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Histopathological Changes on Heart Tissues in Male Rats induced by Sodium Benzoate and *Ephedra alata*

Amany Y. A. Tayeb[1], Fareha G. S. Elshokri[2], Mohammed H. Bouleefah[3], Ebtesam M. M. Gheth[4], Ibrahim S. Eldurssi[4*] and Noura A. A. Alhissade[5]

[1]High Institute of Medical Sciences and Technologies, El-Marj, Libya
[2]Zoology Department, Faculty of Art's and Science - Sulug, University of Benghazi, Libya
[3]Department of Anatomy, Histology and Embryology, Faculty of Veterinary Medicine, Omer Al-Mukhtar University, El-Beida, Libya
[4]Zoology Department, Faculty of Science, Omar Al Mukhtar University, El-Beida, Libya
[5]Biology Department, Faculty of Education, Derna University, Derna, Libya
Correspondence author: ibrahim.eldurssi@omu.edu.ly

Abstract:

Food additives are substances that are added to fundamental foods in order to enhance their flavor, texture, color, appearance, and food value as well as their preservation. A genus of nonflowering plants in the Ephedraceae family, *Ephedra alata* (*E. alata*) is used medicinally. The current investigation sought to determine whether Ephedra alata could shield rats' hearts from sodium benzoate-induced cardiac histopathology. 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. The current study's findings showed that sodium benzoate generated severe areas of necrotic tissue and distorted cardiac architecture, which resulted in histological examinations showing detrimental modifications in the heart tissues. Vacuolation, myofiber enlargement, and striation loss were noted. There was evidence of fibrosis, significant vascular dilatation, hypertrophied myocyte nuclei, and blood vessel

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congestion. In addition, inflammatory cellular infiltration, hyaline degeneration, and bleeding were all seen in the treated rat's heart. In addition to fibrosis and an uneven distribution of myocyte nuclei in the heart tissue, the *Ephedra alata* group displayed severe damage, myocardial fiber rupture, and dilated, clogged blood vessels. Additionally, noted were pyknotic nuclei, vacuolation, necrosis, interstitial odema, bleeding, and hyaline degeneration. Cardiac tissue distortion, myofiber enlargement, myocardial blood vessel dilatation, and muscle fiber swelling were all evident in the combo group. There were numerous localized necrotic fibers linked to pyknosis, hyaline degeneration, and muscle fiber splitting with loss of transverse striations. The study's findings demonstrated that Ephedra alata and sodium benzoate by themselves were cardiotoxic. Furthermore, it was discovered that ephedra did not help to reverse the cardiotoxicity caused by sodium benzoate when taken with it.

Keywords: Sodium Benzoate, *Ephedra alata*, Heart histopathology.

التغيرات النسيجية المرضية في أنسجة قلب ذكور الجرذان المُستحثة بواسطة بنزوات الصوديوم ونبات العلندا

أماني يونس علي طيب[1]، فريحة جمعة سالم الشكري[2]، محمد حسن بوليفة[3]، ابتسام مفتاح محمد غيث[4]، إبراهيم سالم الدرسي[4]*، ونورا أمراجع عبدالحميد الحصادي[5]

[1]المعهد العالي للعلوم الطبية والتقنية، المرج، ليبيا

[2]قسم علم الحيوان، كلية الآداب والعلوم – سلوق، جامعة بنغازي، ليبي

[3]قسم التشريح والأنسجة والأجنة، كلية الطب البيطري، جامعة عمر المختار، البيضاء، ليبيا

[4]قسم علم الحيوان، كلية العلوم، جامعة عمر المختار، البيضاء، ليبيا

[5]قسم الأحياء، كلية التربية، جامعة درنة، درنة، ليبيا

البريد الإليكتروني للباحث الرئيسي: ibrahim.eldurssi@omu.edu.ly

الملخص:

