TARGETED BRAIN ANTIOXIDANT MODULATION AND CA1 NEUROPROTECTION BY OCIMUM SANCTUM IN ENDOTOXEMIA-INDUCED BRAIN INJURY

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ABSTRACT

Currently, there is no specific effective management strategy for septic shock, and only a limited number of potential therapeutic agents are undergoing clinical evaluation. Systemic administration of lipopolysaccharide (LPS) is known to induce neuronal death by increasing glutamate release and nitric oxide production, ultimately leading to endotoxin shock due to the elevated levels of free radicals, lipid peroxidation, mitochondrial dysfunction and excessive cytokine release. *Ocimum sanctum (OS)* is well-recognized medicinal herb in the Indian System of Medicine, has been widely reported to exhibit neuroprotective besides antioxidant activities. In this study, 90% ethanol extract of *OS* (EEOS) was evaluated neuroprotective effects in female rats. A single IP of LPS 1mg/kg resulted in significant oxidative stress, as evidenced by the altered antioxidant enzyme activities and elevated lipid peroxidation in discrete regions of the brain, including the cerebral cortex, cerebellum, hippocampus, and corpus striatum. The activity of superoxide dismutase in various brain regions was markedly affected compared to the control group (cortex: 1.35 ± 0.02, striatum: 0.94 ± 0.01, hippocampus: 1.38 ± 0.11, cerebellum: 0.86 ± 0.08). Catalase activity, was significantly elevated in the striatum 43.89 ± 1.53 $P < 0.00$) and cortex 39.56 ± 1.43, $P < 0.001$ compared to control animals. Conversely, total glutathione levels were significantly reduced in the LPS-treated group cortex 5.31 ± 0.10 $P < 0.001$), striatum 13.69 ± 0.38, $p < 0.001$, hippocampus 3.36 ± 0.02 $P < 0.001$ and cerebellum 4.46 ± 0.06 $P < 0.001$. Thiobarbituric acid reactive substances a marker of lipid peroxidation, were significantly elevated in the cortex (7.54 ± 0.61 $P < 0.001$), striatum 5.20 ± 0.52 $P < 0.001$ hippocampus 4.80 ± 0.21 $P < 0.001$ and cerebellum 2.37 ± 0.43 $P < 0.001$ of rats exposed to LPS. However, EEOS treatment provided significant protection, preserving neuronal integrity and preventing structural degeneration in this region. Future clinical studies are warranted to further investigate its therapeutic potential and to develop formulations as adjunct therapies for managing oxidative stress related neurological disorders and septic shock associated neurotoxicity.

Keywords: Septic Shock, Lipopolysaccharide (LPS), Oxidative Stress, *Ocimum Sanctum* Neuroprotection and Antioxidant Enzymes

INTRODUCTION

Lipopolysaccharide (LPS) is one of the most common inflammogen used to investigate the impact of inflammation on neuronal death.[12] LPS function has been under experimental research for several years due to its role in activating many transcription factors, which become active after stimulation with LPS environmental toxins endogenous disease proteins; neuronal injury; through which microglia are activated to exert their neurotoxicity. LPS-induced prototypical gram-negative endotoxemia is accompanied by contact system activation, complement activation, production of cytokines and other evidence of unregulated inflammatory responses.[13] LPS activates mononuclear phagocytes to produce and release inflammatory mediators, of which TNF-α appears to be very important for the development of endotoxin

