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Histopathological Evaluation of Aspartame-Induced Cardiotoxicity and the Protective Role of Libyan Sidr Honey in Albino Rats

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Abstract

Aspartame (ASP) is one of the most commonly used artificial sweeteners worldwide. Although it is generally regarded as safe when consumed within recommended limits, growing evidence suggests that prolonged exposure may contribute to oxidative stress and tissue damage. The present study was designed to investigate the potential cardiotoxic effects of ASP, as well as the protective role of Libyan Sidr honey (SH), in female albino rats through histopathological assessment. A total of twenty-five adult female albino rats were randomly divided into five groups (n = 5 per group): a control group, an SH-treated group (100 mg/kg/day), an ASP-treated group (75 mg/kg/day), a protective group (SH administered for two weeks followed by ASP for four weeks), and a combination group receiving both SH and ASP simultaneously for four weeks. All treatments were administered orally. Histopathological examination, supported by semi-quantitative scoring (– = absent, + = mild, ++ = moderate, +++ = severe), revealed that ASP exposure induced marked myocardial damage. These alterations included disruption of cardiac muscle fibers, pronounced vascular congestion (+++), inflammatory cell penetration (++), hemorrhage (+++), and areas of focal necrosis. In contrast, rats treated with SH alone maintained normal cardiac tissue architecture. The protective group demonstrated partial improvement, with moderate levels of vascular congestion (++) and hemorrhage (++). Notably, the combination group showed the most significant preservation of myocardial structure, with only mild changes observed across all evaluated parameters (+). Overall, these findings suggest that concurrent administration of Libyan SH can effectively attenuate ASP-induced cardiotoxicity. This highlights its potential as a natural cardioprotective agent. However, further investigations incorporating biochemical and molecular analyses are needed to better understand the mechanisms underlying these protective effects.

Keywords: Aspartame; Sidr honey; Cardiotoxicity; Histopathology; Albino rats.

التقييم النسيجي المرضي لسمية القلب الناجمة عن الأسبارتام والدور الوقائي لعسل السدر الليبي في الجرذان البيضاء

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ملخص

يُعد الأسبارتام من أكثر المُحلّيات الصناعية استخدامًا على مستوى العالم. وعلى الرغم من اعتباره آمنًا ضمن الحدود الموصى بها، إلا أن التعرض المزمن له قد يرتبط بحدوث إجهاد تأكسدي وتلف في الأنسجة. هدفت هذه الدراسة إلى تقييم التأثيرات السمية القلبية للأسبارتام، بالإضافة إلى دراسة الدور الوقائي لعسل السدر الليبي في إناث الجرذان البيضاء، وذلك بالاعتماد على الفحص النسيجي الوصفي. تم استخدام خمسة وعشرين جرذًا أبيض بالغًا من الإناث، قُسمت عشوائيًا إلى خمس مجموعات (5 حيوانات لكل مجموعة): مجموعة ضابطة، مجموعة معالجة بعسل السدر (100 ملغم/كغم/يوم)، مجموعة معالجة بالأسبارتام (75 ملغم/كغم/يوم)، مجموعة وقائية (عسل السدر لمدة أسبوعين تلاه الأسبارتام لمدة أربعة أسابيع)، ومجموعة مشتركة (إعطاء عسل السدر والأسبارتام معًا لمدة أربعة أسابيع). تم إعطاء جميع المعالجات عن طريق الفم. أظهرت نتائج الفحص النسيجي، باستخدام نظام تقييم شبه كمي (– = غياب، + = خفيف، ++ = متوسط، +++ = شديد)، أن الأسبارتام تسبب في تغيرات واضحة في عضلة القلب، تمثلت في اضطراب ترتيب الألياف العضلية، واحتقان وعائي شديد (+++)، وارتشاح خلايا التهابية (++)، ونزيف (+++)، بالإضافة إلى نخر بؤري. في المقابل، حافظت مجموعة عسل السدر على البنية الطبيعية لأنسجة القلب. أما المجموعة الوقائية فقد أظهرت تحسنًا جزئيًا، حيث انخفضت شدة الاحتقان والنزيف إلى مستوى متوسط (++). في حين أظهرت المجموعة المشتركة أفضل تحسن، إذ اقتصر ظهور التغيرات المرضية على درجات خفيفة (+) في جميع المؤشرات المدروسة. تشير هذه النتائج إلى أن إعطاء عسل السدر الليبي بالتزامن مع الأسبارتام يمكن أن يخفف بشكل ملحوظ من السمية القلبية الناتجة عنه، مما يدعم دوره كمادة طبيعية ذات تأثير وقائي محتمل. ومع ذلك، توصي الدراسة بإجراء مزيد من الأبحاث التي تتضمن مؤشرات بيوكيميائية وجزيئية لفهم الآليات الكامنة وراء هذه التأثيرات بشكل أعمق.