المضافات الغذائية هي مواد تُضاف إلى الأطعمة الأساسية لتحسين نكهتها وملمسها ولونها ومظهرها وقيمتها الغذائية، بالإضافة إلى حفظها. نبات العلندا هو جنس من النباتات غير المزهرة، نبات العلندا (*E. alata*)، وله استخدامات طبية. الدراسة الحالية

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تهدف إلى تحديد ما إذا كان نبات العلندا قادرًا على حماية قلوب الجرذان من التغيرات النسيجية المرضية الناتجة عن بنزوات الصوديوم. استخدمت في هذه عشرون من ذكور الجرذان، تراوحت أوزانها بين 195 و300 غرام، وقسمت إلى أربع مجموعات متساوية، تضم كل منها خمسة جرذان. أُعطيت المجموعة الأولى ماء مقطر يومياً، واحتفظت بها كمجموعة ضابطة. أُعطيت المجموعة الثانية جرعة فمية من بنزوات الصوديوم (100 ملغم/كغم/وزن الجسم) لمدة أسبوعين. أُعطيت المجموعة الثالثة مستخلص مائي لنبات العلندا (1 جم/كجم/وزن الجسم) عن طريق الفم لمدة أسبوعين، أُعطيت المجموعة الرابعة (المجموعة المركبة)، بنزوات الصوديوم والمستخلص المائي لنبات العلندا لمدة أسبوعين. أظهرت نتائج الدراسة الحالية أن بنزوات الصوديوم أحدثت مناطق نخرية شديدة في الأنسجة وتشوهات في بنية القلب. كما أظهرت الفحوصات النسيجية تغيرات ضارة في أنسجة القلب. ولوحظ حدوث فجوات وتضخم في الألياف العضلية وفقدان لتخطيط عضلات القلب. وكان هناك دليل على التليف وتوسع وعائي كبير ونوى عضلية متضخمة واحتقان في الأوعية الدموية. بالإضافة إلى ذلك، لوحظ ارتشاح بالخلايا الالتهابية وتنكس زجاجي ونزيف في قلب الفئران المعالجة ببنزوات الصوديوم. بالإضافة إلى التليف والتوزيع غير المتساوي لنوى الخلايا العضلية في أنسجة القلب، أظهرت مجموعة العلندا تلفاً شديداً وتمزقاً في ألياف عضلة القلب والأوعية الدموية كان بعضها متوسع أخرى مسدودة. بالإضافة إلى ذلك، لوحظ تغلظ في الأنوية، وفجوات، ونخر، ووذمة في بعض الخلايا، ونزف، وتنكس زجاجي. في المجموعة المُركبة ظهرت تشوهات في أنسجة القلب، وتضخم في الألياف العضلية، وتوسع في الأوعية الدموية في عضلة القلب، وانتفاخ في ألياف العضلات. كما وجدت العديد من الألياف النخرية الموضعية مرتبطة بتغلظ في الأنوية، تنكس زجاجي، وتمزق في ألياف العضلات مع فقدان مظهر الخطوط العرضية. وأظهرت نتائج الدراسة أن العلندا وبنزوات الصوديوم بحد ذاتهما سامان للقلب. علاوة على ذلك، وُجد أن العلندا لا تُساعد في عكس السمية القلبية التي تُسببها بنزوات الصوديوم عند تناولهما معاً.

الكلمات المفتاحية: بنزوات الصوديوم، العلندا، التغيرات النسيجية المرضية للقلب.

Introduction:

In today's abundant and nourishing food supply, food additives are essential. They enable our expanding population to eat a wide range of nutritious and delectable foods all year round (Amin *et al*., 2010).

