory model. A single intraperitoneal (i.p.) dose of LPS (0.8 mg/kg) was injected to induce cognitive dysfunction. The LPS-treated mice were administered for 7 days with either AKBA or DEX at intraperitoneal doses of 5 and 1 mg/kg, respectively. Cognitive, locomotor functions, and anxiety level were first examined. The level of the phosphorylated inhibitory protein for NF-κB, IκB-α (P-IκB-α), was measured, and the expression levels of the inflammatory microRNA-155 (miR-155) and its target gene, suppressor of cytokine signaling-1 (SOCS-1), were determined in the brain. Moreover, the level of carbonyl proteins as a measure of oxidative stress and several cytokines as well as markers for apoptosis and amyloidogenesis was detected. Results showed that AKBA and DEX reversed the behavioral dysfunction induced by LPS. AKBA decreased P-IκB-α, miRNA-155 expression level, and carbonyl protein content. It restored normal cytokine level and increased SOCS-1 expression level. It also showed anti-apoptotic and anti-amyloidogenic effects in LPS-injected mice. These findings suggest AKBA as a therapeutic drug for alleviating the symptoms of neuroinflammatory disorders.

Keywords LPS · AKBA · DEX · Molecular markers · Inflammatory markers

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Introduction

Neuroinflammation and oxidative stress are main key players in the disruption of central nervous system (CNS) homeostasis. Activated microglia progressively release inflammatory cytokines, chemokines, and reactive oxygen species (ROS), contributing to the development of chronic neurodegenerative disorders [1, 2]. One of the products of oxidative stress is the carbonylation of proteins which proceeds to damaging effects and subsequent protein dysfunction. These carbonylated

proteins are associated with the pathogenesis of chronic neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), progressively causing the appearance of aggregate-like structures which are readily detected [3, 4].

LPS is a gram-negative bacterial endotoxin, present in the outer membrane. It causes a neuroinflammatory state [5]. LPS mediates its action by binding to Toll-like receptor-4 which is known to be abundant on microglia in the CNS [6]. As a result of this binding, nuclear factor kappa B (NF-κB) pathway is activated initiating a neuroinflammatory process. This process is characterized by the release of inflammatory mediators consequently resulting in neurodegeneration [7, 8]. This activation of NF-κB is mediated by the action of the IκB kinases (IKK), which act through IκB protein phosphorylation in the N-terminal domain (P-IκB) followed by polyubiquitination and proteasomal degradation. Finally, NF-κB binds to DNA motifs in target genes after translocation to the nucleus controlling their transcription [9]. Moreover, it was recently shown that LPS stimulates apoptotic neurodegenerative process via elevating caspase-3. LPS was proven to up regulate the expression level of amyloid beta (Aβ), amyloid precursor protein (APP), β-secretase (BACE-1), and P-Tau; all are possible markers of AD [10].

MicroRNAs (miR) are single-stranded non-coding RNA and function to control gene expression at a post-transcriptional level [11], promoting degradation and translational repression of their target mRNA as well as downregulation of the gene product [12]. Additionally, it was found that miRs are among the epigenetic factors regulating the expression of genes in the inflammatory process [13]. MiR-155 is a pro-inflammatory miR as it is known to target proteins having anti-inflammatory functions [14]. MiR-155 is transcribed from an exon of non-coding RNA in the B cell integration cluster (BIC) region on human chromosome 21 [15, 16]. It was shown that miR-155 targets suppressor of cytokine signaling (SOCS-1), an anti-inflammatory protein in the microglia, causing upregulation of several inflammatory pathways [17].

Glucocorticoids exert neuroprotective effects. One of the commonly used therapeutic glucocorticoids is dexamethasone (DEX) [18]. Long time ago, it was shown that DEX inhibited NF-κB activity, by increasing the expression of inhibitor of kappa B (IκB) [19]. Thereby, DEX reduced blood-brain barrier permeability [20]. As an anti-inflammatory drug, DEX can act on glucocorticoid receptors and regulates neuroinflammation in vitro [21]. It was proven that DEX reduced the expression of miR-155 in mice liver after the induction of sepsis using LPS [22].

The gum-resin of *Boswellia serrata* or "frankincense" is known for its anti-inflammatory effect in vivo [23]. Boswellic acids are the main active constituents of the oleo-gum-resin of the plant. From the boswellic acids, 3-acetyl-11-keto-β-boswellic acid (AKBA) has the most potent anti-inflammatory action by inhibiting 5 lipooxygenase (5-LO) enzyme [24]. Boswellic acids such as AKBA readily pass the blood-brain barrier as they are highly lipophilic compounds [25].

The *Boswellia* extract is well known to enhance memory formation via brain-derived neurotrophic factor [26] and learning abilities [27]. It was shown that different extracts from *Boswellia* can act as a preventive therapy against several brain disorders including neurodegenerative diseases [28]. In addition, *Boswellia serrata* exhibits a potential anti-oxidant action in the cerebrovascular system [29].

A previous study done on AKBA showed its protective activity against LPS-induced neuroinflammation, having potential anti-inflammatory, anti-glutamatergic, and anti-amyloidogenic effects [30]. The aim of the current study is to investigate the possible protection mechanism of AKBA through modulation of NF-κB-regulated miR-155/SOCS-1 expression, and thereby affecting oxidative, apoptotic, and amyloidogenic markers, in comparison to DEX.

Materials and Methods

Animals

Adult male Swiss albino mice weighing between 25 and 30 g, aged 3–4 months, were used. Animals were obtained from the animal colony of the National Research Center (NRC) (Giza, Egypt) and housed in a temperature-controlled room (23–24 °C), with 12-h dark/light cycles. Free access to food and water was allowed. Experimental procedures were performed according to the guidelines of the Animals Ethics Committee at the German University in Cairo in association with the recommendations of the National Institutes of Health (NIH) Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

Treatments and Experimental Groups

Animals were divided into six groups (n = 10–13 mice/group). The untreated control group was injected with 0.9% saline and neuroinflammation control group was induced by the intraperitoneal injection of LPS-B8 (L3129, Sigma-Aldrich GmbH, Steinheim, Germany) at a dose of 0.8 mg/kg [31, 32]. Treated groups with either AKBA or DEX were injected 1-h post-LPS injection with either 5 mg/kg AKBA (sc-221208, Santa Cruz Biotechnology, Germany) or 1 mg/kg DEX (sc-204715, Santa Cruz Biotechnology, Germany), for 7 days [30, 33–35]. Drug control groups were injected with either AKBA or DEX at the same dose and duration as in the treated groups, but without pre-injection with LPS.

Modified Y-Maze

Y-maze is considered a well-known test to measure the short-term spatial memory of rodents. The maze is composed of Y-shaped white wood with three identical arms. Animals were trained on the 7th day of injection. During the training session, one arm was blocked and the animal was allowed to explore the other two arms for 15–30 min. After 1–2 h, the test trial was performed in which all arms were opened to be explored for 5 min. [36, 37]. The percentage of time spent in novel arm was calculated as percentage of the total arm time [38].

Elevated plus Maze

The elevated plus maze (EPM) was proven to be a suitable test to evaluate the anxiety-related behavior [39]. Mice were located in the central square of the plus maze facing an open arm, and then they were allowed to explore the maze freely for 5 min immediately after the 7th day of injection. The parameter calculated is the percentage of time spent in the open arms during 5 min as percentage of the total time [40].

