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Original article

Effects of Sodium Benzoate and *Ephedra alata* on Some Cardiac Enzymes in Male Rats

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Sodium Benzoate, Ephedra alata, Cardiac enzymes, Male Rats.

ABSTRACT

Sodium benzoate is a common food preservative found in a wide range of items, including milk, toothpaste, mouthwash, fluids, and cosmetics. In Greco-Arab traditional medicine, *Ephedra alata* (*E. alata*) is used to treat respiratory issues, asthma, and cancer. The current investigation sought to determine whether *Ephedra alata* may shield rats from sodium benzoate-induced cardiotoxicity. Twenty male albino rats weighing between 195 and 300 g were split up into four equal groups, each of which had five male rats: Every day, distilled water was given to the first group, which was retained as the control. For two weeks, the second group was given an oral dosage of sodium benzoate (100 mg/kg/b. w.). For two weeks, *E. alata* (1 g/kg/b. w.) was administered orally to the third group. For two weeks, sodium benzoate and ephedra were given to the fourth group, also known as the combination group. According to the study's findings, there were no appreciable differences in the mean levels of CKMB, troponin, or LDH between the treatment and control groups; however, the combination group's troponin levels significantly increased in comparison to the control group. In summary, the study's findings demonstrated that ephedra did not effectively reverse the cardiotoxicity caused by sodium benzoate when taken alongside it.

Introduction

Sodium benzoate is a white, crystalline substance that is a salt of benzoic acid. While it dissolves readily in water, it barely dissolves in ethanol. It has a molecular weight of 114.11 and becomes more soluble when the water temperature rises [1]. Previous research has shown that sodium benzoate negatively impacts several physiological systems in a variety of animals [2].

Sodium benzoate significantly reduced hemoglobin levels in a dose-dependent manner and significantly decreased WBC counts at 60 and 120 mg/kg. However, there was no discernible change in body weight when 30 mg/kg b. w. of sodium benzoate was administered. The preservative did not substantially impact total plasma protein concentrations. Bicarbonate and chloride did not significantly change at the different preservative concentrations, whereas sodium and potassium showed notable increases from the sixth day [3]. Furthermore, giving male rats larger doses of sodium benzoate (6–8 mg/kg b. w./day) resulted in a significant drop in their RBC count, hemoglobin concentration, hematocrit values, lipoprotein, albumin, triglycerides, cholesterol, and total protein [4]. WBC counts, total bilirubin, ALT, AST, urea, creatinine, LDH, CPK, CKMB, and MDA all significantly increased over this time [5]. The pro-inflammatory cytokines TNF-α and IL-6 of heart tissue were significantly reduced by sodium benzoate [6]. There was no significant difference at 150 mg/kg b. w., but there was a significant decrease in cholesterol levels at doses of 5 for 250 and 500 mg/kg b. w. Ephedra herb contains analgesic, anti-inflammatory, and anti-influenza properties [7, 8].

Due to health concerns, the US Food and Drug Administration (FDA) prohibited the sale of nutritional supplements containing ephedra plants in 2004 [9]. Ephedrine's effects on the heart can last up to ten times as long as those of adrenaline. Additionally, ephedrine raises the pulse rate and the systolic and diastolic values. Blood flow in the heart, brain, and muscles increases while that in the kidneys and viscera decreases [10]. *E. sinica* stimulates the heart and functions as an epinephrine-like chemical [11]. Ephedra has been shown to raise blood pressure and strain the circulatory system, which can result in major illnesses like stroke, myocardial infarction, and other cardiac problems. Fasting or dieting could intensify this impact even more, increasing the chance of a fatal cardiac arrhythmia, particularly when combined with drugs that

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have a sympathomimetic effect [12]. Additionally, *E. nebrodensis* treatment reversed the abnormalities in electrocardiography (ECG), raised levels of other antioxidant defense enzymes, such as GSH and SOD, and significantly reduced levels of cardiac marker enzymes and lipid peroxidation. Additionally, *E. nebrodensis* may be able to stop the cardiotoxic effects that doxorubicin causes. Animals treated with DOX saw a marked reduction in heart weight, which was avoided after two weeks of treatment with *E. nebrodensis* extract (100 and 200 mg/kg) [13]. However, after three weeks, *E. sinica* significantly reduced the weight of the kidney, heart, liver, lung, and spleen in mice, according to [14].