لكلمات المفتاحية: الأسبارتام؛ عسل السدر ؛ سمية القلب؛ علم الأمراض النسيجية؛ الجرذان البيضاء.

Introduction

Artificial sweeteners have become increasingly popular as substitutes for sugar, particularly among individuals seeking to reduce caloric intake and maintain metabolic health [1, 2]. Among these, aspartame (ASP) remains one of the most widely consumed, largely due to its high sweetening potency and minimal caloric contribution [1, 3]. As a result, it is commonly used in a variety of products, including beverages, pharmaceutical formulations, and diet-related foods [4]. Although regulatory authorities have approved ASP within established acceptable daily intake limits [5], concerns about its safety have increased, particularly regarding long-term consumption [1, 6]. Once ingested, ASP is hydrolyzed into phenylalanine, aspartic acid, and methanol. Methanol is then further metabolized into formaldehyde and formic acid, both of which have been linked to the production of reactive oxygen species (ROS) and subsequent cellular damage [7]. An excess of ROS can disrupt normal cellular function, contributing to lipid peroxidation, protein oxidation, and mitochondrial impairment [1, 8].

The heart is especially vulnerable to oxidative stress (OS), given its high metabolic demands and continuous contractile activity [9, 10]. Evidence from experimental studies indicates that prolonged exposure to ASP can lead to both structural and functional alterations in cardiac tissue. Reported changes include deterioration of myocardial fibers, vascular congestion, infiltration of inflammatory cells, and areas of necrosis [6, 11, 12]. Collectively, these observations point to OS as a key factor in the development of ASP-induced cardiotoxicity. At the same time, there has been growing interest in natural products rich in antioxidants as potential protective agents against chemically induced tissue damage [13, 14]. In this regard, medicinal plants have attracted particular attention as complementary or alternative therapeutic options, owing to their wide availability, long-standing use in traditional medicine, and their richness in diverse bioactive compounds [15].

Among these natural products, honey stands out as a complex biological substance rich in flavonoids, phenolic acids, enzymes, vitamins, and minerals, all of which contribute to its antioxidant and anti-inflammatory properties [16, 17]. In particular, Libyan Sidr honey (SH), derived from *Ziziphus spina-christi*, has been reported to possess a higher phenolic content and greater antioxidant capacity compared to other regional honey types [18–20]. Although a growing body of evidence has addressed the toxic effects of ASP and the protective potential of natural antioxidants, relatively few studies have specifically examined the cardioprotective effects of Libyan SH against ASP-induced cardiac injury, particularly using histopathological approaches. Therefore, the present study was designed to investigate the histopathological effects of ASP on cardiac tissue and to assess the potential protective role of Libyan SH in an experimental rat model.

Hypothesis: We hypothesize that chronic exposure to aspartame induces cardiotoxicity through OS and lipid peroxidation, and that Libyan SH protects cardiac tissue by enhancing endogenous antioxidant defenses and activating the Nrf2-mediated cytoprotective pathway.

Null Hypothesis (H0): Administration of Libyan SH does not affect aspartame-induced histopathological changes in cardiac tissue of albino rats.

Materials and Methods

Chemicals

- ASP was obtained from Sigma-Aldrich Corporation (St. Louis, MO, USA). Before each administration, it was freshly dissolved in distilled water to ensure stability and accurate dosing.
- Libyan SH was supplied by the Natural Food and Honey Production Company in Benghazi, Libya. Before use, the honey was freshly diluted with distilled water to obtain the required concentration. It was then stored in dark, airtight containers at room temperature to preserve its bioactive constituents until administration.

Experimental Animals

Twenty-five healthy adult female albino rats, weighing 100–200 g, were used in this study. The animals were obtained from the Department of Zoology's animal house at the University of Derna, Libya. They were housed under standard laboratory conditions in well-ventilated cages and maintained on a 12-hour light/dark cycle, with stable environmental conditions throughout the experimental period. Before the start of the experiment, the rats were allowed a ten-day acclimatization period to ensure physiological adaptation and reduce stress-related variability. Throughout the study, the animals had free access to water and were provided with a standard laboratory diet containing 21.27% protein, 2.83% fat, and 2.46% fiber. All experimental procedures were carried out in accordance with institutional ethical guidelines for the care and use of laboratory animals.

Female albino rats were selected to maintain a consistent baseline in cardiac morphology and to reduce variability associated with sex-related physiological differences. Although the estrous cycle was not specifically monitored, previous research suggests that cardiac histology in female rats does not show marked variation across the cycle, supporting their suitability for this experimental design [21].