Ladder Rung

The test is a skilled walking test performed to investigate rodents' motor activity. Ladder rung consists of a horizontal ladder made of clear plexiglass with metal rungs which are regularly or irregularly spaced, 1–5 cm apart from each other according to the trial session. Training was performed on the 7th day of injection. Mice were allowed to walk freely at one side along the ladder using regularly arranged rungs of 1-cm spacing between each, in order for the mice to anticipate the position of the rungs over three trials. On the 8th day, three trials were performed by each mouse with different irregular rung spacing patterns, each time to increase the difficulty of the test by modifying the position of the metal rungs. Foot placement accuracy was recorded. Errors were defined as any attempt of foot slip or total miss as mentioned by the foot fault scoring system. Average errors for three trials were evaluated [41, 42].

Brain Sample Collection

At the end of the behavioral tests, animals were sacrificed; their brains were harvested and washed with phosphate-buffered saline (PBS), pH 7.4. Brains were frozen at − 80 °C for further assays. Brains were divided into two halves. Half brain from each group was homogenized in radioimmunoprecipitation assay (RIPA) buffer to be used in western blot experiments ($n = 3$). The second half was homogenized in PBS for the carbonyl protein assay ($n = 5$), the enzyme-linked immunosorbent assay (ELISA) ($n = 6$), and for the analysis of gene expression levels by qPCR ($n = 5$).

Real-time PCR

To assay the expression levels of miR-155 and its target gene, SOCS-1, total RNA was extracted from the brain samples using mirVana miRNA extraction kit (Cat. No. AM1560, Ambion®, USA). For miR-155 assay, 10 ng of total RNA was converted into cDNA using TaqMan Reverse Transcriptase kit (Cat. No. 4366597, Applied Biosystems®, USA). For SOCS-1 assay, high-capacity cDNA reverse transcription kit (Cat. No. 4368814, Applied Biosystems®, USA) was used where 2 μg RNA was converted to cDNA.

Quantitative RT-PCR (qRT-PCR) of miR-155 was performed by TaqMan® microRNA assays (Cat. No. 4427975, 002571, Applied Biosystems®, USA) relative to snoRNA-202 (Cat. No. 4427975, 001232, Applied Biosystems®, USA), which serves as a reference gene. For SOCS-1 measurement, the amplification was performed using TaqMan® gene expression assays (Cat. No. 4331182, Applied Biosystems®, USA) relative to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as a housekeeping gene. Results of qRT-PCR measurement were expressed as Ct values calculated by Applied Biosystems® StepOne™ (Applied Biosystems®, USA). Data were normalized to either snoRNA-202 or GAPDH expression and calculated as relative expression for LPS group compared to control group or treated group compared to LPS. Comparative Ct method ($2^{-\Delta\Delta Ct}$) was used to estimate differences between groups [43].

Western Blotting

Brain tissues were lysed using RIPA buffer with the subsequent addition of complete™ protease inhibitor cocktail (Roche, USA) and Phoso-stop easy pack (Roche, USA). Sonication was performed followed by centrifugation for 10 min at a maximum speed, 4 °C and then the supernatants were retained. Protein concentration was determined in the supernatant using Bradford assay. Samples mixed with loading buffer were incubated at 90 °C for 5 min for proteins denaturation. Equivalent amounts of brain lysate to 50 μg protein were loaded and electrophoresed on 12% separating gel. Proteins were transferred onto polyvinylidene fluoride (PVDF) membrane (Biorad, USA), then blocked with odyssey blocking reagent for 1 h with continuous shaking. Membranes were incubated overnight at 4 °C with primary antibodies diluted 1:1000 with tris-buffered saline and tween 20 (TBST) for the total IκB-α (anti-IκB-α anti-mouse antibody (H-4) Santa Cruz Biotechnology, Germany), and the phosphorylated IκB-α (anti-P-IκB-α anti-rabbit antibody (ser 32/36), Santa Cruz Biotechnology, Germany). The housekeeping protein GAPDH was used as a reference control detected by (14 C10, Cell Signaling, USA) anti-GAPDH anti-rabbit antibody at a concentration of 1:5000. On the following

day, membranes were washed of excess primary antibodies and incubated for 1 h in dark with 1:10,000 diluted secondary antibodies (anti-IκB-α anti-mouse; IR 800CW DαM and anti-P-IκB-α anti-rabbit; IR 800CW DαR). The amount of fluorescence emerging from each antibody was detected by Odyssey quantitative western blot near infrared system (Li-Cor Biosciences, USA). Each protein band was normalized to that of the GAPDH housekeeping protein. Finally, the relative intensity of P-IκB-α to total IκB-α was determined.

Carbonyl Protein Content

Before assaying the carbonyl content in the brain samples, protein concentrations were determined by Pierce® bicinchoninic acid (BCA) protein assay kit (Cat. No. 23227, Thermo Fisher Scientific, USA). Brain tissues were homogenized in PBS to reach a protein content in the range of 0.5–2 mg protein. The carbonyl content was quantified spectrophotometrically by a commercially available kit (Cat. No. ab126287, Abcam, UK) according to the manufacturer's instructions. The carbonyl content was calculated in n moles divided by the protein concentration in milligram.

ELISA Measurements of IL-6, IL-10, Caspase-3, and Aβ (1-42)

To investigate the effect of neuroinflammation on the levels of cytokines, the inflammatory cytokine interleukin-6 (IL-6) and the anti-inflammatory cytokine IL-10 were measured using ELISA kits (RayBio® Mouse IL-6 ELISA kit (ELM-IL6-CL, RayBiotech, Inc., USA) and *Mus musculus* ELISA kit for IL-10 (SEA056Mu, Cloud-Clone Corp., USA)) according to the manufacturers' instructions.

Furthermore, in order to investigate the apoptosis and amyloidogenesis, caspase-3 and Aβ (1-42) were assayed by mouse caspase-3 (Casp-3) ELISA kit (CSB-E08858m, Cusabio, USA) and mouse amyloid beta peptide 1-42 (Aβ1-42) ELISA kit (CSB-E10787m, Cusabio, USA), respectively, following the manufacturer's instructions. Results were expressed in gram tissues.

Statistical Analysis

Statistical analysis was performed using instant automated software (Graph Pad Prism version 5.01, Inc., California, USA). Results were expressed as mean ± standard error of mean (SEM). One-way ANOVA followed by the Tukey-Kramer multiple comparison test was selected for analysis of all tests. P value less than 0.05 was considered significant.

Results

Behavioral Improvement by AKBA and DEX Treatment

Administration of a single dose of LPS (0.8 mg/kg) induced behavioral impairment, which was reversed using AKBA (5 mg/kg) and DEX (1 mg/kg) treatment. Three tests were used to assess behavioral functions: modified Y-maze to test spatial memory, EPM to test anxiety level, and ladder rung to assess locomotor functions. Results were normalized to the untreated controls.

Effect of AKBA and DEX on the Spatial Memory Impairment by LPS

LPS treatment resulted in a significant decrease in the percentage of time spent in the novel arm of the Y-maze compared to the control mice (39.22 ± 5.41%) versus (100.70 ± 10.56%) (Fig. 1a). AKBA treatment significantly increased the percentage of time spent in the novel arm (90.03 ± 8.86%) compared to LPS-treated group. The same effect was observed after DEX treatment compared to LPS group (85.93 ± 5.50%).