shock Administration of LPS laboratory animals induces a variety of physiological responses.[49] neuroendocrine changes[11&24] and modifications of behavior consisting of fever[117&118] and social behavior,[373&374] sleepiness, depression (sickness behavior).[11&73] Thus it has been suggested that immunological activation with LPS or cytokines themselves and may be interpreted by the CNS as a stressor, and that the immune system may act as a sensory organ for non-cognitive stimuli such as bacteria, tumors, viruses.[3,94&23] Numerous cytokines and their receptors have been shown to be upregulated by LPS in microglia, astrocytes and neurons[326] in many regions of the CNS in response to LPS challenge[276]. Many laboratories have reported that LPS treatment induces neurotoxicity via microglia activation in mixed neuron / glia cultures. Activated microglia produce large amounts of prostanoids, ROS, NO and proinflammatory cytokines such as TNF- α, IL-1, IL-6 and IL-8, AA metabolites, and quinolinic acid which are capable of sustaining inflammatory state and in turn, cause neuronal damage.[127,174& 382] One of the widely used medicinal herbs in indigenous systems of medicine is *Ocimum sanctum* Linn (OS) which belongs to the family *Lamicaceae* and commonly known as "sacred basil" or "Tulsi." Epidemiological studies have suggested positive associations between the consumption of phenolic-rich foods or beverages and the prevention of diseases.[275] These effects have been attributed to antioxidant components such as plant phenolics, flavonoids and phenyl propanoids among others.[251] Basils (*Ocimum* spp., *Lamiaceae*) contain a wide range of essential oils rich in phenolic compounds[228] and a wide array of other natural products including polyphenols such as flavonoids and anthocynanins. Hypotension associated with septic shock is a major cause of inadequate tissue perfusion and compromised peripheral circulation facilitating anaerobic metabolism, leading to multiple organ dysfunction and death. Therefore, a number of therapeutic agent modifying the above-mentioned parameters may be tried in order to improve the outcome of endotoxemic injury. This work aims at investigating the potential therapeutic value of OS leaves on brain metabolism in shocked rats. For that purpose, brain MDA, GSH, CAT and SOD levels/activities were measured. However, there have been no studies on the effects of ethanolic extract of OS leaves on the central protective role in discrete regions of rat brain like the cerebral cortex, cerebellum, hippocampus and corpus striatum. Therefore, this study focuses the possible protective role of OS in attenuating LPS-induced endotoxic shock.

MATERIAL AND METHODS

Drugs and chemicals

Chemicals were purchased from Sigma Aldrich Co., St Louis, USA and S.D.Fine Chem Ltd., Biosar, India. Ammonium thiocyanate was purchased from E Merck Ltd., Mumbai, India. Lyophilized lipopolysaccharide powder from *Escherichia Coli*, serotype 055:B5 (containing ≥ 10,000 endotoxin units / mg LPS) and potassium dihydrogen orthophosphate (AR grade) were purchased from Sigma Chemical Company, New Delhi, India.

Animals

Healthy inbred female Sprague-Dawley rats weighing between 125-170 g, procured from the Central Animal House of the institute, housed in colony cages at an ambient temperature of 25 ± 2°C and 45-55% maintain standard procedures followed by the CCSEA protocol for the use of animal studies was approved by the Institutional Animal Ethical Committee, under the regulation of CCSEA, New Delhi (JKKN/IAEC//PhCology/02/2004-05).

Plant material and extraction

The aerial parts of the plant *OS* were collected from Bhavani, Erode district, Tamil Nadu, India. It was taxonomically identified by the Survey of Medicinal Plants and Collection Unit, Ooty, Tamil Nadu, India, and a herbarium of the plant is preserved in the Department of Pharmacognosy, The whole plant was washed, and leaves were separated from other aerial parts, freed from earthy material and shade dried with occasional sifting at room temperature. Dried leaves were coarsely powdered and subjected to extraction by cold maceration with 90% ethanol at room temperature

Biochemical analysis

At the end of the behavioral studies, the animals of each group were anesthetized with ether and sacrificed by cervical dislocation; the brains were quickly removed, weighed, rinsed in ice-cold isotonic saline and one half of the brain was processed as follows: Various parts of the brain such as cerebral cortex, cerebellum, corpus striatum and hippocampus were dissected out in ice cold condition according to the method.[383] A 10% (w/v) tissue homogenate was prepared using ice cold Tris-KCl buffer (0.05M Tris and 1.15% KCl, pH 7.4) using Elvehjem hand homogenizer fitted with Teflon pestle. The homogenate was centrifuged at 2000 rpm at 4°C for 15 minutes and the supernatant was used for the biochemical analysis.

