Journal of King Saud University – Science 32 (2020) 1764–1771

Contents lists available at ScienceDirect

Journal of King Saud University – Science

journal homepage: www.sciencedirect.com

Original article

Celery ameliorating against neurobehavioral and neurochemical disorders of perinatal lipopolysaccharides exposure in mice offspring

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ARTICLE INFO

Article history:
Received 23 September 2019
Revised 30 November 2019
Accepted 6 January 2020
Available online 14 January 2020

Keywords:
Neurobehavioral disorders
Behavior
Dopamine
Serotonin
Acetylcholinesterase
Celery

ABSTRACT

In this study, the role of Lipopolysaccharide (LPS) on the neurochemical disruption and neurobehavioural changes in offspring of mice was analyzed. Totally 30 pregnant mice was selected and divided in to six groups. *Apium graveolens* was supplemented at various doses to the experimental animals. This experiment was started at the day of pregnancy and was continued up to post-natal day 15. In our experiment three pups from each set of experiment were carefully marked and analyzed its physical, biochemical and behavioral changes. The experimental animals showed decreased body weight, delayed eye opening and delayed hair growth. Also, LPS treated pups showed cliff avoidance and rotating reflexes. Pups exposed to LPS showed heavy learning deficits and memory loss. In the treated pups, decreased level of dopamine, acetylcholinesterase and serotonin in forebrain was observed than celery groups. The present finding showed that the treatment of Celery revealed potent activity on behavior and biochemical disorders. Administration of celery enhanced cognition behavior in experimental animals.

1. Introduction

Lipopolysaccharide (LPS) is the outer membrane of Gram-negative bacteria and has hydrophobic lipid and hydrophilic polysaccharide moieties. LPS has amphiphilic properties. The toxicity of LPS is called as "endotoxin" (Hamesch et al., 2015). The structure of LPS consists of O-polysaccharide, core sugar and lipid A component. Lipid A is mainly included 4to 7 fatty acid chains strictly bound to glucosamines, a main sugar component that is consisted of eight carbon sugar namely, keto-deoxyoctonate (KDO). In bacterial species KDO is a highly conserved region (Inagawa et al., 2011). LPS is mainly believed to be an important trigger of septic shock in Gram's-negative bacterial isolates and has been frequently used in analysis of infection due to bacterial pathogens induced various inflammatory response. Also, LPS induce septic shock due to severe oxidative damage. LPS enhance the suppression of antioxidant properties and enhance lipid peroxidation products (Ebaid et al., 2012; Zhu et al., 2007). It was previously stated that treatment of LPS in prenatal condition critically enhanced oxidative stress and considerably reduced the antioxidant glutathione in the organ and tissues of LPS-tested pups and mother animals. Also, exposure of LPS to the experimental animal effectively decreased the locomotors activity of pups. LPS treated animals showed various behavior responses, including, threat, social contact and attack. LPS treated animals was found to inhibit sensory activity. Prenatal exposure of LPS-allowed inflammation in experimental animals and enhanced the chance to develop behavioral disorder (Abu-Taweel et al., 2013; Gurusamy et al., 2019; Kannan and Agastian, 2015). *Apium graveolens* is green branched leaf stalks from the family Apiaceae. It was found in Asia, Africa, Southern Europe, North and South America (Tanasawet et al., 2016; Rathi et al., 2015; Valsalam et al., 2019a,b). This plant is rich of L-3-n-butylphthalide, flavonoids, volatile oil, sedanolide, phenolic compounds, flavonoids and linoleic acid (Uddin et al., 2015; Sowbhagya, 2014; Tanasawet et al., 2016). Several pharmacological properties such as, anti-inflammatory, antimicrobial, antihyperlipidemia, antiulcerogenic and antihypertension activity were reported from this plant (Rajkumari et al., 2019; Sowbhagya, 2014; Dianat et al., 2015; Powanda et al., 2015; Tanasawet et al., 2016). Recently, a potent compound was isolated from *A. graveolens* and this compound improved cognitive impairment in the Alzheimer's mouse in experimental mouse (Peng et al., 2010). Also, the isolated compound DL-3-n-butylphthalide which was isolated from *A. graveolens* showed neuroprotective effects (Li et al., 2010;

Peer review under responsibility of King Saud University.

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https://doi.org/10.1016/j.jksus.2020.01.014
1018-3647/

Huang et al., 2010; Balamurugan, 2015; Arokiyaraj et al., 2015; Antonisamy et al., 2015). The aim of our study is to evaluate the oral perinatal administration of Lipopolysaccharide, LPS on developmental, neurobehavioral and biochemical parameters in mice pups. It also aimed to study the attenuating effects of celery to improve LPS induced developmental, neurobehavioral and biochemical toxicity.