Impact of LPS, AKBA, and DEX on Anxiety Level

A significant decrease in the percentage of time spent by the mice in open arms was observed following LPS administration (22.22 ± 4.95%), as compared to untreated mice (100.00 ± 17.50%) (Fig. 1b). However, the treatment of LPS-injected mice with a daily dose of AKBA or DEX for a week resulted in a significant increase in the percentage of time spent in open arms to 83.32 ± 8.94% and 73.80 ± 2.76%, respectively, compared to LPS group.

Effect of LPS, AKBA, and DEX on Locomotor Function Using Ladder Rung Test

LPS caused locomotor dysfunction revealed by a significant increase in the stepping errors (7.11 ± 0.60) compared to control mice (1.00 ± 0.12) (Fig. 1c). However, treatment of LPS-injected mice with either AKBA or DEX resulted in a significant decrease in the stepping errors to 1.37 ± 0.39 and 1.32 ± 0.46, respectively, compared to LPS.

Molecular Mechanisms Mediating the Neuroprotective Effects of AKBA and DEX

Administration of a single dose of LPS (0.8 mg/kg) resulted in an increase in inflammation and oxidative stress, apoptosis, and amyloidogenesis. AKBA (5 mg/kg) and DEX (1 mg/kg) acted as anti-inflammatory drugs and counteracted the LPS-induced neurotoxic effects. This was obvious in each of the following assays.

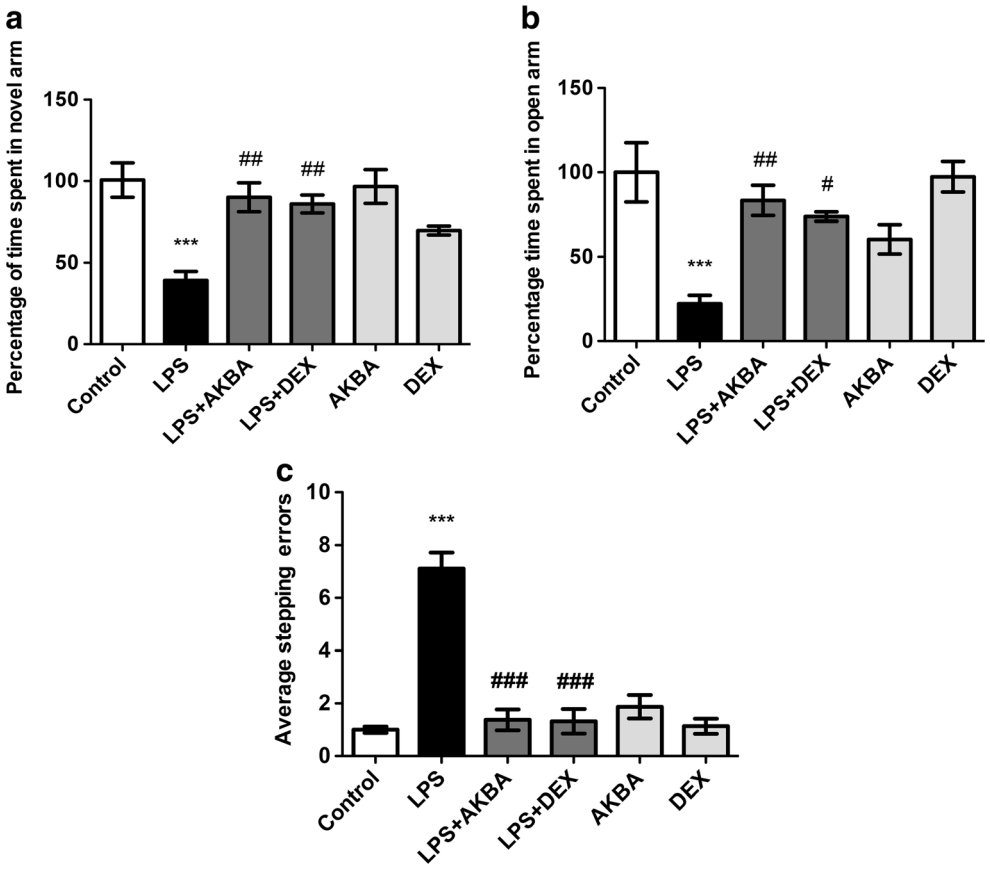

Fig. 1 Behavioral functions evaluation. Modified Y-maze (**a**), EPM (**b**), and ladder rung (**c**) tests. LPS showed significant decrease in percentage of time spent in novel and open arms of Y-maze and EPM tests, respectively, and a significant increase in error choices at ladder rung test. Both DEX and AKBA showed significant recovery of the behavioral changes. Data is represented as mean ± SEM (n = 10–13 mice/group). $^{***}P < 0.001$ versus control group, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ versus LPS group

Anti-inflammatory Effect of AKBA and DEX by Modulation of miR-155 and its Target Gene SOCS-1

Administration of LPS caused a significant increase in the relative miR-155 expression level (6.51 ± 0.64) in comparison to the control mice (1.13 ± 0.25) (Fig. 2a). The treatment of LPS-injected mice with either AKBA or DEX led to a significant decrease in the relative miR-155 expression by 2.52 ± 0.33 and 3.78 ± 0.44, respectively, compared to LPS group.

On the other hand, there was a significant decrease in the relative expression level of SOCS-1 following injection of LPS (0.32 ± 0.02) as compared to control mice (1.15 ± 0.04) (Fig. 2b). Furthermore, treatment of LPS-injected mice with 5 mg/kg AKBA or 1 mg/kg DEX showed a significant increase in the relative SOCS-1 expression by 0.56 ± 0.05 and 0.69 ± 0.08 for AKBA and DEX, respectively, compared to LPS-injected mice.

Effect of AKBA and DEX on NF-κB

Western blot analysis of the IκB-phosphorylated form revealed that LPS resulted in a significant increase in P-IκB-α compared to control mice (6.02 ± 0.40 versus 1.00 ± 0.37) (Fig. 3). Meanwhile, treatment with 5 mg/kg AKBA significantly decreased P-IκB-α protein expression (2.46 ± 0.22) compared to LPS-injected mice (6.02 ± 0.40). In a similar manner, 1 mg/kg DEX treatment significantly decreased P-IκB-α protein (2.02 ± 0.20) compared to LPS group. Results were normalized to the untreated control group.

Effects of AKBA and DEX on the Levels of Cytokines: IL-6 and IL-10

The role of LPS in the regulation of inflammatory mediators was investigated. LPS injection resulted in a significant increase in the inflammatory cytokine: IL-6 up to 4.83 ± 0.30 compared to the control untreated mice (1.00 ± 0.04) (Fig. 4a). The treatment of LPS-injected mice with AKBA or DEX for 7 consecutive days caused a significant decrease by 1.65 ± 0.07 or 2.21 ± 0.07, respectively, as compared to LPS-injected mice (4.83 ± 0.30).