Superoxide dismutase (SOD)

The measurement of SOD[115] involves the inhibition of the formation of the blue colored formozan dye from nitro blue tetrazolium (NBT), in the presence of phenazine methosulphate (PMS) and reduced nicotinamide adenine dinucleotide (NADH). followed by incubation for 90 seconds at 37°C. The reaction was terminated by the addition of glacial acetic acid (1ml), n-butanol (4ml), shaken vigorously, centrifuged at 4000 rpm for 1 minute and the upper butanol layer was read at 560nm, against butanol blank.[8.] CAT measurement was done based on the ability of CAT to inhibit oxidation of hydrogen peroxide (H_2O_2). 2.25ml of potassium phosphate buffer (65 mM, pH 7.8) and 100 µl of the brain homogenate or sucrose (0.32 M) were incubated at 25°C for 30 minutes. H_2O_2 (7.5 mM; 650 µl) was added to initiate the reaction. The change in absorption at 240 nm was measured for 2-3 minutes. dy/dx for every minute for each assay was calculated and the results are expressed as CAT units of protein.

CAT (U) in 100 µl of sample = dy/dx **X** 0.0003 / 38.3956 **X** 10^{-6}

Total glutathione (GSH)

The following working solutions were prepared from the stock buffer for the estimation of GSH as follows: (1) 125 mM sodium phosphate, 6.3 mM sodium EDTA, adjusted to pH 7.5; (2) 0.3 mM NADPH, 6 mM dinitrothiobisnitroso benzoic acid (DTNB) and (3) approximately 50 units of glutathione reductase per ml and stored at 4°C. During the assay, 700 µl of NADPH, 100 µl of DTNB, 25 µl of glutathione sample, 10 µl of glutathione reductase were incubated at 30°C and 165 µl of deionized water were incubated at 30°C and the absorbance was read immediately at 420nm[2].

Lipid peroxide (TBARS)

LPO was estimated in terms of TBARS and malondialdehyde (MDA) was taken to represent the TBARS[204]. The incubation mixture consisting of 0.5ml of supernatant brain homogenate, 0.2 ml of 8% sodium dodecyl sulphate, 1.5 ml of 20% acetic acid solution (adjusted to pH 3.5 with 1NaOH / 0.1N HCl) and 1.5 ml of 0.9% aqueous solution of thiobarbituric acid (adjusted to pH 7.4 with 1N NaOH / 0.1N HCl) was made up to 5.0 ml with double distilled water and then heated in boiling water bath for 30 minutes. After cooling, the red chromogen was extracted into 5 ml of the mixture of n-butanol and pyridine (15.1v/v) centrifuged at 4000 rpm for 10 minutes. The absorbance of organic layer was measured at 532 nm. 1, 2, 3, 3-tetraethoxypropane (TEP) was standard

Statistical analysis

The data are expressed as mean ± SEM from six observations in each group. The general behavioral data was subjected to one-way analysis of variance (ANOVA), followed by Dunnet's multiple comparison posttests. (GraphPad Prism Software, San Diego, California, USA).

RESULTS & DISCUSSION

The activities of SOD in different brain regions are depicted in Table 1. In comparison to control group (cortex 1.35 ± 0.02, striatum 0.94 ± 0.01, hippocampus 1.38 ± 0.11 and cerebellum 0.86 ± 0.08), endotoxemic neurodegeneration induced by LPS did not manifest any significant changes in the levels of SOD (cortex 1.52 ± 0.03, striatum 1.00 ± 0.02, hippocampus 1.97 ± 0.29 and cerebellum 0.99 ± 0.11) of LPS-treated group. Activity of CAT on various regions of rat brain is shown in Table 9. In comparison to control group animals, a significant increase in the level of CAT in striatum (43.89 ± 1.53, $p<0.001$) and cortex (39.56 ± 1.43, $p<0.001$) was observed. A moderate increase in hippocampus (23.27 ± 0.38, $p<0.001$) and cerebellum (16.74 ± 1.02, $p<0.001$) CAT status was recorded in LPS-treated group. A dose dependent decrease in CAT level were observed following post-treatment with EEOS studied and the restoration of antioxidant enzyme status was most effective at the dose of EEOS 200 mg/kg dose level: striatum (26.08 ± 0.54, $p<0.001$), cortex (21.56 ± 0.53, $p<0.01$), hippocampus (16.28 ± 0.20, $p<0.001$) and cerebellum (11.50 ± 0.32, $p<0.001$). STD significantly decreased the CAT level in cortex and cerebellum among the regions studied ($p<0.001$) and an increased activity was observed in striatum and hippocampus regions. TBARS levels were significantly elevated in cortex (7.54 ± 0.61, $p<0.001$),