2. Materials and methods

2.1. Experimental animal

In our study, female and male experimental mice (Swiss-Webster rat) were maintained in plastic cages. In each cage, animals were maintained as, 3: 1 ratio (three females and a male). All experimental animals were checked and disease free experimental animals were obtained from Central Animal House Facility, Faculty of Pharmacy, King Saud University. This experimental setup was approved by the Ethical Committee, King Saud University. Adequate food and water was provided and male animal was removed once the female attained pregnancy.

2.2. Lipopolysaccharides (LPS) and administration of celery

In this experiment, pregnant Swiss-Webster was divided into various experimental groups. To the control group only water was provided, however the experimental group of animals received celery at various doses (300 and 600 mg/kg). Also, LPS was administered intravenously in one set of experimental animal at the dose of 2.5 mg/kg. Also, celery was administered to the LPS administered animal in order to analyze the protective role (Zhu et al., 2014; Mansouri et al., 2017). This experiment was performed as suggested by Abu-Taweel (2019).

2.3. Evaluation of off spring in weaning period

In this study, opening of eye, total body weight and body hair fuzz were analyzed in the Swiss-Webster off spring from PD1 to PD21.

2.4. Neuromotor maturation assessment

This study was performed as suggested by Binjumah et al. (2018).

2.5. Observation of behavioral changes

2.5.1. Active avoidance responses

Active avoidance response analyses was performed using a shuttle box" (UgoBasile, Comerio, and Varese, Italy). An automatic shuttle box registered the response and the experiment was performed up to 50 different trials (Abu-Taweel, 2018; Ahmed et al., 2016). All experiments were performed as suggested previously (Abu-Taweel et al., 2014, 2012).

2.5.2. Morris water-maze test

In this study cognitive functions of the mice was analyzed as described by Tariq et al. (2008), Ahmed et al. (2016), Rutten et al. (2002), Morris (1984), and Abu-Taweel (2018). The experimental procedures were performed for four days (Spiers et al., 2001; Jeltsch et al., 2001).

2.5.3. T-maze test

All six experimental groups of animals were subjected to T-maze test. This experiment was performed as suggested by Maodaa et al. (2015) and Leret et al. (2003).

2.6. Biochemical studies

In our study, forebrain of the experimental animal was carefully dissected out and neurotransmitter analysis was performed. Serotoninor 5-hydroxytryptamine (5-HT), dopamine (DA) and Acetylcholinesterase (AChE) were analyzed.

2.7. Statistical analysis

All experiments were subjected to analysis of variance as described earlier.

3. Results

3.1. Impact of LPS and physical assessment

In this analysis physical assessment was made during weaning period. Results revealed that exposture of LPS during perinatal stage reduced body weight (Fig. 1a). In this study, body and eyes opening was delayed ($P < 0.001$) than that of control group of

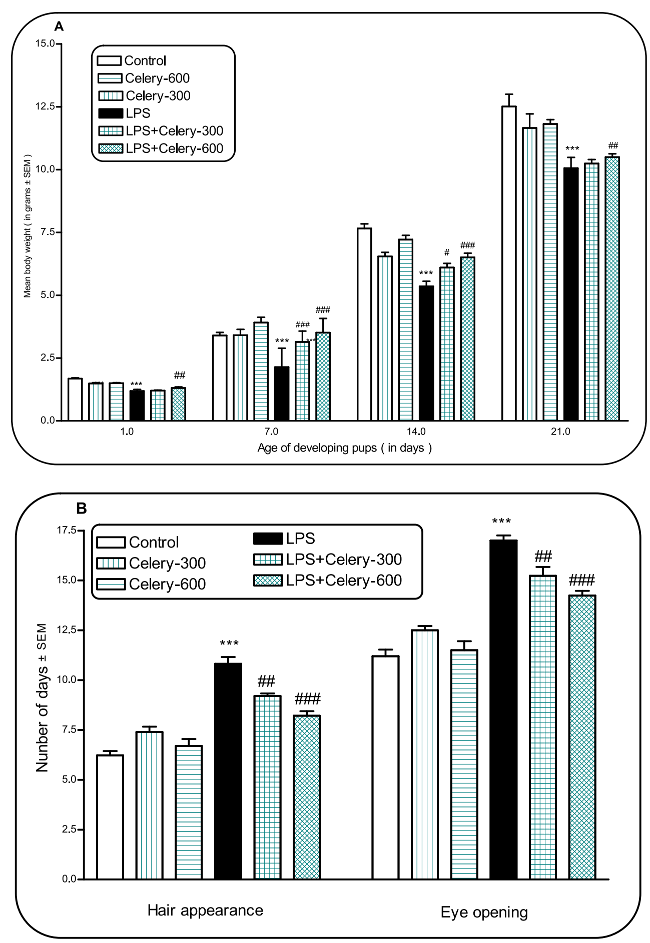


Fig. 1. Perinatal exposure of LPS and celery in mice offspring. (A) Effect on body weight. (B) effect on opening of the eyes and appearance of body hair fuzz. ***represent statistically significant at $P < 0.001$ from the control and celery groups. ##, ## and ### represent statistically significant at $P < 0.05$, $P < 0.01$ and $P < 0.001$ respectively from LPS group.

animals (Fig. 1B). However, celery administered animal at the same age group prevented body weight loss (Fig. 1. A). Celery positively regulate body metabolism and attenuates eye opening and development of body hair fuzz (Fig. 1. B).