Experimental Design

Animals were randomly divided into five groups (n = 5 each):

- **Group I (Control):** Received distilled water orally for four weeks.
- **Group II (SH):** Received Libyan SH (100 mg/kg body weight/day) orally for four weeks [20].
- **Group III (ASP):** Received ASP (75 mg/kg body weight/day) orally for four weeks [2, 8].
- **Group IV (Protective):** Received SH (100 mg/kg/day) for two weeks, followed by ASP (75 mg/kg/day) for four weeks.
- **Group V (Combination):** Received SH (100 mg/kg/day) concurrently with ASP (75 mg/kg/day) for four weeks.

All treatments were administered orally once daily using a stainless-steel gastric gavage tube. The administered volume was adjusted to each animal's body weight to ensure accurate and consistent dosing.

Histopathological Examination

At the end of the experimental period, the rats were humanely sacrificed under appropriate anesthesia. The hearts were carefully excised, rinsed with saline solution, and fixed in 10% neutral buffered formalin. After routine tissue processing, the samples were embedded in paraffin, sectioned at 5 µm thickness, and stained with hematoxylin and eosin (H&E). The prepared slides were then examined under a light microscope using standard histopathological methods [22]. For each animal, three tissue sections were evaluated, and at least ten randomly selected fields per section were analyzed [23]. Histopathological changes were assessed using a semi-quantitative scoring system classified as absent (–), mild (+), moderate (++), or severe (+++) [24, 25]. Given the descriptive nature of the study and the reliance on semi-quantitative histological evaluation, formal statistical analysis was not performed. Instead, comparisons were based on consistent patterns observed across multiple sections and fields, allowing an overall assessment of the relative severity of myocardial alterations.

Theoretical Experimental Design Diagram

A schematic diagram illustrating the experimental groups, treatments, and timeline is included as Figure 1, providing a visual overview of the study design.

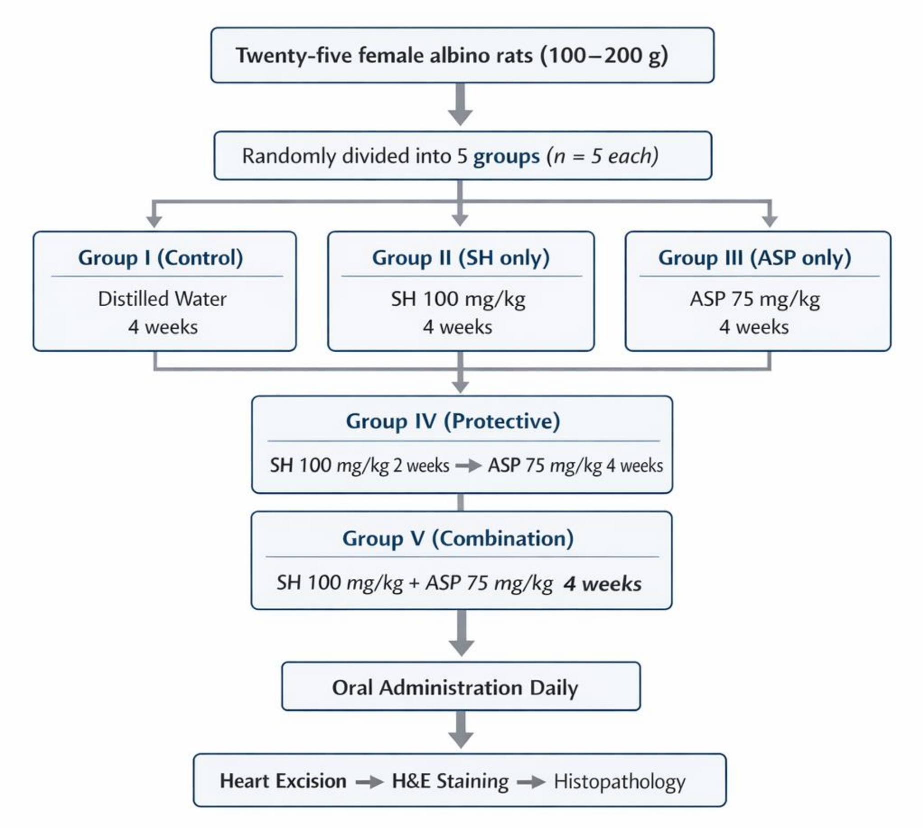

Fig 1. Experimental design for evaluating ASP-induced cardiotoxicity and the protective role of Libyan SH in albino rats.