On the other hand, a significant decrease in the anti-inflammatory cytokine: IL-10 was observed after administration of LPS down to 0.10 ± 0.008 compared to untreated mice (1.00 ± 0.04) (Fig. 4b). Meanwhile, treatment of LPS-injected mice with seven doses of AKBA or DEX significantly increased IL-10 level to 0.57 ± 0.02 or 0.44 ± 0.01, respectively, as compared to LPS-injected mice (0.10 ± 0.008). Variation in

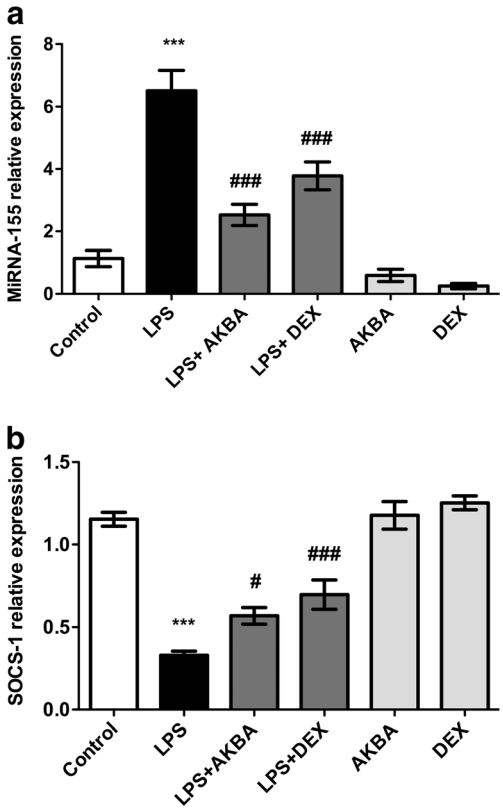

Fig. 2 Relative expression of miR-155 and its target gene, SOCS-1 by qPCR Taqman assays. Relative expression of miR-155 with reference to the control and LPS-treated mice (**a**). Relative expression of SOCS-1 with reference to the control and LPS-treated mice (**b**). Treatment with AKBA and DEX reversed the inflammatory action of LPS on miR-155 and SOCS-1. Data is represented as mean ± SEM (n = 5 mice/ group). $^{***}P < 0.001$ versus control group, $^{\#}P < 0.05$ and $^{\#\#\#}P < 0.001$ versus LPS group

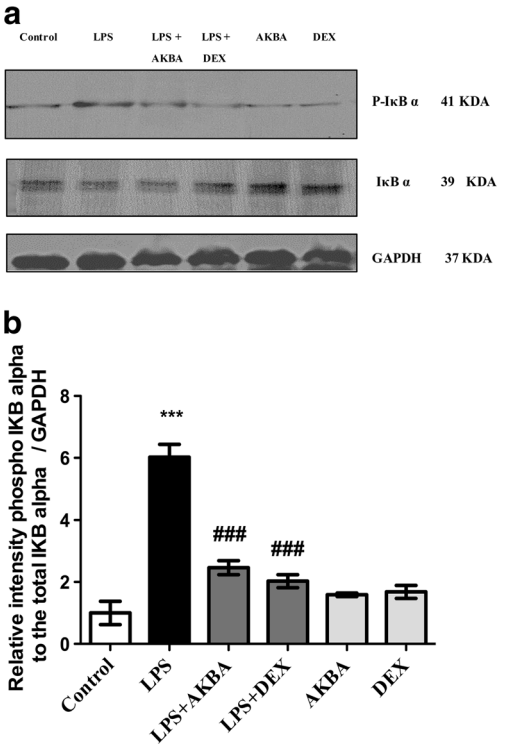

Fig. 3 Western blot analysis of P-IκB-α and IκB-α expression. Immunoblotting of P-IκB-α and IκB-α from brain tissues of mice (**a**). Quantification of P-IκB-α and IκB-α expression levels normalized to GAPDH reference protein (**b**). LPS caused a significant increase in the relative band intensity of P-IκB-α. Treatment with AKBA and DEX reversed the action of LPS. Data is represented as mean ± SEM (n = 3 mice/group). $^{***}P < 0.001$ versus control group. $^{\#\#\#}P < 0.001$ versus LPS group

cytokines expression levels has been normalized to the untreated control group.

Effect of AKBA and DEX on Carbonyl Protein Content

A significant increase in the carbonyl protein content was observed in LPS-treated mice up to 4.33 ± 0.48 compared to the control untreated mice (1.00 ± 0.18) (Fig. 5). The treatment of LPS-injected mice with seven doses of AKBA or DEX decreased the carbonyl protein level significantly to 1.35 ± 0.24 or 1.09 ± 0.07, respectively, compared to LPS. Values are normalized to the untreated control group.

Effect of AKBA and DEX on LPS-Induced Apoptosis and Amyloidogenesis

Neuroinflammation may result into cell apoptosis. Therefore, caspase-3 protein level was evaluated after injection of LPS and revealed a significant increase to 5.46 ± 0.29 compared to the control untreated mice (1.00 ± 0.03) (Fig. 6a). In addition, treatment with AKBA or DEX after LPS showed a significant decrease in caspase-3 level by 1.44 ± 0.09 or 2.45 ± 0.17, respectively, as compared to LPS-injected mice.

Similarly, LPS injection enhanced amyloidogenesis by significantly increasing Aβ (1-42) protein level up to 5.48 ± 0.37 compared to the control untreated mice (1.03 ± 0.04) (Fig. 6b). Conversely, treatment of LPS-injected mice with seven doses of 5 mg/kg AKBA or 1 mg/kg DEX revealed a significant decrease in the Aβ (1-42) protein expression level by 1.67 ± 0.07 or 2.31 ± 0.08, respectively, as compared to LPS-injected mice. Values for both parameters are represented after normalization to the control untreated group.

Discussion

The neuroinflammatory state was proven to cause behavioral dysfunction. In the current study, LPS caused deterioration of spatial memory in the Y-maze test, which was restored by AKBA and DEX. It was previously found that LPS decreased spatial recognition memory in the Y-maze test. The behavioral deficits observed were a consequence of increased microglial count within the hippocampus [38]. Recently, the injection of mice with LPS for 1 week resulted in impairment of spatial

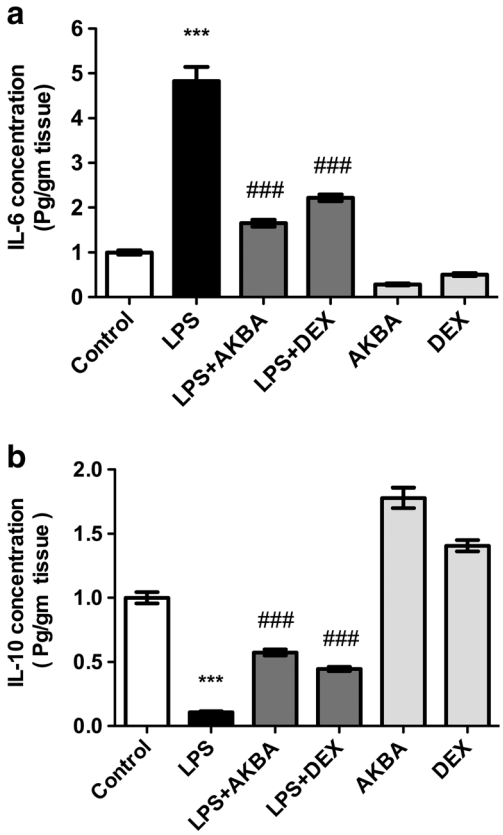

Fig. 4 Evaluation of IL-6 (**a**) and IL-10 (**b**) cytokine inflammatory markers by ELISA assay. LPS caused significant increase in IL-6 level and a decrease in IL-10 level. AKBA and DEX treatments significantly decreased IL-6 level and increased IL-10 level. Data is represented as mean ± SEM (n = 6 mice/group). $^{***}P < 0.001$ versus control group, $^{###}P < 0.001$ versus LPS group

memory. This result was caused by LPS-induced NF-κB-dependent neuroinflammatory mechanisms which predispose the animals to synaptic dysfunction [10]. In the radial maze test, DEX increased novel arm entry [44]. In a recent study, the

