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Quinic acid through mitigation of oxidative stress in the hippocampus exerts analgesic effect in male mice

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Original Article

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Abstract:

Background and aims: Pain is a human societies problems that has always had a lot of attention to control. However, some patients became resistance to analgesic effect of common analgesics. A main goal of the researches on the field of pain is to find effective medications with less side effects. In this regards, natural derivatives of medicinal plants are under considering of researchers. It has been determined that oxidative stress involved in the pathophysiology of pain. The aim of this study is to investigate the analgesic effect of quinic acid considering its possible antioxidative effects in male mice**.**

Methods: In this experimental study, 40 male mice were divided into 4 groups (N=10) received normal saline (1 ml/kg), dexamethasone (5 mg/ kg), quinic acid (QA) (10 mg/kg) and QA (50 mg/kg) for 7 constant days via intraperitoneal route. Then, the pain response was assessed using hot plate test. Finally, mice were euthanized and hippocampi dissected out. The levels of malondialdehyde (MDA), nitrite as well as antioxidant capacity were measure in the hippocampus.

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Results: The results showed that QA significantly increased the duration of delay in pain response to heat. Furthermore, QA significantly increased the antioxidant capacity as well as decreased the levels of MDA and nitrite in the hippocampus.

Conclusion: we concluded that QA, partially at least, through mitigation of oxidative stress (increased the antioxidant capacity as well as decreased the levels of MDA and nitrite) exerts analgesic effect in the hot plate test in male mice.

Keywords: Quinic acid, pain, hot plate, oxidative stress, mice

INTRODUCTION

Pain is an unpleasant sensation, an emotional experience, and a physical problem caused by various stimulant including trauma, heat, rupture, necrosis, inflammation and spasm (1, 2). Pain leads to complications such as sleep disorders, insomnia, fatigue and depression (3). Pain is a defense mechanism that alerts the body to injury (4).

Various hypotheses have been proposed about the pathophysiology of pain, including biochemical reactions such as oxidative stress (5). Previous studies have been determined that oxidative stress is involved in the pathophysiology of pain (6). In this regards, it has been demonstrated that inhibition of oxidative stress could mitigated the pain response (7). Ample evidences showed that decrease in the MDA and nitrite levels is associated with analgesic effects of some agents (8-10).

Nowadays, drugs commonly use to relieve pain are either narcotic, such as opioids, or non-narcotic, such as salicylates and corticosteroids (e.g., hydrocortisone) which are associated with various side effects (11). Thus, finding new agents with high efficacy and low side effects is interesting and is a pressing need.

Few side effects of medicinal plants attracted the attention of researchers across the globe in recent decades. Herbal compounds can be used alone or as a supplement with chemical drugs in treatment of diseases (12).

Quinic acid with the chemical formula of C7H12O6, obtained from the bark of cinchona, beans, coffee, tobacco leaves, carrot leaves, apples, peaches, pears, plums, vegetables, etc (12). Previous studies have demonstrated that QA exerted antioxidant effects in various disease in animal models (12-15).

Due to the antioxidant activity of QA as well as role of oxidative stress in the pathophysiology of pain, the present study was conducted to investigate the analgesic effect of QA in the hot plate test in male mice considering its possible role on oxidative stress**.**

MATERIALS AND METHODS

Animals

All stages of experiments on mice were performed in accordance with the regulations of the Ehics Committee of Shahrekord University. In this experimental study, 40 male mice weighing approximately 25-30 g, under suitable temperature conditions (22±1 °C) and cycles of 12 hours of light and 12 hours of darkness with free access to the same water and food were used.

Mice were randomly divided into four groups (n=10), including the group received normal saline (1 ml/kg), the group received dexamethasone (5 mg/kg), the group received quinic acid (10 mg/kg) and the group received quinic acid at dose of 50 mg/kg (16).

Quinic acid was injected intraperitoneally for three constant days and the pain response was assessed by the hot plate test. The mice were then placed under deep anesthesia and brains were isolated to measure the levels of oxidative factors including antioxidant capacity, malondialdehyde (MDA) and nitrite in the hippocampus.

Hot plate test

In this test, the mouse was placed on a hot plate at 50 °C with a cut-off time of 60 seconds, and the time that the mouse takes to exhibit the signs of pain, including jumping, licking, and rearing was recorded. An increase in this time indicates an analgesic effect (17).

Antioxidant capacity

After behavioral assessments, hippocampus tissue was isolated and a homogenates was prepared. The antioxidant capacity was determined by measuring its ability to reduce Fe^{3+} to Fe^{2+} using the FRAP method.

Three solutions were used to determine the antioxidant capacity. Solution 1 contained 1.5 ml of sodium acetate and 8 ml of acetic acid dissolved in 500 ml of distilled water, solution 2 contained 270 mg of iron (III) chloride dissolved in 50 ml of distilled water, and solution 3 contained 47 mg of trioxene dissolved in 40 ml of HCL.