Results

Histopathological Findings

Microscopic examination of cardiac tissue sections from the control group showed normal myocardial architecture. The cardiac muscle fibers were well organized and branched, with centrally located oval nuclei. The interstitial connective tissue was minimal, and only a few fibroblasts were observed between myocardial fibers, with no signs of deterioration, inflammation, or vascular congestion (Fig. 2). Similarly, sections from the SH-treated group exhibited histological features comparable to those of the control group. The myocardial fibers remained regularly arranged with clearly defined central nuclei, and the interstitial spaces were minimal, indicating preservation of normal cardiac structure (Fig. 3). In contrast, the ASP-treated group showed pronounced histopathological alterations. These included severe vascular dilation and congestion, fragmentation of the sarcoplasm, and degenerative changes in myocardial fibers (Figs. 4 and 5). Inflammatory cell penetration was also evident between myocardial fibers, along with disruption of the normal tissue organization (Fig. 6). In addition, irregular arrangement of cardiac fibers and extensive hemorrhagic areas were observed (Fig. 7), reflecting marked myocardial injury following ASP exposure.

Histological examination of the protective group (SH pre-treatment followed by ASP exposure) revealed partial restoration of myocardial structure compared with the ASP group. Although the myocardial fibers appeared relatively more organized, several pathological features were still present, including vascular congestion, dilated blood vessels, and sarcoplasmic fragmentation (Figs. 8 and 9). Mild inflammatory infiltration and hemorrhagic lesions were also observed, though less severe than in the ASP group (Fig. 10). Some blood vessels showed thickened walls with limited areas of necrosis, suggesting incomplete structural recovery (Fig. 11).

In the combination group (simultaneous administration of SH and ASP), the cardiac tissue demonstrated marked improvement compared with the ASP group. The myocardial fibers were more regularly arranged and closely resembled the normal architecture seen in the control group (Figs. 12 and 13). Inflammatory cell penetration was minimal, while hemorrhage and vascular congestion were notably reduced relative to both the ASP and protective groups. Although mild vascular dilation persisted in certain areas, the overall myocardial structure appeared largely preserved (Fig. 14).

Overall, ASP exposure induced severe structural damage in cardiac tissue, whereas SH administration alleviated these effects. Notably, concurrent administration of SH with ASP provided greater protection and better preservation of myocardial architecture compared with SH pre-treatment alone.

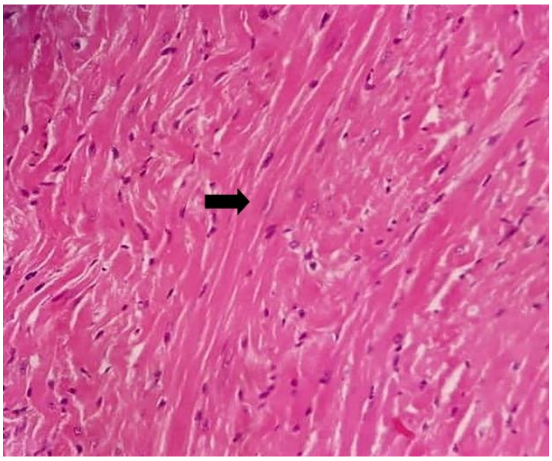

Fig. 2: The cardiac tissue from the control group demonstrates preserved myocardial architecture. Cardiac myofibers are well-organized and branched, with centrally located oval nuclei (arrow). Minimal interstitial connective tissue and sparse fibroblasts are observed

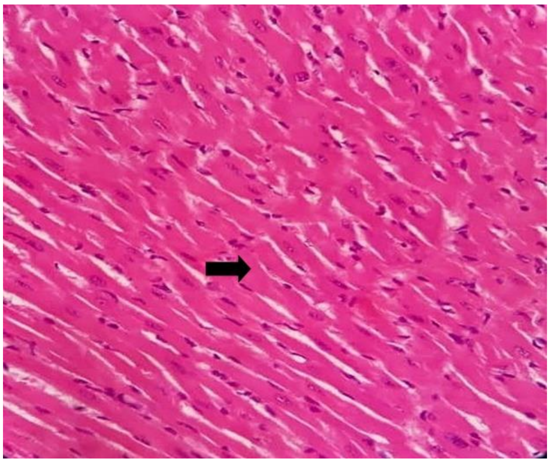

Fig. 3: The cardiac tissue from the SH group demonstrates preserved myocardial architecture. Cardiac myofibers are well-organized and branched, with centrally located oval nuclei (arrow). Minimal interstitial connective tissue and sparse

between the myocardial fibers. (H&E, ×400).

fibroblasts are observed between the myocardial fibers. (H&E, ×400).

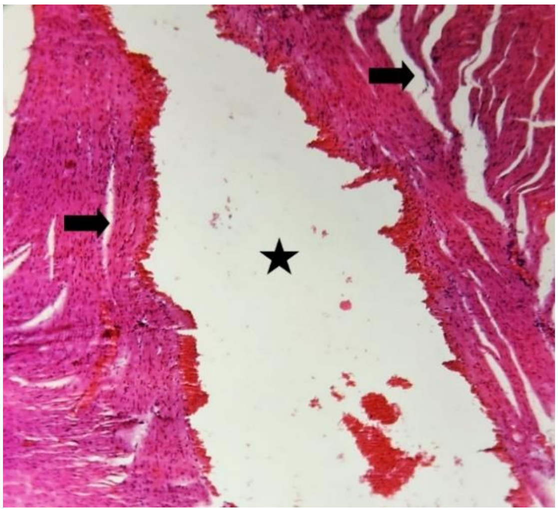

Fig. 4: The cardiac tissue from the ASP group showed severely dilated blood vessels (star), and fragmentation of sarcoplasm and deteriorating changes (H&E, ×100).