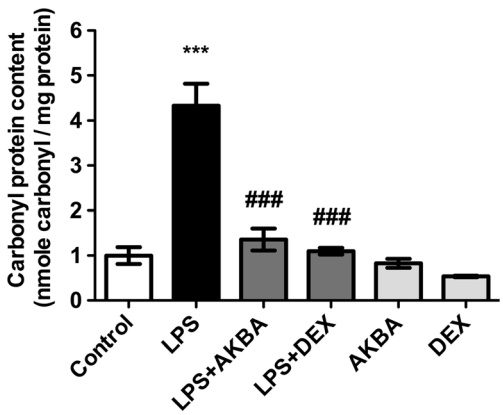

Fig. 5 Carbonyl protein content determination by DNPH assay. LPS caused a significant increase in carbonyl protein content normalized by mg protein in BCA assay. AKBA and DEX significantly decreased the carbonyl protein content in LPS-treated mice. Data is represented as mean ± SEM (n = 5 mice/group). $^{***}P < 0.001$ versus control group, $^{###}P < 0.001$ versus LPS group

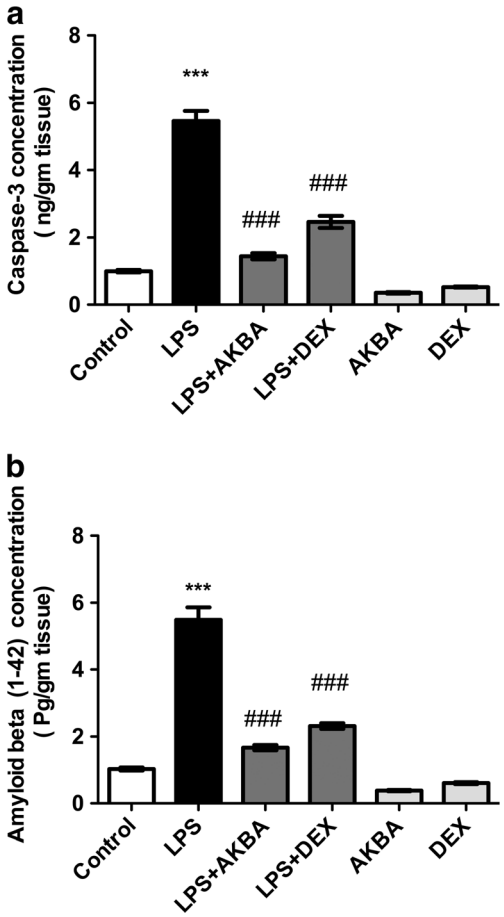

Fig. 6 Quantification of apoptotic and amyloidogenic markers by ELISA assay. Expression of caspase-3 (**a**), and Aβ (1-42) (**b**) in the brain biopsies of mice exposed to different treatments. LPS injection caused significant increase in caspase-3 apoptotic marker, and Aβ (1-42) amyloidogenic marker. Treatment with AKBA and DEX significantly decreased both markers. Data is represented as mean ± SEM (n = 6 mice/group). $^{***}P < 0.001$ versus control group, $^{###}P < 0.001$ versus LPS group

resin extract of *Boswellia carteri* showed considerable memory recovery mediated by counteracting the inflammatory mechanism in LPS-injected rats [45]. LPS also modulated the anxiety level. In a previous study, LPS increased anxiety-like behavior in the elevated zero maze (a circular version of the EPM). The anxiety-stimulating effect may be due to the release of TNF-α [38] which triggers microglial activation and thus neurotoxicity and cell death [46]. In addition, LPS caused a significant decrease in open-field locomotor activity after 2 h [47]. DEX showed an anxiolytic controversial effect. Acute administration of DEX increased open arm time and showed a slight anxiolytic effect, whereas chronic doses were anxiogenic. The anxiogenic action was suggested to be due to increased glutamate release and imbalance between GABA and glutamate neurotransmitters [44]. In the present study, AKBA showed significant anxiolytic effect and this result is in accordance with a previous study in which animals administered *Boswellia serrata* extract spent more

time in the open arms than the closed arms of the EPM [48] and showed significant improvement of motor functions in rotarod test [49]. These results are consistent with the current study in which LPS caused anxiogenic effect and decreased motor functions which were reversed by administration of AKBA and DEX.

Some anti-inflammatory drugs played a role in miR expression. In the present study, DEX modulated the effect of LPS on miR-155 and SOCS-1. On a similar basis, DEX showed protective effect in mice treated with LPS, mediated by a decrease in TNF-α and IL-6 in the liver. Furthermore, DEX injection resulted in a decrease in miR-155 level in a dose-dependent manner. It was suggested that DEX may act directly by binding to the BIC genes [22]. The inhibitory effect of glucocorticoids was regulated particularly by NF-κB binding sites located on the promoters of the BIC genes [50]. In an in vitro study, the transfection of miR-155 followed by DEX caused a great increase in the expression level of SOCS-1 [51]. Recently, in an intracerebral hemorrhage mouse model, DEX modulates inflammatory state via miR-155/SOCS-1 signaling pathway [52]. To our knowledge, this study is the first to prove the anti-inflammatory effect of AKBA by downregulating miR-155.

The pathogenic mechanisms of LPS-induced neuroinflammation were shown to be involved in the modulation of cytokines levels. Mice treated with LPS had elevated levels of cytokines: IL1-β, IL-6, TNF-α, and interferon-γ (IFN-γ) with an opposing effect on IL-10, both appeared in the cerebral cortex and hippocampus [53]. In the current study, DEX decreased P-IκB-α as well as IL-6 and increased IL-10. In accordance, DEX-treated rats revealed a decrease in the pro-inflammatory cytokines such as IL-6 and an increase in IL-10 [54]. A decrease in NF-κB subunit, p65 on protein and mRNA levels was observed. This was associated with a protective effect against oxidative damage [55].

AKBA showed strong anti-inflammatory effects in the present study. This is in agreement with previous studies showing that the plant extract revealed anti-oxidant and anti-inflammatory effects shown by a rise in the level of IL-10 accompanied by reduction of the inflammatory mediators: IL-1β, IL-6, TNF-α, and IFN-γ [56]. The terpenoids mediated the inhibition of NF-κB pathway through decreasing IκB-α degradation, along with phosphorylation and nuclear translocation of p65 [57].

The injection of LPS previously showed significant increase in protein carbonyl content in the serum of mice [58]. In contrary, a decrease in the level of carbonylated proteins was observed in rats after DEX treatment [59]. Moreover, AKBA was proven to alleviate oxidative stress markers [60]. The powerful anti-oxidant and accordingly neuroprotective effects of *Boswellia* could explain the observed enhancement of cognitive functions [61, 62]. These effects were confirmed in a previous study using AD-induced rats [49]. Consistent with these findings, LPS injection in the present study resulted in an inflammatory state and oxidative damage, which were improved by the administration of the anti-inflammatory drugs: AKBA and DEX.