3.2. Assessment of neuromotor in mice

In this study exposure of LPS results parentally delayed neuromotor maturation reflexes such as, cliff avoidance, righting, and rotating reflexes and was statistically significant (Fig. 2A, B and C). Results revealed that celery significantly improved disruptions in neuromotor maturation reflexes than untreated animal.

3.3. Behavioral response of mice

3.3.1. Active avoidance responses

LPS administered during perinatal stage induced various disorders in memory and learning of Swiss-Webster rat. Shuttle box experiments revealed that exposure of LPS cause impaired learning (Fig. 3A, B, C and D). Administration of celery saved changes caused by LPS significantly (Fig. 3A, B, C).

3.3.2. Morris water-maze experiment

In this experiment, exposure of LPS significantly induced various disturbances in Morris water-maze test (Fig. 4A–C). However, celery reversed the changes caused by LPS and the result was statistically significant ($P < 0.001$).

3.3.3. T-maze test

T-maze experiment was performed to analyze memory and learning of experimental and control animal. The present finding revealed that exposure of LPS affects learning and memory in offspring and was statistically significant ($P < 0.001$) (Fig. 5A–D). Administered celery showed protective role in experimental animal.

3.4. Biochemical analysis

LPS exposure led to reduce neurotransmitters and increase oxidative stress in treated offspring compared to control group (Figs. 6 - 8). Fig. 6A–C showed the decreasing level of ($P < 0.001$) dopamine, serotonin and Acetylcholinesterase (AChE), respectively. LPS exposure increased TBARS while GSH was decreased significantly ($P < 0.001$) than control (Fig. 7A and B). LPS exposure decreased GST, CAT and SOD activity and the result was significant (Fig. 8A, B and C). Figs. 6–8 indicated that exposure to celery reversed the disturbances which induced by LPS significantly ($P < 0.001$).

4. Discussion

Ebaid et al. (2012) previously studied prenatal exposure of LPS in gestated mice at PL stage. The prenatal exposure to LPS is highly dangerous to the developing pups clearly indicating a transfer of LPS from mother to their young ones. The results indicated that exposure to LPS led to reduced total weight gain and the process such as, appearance of body hair fuzz and eye opening is also delayed. Also, cliff avoidance and rotating reflexes were significantly delayed. LPS exposure significantly induced disorders in memory function and learning ability in tests of shuttle box, Mores water and T-Mazes. Neurobiochemical parameters were affected significantly after the LPS exposing at various doses. The treatment with celery served as protective role against LPS behavioral and biochemical disorders. These results are in line with Abu-Taweel et al. (2013) on Pregnant Swiss female mice injected with the bacterial lipopolysaccharides at a single dose of 2.5 mg/kg of body weight. These experiments showed that LPS very much reduced the locomotors activity of mice pups than those saline-control mice. Highly distributed focal areas indicating many phagocytic activities with a marked depletion of lymphocytes was observed insection from thymus of pups born to LPS-treated mice, indicating an intense inflammation. In the present study, body weight gain