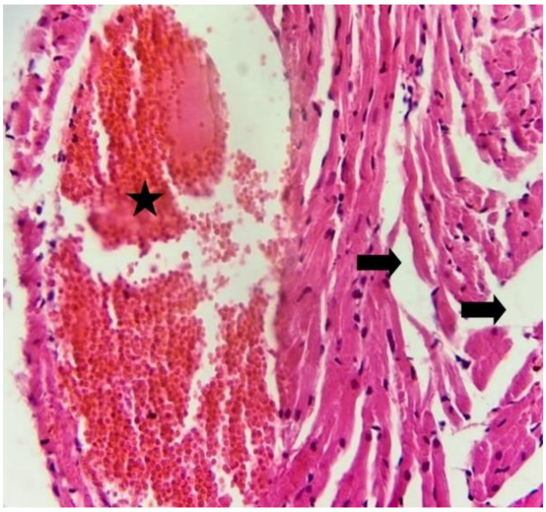

Fig. 5: The cardiac tissue from the ASP group showed severe congestion and dilated blood vessels (star), with fragmented sarcoplasm and deteriorating changes (thick arrows). (H&E, ×400).

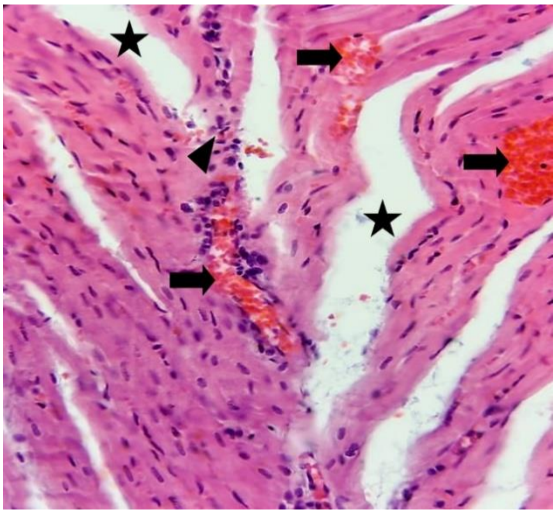

Fig. 6: The cardiac tissue from the ASP group showed congested blood vessels (arrows), fragmented sarcoplasm and degenerative

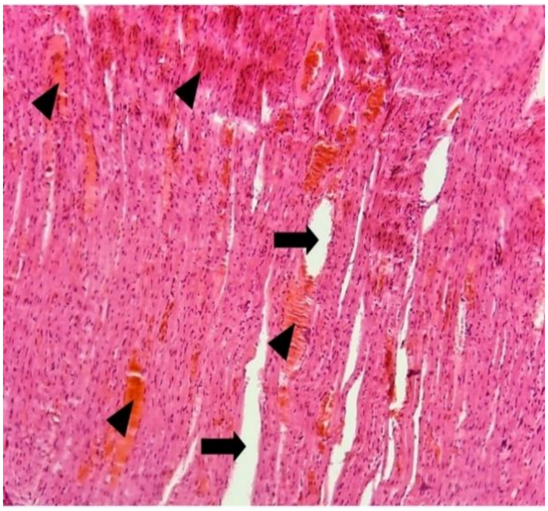

Fig. 7: The cardiac tissue from the ASP group showed irregular arrangement of cardiac fibers

changes (star), and infiltration of inflammatory cells (arrowhead). (H&E, ×400).

(arrows) and severe hemorrhagic lesions (arrowhead). (H&E, ×100).

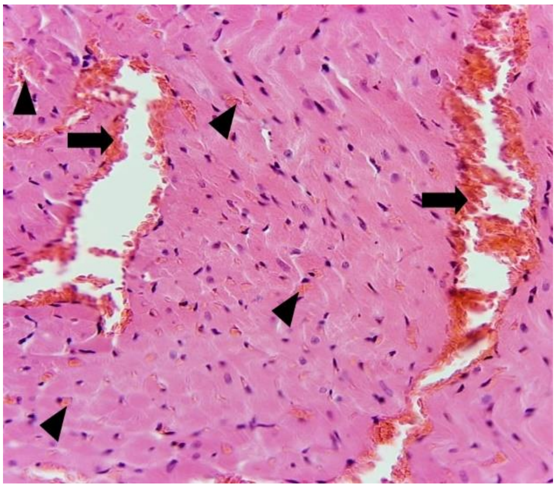

Fig. 8: The cardiac tissue from the protective group showed significant improvement in cardiac fibers, with congestion and dilated blood vessels (arrows), and hemorrhagic lesions (arrowheads). (H&E, ×400).