striatum (5.20 ± 0.52, p<0.001), hippocampus (4.80 ± 0.21, p<0.001) and cerebellum (2.37 ± 0.43, (p<0.001),

Table3 summarizes the perturbations in level of GSH in the brain of control and drug-treated rats. In comparison to control group, the level of GSH was found to be significantly decreased in the LPS group, in cortex (5.31 ± 0.10, p<0.001), striatum (13.69 ± 0.38, p<0.001), hippocampus (3.36 ± 0.02, p<0.001) and cerebellum (4.46 ± 0.06, p<0.001), following a single endotoxic shock with LPS. A significant dose dependent increase in GSH levels was observed in EEOS comparison to control. Table 4 shows the effect of LPS and EEOS post-treatment on lipid peroxidation status (TBARS) in the various brain regions studied. In comparison to control rats, TBARS levels were significantly elevated in cortex (7.54 ± 0.61, p<0.001), striatum (5.20 ± 0.52, p<0.001), hippocampus (4.80 ± 0.21, p<0.001) and cerebellum (2.37 ± 0.43, (p<0.001), regions of the rat exposed to LPS. The levels of TBARS were significantly diminished following EEOS post-treatment for 21 days and, a profound effect was observed at EEOS 200 mg/kg dose level, in cortex (1.18 ± 0.61, p<0.001), striatum (1.54 ± 0.23, p<0.001), hippocampus (1.24 ± 0.15, p<0.001) and cerebellum (1.01 ± 0.08, p<0.001), in comparison to MSG-treated animals. Indomethacin significantly (p<0.001) decreased the TBAR levels in all the regions observed on day 21, in comparison to control and LPS-treated groups. All cells in the body are exposed chronically to oxidants from both endogenous and exogenous sources but are also equipped with an antioxidant system. Reactive oxygen and nitrogen species, if unchecked, can contribute to chronic disease development by oxidatively modifying lipids, nucleic acids and proteins. Of all the organs, the brain is thought to be most vulnerable to oxidative damage due to high oxygen consumption, presence of high levels of PUFA and nondegenerative nature of neurons, leading to various neurodegenerative diseases,[34] making them the primary target for different stressors that initiate lipid peroxidation, a self-propagating chain reaction resulting in significant tissue damage and disease. Under normal conditions, brain microglias are involved in immune surveillance and host defense against infectious agents. Activation of the immune system in response to infection produces neural, neuroendocrine, and behavioral effects. However, microglia readily become activated in response to injury or immunological challenges, as indicated by a change in morphology from a ramified resting state to an amoeboid appearance with an increase in the expression of major histocompatibility complex (MHC) molecules and complement type 3 receptor.[53&104] Endotoxin-mediators induced activation of microglia is believed to contribute to neurodegenerative process through the release of proinflammatory and/or cytotoxic factors, including IL-1ß, IL-6, TNF-α, INF-γ, induction of NF-κB, macrophage inflammatory protein (MIP), NO, ROS, histamine, proteases, neuropeptides, quinolinic acid and AA metabolites.[16,321,27,126&21] Among the AA metabolites, prostaglandin E_2 (PGE_2) levels of brain interstitial fluid was found to rise following peripheral injection of LPS.[280] Pharmacological blockade of PGE_2 synthesis attenuates many peripheral LPS-induced responses, such as fever,[280] brain c-*fos* expression, HPA axis activation (Parrott et al., 1995)[223], increased splenic sympathetic activity,[148] activation of 5-HT and NA