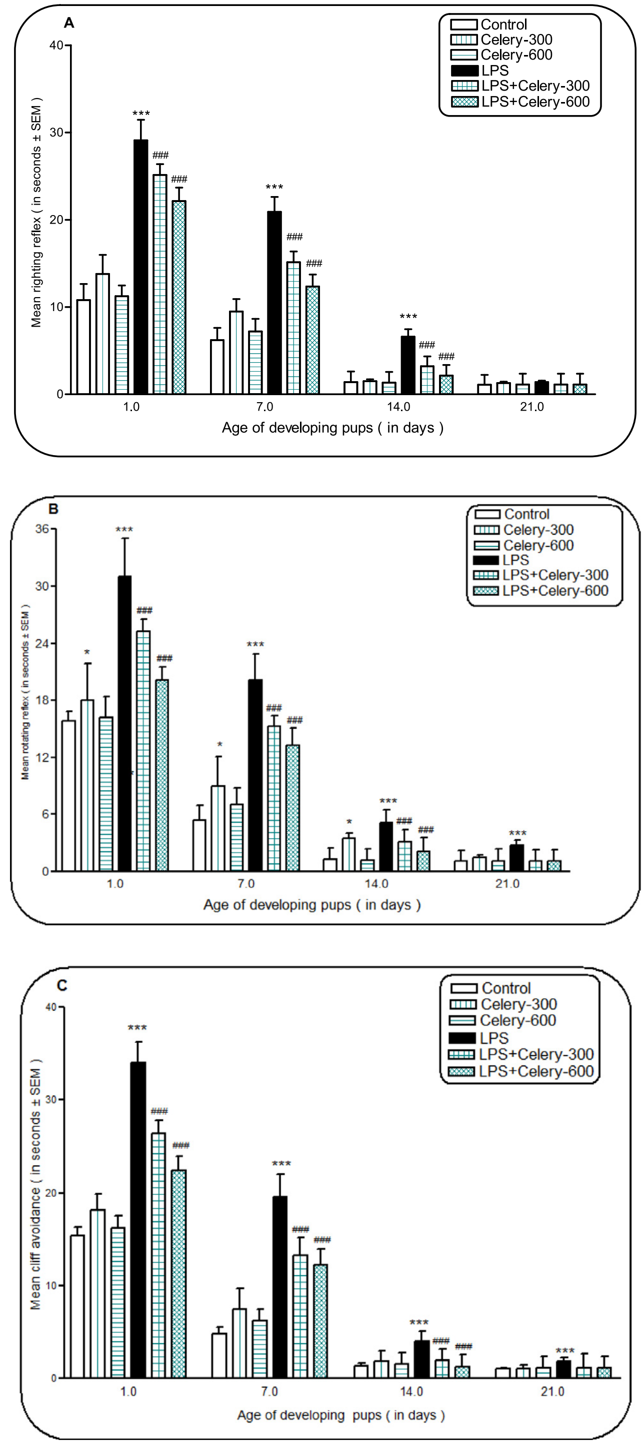


Fig. 2. A, B and C: Effects of L[S and celery perinatal exposure on neuromotor maturation reflexes of mice offspring > A, righting; B, rotating and cliff avoidance reflexes. *** represent statistically significant at $P < 0.001$ from the control and celery groups. ### represent statistically significant at $P < 0.001$ respectively from LPS group.

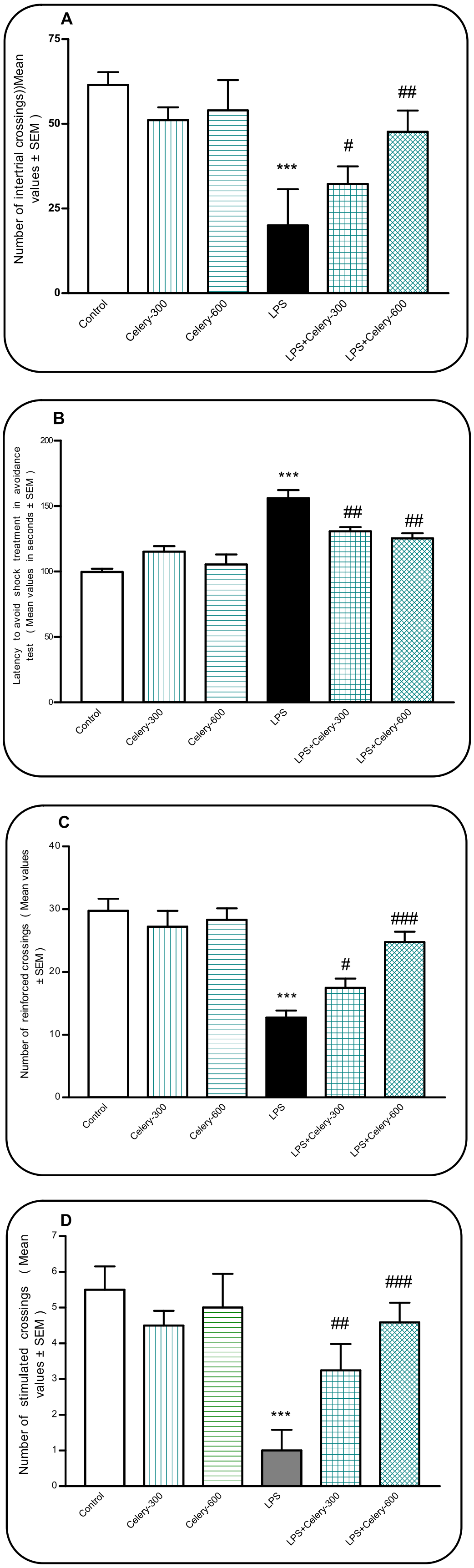


Fig. 3. A, B, C and D: Perinatal exposure effects of LPS and celery in shuttle box tests. A, Number of intertrial crossings. B, Latency to avoid shock treatment, C, Number of reinforced crossings. D, Number of stimulated crossings. *** represent statistically significant at P < 0.001 from the control and celery groups. ##, ## and ### represent statistically significant at P < 0.05, P < 0.01 and P < 0.001 respectively from LPS group.