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Studies on food additives that include biochemical, physiological, genotoxic, and embryological aspects (Türkoğlu, 2007; Chen *et al*., 2009). Cats' liver, kidneys, and lungs had degenerative alterations as a result of diets containing 630 mg/kg b. w. sodium benzoate (Bedford and Clarke, 1972). Additionally, the liver, heart, kidneys, spleen, and brain experienced congestion and hyperemia due to sodium benzoate (Dewangan, 2009). Additionally, compared to control, sodium benzoate therapy markedly changed the cytoarchitecture of testicular tissue and sperm quality (Kehinde *et al*., 2018). Khan *et al*. (2020) demonstrated that 700 mg/kg b. w. of sodium benzoate caused significant histological damage to the hepatic tissue. Ephedra are xerophytic plants that typically grow wild in arid and semiarid regions, primarily in North Africa, Asia, America, and Europe's desert regions. Perennial, evergreen, and dioecious sub-shrubs, shrubs, or climbers make up the ephedra group (Zhang *et al*., 2018). Both ischemic and hemorrhagic stroke, cardiac arrhythmias such as ventricular tachycardia, coronary vasospasm, acute myocardial infarction, tachycardia-induced cardiomyopathy, and sudden death are linked to the risk of cardiovascular events when using ephedra (Samenuk *et al*., 2002; Foxford *et al*., 2003). Patients with coronary thrombosis, diabetes, glaucoma, heart illness, hypertension, thyroid disorders, impaired cerebrum circulation, phaeochromocytoma, or prostate hyperplasia should not take ephedra (Goodman, 1996). Nyska *et al*. (2005) found that the left and right ventricular walls, as well as the interventricular septum, changed primarily. The subendocardial myocardium of the left ventricle and the interventricular septum experienced massive interstitial bleeding accompanied by myofiber degeneration. Ephedra can result in a variety of cardiovascular toxicities, such as myocarditis, arrhythmias, myocardial infarction, cardiac arrest, and sudden death, according to Naik and Freudenberger (2004). Additionally, Dunnick *et al*. (2007) shown that within 2-4 hours of treatment with ma huang (ephedra)/caffeine or ephedrine/caffeine, cardiotoxicity included bleeding, necrosis, and degeneration in the ventricles or interventricular septum. The purpose of the current study was to ascertain if *Ephedra alata* could protect rats' hearts against cardiac histopathology caused by sodium benzoate.

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Materials and Methods:

Animals:

Throughout the current investigation, twenty male albino rats weighing between 195 and 300 g were employed. They were acquired from the Zoology Department's animal home at the University of Omar Al-Mukhtar's Science Faculty. The mice 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 adequate rate 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.

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.

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 (Tawfek *et al*., 2015).

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. (Jahromi et al., 2016).

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

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mg/kg/b. w. of sodium benzoate every day. ***E. alata* treated group (G3):** Rats in this group received an oral daily dose of 1g/kg b. w. of E. alata for two weeks. **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.).

Preparation of tissue samples

After the thoracic cavity was opened during the sacrifice, the heart was quickly removed, cleaned in saline to get rid of blood and other debris, and weighed to determine its relative weight. For histological analysis, heart tissue samples were stored in a 10% neutral buffered formalin solution.

Histopathological method

10% buffered neutral formalin solution was used to fix the heart specimens (Lillie, 1954). For a general histological analysis, sections were then stained using Harris's hematoxylin and eosin stain (Harris, 1900).

Results:

Control group: The histological appearance of the cardiac tissue slice control group was normal, there was no visible degeneration or necrosis in figure (1), and the cardiac fibers were organized consistently with distinct striations.

Sodium benzoate group: Rats given sodium benzoate (100 mg/kg) for two weeks showed a significant amount of muscle fiber damage, as seen in figure (2), with obvious vacuolation and necrosis. There were fibrosis areas, cellular infiltration, and hypertrophied nuclei in some myocytes. Furthermore, the rat heart's histological changes revealed significant arterial dilatation and blood vessel congestion. Additionally, the treated rat's myocardium showed evident signs of mononuclear cellular infiltration between the muscle fibers and the intracellular bleeding region (Figures 3). As seen in pictures (4), which reveal abnormalities in heart tissue, hyaline degeneration, and some hemorrhagic patches, the same treated specimens displayed severe cardiotoxicity.