In the current study, LPS revealed significant increase in apoptotic and amyloidogenic markers. Previous studies showed an increase in caspase-3 activation after LPS administration [63]. Lately, LPS elevates the underlying factors and markers of AD as APP, BACE-1, and Aβ in the hippocampus and induces immunoinflammatory changes in the cortex [10, 64] which could be a reason for cognitive dysfunction in rodents [65]. It was suggested that the apoptotic neurodegenerative mechanism is a causative factor of elevation of caspase-3 [10].

DEX showed a decrease in caspase-3 level in the present study. In a similar manner, DEX administration significantly decreased the apoptotic markers and increased the number of surviving neurons. The steroid expressed high ratio of Bcl-2/Bax and downregulated the expression of cleaved caspase-3, thus acting as anti-apoptotic drug [66]. It was shown that DEX is capable to antagonize LPS effect to trigger neuronal apoptosis in a caspase-3-dependent manner [67]. Parallel to this, in the current study, AKBA had a noticeable effect to decrease apoptotic and amyloidogenic parameters. AKBA decreased the level of infarction and apoptosis in primary cortical neurons [60]. Similarly, β boswellic acids enhanced neuronal hippocampal branching in CA1 region [68]. A minimal damage in the hippocampus and striatum of AD-induced rats was observed by histological investigation after administration of *Boswellia serrata* extract. This effect was coupled with decreased inflammatory markers as NF-κB and a noticed elevation in Bcl-2 in the brain and serum [69].

Conclusion

In conclusion, LPS administration caused an increase in the anxiety level, decreased spatial memory, and locomotor function in mice. Moreover, LPS led to an increase in inflammatory, oxidative stress, apoptotic, and amyloidogenic markers, associated with modulation of the miR-155/SOCS-1 pathway. AKBA, a constituent of *Boswellia serrata*, efficiently decreased all signs of behavioral dysfunction, inflammation, oxidative stress, and apoptosis as a result of injection of LPS in mice, in a similar manner as DEX. Thus, AKBA exhibited neuroprotective effects which may be therapeutically exploited to counteract inflammation-associated neurological diseases.

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Authors' Contribution German University in Cairo (GUC) led the conception, design acquisition of all experimental work, and the manuscript preparation. All authors read and approved the final manuscript. Conceived and designed the experiments: IG, MB, and NS. Participated at the experimental work: AS and IG. Contributed with reagents/materials/analysis equipment and tools: AS, IG, and MB. Analyzed the data: AS and IG. Wrote the paper: AS, IG, MB, and NS.Funding InformationThis work has been partially supported by equipment grants from the Centre for Special Studies and Programs (CSSP), Bibliotheca Alexandrina, grant no. "145", as well as DAAD equipment funding, project no. "134.104401.347", grant no. "ga43213."

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Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Agostinho P, Cunha RA, Oliveira C (2010) Neuroinflammation, oxidative stress and the pathogenesis of Alzheimer's disease. Curr Pharm Des 16(25):2766–2778
2. Fischer R, Maier O (2015) Interrelation of oxidative stress and inflammation in neurodegenerative disease: role of TNF. Oxidative Med Cell Longev 2015:610813. https://doi.org/10.1155/2015/610813
3. Dalle-Donne I, Aldini G, Carini M, Colombo R, Rossi R, Milzani A (2006) Protein carbonylation, cellular dysfunction, and disease progression. J Cell Mol Med 10(2):389–406
4. Bizzozero OA (2009) Protein carbonylation in neurodegenerative and demyelinating CNS diseases. In: Lajtha A (ed) Handbook of neurochemistry and molecular neurobiology: brain and spinal cord trauma. 3rd edn. Springer Science & Business Media, 543–562
5. Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM (2005) Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. J Neurosci 25(39):8843–8853. https://doi.org/10.1523/JNEUROSCI.2868-05.2005
6. Lehnardt S, Massillon L, Follett P, Jensen FE, Ratan R, Rosenberg PA, Volpe JJ, Vartanian T (2003) Activation of innate immunity in the CNS triggers neurodegeneration through a Toll-like receptor 4-dependent pathway. Proc Natl Acad Sci U S A 100(14):8514–8519. https://doi.org/10.1073/pnas.1432609100
7. Zhao M, Zhou A, Xu L, Zhang X (2014) The role of TLR4-mediated PTEN/PI3K/AKT/NF-kappaB signaling pathway in neuroinflammation in hippocampal neurons. Neuroscience 269:93–101. https://doi.org/10.1016/j.neuroscience.2014.03.039
8. Garate I, Garcia-Bueno B, Madrigal JL, Caso JR, Alou L, Gomez-Lus ML, Leza JC (2014) Toll-like 4 receptor inhibitor TAK-242 decreases neuroinflammation in rat brain frontal cortex after stress. J Neuroinflammation 11:8. https://doi.org/10.1186/1742-2094-11-8
9. Kempe S, Kestler H, Lasar A, Wirth T (2005) NF-kappaB controls the global pro-inflammatory response in endothelial cells: evidence for the regulation of a pro-atherogenic program. Nucleic Acids Res 33(16):5308–5319. https://doi.org/10.1093/nar/gki836
10. Badshah H, Ali T, Kim MO (2016) Osmotin attenuates LPS-induced neuroinflammation and memory impairments via the TLR4/NFkappaB signaling pathway. Sci Rep 6:24493. https://doi.org/10.1038/srep24493
11. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116(2):281–297
12. Kutter C, Svoboda P (2008) miRNA, siRNA, piRNA: knowns of the unknown. RNA Biol 5(4):181–188
13. Dai R, Ahmed SA (2011) MicroRNA, a new paradigm for understanding immunoregulation, inflammation, and autoimmune diseases. Transl Res 157(4):163–179. https://doi.org/10.1016/j.trsl.2011.01.007
14. Martinez-Nunez RT, Louafi F, Sanchez-Elsner T (2011) The interleukin 13 (IL-13) pathway in human macrophages is modulated by microRNA-155 via direct targeting of interleukin 13 receptor alpha1 (IL13Ralpha1). J Biol Chem 286(3):1786–1794. https://doi.org/10.1074/jbc.M110.169367
15. Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T (2002) Identification of tissue-specific microRNAs from mouse. Curr Biol 12(9):735–739
16. Tam W (2001) Identification and characterization of human BIC, a gene on chromosome 21 that encodes a noncoding RNA. Gene 274(1–2):157–167
17. Guedes J, Cardoso AL, Pedroso de Lima MC (2013) Involvement of microRNA in microglia-mediated immune response. Clin Dev Immunol 2013:186872. https://doi.org/10.1155/2013/186872
18. Liu CC, Chien CH, Lin MT (2000) Glucocorticoids reduce interleukin-1 concentration and result in neuroprotective effects in rat heatstroke. J Physiol 527(Pt 2):333–343
19. Auphan N, DiDonato JA, Rosette C, Helmberg A, Karin M (1995) Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. Science 270(5234):286–290
20. Rosa L, Galant LS, Dall'Igna DM, Kolling J, Siebert C, Schuck PF, Ferreira GC, Wyse AT et al (2016) Cerebral oedema, blood-brain barrier breakdown and the decrease in Na(+),K(+)-ATPase activity in the cerebral cortex and hippocampus are prevented by dexamethasone in an animal model of maple syrup urine disease. Mol Neurobiol 53(6):3714–3723. https://doi.org/10.1007/s12035-015-9313-0
21. Chantong B, Kratschmar DV, Nashev LG, Balazs Z, Odermatt A (2012) Mineralocorticoid and glucocorticoid receptors differentially regulate NF-kappaB activity and pro-inflammatory cytokine production in murine BV-2 microglial cells. J Neuroinflammation 9:260. https://doi.org/10.1186/1742-2094-9-260
22. Wang ZH, Liang YB, Tang H, Chen ZB, Li ZY, Hu XC, Ma ZF (2013) Dexamethasone down-regulates the expression of microRNA-155 in the livers of septic mice. PLoS One 8(11):e80547. https://doi.org/10.1371/journal.pone.0080547
23. Singh GB, Atal CK (1986) Pharmacology of an extract of salai guggal ex-Boswellia serrata, a new non-steroidal anti-inflammatory agent. Agents Actions 18(3–4):407–412
24. Siddiqui MZ (2011) Boswellia serrata, a potential antiinflammatory agent: an overview. Indian J Pharm Sci 73(3):255–261. https://doi.org/10.4103/0250-474X.93507
25. Kruger P, Daneshfar R, Eckert GP, Klein J, Volmer DA, Bahr U, Muller WE, Karas M et al (2008) Metabolism of boswellic acids in vitro and in vivo. Drug Metab Dispos 36(6):1135–1142. https://doi.org/10.1124/dmd.107.018424
26. Khalaj-Kondori M, Sadeghi F, Hosseinpourfeizi MA, Shaikhzadeh-Hesari F, Nakhlband A, Rahmati-Yamchi M (2016) Boswellia serrata gum resin aqueous extract upregulates BDNF but not CREB expression in adult male rat hippocampus. Turk J Med Sci 46(5):1573–1578. https://doi.org/10.3906/sag-1503-43
27. Jalili C, Salahshoor MR, Moradi S, Pourmotabbed A, Motaghi M (2014) The therapeutic effect of the aqueous extract of boswellia serrata on the learning deficit in kindled rats. Int J Prev Med 5(5):563–568