neurotransmission in hippocampus,[135] and increased BBB permeabili.[19] Increased production of PGE_2 in brain, therefore, is critically involved in the CNS-linked responses to peripheral LPS. There are three enzymes that are essential for the production of PGE_2: PLA_2, COX, and PGE_2 isomerase. COX-1 levels are relatively insensitive to inflammatory stimulation. COX-2, on the other hand, is strongly induced by inflammatory factors such as LPS.[20] The induced expression of COX-2 in the brain is thought to play an important role in the elevation of central PGE_2 levels in response to peripheral LPS.[14&15] Over expression of COX-2 has been found in the AD brains and a number of epidemiological studies have indicated that NSAIDs, inhibitors of COX, are beneficial for AD patients in delaying the clinical progression.[377] Several previous reports have demonstrated a number of antioxidant, antihistaminic and antiinflammatory activity as due to its COX and LOX inhibitory potential of OS and researchers have associated these effects to the presence of phenolic compounds in OS.[106] OS has also been reported to possess significant antiinflammatory activity against a numbers of mediators of inflammation, in particular, against PGE_2, leukotirenes (LT) and AA-induced paw edema in rats[310] by virtue of their capacity to block both cyclooxygenase[165&106] and lipooxygenase pathways of AA metabolism.[305, 309,308&316] In addition, the capacity of OS to inhibit vascular / capillary permeability & leukocyte migration following inflammatory stimulus was also reported.[314] Pharmacological blockade of PGE_2 synthesis attenuates many peripheral LPS-induced responses, as described.[18] In view of these reported data of OS on COX and LOX, it may be suggested that OS may act as neuroprotective agent by virtue of its inhibitory effect of AA metabolic products leading to down regulation of PGE_2 and COX enzymes and act as a potent antiinflammatory agent. Several lines of investigations now suggest that primary action of LPS in the brain may be mediated by an increase in the concentrations of pro-inflammatory cytokines and several autocoid factor.[82&195] Moreover, they have shown that inhibition of mast cell degranulation by treatment with cromoglycate sodium salt, an agent with antiinflammatory and membrane-stabilizing activity, antagonized the behavioral and pyrogenic effects induced by LPS administration. Several *in vitro* studies have shown that chemokines and growth factors can induce mast cell degranulation.[170] On this basis, it is believable that systemic LPS administration may affect brain mast cells through a cytokine- and autocoid-mediated process. On the other hand, following LPS administration, mast cell degranulation may contribute to affect water and food intake, body temperature, locomotion and anxiety by increasing brain release of cytokines, autocoid factors and free radicals. Moreover, LPS could induce direct activation of brain mast cells through a receptor-dependent mechanism.[346] It is well known that intense stress response results in the generation of ROS. In this study the lipid peroxidation levels increased markedly following LPS treatment, which is in agreement with the findings.[1] In order to neutralize ROS, the body uses enzymatic copper-, zinc-SOD, CAT and selenium dependent GSHPx and non-enzymatic (reduced glutathione) antioxidants.[267] The increase in the levels of SOD, and CAT observed following LPS exposure is an indicator of a relative increase in the superoxide radical production. The increased SOD activity is therefore an indication that the brain's antioxidant