***Ephedra alata* group:** After two weeks of the trial, some histopathological changes were seen between the hearts of rats given *E. alata* (1 g/kg) and controls. E. alata treatment of rats resulted in histological changes, including fibrosis and an uneven distribution of myocyte nuclei in the heart tissue, as well as regions of extravascular red blood cells in the myocardium (figure 5).

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Additionally, some specimens had hemorrhagic patches and dilated, clogged blood arteries. Additionally, figure (6) shows that the nuclei of some myocytes are hypertrophied. Figure (7) illustrates the severe destruction, hyaline degeneration, bleeding, necrosis, vacuolation, and pyknotic nuclei that were seen in a group that received *E. alata* treatment. Figure (8) illustrates the same group's myocardial fiber rupture, dense fibrous scar that replaces myocyte loss, vacuolation, interstitial odema, necrotic region, and severe areas of bleeding and congestion in between the heart muscle.

Combination group: Figure (9) illustrates the significant degree of heart tissue deterioration in animal specimens administered sodium benzoate (100 mg/kg b. w.) and E. alata (1 g/kg b. w.) (combination group). This includes cardiac tissue distortion, myofibril widening, and an irregular wavy appearance of myocardial fibers. Rat heart sections treated similarly to the above therapy showed increased muscle fiber fragility and swelling. In addition to the loss of transverse striations, there were several localized necrotic fibers linked to muscle fiber disarray, fragmentation, and splitting. The myocardial fibers are greatly lysed (Figure 10). Additionally, figure (11) displayed areas of deteriorated heart tissue as well as muscle fiber splitting and loss of striations. Rounding of some fibers also caused variations in their size and shape. Animals in the same group had their hearts examined, and the results showed twisted cardiac muscle fibers, enlarged myocardial blood vessels, hyaline degeneration, and pyknosis of the nucleus (figure 12).

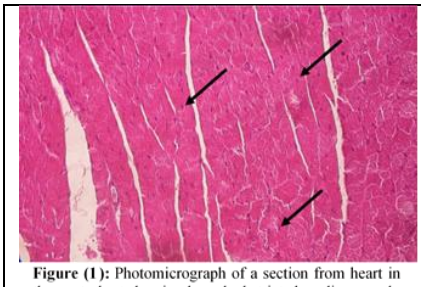

Figure (1): Photomicrograph of a section from heart in the control rat showing branched striated cardiac muscle fibers with acidophilic cytoplasm and central, vesicular and oval nuclei (Arrows) (H & E, X 400).

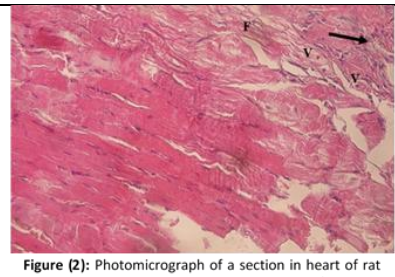

Figure (2): Photomicrograph of a section in heart of rat treated daily with sodium benzoate (100 mg/kg) for 2 weeks showing clear vacuolation (V) and necrosis. Nuclei of some myocytes are hypertrophied, cellular infiltration (Arrow) and fibrosis area (F) (H & E, X 400).

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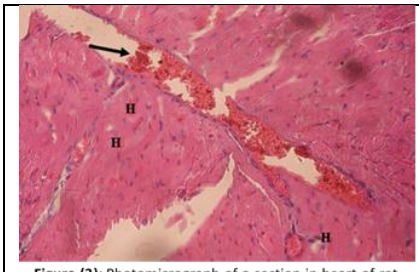

Figure (3): Photomicrograph of a section in heart of rat treated daily with sodium benzoate (100 mg/kg) for 2 weeks showing marked vascular dilation and congestion, cellular infiltration and area of hemorrhage (H) (H & E, X 400).