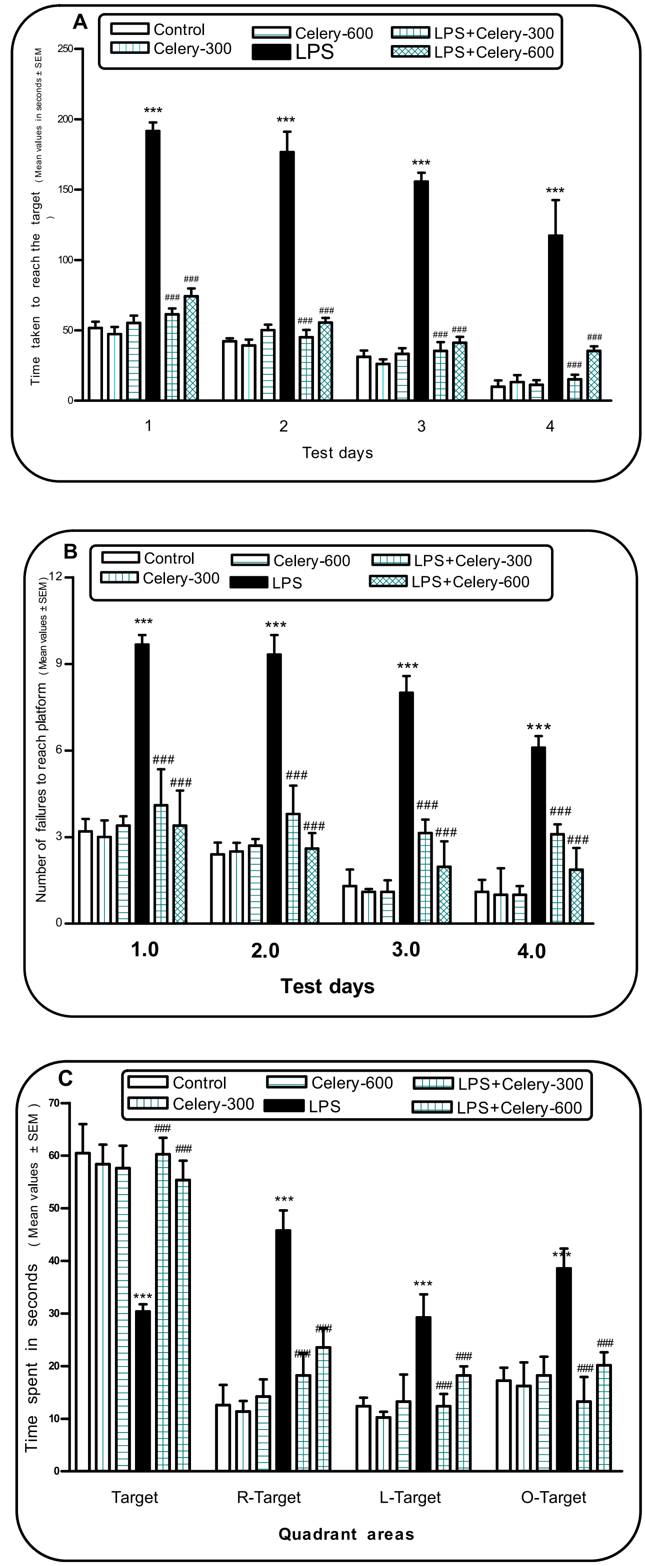
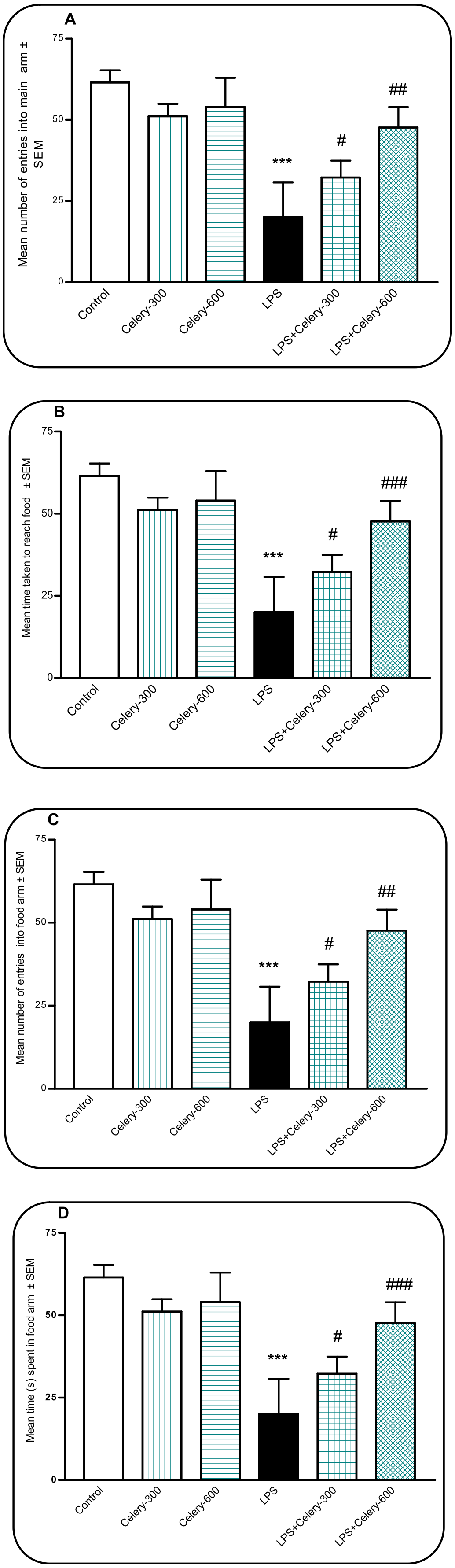