Materials and Methods

Experimental animals

For this investigation, twenty male albino rats (*Rattus norvegicus*) weighing between 195 and 300 g were employed. They were acquired from the Zoology Department's animal house at the University of Omar Al-Mukhtar's Science Faculty. The rats were kept in four groups in identical cages in the same room with consistent environmental parameters, including humidity (50-60 %) and temperature (22±3°C). Ad libitum drinking water and an adequate rate of feed were provided to them. Prior to the study's two-week start, all animals were given two weeks to become acclimated to their surroundings.

Chemical

Sodium benzoate

The chemical formula for the material utilized is C6H5COONa, or sodium benzoate. BDH Chemicals Ltd. (England) provided it.

Medical Plant

Ephedra alata

On Libya's east coast, in the Al-jabal Al-Akhdar region, *Ephedra alata* leaves were gathered. The *E. alata* extraction procedure was carried out in accordance with the Dahiru *et al.* (2006) approach [15].

Preparation of sodium benzoate

According to the group distribution, sodium benzoate was administered orally every day for two weeks at a dose of 100 mg/kg/b. w. dissolved in freshly made distilled water [16].

Preparation of Ephedra alata

The gathered leaves were weighed, cleaned with water, dried, and then chopped into little pieces before being weighed one more. Use a funnel to sieve the mixture after an hour of beating it in the mixer. A rotary evaporator was used to remove the solvent from the samples, and the heavy extract was then collected. Over the course of the entire trial, *E. alata* was administered orally every day for two weeks at a dose of 1 g/kg/b. w. [17]. A customized gastric tube with a smooth tip was used to administer both doses orally in order to prevent damage to the buccal and oral cavity's inner lining.

Experimental design

A total of twenty male albino rats were used in this experiment. The rats were divided into four equal groups at random using the following methodology, with five male rats in each group: Control group (G1): For two weeks, the animals in this group were given distilled water orally every day. Sodium benzoate-treated group (G2): For two weeks, rats were given an oral dosage of 100 mg/kg/b. w. of sodium benzoate every day. *E. alata* treated group (G3): Rats that received a daily dose of 1g/kg b. w. of *E. alata* for two weeks were included in this group. Combination Group (G4): For a period of two weeks, the animals in this group were given an oral dose of Ephedra (1 g/kg b. w.) along with a dose of sodium benzoate (100 mg/kg b. w.).

Cardiac enzymes methods

Using the Elisa Kit from My Biosource Company, a competitive enzyme immunoassay approach was used to measure the levels of creatine kinase myocardial band (CKMB), troponin I, and lactate dehydrogenase (LDH) in each animal's serum.

Results

Cardiac enzyme levels in serum

(Table 1 and figures 1, 2, and 3) showed the mean levels of CKMB, troponin, and LDH for the control and experimental groups. When compared to the control group, the mean CKMB values for each treated group were as follows: 29.40±2.44 for the control group, 27.80±3.48 for the sodium benzoate group, 22.00±3.21 for the *E. alata* group, and 26.20±1.46 for the combination group (Table 1 and Figure 1). Troponin levels in

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the sodium benzoate and *E. alata* groups did not significantly change (0.156±0.023 and 0.142±0.017, respectively). Troponin levels in the combination group were significantly higher (0.302±0.10) than in the control group (0.132±0.018) (Table 1 and Figure 2). (Table 1 and Figure 3) Exhibit the data collected for the mean of LDH. When compared to control animals, there were no notable changes in the mean LDH levels, which were recorded as follows: 479.8±39.33 in the control group, 466.4±49.3 in the sodium benzoate group, 342.2±22.99 in the *E. alata* group, and 441.2±9.86 in the combination group.