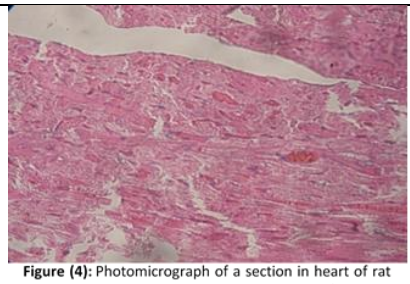

Figure (4): Photomicrograph of a section in heart of rat treated daily with sodium benzoate (100 mg/kg) for 2 weeks showing hyaline degeneration, and some hemorrhagic spots (H & E, X 400).

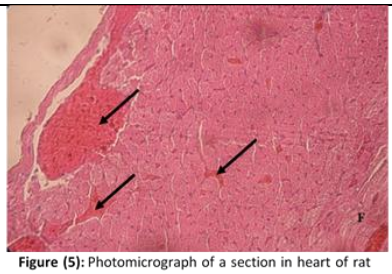

Figure (5): Photomicrograph of a section in heart of rat treated daily with *Ephedra alata* (1 g/kg) for 2 weeks showing large areas of extravascular red blood cells in the myocardium (Arrows), fibrosis (F) and irregular distribution of nuclei of myocytes of cardiac tissue (H & E, X 400).

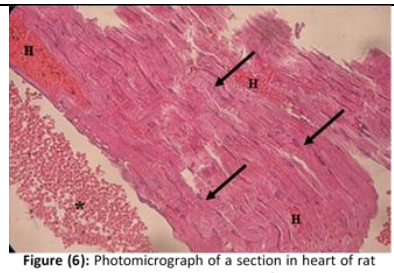

Figure (6): Photomicrograph of a section in heart of rat treated daily with *Ephedra alata* (1 g/kg) for 2 weeks showing dilated congested blood vessels (*) and some hemorrhagic spots (H). Notice nuclei of some myocytes are hypertrophied (Arrows) (H & E, X 400).

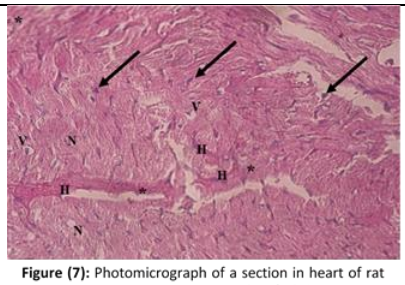

Figure (7): Photomicrograph of a section in heart of rat treated daily with *Ephedra alata* (1 g/kg) for 2 weeks showing hyaline degeneration (*), hemorrhage (H), necrosis (N), vacuolation (V) and pyknotic nuclei (arrows) (H & E, X 400).

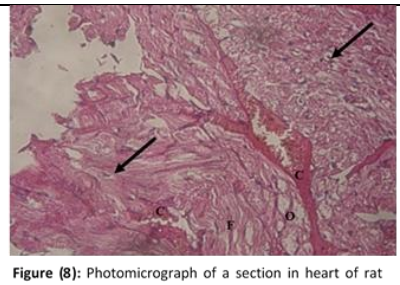

Figure (8): Photomicrograph of a section in heart of rat treated daily with *Ephedra alata* (1 g/kg) for 2 weeks showing rupture of myocardial fiber, fibrosis (F), vacuolation (Arrows), interstitial odema (O) and necrotic area as well as severe areas of hemorrhage and congestion (C) in between the cardiac muscle (H & E, X 400).

Figure (9): Photomicrograph of a section in heart of rat from combination group after 2 weeks showing distortion of cardiac tissue and widening of myofibrils (H & E, X 100).

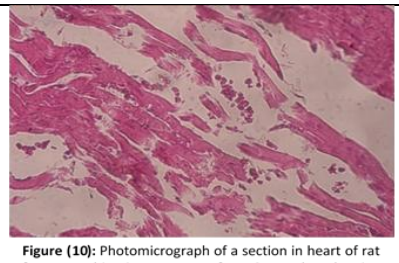

Figure (10): Photomicrograph of a section in heart of rat from combination group after 2 weeks showing disorganization and fragmentation, splitting of muscle fibers with loss of transverse striations. There is great lysis of the cells (H & E, X 400).