machinery is activated in response to excessive generation of free radicals. Enhanced SOD activity catalyzes the conversion of superoxide anions to H_2O_2 which in turn could stimulate the second line of defense which includes GSHPx and CAT. The significant reduction in GSH levels in LPS exposed animals may be justifiable as due to increased production of free radicals. Furthermore it is also suggests that the ratio of reduced/oxidized glutathione in the cell is a good indicator of the level of oxidative stress [1]. Therefore, the significant decrease in the GSH observed in this study indicates the oxidative stress in discrete regions of brain due to LPS exposure. The glutathione status of a cell could be taken as the most accurate single indicator of the health of the cell as the GSH depletion determines the vulnerability to oxidant attack. Animals exposed to LPS-stress showed depletion of GSH level in brain while treatment with EEOS attenuated this depletion, possibly by reducing oxidative stress-induced generation of ROS. The enhanced production of brain TBARS observed in our study by LPS injection is in agreement with previous reports.[186&287] Several mechanisms were postulated to explain this phenomenon. One depends on the enhanced release of cytokines that promote the formation and release of ROS and NO from microglial cells.[364] Another mechanism is based on the release of excitatory amino acids (EEAs), aspartate and glutamate that induce free radical formation during their physiological action[183]. These results may be interpreted through microglial activation associated with the production of NO and ROS in response to glutamatergic stimulation.[42] A third mechanism is related to the LPS-induced mobilization of mitochondrial calcium, which in turn, activates the AA cascade that produces pro-inflammatory agents[252]. It has been found that LPS stimulates the production of Ca^{2+}-independent NOS with different time courses in various tissues.[54] Regardless of the source of NO, high levels of NO have been associated with membrane lipid peroxidation.[236] The fall in brain GSH content following LPS injection is supported by a similar study (Mostafa et al, 1994).[186] The increased oxidative stress depletes cellular stores of brain antioxidants such as GSH and vitamin E.[337] The over production of free radicals can be detoxified by the endogenous antioxidants causing their cellular stores to be depleted.[337] This is in accordance with our results as manifested by diminishing GSH content in shocked rats. GSH depletion has been found to dramatically increase cellular sensitivity toward NO, suggesting that intracellular GSH pools act to scavenge NO or NO-derived species.[356&144] Shock was also associated with elevated brain GSHPx activity that acts as a crucial enzymatic defense mechanism against hydrogen peroxide and organic peroxides. Previous reports describing the response of SOD to different types of oxidative stresses were conflicting. Our results are in agreement with a number of reports indicating mild increase of no change in brain SOD levels following LPS-induced endotoxemic stress.[224&78] Measuring SOD activity in whole brain homogenate may not reflect specific localized changes in the activity of this enzyme since it varies significantly between different brain regions.[33] In this respect, it is worthy to note that a brain antioxidant system is the main target of ROS toxicity due to its high oxygen consumption.[318] The free radical mediated lipid peroxidation has been proposed to be critically involved in many neurological disorders and in

the degenerative process associated with stress[5,155&6] concluded that the vulnerability to oxidative stress in the brain is region specific and is dependent upon local endogenous iron content and their ability to produce lipid peroxides[154] reported that regions like cortex, hypothalamus, hippocampus and striatum are more susceptible to oxidative damage when compared to cerebellum. In this study, we have observed that cerebellum, was also equally susceptible to oxidative damage induced by LPS. This is also in agreement with previous conflicting report.[1] Increase in TBARS and decrease in the activity of CAT, and GSH, observed in the rat brain following LPS treatment, were similar to that of earlier reports, wherein different stressors have been reported to induce similar changes.[9] The potential of OS to inhibit COX and LOX pathways of AA metabolism (dual inhibitor property), may also be supplemented by antihistaminic property of OS, because over expression of COX is seen in brain of AD patients. In addition to this, PGE_2, and LTB_4 inhibitory properties were also found to be observed with OS, which was suggested to be due to COX and LOX inhibitory property of OS[314&87] reported the anticonvulsant potential of OS and suggested that the amount of active compounds like saponins, triterpenoids, flavonoids, tannins, proteins and carbohydrates present in the extract may be responsible for the action. On the basis of published reports, and from our study, we can speculate that LPS-induced effects of indomethacin, used as a standard drug in this model, involve alterations of neuroendocrine, neuroimmune, and neurochemical function[44] and that NSAIDs counteract stress hormone[24&206] pro-inflammatory cytokine release, and neurochemical effects[18] produced by endotoxin or cytokine exposure. The observed neuroendocrine and behavioral effects produced by NSAIDs may be the result of its actions as a COX-1 inhibitor. The effects produced by indomethacin may also result from its actions on PGE_2, which is a major COX product at inflammatory sites. In a recent study, LPS-induced increases in PGE_2 production were significantly attenuated by diclofenac, but not by a COX-2-selective inhibitor.[48] Future studies should address NSAID selectivity (a comparison of non-selective COX inhibitors vs. COX-2 inhibitors). Overall, these findings compliment emerging data that implicate a novel role for NSAIDs in the treatment of depressive-like behavior or symptoms associated with neuroendocrine or neuroimmune dysfunction.[3&18] In addition, phenolic flavonoids present a strong affinity for iron ions, which are known to catalyze many processes leading to the appearance of free radicals.[99] It is well established that LPS induces protein tyrosine phosphorylation.[202] The phosphorylation is an early event of the LPS-induced cytotoxicity and results in the production of inflammatory cytokines.[4] Therefore, LPS-induced cytotoxicity could be prevented by tyrosine kinase inhibitors. The antitoxic and organ-protective effects of flavonoids [175] and their inhibitory activity against tyrosine protein and serine / threonine protein kinases[66] may provide a plausible explanation for the protective action of OS in LPS-induced shock. The antioxidants interrupt the free-radical chain of oxidation by donating hydrogen from phenolic's hydroxyl groups, thereby forming stable free radicals, which do not initiate or propagate further oxidation of lipids. Therefore, it can be assumed that EEOS may also be acting on similar lines. Moreover the antioxidant property of OS has been confirmed by many studies.[348] Apart from this,