Table 1. Ephedra alata aqueous extract's ability to protect serum CKMB (U/L), Troponin (ng/ml), and LDH (U/L) levels against sodium benzoate toxicity

Parameters	Group Duration		Control group	Sodium benzoate group	*E. alata* group	Comb. group
CKMB	2nd week	Mean ± S. E. % of change	29.40A±2.44	27.80A±3.48 -1.6	22.00A±3.21 -7.4	26.20A±1.46 -3.2
Troponin	2nd week	Mean ± S. E. % of change	0.132B±0.018	0.156B±0.023 0.024	0.142B±0.017 0.010	0.302A±0.010 0.170
LDH	2nd week	Mean ± S. E. % of change	479.8A±39.33	466.4A±49.33 -13.4	342.2A±22.99 -137.6	441.2A±9.86 -38.6

A, B: The groups in the same row with different letters are statistically significant ($p < 0.05$).

Discussion

Although sodium benzoate is recognized as a safe drug, prolonged or frequent contact may result in significant skin sensitivity, while brief exposure may irritate the eyes, skin, and respiratory tract [18]. The well-known Chinese herbal product ephedra contains 0.5 to 2.5 % sympathomimetic alkaloids, mostly ephedrine and pseudoephedrine. Vasculitis brought on by ephedrine and other sympathomimetics has mostly affected the cerebral arteries, whereas cardiotoxicity is typically caused by dose-related alpha and beta receptor activation [19, 20]. CKMB, troponin, and LDH levels in all treated groups were not significantly different from the control group in the current investigation; however, the combination group's troponin levels were significantly higher than those of the control group. Troponin, LDH, and CKMB levels in the sodium benzoate group did not significantly differ from those in the control group. The current result appears to contradict the findings of Ahmad *et al.* (2018), who found that giving male rats 6–8 mg/kg b. w./day of sodium benzoate significantly increased their levels of LDH, CPK, CKMB, and MDA [5]. Additionally, compared to control, high sodium benzoate concentrations (200, 400, and 700 mg/kg b. w..) result in a notable rise in inflammatory cytokine markers (TNF-α, IFN-γ, IL-1β, and IL-6). At a dosage of 70 mg/kg b. w., sodium benzoate did not significantly alter any of the previously examined parameters. Thus, there may be large variations in the levels of CKMB, troponin, and LDH that are related to both dose and time [21]. As a result, additional research may be conducted to ascertain any potential harmful effects from prolonged administration times.

It is noteworthy that the sodium benzoate concentrations employed in this investigation were far lower than those reported in other studies and well below the 0.1% "safe" limits in foods [22]. It is noteworthy that the sodium benzoate concentrations employed in this investigation were far lower than those reported in other studies and well below the 0.1% "safe" limits in foods [22]. Serum levels have not changed significantly, which could be because there hasn't been any heart tissue damage. Furthermore, we were unable to locate any prior research that assessed the impact of sodium benzoate on alterations in cardiac enzymes. With the exception of a notable rise in the combination group's troponin levels relative to the control group, there were no discernible changes in the CKMB, troponin, or LDH levels in the *E. alata* and combination groups. By standardizing the biochemical parameters under investigation, the effects of *E. alata* on male rats provide outcomes comparable to numerous controls [23]. These findings contradicted those demonstrating that E. nebrodensis therapy markedly elevated cardiac marker enzyme levels [13].

Myocardial infarction and cardiac damage could be the cause of the elevated troponin levels. It suggests a higher chance of experiencing heart attacks or other cardiac problems in the future. In light of the current work, the contentious findings from earlier research could be explained by variations in various experimental settings, such as *E. alata* dosages.