28. Gokaraju GR, Gokaraju RR, Gokaraju VK, Golakoti T, Bhupathiraju K, Alluri VK (2013) Boswellia oil, its fractions and compositions for enhancing brain function
29. Assimopoulou A, Zlatanos S, Papageorgiou V (2005) Antioxidant activity of natural resins and bioactive triterpenes in oil substrates. Food Chem 92(4):721–727. https://doi.org/10.1016/j.foodchem.2004.08.033
30. Sayed AS, El Sayed NS (2016) Co-administration of 3-acetyl-11-keto-beta-boswellic acid potentiates the protective effect of celecoxib in lipopolysaccharide-induced cognitive impairment in mice: possible implication of anti-inflammatory and antiglutamatergic pathways. J Mol Neurosci 59(1):58–67. https://doi.org/10.1007/s12031-016-0734-7
31. Arai K, Matsuki N, Ikegaya Y, Nishiyama N (2001) Deterioration of spatial learning performances in lipopolysaccharide-treated mice. Jpn J Pharmacol 87(3):195–201
32. Sheng JG, Bora SH, Xu G, Borchelt DR, Price DL, Koliatsos VE (2003) Lipopolysaccharide-induced-neuroinflammation increases intracellular accumulation of amyloid precursor protein and amyloid beta peptide in APPswe transgenic mice. Neurobiol Dis 14(1):133–145
33. Anthoni C, Laukoetter MG, Rijcken E, Vowinkel T, Mennigen R, Muller S, Senninger N, Russell J et al (2006) Mechanisms underlying the anti-inflammatory actions of boswellic acid derivatives in experimental colitis. Am J Physiol Gastrointest Liver Physiol 290(6):G1131–G1137. https://doi.org/10.1152/ajpgi.00562.2005
34. Cuaz-Perolin C, Billiet L, Bauge E, Copin C, Scott-Algara D, Genze F, Buchele B, Syrovets T et al (2008) Antiinflammatory and antiatherogenic effects of the NF-kappaB inhibitor acetyl-11-keto-beta-boswellic acid in LPS-challenged ApoE-/- mice. Arterioscler Thromb Vasc Biol 28(2):272–277. https://doi.org/10.1161/ATVBAHA.107.155606
35. Puccio S, Chu J, Pratico D (2011) Involvement of 5-lipoxygenase in the corticosteroid-dependent amyloid beta formation: in vitro and in vivo evidence. PLoS One 6 (1):e15163. doi:https://doi.org/10.1371/journal.pone.0015163
36. Bryan KJ, Lee H, Perry G, Smith MA, Casadesus G (2009) Transgenic mouse models of Alzheimer's disease: behavioral testing and considerations. In: Buccafusco JJ (ed) Methods of behavior analysis in neuroscience. 2nd edn. Frontiers in neuroscience
37. Jackson LL (1943) VTE on an elevated T-maze. J Comp Psychol 36(2):99–107
38. Camara ML, Corrigan F, Jaehne EJ, Jawahar MC, Anscomb H, Baune BT (2015) Effects of centrally administered etanercept on behavior, microglia, and astrocytes in mice following a peripheral immune challenge. Neuropsychopharmacology 40(2):502–512. https://doi.org/10.1038/npp.2014.199
39. Walf AA, Frye CA (2007) The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. Nat Protoc 2(2):322–328. https://doi.org/10.1038/nprot.2007.44
40. Onaolapo OJ, Onaolapo AY, Mosaku TJ, Akanji OO, Abiodun OR (2012) Elevated plus maze and Y-maze behavioral effects of subchronic, oral low dose monosodium glutamate in Swiss albino mice. J Pharm Biol Sci 3:21–27. https://doi.org/10.9790/3008-0342127
41. Metz GA, Whishaw IQ (2009) The ladder rung walking task: a scoring system and its practical application. J Vis Exp (28). doi: https://doi.org/10.3791/1204
42. Scali M, Begenisic T, Mainardi M, Milanese M, Bonifacino T, Bonanno G, Sale A, Maffei L (2013) Fluoxetine treatment promotes functional recovery in a rat model of cervical spinal cord injury. Sci Rep 3:2217. https://doi.org/10.1038/srep02217
43. Couch Y, Anthony DC, Dolgov O, Revischin A, Festoff B, Santos AI, Steinbusch HW, Strekalova T (2013) Microglial activation, increased TNF and SERT expression in the prefrontal cortex define stress-altered behaviour in mice susceptible to anhedonia. Brain Behav Immun 29:136–146. https://doi.org/10.1016/j.bbi.2012.12.017
44. Onaolapo OJ, Onaolapo AY, Akinola OR, Anisulowo TO (2014) Dexamethasone regimens alter spatial memory and anxiety levels in mice. J Behav Brain Sci 04:159–167. https://doi.org/10.4236/jbbs.2014.44019
45. Beheshti S, Karimi B (2016) Frankincense improves memory retrieval in rats treated with lipopolysaccharide. J HerbMed Pharmacol 5(1):12–16
46. Takeuchi H, Jin S, Wang J, Zhang G, Kawanokuchi J, Kuno R, Sonobe Y, Mizuno T et al (2006) Tumor necrosis factor-alpha induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner. J Biol Chem 281(30):21362–21368. https://doi.org/10.1074/jbc.M600504200
47. Skelly DT, Hennessy E, Dansereau MA, Cunningham C (2013) A systematic analysis of the peripheral and CNS effects of systemic LPS, IL-1beta, [corrected] TNF-alpha and IL-6 challenges in C57BL/6 mice. PLoS One 8(7):e69123. https://doi.org/10.1371/journal.pone.0069123
48. Adake P, Petimani MS, Jayaraj M, Rao SN (2015) Preclinical evaluation of Boswellia serrata for anxiolytic activity. Int J Basic Clin Pharmacol 4(3):551–555
49. Yassin N, El-Shenawy S, Mahdy KA, Gouda N, Marrie A, Farrag A, Ibrahim BMM (2013) Effect of Boswellia serrata on Alzheimer's disease induced in rats. J Arab Soc Med Res 8:1–11. https://doi.org/10.7123/01.JASMR.0000429323.25743.cc
50. Zheng Y, Xiong S, Jiang P, Liu R, Liu X, Qian J, Zheng X, Chu Y (2012) Glucocorticoids inhibit lipopolysaccharide-mediated inflammatory response by downregulating microRNA-155: a novel anti-inflammation mechanism. Free Radic Biol Med 52(8):1307–1317. https://doi.org/10.1016/j.freeradbiomed.2012.01.031
51. Li X, Tian F, Wang F (2013) Rheumatoid arthritis-associated microRNA-155 targets SOCS1 and upregulates TNF-alpha and IL-1beta in PBMCs. Int J Mol Sci 14(12):23910–23921. https://doi.org/10.3390/ijms141223910
52. Xu HF, Fang XY, Zhu SH, Xu XH, Zhang ZX, Wang ZF, Zhao ZQ, Ding YJ et al (2016) Glucocorticoid treatment inhibits intracerebral hemorrhage induced inflammation by targeting the microRNA155/SOCS1 signaling pathway. Mol Med Rep 14(4):3798–3804. https://doi.org/10.3892/mmr.2016.5716
53. Fruhauf PK, Ineu RP, Tomazi L, Duarte T, Mello CF, Rubin MA (2015) Spermine reverses lipopolysaccharide-induced memory deficit in mice. J Neuroinflammation 12:3. https://doi.org/10.1186/s12974-014-0220-5
54. Gamal M, Abdel Wahab Z, Eshra M, Rashed L, Sharawy N (2014) Comparative neuroprotective effects of dexamethasone and minocycline during hepatic encephalopathy. Neurol Res Int 2014:254683. https://doi.org/10.1155/2014/254683
55. Al-Harbi NO, Imam F, Al-Harbi MM, Ansari MA, Zoheir KM, Korashy HM, Sayed-Ahmed MM, Attia SM et al (2016) Dexamethasone attenuates LPS-induced acute lung injury through inhibition of NF-kappaB, COX-2, and pro-inflammatory mediators. Immunol Investig 45(4):349–369. https://doi.org/10.3109/08820139.2016.1157814
56. Umar S, Umar K, Sarwar AH, Khan A, Ahmad N, Ahmad S, Katiyar CK, Husain SA et al (2014) Boswellia serrata extract attenuates inflammatory mediators and oxidative stress in collagen induced arthritis. Phytomedicine 21(6):847–856. https://doi.org/10.1016/j.phymed.2014.02.001
57. Syrovets T, Buchele B, Krauss C, Laumonnier Y, Simmet T (2005) Acetyl-boswellic acids inhibit lipopolysaccharide-mediated TNF-alpha induction in monocytes by direct interaction with IkappaB kinases. J Immunol 174(1):498–506
58. Erickson MA, Hansen K, Banks WA (2012) Inflammation-induced dysfunction of the low-density lipoprotein receptor-related protein-1 at the blood-brain barrier: protection by the antioxidant N-