flavonoids and terpenoids have been reported as potentially useful exogenous agents in protecting the ageing brain, other organs and tissues of the body against free-radical induced damage.[10] Therefore, it appears that these phytconstituents contents of OS may be responsible for the observed attenuation of oxidative damage due to LPS exposure. In conclusion, these findings extend several other lines of evidence for the association between immune activation and depression. Our data support the potential value of these agents for the therapy of septic shock. Further studies are needed to explore the role of RA & UA as neuroprotective during the early phase of experimental endotoxemia before extrapolating results to humans. Future studies should determine the molecular mechanisms that link LPS-induced HPA- axis activation and behavioral changes and the means by which EEOS attenuates these responses. On the basis of the published reports, and especially, on the ability of OS to act as a potent antiinflammatory agent, acting through diverse pathways, we can speculate that the neuroprotective effects of OS in LPS-induced effects may be mediated by following distinct mechanisms.

Table 1. Effect of EEOS, indomethacin (INDO) on SOD (U/mg protein) level in LPS-treated rat brain

Groups	Cortex	Striatum	Hippocampus	Cerebellum
Control	1.35 ± 0.02	0.94 ± 0.01	1.38 ± 0.11	0.86 ± 0.08
LPS	1.52 ± 0.03	1.00 ± 0.02	1.97 ± 0.29	0.99 ± 0.11
OS 50	1.38 ± 0.04	0.94 ± 0.07	1.62 ± 0.17	0.94 ± 0.06
OS 100	1.56 ± 0.04[a]	0.88 ± 0.09	1.76 ± 0.14	0.93 ± 0.05
OS 200	1.89 ± 0.06[cz]	0.89 ± 0.19	1.67 ± 0.03	0.98 ± 0.20
INDO	1.70 ± 0.07c	1.02 ± 0.14	1.74 ± 0.13	0.94 ± 0.05

Table 2. Effect of EEOS, indomethacin (INDO) on CAT (U/mg protein) level in LPS-treated rat brain

Groups	Cortex	Striatum	Hippocampus	Cerebellum
Control	16.20 ± 1.52	19.30 ± 0.53	12.05 ± 0.45	10.74 ± 1.48
LPS	39.56 ± 1.43[c]	43.89 ± 1.53[c]	23.27 ± 0.38[c]	16.74 ± 1.02[c]
OS 50	35.95 ± 1.67[c]	38.60 ± 1.73[cy]	19.45 ± 0.42[cz]	14.34 ± 0.37[a]

OS 100	25.15 ± 0.25^{cz}	29.00 ± 0.47^{cz}	16.74 ± 0.32^{cz}	12.78 ± 0.35^{y}
OS 200	21.56 ± 0.53^{bz}	26.08 ± 0.54^{cz}	16.28 ± 0.20^{cz}	11.50 ± 0.32^{z}
INDO	33.00 ± 0.42^{cy}	34.62 ± 0.43^{cz}	17.39 ± 0.30^{cz}	14.23 ± 0.44^{a}