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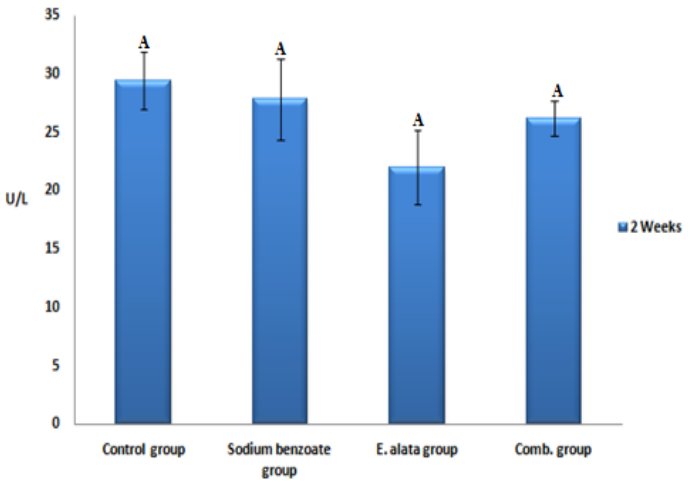

***Figure 1. The safeguarding function of Ephedra alata aqueous extract against sodium benzoate effects on serum* CKMB (U/L) levels**

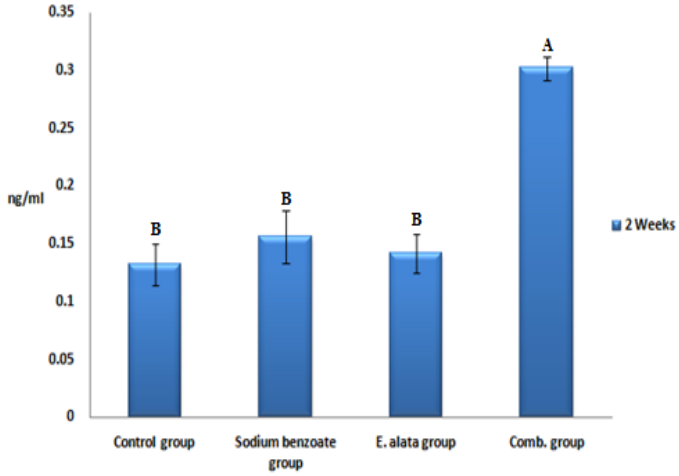

Figure 2. Ephedra alata aqueous extract's ability to shield serum Troponin (ng/m) levels from sodium benzoate's effects.

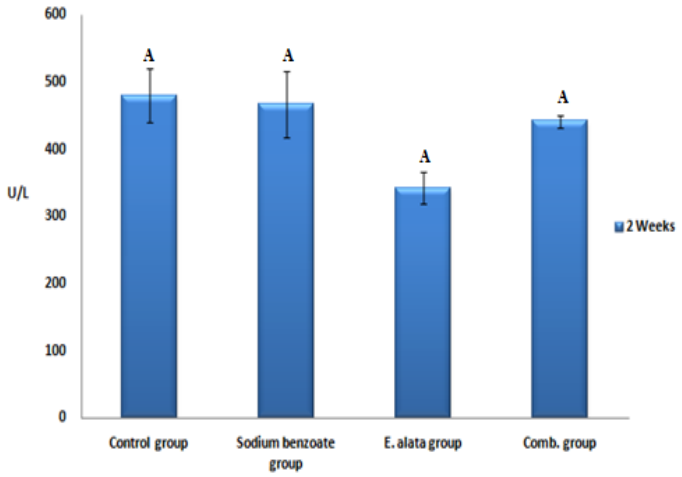

Figure 3. The protective role of Ephedra alata aqueous extract against sodium benzoate effects on serum LDH (U/L) levels

Conclusion

The study's findings, taken together, demonstrate that sodium benzoate and *E. alata* extract have no influence on the levels of cardiac enzymes.

Conflicts of Interest

The authors declare no conflicts of interest.

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