The working solution was prepared by mixing 10 ml of solution 1, 1 ml of solution 2 and 1 ml of solution 3. 2.5 ml of the working solution was mixed with 25 µl of homogenized tissue tissue and after 15 minutes incubation at 37 °C, optical absorbance was determined at 593 nm (18).

MDA level

The rate of lipid peroxidation in homogenate of the hippocampus was determined by colorimetric method based on the formation of reactants with thiobarbituric acid. An appropriate volume of tissue homogenate (10% w/v) was incubated in 50 mM phosphate buffer (pH 7.4), 10% TCA and 34% thiobarbituric acid for 15 min. The cooled reaction sample was then centrifuged and the optical absorption of the supernatant was determined by spectrophotometry at 535 nm wavelength (19).

Nitrite level

To measure nitrite level, 300 µl of tissue homogenate and 600 µl of 75 mM $ZnSO_4$ solution was mixed and centrifuged at 1000 g for 5 minutes at room temperature. After incubation of the supernatant with copper cadmium granules in glycine-sodium hydroxide buffer to convert nitrate to nitrite, the amount of total nitrite was measured by Griess reaction. To this, 1 ml of the sample was mixed with a Griess solution (1 ml of 0.5% sulfanilamide and 0.05% n-naphthalene diamine hydrochloride) and after 30 minutes of incubation in the dark place, the absorbance was read at 545 nm (20).

Statistical analysis

After collecting data and entering the data in PRISM statistical software version 8, one-way analysis of variance (ANOVA) and Tukey's post-test were used for analysis. $P<0.05$ was considered significance level.

RESULTS

Quinic acid increases latency to heat response

The results of Tukey's post hoc test (Figure 1) showed that quinic acid at dose of 50 mg/kg, significantly increased the latency to heat response in compared to the control group ($P<0.01$).

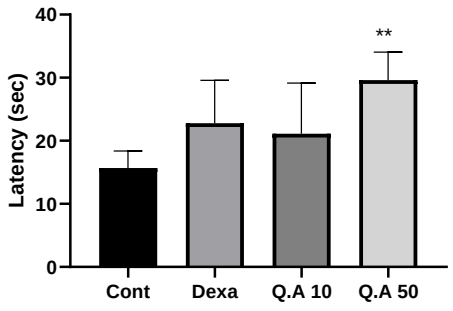

Figure 1. Effect of quinic acid in latency to heat response in the hot plate test; Cont: control group (normal saline); Dexa: Dexamethasone; Q.A: Quinic acid. ** P<0.01 in compared to the control group.

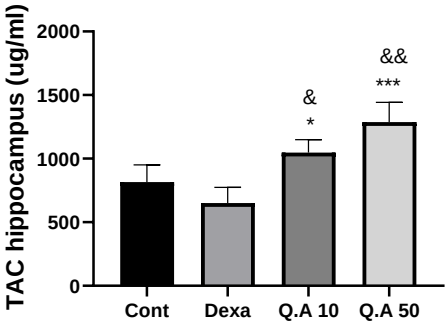

Figure 2. Effect of quinic acid on the hippocampal total antioxidant capacity (TAC); Cont: control group (normal saline); Dexa: Dexamethasone; Q.A: Quinic acid. *P<0.05 and *** P<0.001 in compared with the control group and $^{\&}$P<0.05 and $^{\&\&}$P<0.01 in compared to the dexamethasone-received group.

Quinic acid increases the antioxidant capacity of the hippocampus

The results of Tukey's post hoc test (Figure 2)showed that quinic acid at doses of 10 and 50 mg/kg significantly increased the antioxidant capacity of the hippocampus in compared to the control group (P<0.001 and <0.05, respectively). Finding showed that quinic acid at doses of 10 and 50 mg/kg significantly increased the antioxidant capacity in compared with the dexamethasone treated-group (P<0.05 and P<0.01, respectively).

Quinic acid decreases the hippocampal MDA level

The results of Tukey's post hoc test (Figure 3) showed that quinic acid at doses of 10 and 50 mg/kg significantly reduced the hippocampal MDA level in compared to the control group (P<0.001). Finding showed that quinic acid at doses of 10 and 50 mg/kg significantly decreased the MDA level in compared to the dexamethasone treated-group (P<0.05 and P<0.001, respectively).

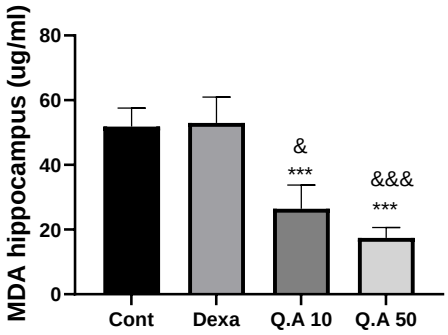

Figure 3. Effect of quinic acid on the hippocampal MDA level; Cont: control group (normal saline); Dexa: Dexamethasone; Q.A: Quinic acid. *** P<0.001 in compared with the control group and $^{\&}$P<0.05 and $^{\&\&\&}$P<0.001 in compared to the dexamethasone-received group.