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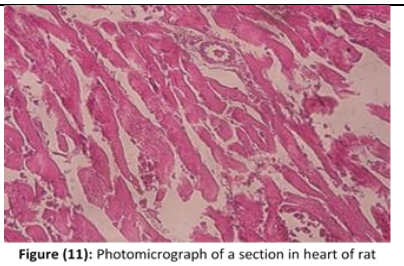

Figure (11): Photomicrograph of a section in heart of rat from combination group after 2 weeks showing splitting and loss of striations of muscle fibers. Variation in fiber size and shape with rounding of some fibers (H & E, X 400).

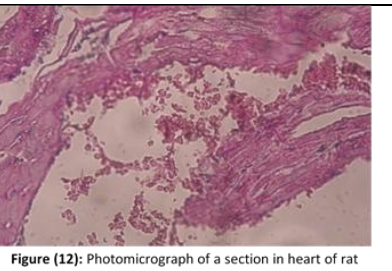

Figure (12): Photomicrograph of a section in heart of rat from combination group after 2 weeks showing distorted cardiac muscle fibers, dilation of the myocardial blood vessels, hyaline degeneration and pyknotic nuclei (H & E, X 400).

Discussion:

In the current investigation, the histological analysis of heart tissues treated with sodium benzoate at a dose of 100 mg/kg showed severe regions of necrotic tissue and twisted cardiac muscle fibers. Vacuolation, myofibril enlargement, and striation loss were noted. There was evidence of fibrosis, significant vascular dilatation, hypertrophied myocyte nuclei, and blood vessel congestion. Also seen in the treated rat's myocardium were cellular infiltration, hyaline degeneration, and bleeding. Dewangan's (2009) findings, which showed that sodium benzoate induced congestion and hyperaemia in the liver, heart, kidneys, spleen, and brain, corroborated these conclusions. Oxidative stress may be the cause of the damaged and deformed heart muscle fibers seen in this investigation. These findings concur with those of El-Habit et al. (2000) and Helen and Khaled (2001), who suggested that a rise in lipid peroxidation and a fall in antioxidant enzyme activity could cause histological damage and cellular membrane damage. According to our findings, the cardiac tissue had fibrosis. This finding supports the findings of Graham-Brown et al. (2017) and Disertori et al. (2017), who claimed that replacement fibrosis develops during cardiac injury, such as myocardial infarction, in which cardiac cells are harmed. Here, dead cells are replaced, and the scar is primarily composed of collagen type I. A reactive alteration that might be connected to the inhibitory effect on the vascular smooth muscles that caused relaxation and ensuing vasodilatation could be the vascular dilatation, blood vessel congestion with hemorrhage, and necrotic tissue in the cardiac tissue seen in this investigation. Melamed *et al*. (2003) provide support for this finding, stating that vasodilatation and greater vascular permeability should result in blood fluid loss. Therefore, the vessels were filled with blood cells, which caused the blood flow to slow