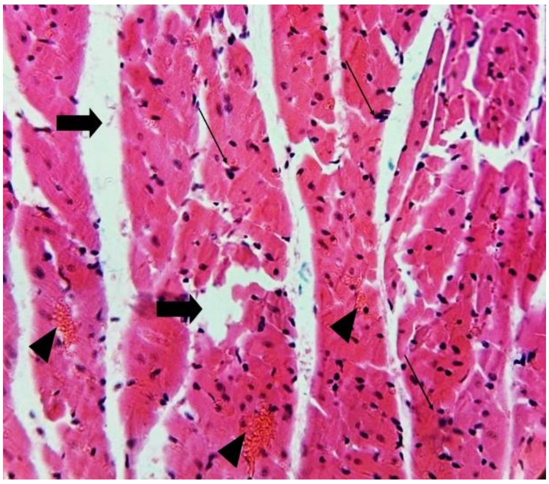

Fig. 9: The cardiac tissue from the protective group showed fragmentation of the sarcoplasm and degenerative changes (thick arrows), hemorrhagic lesions (arrowheads), and an irregular arrangement of cardiac fibers (thin arrows). (H&E, ×400).

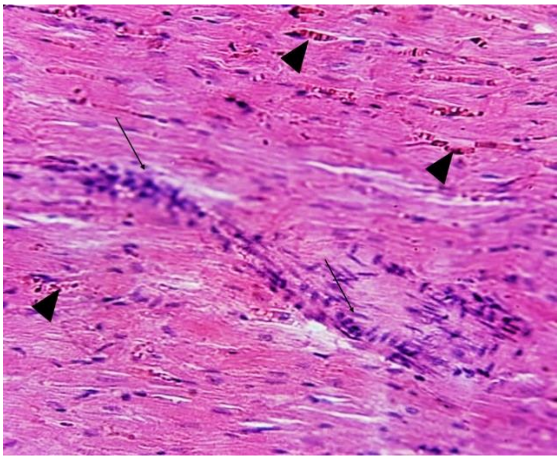

Fig. 10: The cardiac tissue from the protective group showed significant

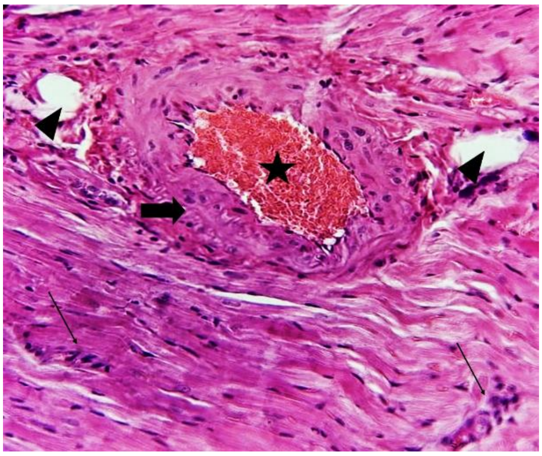

Fig. 11: The cardiac tissue from the protective group showed significant

improvement in cardiac fibers with inflammatory cells (thin arrows), and hemorrhagic lesions (arrowheads). (H&E, ×400).

improvement in cardiac fibers with blood vessel congestion (star), surrounded by a significantly thicker wall (thick arrow), inflammatory cells (thin arrows), and little necrosis (arrowheads). (H&E, ×400).

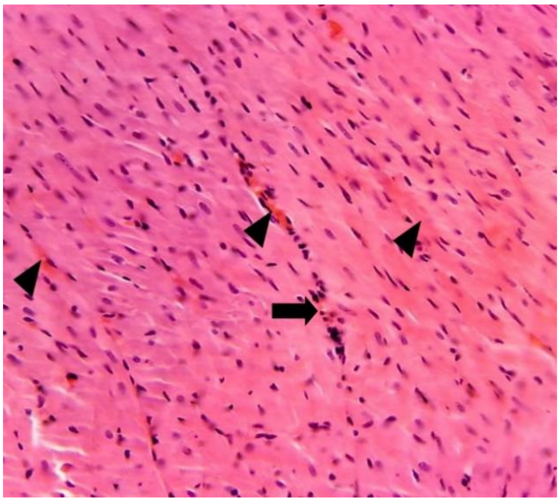

Fig. 12: The cardiac tissue from the combination group showed significant improvement in cardiac fibers with some inflammatory cells (arrows), and hemorrhagic lesions (arrowheads). (H&E, ×400).