Fig. 4. A, B and C: Effects of LPS and celery perinatally exposure in water maze. (A) Time taken to reach the target. (B) Number of failures to reach platform. (C) Time spent in quadrant areas. *** represent statistically significant at P < 0.001 from the control and celery groups. ### represent statistically significant at P < 0.001 respectively from LPS group.

was significantly affected by the activity of LPS. Also, behavior changes were also observed in this study due to poor feeding capabilities. In most of the animals, dopamine plays a critical role and administration of LPS affect the function of dopamine (Lee et al.,



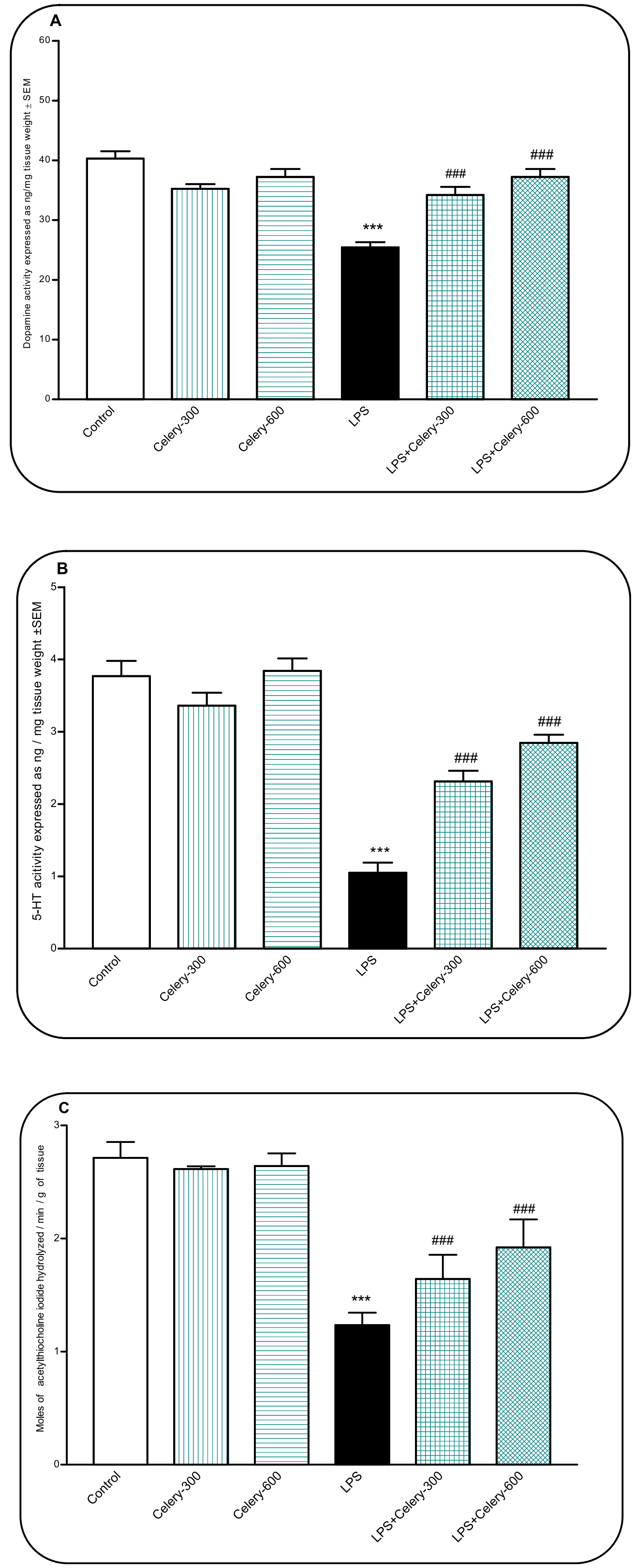


Fig. 6. A–C. Effects of LPS and celery exposure on neurotransmitters. (A) Dopamine. (B) Serotonin. (C) Acetylcholinesterase (AChE). *** represent statistically significant at P < 0.001 from the control and celery groups. ### represent statistically significant at P < 0.001 respectively from LPS group.