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down. This would cause the heart tissues to degenerate and necrotize. Additionally, the current study observed cellular deterioration followed by necrosis, particularly following two weeks of sodium benzoate delivery. Mice were reported to exhibit similar alternations (EL-Shamy *et al*., 1999). Furthermore, the bleeding may be caused by the drug's toxic effects that break the arterial wall, and it may be dose-dependent and dependent on how long the drug is administered (Agarwal *et al*., 2016). According to the current study, oxidative stress brought on by the generation of free radicals may be the cause of the cardiotoxicity that sodium benzoate causes. Furthermore, we were unable to locate any prior research that assessed sodium benzoate's impact on histological alterations in the heart. Administering *E. alata* alone at a dose of 1 g/kg b. w. in the current investigation resulted in severe damage, myocardial fiber rupture, dilated and congested blood vessels, along with fibrosis and uneven distribution of myocyte nuclei in cardiac tissue. Additionally, noted were pyknotic nuclei, vacuolation, necrosis, interstitial odema, bleeding, and hyaline degeneration. According to Nyska *et al*. (2005), these results are consistent with the observation of large interstitial hemorrhage, myofiber degeneration, and foci of cardiac degeneration and necrosis that had previously been infiltrated by mixed inflammatory cells. Similarly, with a single dose of 25 or 50 mg ephedrine/kg combined with 15 or 30 mg caffeine/kg, Dunnick *et al*. (2007) observed considerable cardiotoxicity and morbidity. It's interesting to note that purified ephedrine given in a comparable combined dosage was proven to be less harmful than ephedrine administered as Ephedra. 25 mg/kg of ephedrine was the lowest dose of ephedra alone that might result in clinical toxicity and moribund sacrifice. Furthermore, they discovered that bleeding, necrosis, and degeneration were cardiotoxic lesions caused by ephedra and ephedrine cardiotoxicity. Lesions can cause severe clinical symptoms, including mortality, and have a major impact on heart function. Whether myocardial ischemia, hyperthermia, or other clinical toxicity is the cause of these treatment-related cardiac abnormalities is unknown (Howden *et al*., 2005). Animals exhibiting clinical indications of toxicity followed by moribund sacrifice were more likely to have treatment-related cardiac lesions than rats treated with ephedrine/Ma Huang who survived to terminal sacrifice (4 hours after treatment). This implies a close relationship between cardiac degeneration and necrosis and clinical symptoms of lethargy (Dunnick *et al*., 2007).

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Han *et al*. (2018) found that E. herba exhibits comparatively high toxicity when compared to other herbal remedies in a study involving rats given up to 1000 mg/kg of Ephedra extract including ephedrine and pseudoephedrine. However, ephedrine-containing food supplements can pose serious health hazards, which is why many nations have banned all over-the-counter medications that include ephedrine (Sellami et al., 2018). Myofibril enlargement, myocardial blood vessel dilatation, muscle fiber enlargement, and cardiac tissue deformation were all noticeable in the combo group. There were several localized necrotic fibers, pyknosis, hyaline degeneration, fragmentation, and muscle fiber splitting with loss of transverse striations. However, Azarnia and Ghasemi (2013) found that the application of E. pachyclada extract considerably reduced the inflammation and necrosis in the liver tissue. Additionally, the animal that received carbon tetrachloride had a higher survival rate. Alqasoumi *et al*. (2008) also noted that *E. foliate* treated with CCl4 showed remarkable improvement in the elimination of necrosis and fatty buildup. It only displayed slight portal inflammation, suggesting that the hepatocytes had recovered well. Furthermore, when Djahra *et al*. (2019) investigated the effects of *E. alata* on rats exposed to deltamethrin, the results revealed reforms in some tissue sections, indicating the efficacy of the diluted extract in comparison to boiling, and its complete absence in the liver tissue treated with the powder. By the end of the trial, research revealed that *E. alata* extract (1g/kg) b. w. by itself produced cardiotoxicity and that it was ineffective in reversing sodium benzoate-induced cardiotoxicity when taken with it. Because it was not curative and had negative effects. No discernible protective effects of *E. alata* caused heart damage, most likely as a result of the combination of sodium benzoate and ephedra, and produced a hazardous chemical whose mechanism was unclear because we could not locate a review of the literature on *E. alata* and sodium benzoate. The use of ethanolic or water extracts of E. *alata*, as well as the kind, origin, and composition of *E. alata*, may be the reason for the differences between the current study and earlier research. Additionally, the dose given and the animal's breed and species. Additionally, among the variables influencing the stated difference may be the administration route and duration.

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Conclusion:

In summary, the findings of this investigation support the cardiotoxic impact of sodium benzoate, and cardiac histopathology analyses revealed that sodium benzoate altered cardiac tissue. This study then shown that *E. alata* extract by itself caused cardiotoxicity at the conclusion of the trial period, and that ephedra administered with sodium benzoate was ineffective in reversing the effects of sodium benzoate-induced cardiotoxicity. Since we were unable to locate a literature review on E. alata and sodium benzoate, the mechanism causing the harmful compound's outcomes is unknown.

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