Table 3. Effect of EEOS, indomethacin (INDO) on GSH (mg/g protein) level in LPS-treated rat brain

Groups	**Cortex**	**Striatum**	**Hippocampus**	**Cerebellum**
Control	20.25 ± 0.07	35.95 ± 0.41	18.73 ± 0.13	18.29 ± 0.03
LPS	5.31 ± 0.10^{c}	13.69 ± 0.38^{c}	3.36 ± 0.02^{c}	4.46 ± 0.06^{c}
OS 50	12.33 ± 0.05^{cz}	17.97 ± 0.24^{cz}	5.10 ± 0.01^{cz}	9.11 ± 0.15^{cz}
OS 100	16.48 ± 0.54^{cz}	23.99 ± 0.30^{cz}	12.29 ± 0.11^{cz}	11.94 ± 0.18^{cz}
OS 200	17.65 ± 0.02^{cz}	27.86 ± 0.20^{cz}	14.70 ± 0.02^{cz}	13.01 ± 0.16^{cz}
INDO	12.87 ± 0.03^{cz}	19.08 ± 0.10^{cz}	8.27 ± 0.07^{cz}	7.22 ± 0.14^{cz}

Table 4. Effect of EEOS, indomethacin (INDO) on TBARS (µ Moles of MDA/mg protein) level in LPS-treated rat brain

Groups	**Cortex**	**Striatum**	**Hippocampus**	**Cerebellum**
Control	0.82 ± 0.04	0.72 ± 0.07	0.39 ± 0.02	0.36 ± 0.01
LPS	7.54 ± 0.61^{c}	5.20 ± 0.52^{c}	4.80 ± 0.21^{c}	2.37 ± 0.43^{c}
OS 50	3.51 ± 0.40^{cz}	3.20 ± 0.39^{cz}	2.91 ± 0.28^{cz}	1.85 ± 0.16^{c}
OS 100	1.49 ± 0.13^{z}	1.70 ± 0.23^{z}	2.18 ± 0.22^{cz}	1.17 ± 0.13^{y}
OS 200	1.18 ± 0.61^{z}	1.54 ± 0.23^{z}	1.24 ± 0.15^{az}	1.01 ± 0.08^{z}

INDO	2.19 ± 0.18^{az}	2.21 ± 0.19^{bz}	3.28 ± 0.09^{cz}	2.07 ± 0.20^{c}

SUMMARY AND CONCLUSION

Administration of a single dose of LPS (1 mg/kg; i.p.) resulted in endotoxemia due to microglial and astrocytes activation causing disturbances in general behavior of the animals like increased mean body temperature, decreased body weight, inhibition of food and water consumptions. All these observed effects were antagonized by EEOS. LPS caused a mild increase in the status of SOD along with elevated levels of CAT and TBARS in LPS-treated rats. The level of GSH was significantly decreased. Treatment with EEOS was found to restore the biochemical disturbances caused by LPS, in a dose-dependent manner. Analysis of rat brain tissues revealed extensive derangement of hippocampal CA1 cell texture with LPS exposure, and significant protection of the CA1 region with EEOS treatment. In our experiment, LPS caused an elevation of brain TBARS and CAT while reducing endogenous antioxidant (GSH). In conclusion, administration of EEOS saved brain CC, CS, HT and CB regions from oxidative stress. The main indicator is the decreased TBARS levels, which is the final product of membrane LP. In addition, decrease in SOD, CAT, GSH levels in the brain areas studied indicated a negative trend in oxidative stress. The positive correlations between SOD and CAT may show a protective effect of EEOS in brain. Brain tissue is more vulnerable to oxidative injuries because its lipid ratio is higher and membrane structure is bigger than those of other organelles are. The current report offers compelling, but perhaps not conclusive, arguments for an association between behavioral and brain anatomical changes induced by LPS and its attenuation by EEOS.

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