2000). Also, the treatment offspring with LPs affect appetite (Counter and Buchanan, 2004), critically affected absorption of biomolecules such as amino acids and sugars in the intestine (Chehimi

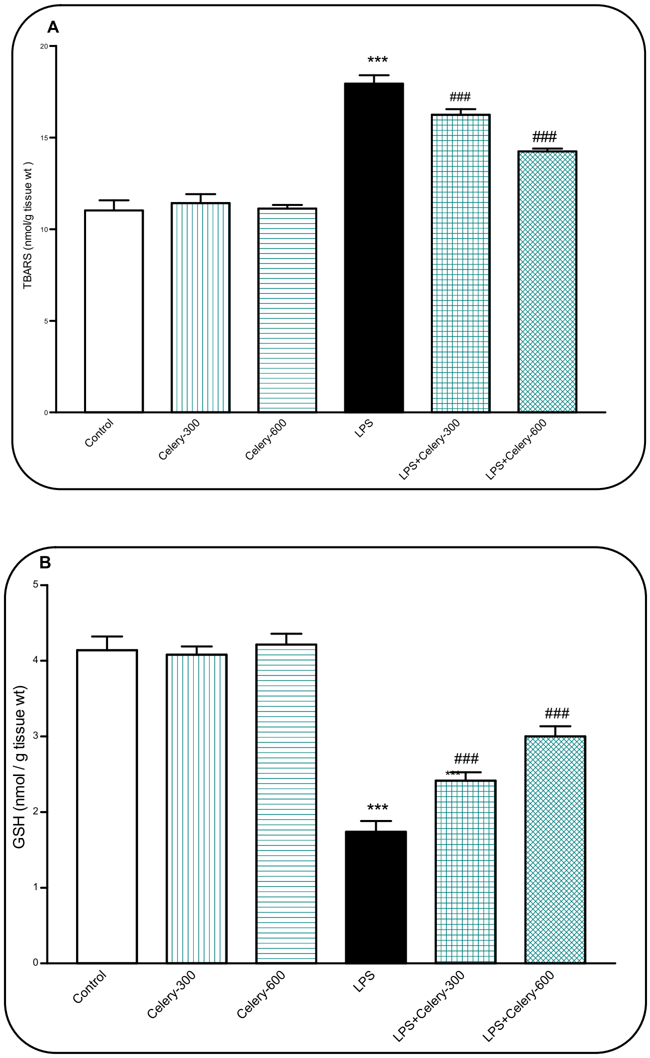


Fig. 7. A and B. Effects of LPS and celery on TBARS and GSH in mice offspring. (A) TBARS, (B) GSH. *** represent statistically significant at P < 0.001 from the control and celery groups. ### represent statistically significant at P < 0.001 respectively from LPS group.

et al., 2012). In the experimental animal eye opening and appearance of hair were delayed in LPS administered animal. Also, LPS affect the development of neural tube. Because of this reason, maturation of motor response was very much delayed (Abu-Taweel, 2019). In our study, LPS exposure during lactation and pregnancy critically affect the development of neuromotors in offsprings. This dysfunction was noted in cliff and rotating reflexes after administration of LPS. The analysis showed that LPS intervene with developing offspring and it passes through placenta or milk (Abu-Taweel et al., 2012). Eddins et al. (2008) reported various metabolic and behavioral changes in animals and humans due to LPS toxicity. In this study, brain was mainly affected due to LPS toxicity and LPS disrupt the functions of neurotransmitters. Stringari et al. (2008) reported increased level of GSH and also the increase of GSH and GPx after PD 21. The present findings revealed antioxidant

Fig. 5. A–D: Memory and learning test in T-Maze. (A) number of entries into main arm. (B) Time taken to reach food. (C) Number of entries into food arm. (D) Time spent in food arm. *** represent statistically significant at P < 0.001 from the control and celery groups. ##, ## and ### represent statistically significant at P < 0.05, P < 0.01 and P < 0.001 respectively from LPS group.