acetylcysteine. Brain Behav Immun 26(7):1085–1094. https://doi.org/10.1016/j.bbi.2012.07.003

59. Pereira DV, Steckert AV, Mina F, Petronilho F, Roesler R, Schwartsmann G, Ritter C, Dal-Pizzol F (2009) Effects of an antagonist of the gastrin-releasing peptide receptor in an animal model of uveitis. Invest Ophthalmol Vis Sci 50(11):5300–5303. https://doi.org/10.1167/iovs.09-3525
60. Ding Y, Chen M, Wang M, Zhang T, Park J, Zhu Y, Guo C, Jia Y et al (2014) Neuroprotection by acetyl-11-keto-beta-Boswellic acid, in ischemic brain injury involves the Nrf2/HO-1 defense pathway. Sci Rep 4:7002. https://doi.org/10.1038/srep07002
61. Moussaieff A, Shein NA, Tsenter J, Grigoriadis S, Simeonidou C, Alexandrovich AG, Trembovler V, Ben-Neriah Y et al (2008) Incensole acetate: a novel neuroprotective agent isolated from Boswellia carterii. J Cereb Blood Flow Metab 28(7):1341–1352. https://doi.org/10.1038/jcbfm.2008.28
62. Omura Y, Horiuchi N, Jones MK, Lu DP, Shimotsuura Y, Duvvi H, Pallos A, Ohki M et al (2009) Temporary anti-cancer & anti-pain effects of mechanical stimulation of any one of 3 front teeth (1st incisor, 2nd incisor, & canine) of right & left side of upper & lower jaws and their possible mechanism, & relatively long term disappearance of pain & cancer parameters by one optimal dose of DHEA, Astragalus, Boswellia Serrata, often with press needle stimulation of True ST. 36. Acupunct Electrother Res 34(3–4):175–203
63. Eklind S, Hagberg H, Wang X, Savman K, Leverin AL, Hedtjarn M, Mallard C (2006) Effect of lipopolysaccharide on global gene expression in the immature rat brain. Pediatr Res 60(2):161–168. https://doi.org/10.1203/01.pdr.0000228323.32445.7d
64. Deng X, Li M, Ai W, He L, Lu D, Patrylo PR, Cai H, Luo X et al (2014) Lipolysaccharide-induced neuroinflammation is associated with Alzheimer-like amyloidogenic axonal pathology and dendritic degeneration in rats. Adv Alzheimer Dis 3(2):78–93. https://doi.org/10.4236/aad.2014.32009
65. Lee YJ, Choi DY, Yun YP, Han SB, Oh KW, Hong JT (2013) Epigallocatechin-3-gallate prevents systemic inflammation-induced memory deficiency and amyloidogenesis via its anti-neuroinflammatory properties. J Nutr Biochem 24(1):298–310. https://doi.org/10.1016/j.jnutbio.2012.06.011
66. Lee IN, Cheng WC, Chung CY, Lee MH, Lin MH, Kuo CH, Weng HH, Yang JT (2015) Dexamethasone reduces brain cell apoptosis and inhibits inflammatory response in rats with intracerebral hemorrhage. J Neurosci Res 93(1):178–188. https://doi.org/10.1002/jnr.23454
67. Wang H, Wu YB, Du XH (2005) Effect of dexamethasone on nitric oxide synthase and caspase-3 gene expressions in endotoxemia in neonate rat brain. Biomed Environ Sci 18(3):181–186
68. Hosseini-sharifabad M, Esfandiari E (2015) Effect of Boswellia serrata gum resin on the morphology of hippocampal CA1 pyramidal cells in aged rat. Anat Sci Int 90(1):47–53. https://doi.org/10.1007/s12565-014-0228-z
69. Ahmed HH, Mohamed EM, El-Dsoki SM (2014) Evidences for the promising therapeutic potential of boswellia serrata against Alzheimer's disease: pre-clinical study. Int J Pharm Pharm Sci 6(11):384–392