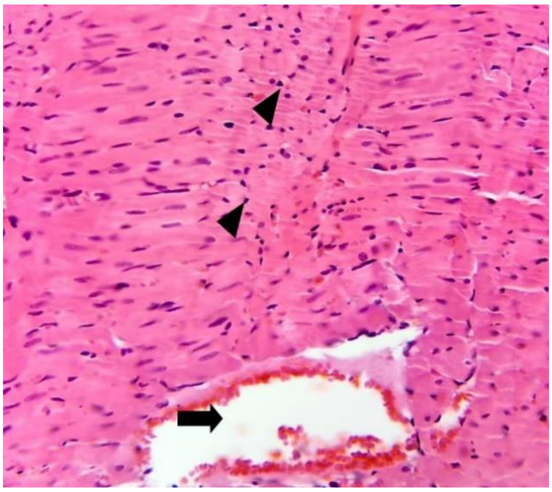

Fig. 13: The cardiac tissue from the combination group showed significant improvement in cardiac fibers with some inflammatory cells (arrowheads), and dilated blood vessels (arrow). (H&E, ×400).

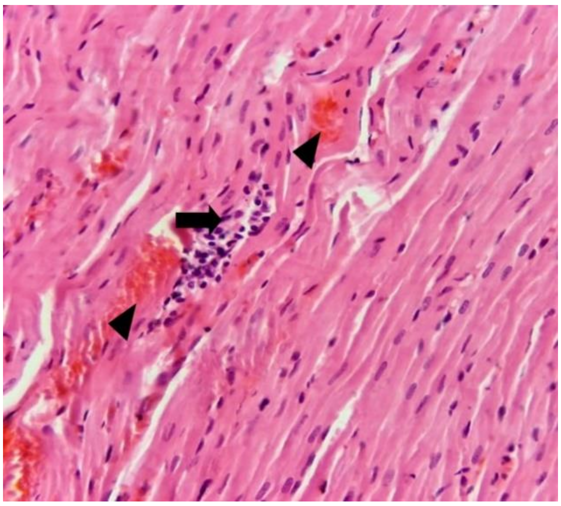

Fig. 14: The cardiac tissue from the combination group showed significant improvement in cardiac fibers with some inflammatory cells (arrow), and hemorrhagic lesions (arrowhead). (H&E, ×400).

Semi-Quantitative Histopathological Scoring

The semi-quantitative evaluation of cardiac lesions is presented in Table 1 and Figure 15. Both the control and SH groups showed normal myocardial architecture, with no detectable histopathological alterations. In contrast, the ASP group exhibited severe structural damage characterized by pronounced vascular congestion, extensive sarcoplasmic degeneration, marked inflammatory cell penetration, and widespread hemorrhagic lesions.

The Protective group demonstrated partial improvement compared with the ASP group. Lesion severity was reduced, with less vascular congestion, milder deterioration of myocardial fibers, and decreased hemorrhagic areas. Although inflammatory cell penetration was still present, it was notably less intense, suggesting partial recovery of cardiac structure.

Notably, the Combination group showed a marked improvement in myocardial histology, with cardiac fibers appearing more regularly organized and closely resembling normal architecture. Vascular congestion was mild, sarcoplasmic damage was minimal, and inflammatory penetration was greatly reduced. Overall, lesion scores in the Combination group were considerably lower than those in the Protective group, indicating a stronger cardioprotective effect of concurrent SH administration.

Table 1. Semi-quantitative histopathological lesion scoring of cardiac tissue in experimental groups.

Group	Vascular congestion	Sarcoplasmic deterioration	Inflammatory penetration	Hemorrhage
Control	–	–	–	–
SH	–	–	–	–
ASP	+++	+++	++	+++
Protective	++	++	+	++
Combination	+	+	+	+

Scoring: – = absent, + = mild, ++ = moderate, +++ = severe.

Note: Statistical analysis was not applied due to the descriptive nature of the study.