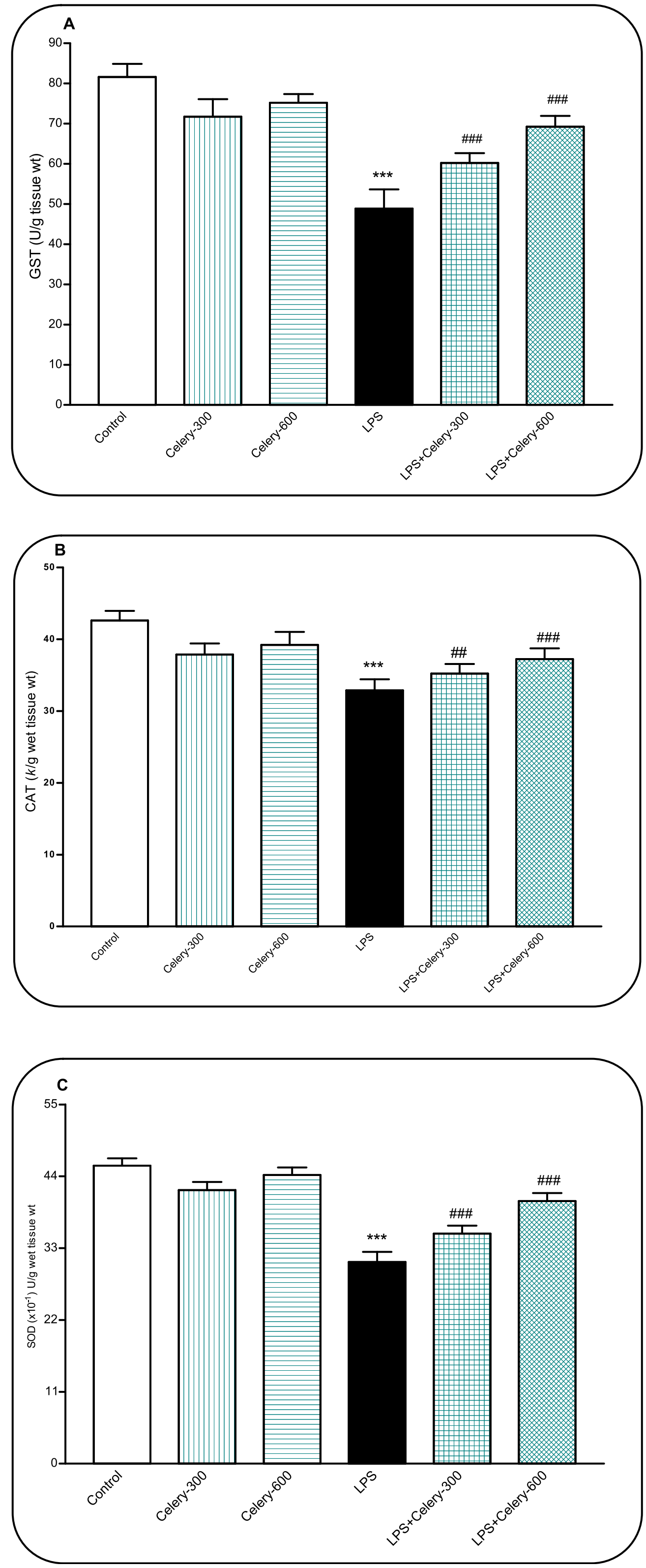


Fig. 8. A–C: Perinatal exposure to LPS and celery on Glutathione-S-Transferase (GST), catalase (CAT) and superoxide dismutase (SOD) activity. (A) GST; (B) CAT; (C), SOD. *** represent statistically significant at P < 0.001 from the control and celery groups. ### represent statistically significant at P < 0.001 respectively from LPS group.

response due to the administration of celery during PD stages. Abu-Taweel (2018) recently reported various non enzymatic stresses in experimental animal due to LPS toxicity. In animals, high level of oxidative stress has been reported in brain (Freitas, 2009) and this stress was mainly associated with cognitive impairment (Reeta et al., 2011; Abu-Taweel, 2019). In general, brain tissues are highly susceptible to oxidative stress (Barros et al., 2014). Many investigations were performed to analyze anti-inflammatory, anti-arthritis, antihypertension and antihyperlipidemia properties from celery (Sowbhagya, 2014; Dianat et al., 2015; Powanda et al., 2015; Tanasawet et al., 2016). Celery contains rich source of flavonoids and involved in various functions (Jung et al., 2011; Li et al., 2014).

5. Conclusion

In this study female mouse treated with LPS toxins during pregnancy showed considerable risk for various complications for their offspring. The use of celery showed protective effect against LPS induced various oxidative stresses. The present finding revealed the protective role of celery against behavioral and biochemical disorders. In conclusion, celery has lot of potential against LPS and other toxins.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The author is thankful to the Deanship of Scientific Research, Department of Biology, College of Sciences, Jazan University for supporting this research.

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