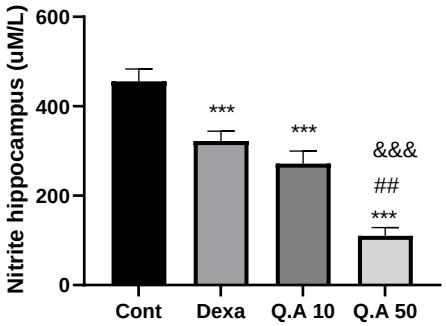

Figure 4. Effect of quinic acid on the hippocampal nitrite level; Cont: control group (normal saline); Dexa: Dexamethasone; Q.A: Quinic acid. *** P<0.001 in compared to the control group, ##P<0.01 in compared to the group received quinic acid at dose of 10 mg/kg and $^{\&\&\&}$P<0.001 in compared to the dexamethasone-received group.

Quinic acid decreases the hippocampal nitrite level

The results of Tukey's post hoc test (Figure 4) showed that dexamethasone group, as well as quinic acid at doses of 10 and 50 mg/kg, significantly reduced the hippocampal nitrite level in compared with the control group (P <0.001). Furthermore, we showed that quinic acid at dose of 50 mg/kg in compared to the dose of 10 mg/kg significantly reduced the nitrite level in the hippocampus. Finding showed that quinic acid at dose of 50 mg/kg significantly decreased the nitrite level in compared to the dexamethasone treated-group (P<0.001).

DISCUSSION

Results of the present study showed that quinic acid increased time latency to heat response in the hot plate test. We observed that quinic acid increased antioxidant capacity as well as decreased levels of MDA and nitrite in the hippocampus. These findings demonstrated that quinic acid partially, at least, through its antioxidant effects exerted analgesic effect in the hot plate test in mouse.

Pain is one of the most common symptoms associated with various

diseases and is a major economic and health stress that may lead to a decrease in quality of life and disability (19, 20).

Oxidative stress causes the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and triggers several destructive mechanisms such as inhibition of mitochondrial function, increased calcium levels, reperfusion injury and inflammation (21). In neuropathic pain, in addition to increase in the ROS level, the amount of antioxidants also decrease (22). The analgesic chemical compounds via effects on the pain processes systems in the brain exert their pain relieving properties. However, these compounds have numerous side effects (9). Herbal compounds have attracted the attention of researchers in this field because of fewer side effects as well as desirable efficacy (23). Given that quinic acid is a natural compound that is widely found in many plants (24). this study aimed to investigate the analgesic effect of quinic acid in mouse hot plate test as a valid test to evaluate pain response in rodent (25). considering possible its antioxidant effect.

There is evidence that oxidative stress plays a major role in the pathogenesis of many diseases, including neurological disorders (26). Various hypotheses have been proposed about the pathophysiology of pain, including biochemical reactions such as oxidative stress (5). Previous studies have been determined that oxidative stress is involved in the pathophysiology of pain (6). In this regards, it has been demonstrated that inhibition of oxidative stress could mitigated the pain response (7).The production of the MDA as a biomarker of lipid peroxidation is considered for measuring oxidative stress levels (27).

NO, as a regulating molecule, plays a key role in the functioning of various systems of the body as well as in a wide range of physiological and pathological processes (28). It has been determined that NO is involved in the pathophysiology of pain and attenuation of nitrite level is associated with analgesic effects of some agents (29).

It has been shown that quinic acids exerted antioxidative properties (28). In another study, it has been observed that quinic acid, as an antioxidant, supports

the synthesis of tryptophan and nicotinamide, leading to increase of DNA repair and inhibition of NF-κB (29). Lee et al. (2013), by studying the neuroinflammatory activity of quinic acid derivatives in microglia-induced lipopolysaccharide, observed that these compounds significantly inhibited NO production (32). In another study, quinic acid derivatives were shown to have inhibitory activity on nitrite formation in murini-induced polysaccharides (30).

In line with aforementioned studies we showed that quinic acid decreased the MDA and nitrite levels as well as increased antioxidant capacity in the hippocampus. We demonstrated that these antioxidative properties of quinic acid are involved in its analgesic effect in the hot plate test. In addition, our results showed that dose of 50 of quinic acid exerted more beneficial effects.

CONCLUSION

The results of the present study showed that quinic acid possibly through antioxidant effects exerted analgesic effects in mouse hot plate test.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

FUNDING

None

CONFLICT OF INTERESTS

None.

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