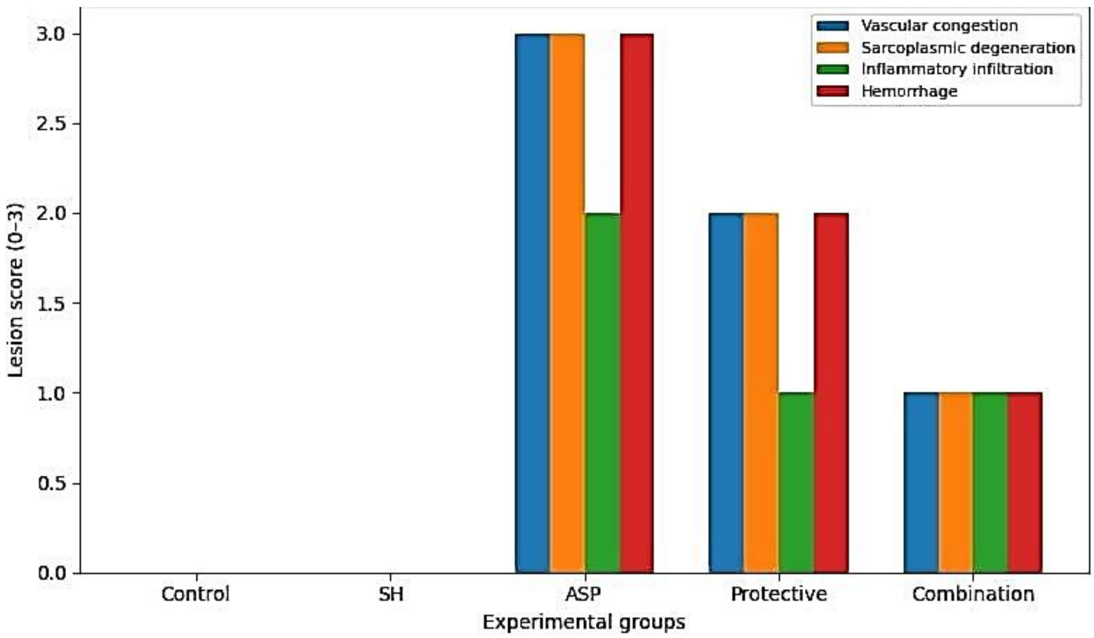

Fig. 15: Semi–quantitative scoring of cardiac tissue lesions in experimental groups.

Discussion

In the present study, ASP administration induced marked histopathological alterations in cardiac tissue, including disorganization of myocardial fibers, vascular congestion, inflammatory cell penetration, and focal necrotic changes. These findings indicate significant myocardial injury following ASP exposure and agree with previous experimental reports [6, 11, 12].

The observed cardiac damage may be related to the metabolic degradation of ASP into methanol and its subsequent conversion into formaldehyde and formic acid, both of which are implicated in OS generation. Excessive ROS production can trigger lipid peroxidation, protein modification, and mitochondrial dysfunction, ultimately disrupting cellular integrity [1, 7]. Given the high metabolic activity of cardiac tissue, such oxidative imbalance can have pronounced effects on myocardial structure and function [9, 26].

In contrast, administration of Libyan SH alone preserved normal myocardial architecture, suggesting its safety and potential protective properties. Both the protective (pre-treatment) and combination (concurrent administration) groups demonstrated varying degrees of histological improvement compared with the ASP group. Notably, the combination group showed greater preservation of myocardial structure, indicating that continuous exposure to SH during ASP treatment may provide enhanced protection.

The cardioprotective effects observed in this study may be largely attributed to the antioxidant properties of honey. Honey contains several bioactive constituents, particularly flavonoids and phenolic compounds, which are known for their free radical scavenging activity and ability to enhance endogenous antioxidant defenses [19, 20, 27]. These components likely contribute to the reduction of oxidative injury, attenuation of inflammatory responses, and preservation of cellular integrity in cardiac tissue. The superior effect observed in the combination group may be explained by sustained antioxidant availability, which potentially reduces cumulative OS more effectively than pre-treatment alone, thereby maintaining myocardial architecture and limiting inflammatory infiltration [11, 17]. Although the exact molecular mechanisms were not directly examined in this study, previous evidence suggests that natural antioxidants can modulate OS pathways and improve tissue resistance to toxic insults [2, 17]. Accordingly, it is reasonable to suggest that the cardioprotective effects of SH are mediated through the reduction of OS and stabilization of cellular structures.

Certain limitations should also be acknowledged. The histopathological evaluation was semi-quantitative and not supported by formal statistical analysis, which may limit precise group comparisons. In addition, the absence of biochemical and molecular assessments restricts deeper insight into the mechanisms underlying the observed tissue changes.

Despite these limitations, the consistent histopathological patterns observed across multiple sections and fields strengthen the reliability of the findings. Future studies should incorporate biochemical markers of OS, such as malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH), in addition to molecular indicators of apoptosis, to better clarify the protective mechanisms involved.

Conclusion

Chronic ASP exposure induces significant histopathological damage in the cardiac tissue of female albino rats, characterized by vascular congestion, deterioration of myocardial fibers, inflammatory penetration, and hemorrhagic changes. Libyan SH demonstrated notable cardioprotective effects, with both pre-treatment and concurrent administration reducing myocardial injury. However, concurrent administration provided superior protection, suggesting that continuous antioxidant support is more effective in preserving cardiac structure during toxic exposure. These findings support the potential role of antioxidant-rich natural products, such as Libyan SH, in mitigating chemically induced cardiac injury.

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