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Protective Effect of *Boswellia Serrata* Resin Extract Against Acetaminophen-Induced Subclinical Hepatic Injury in Rats

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A B S T R A C T

The analgesic and antipyretic effect of acetaminophen has made it one of the most widely used drugs in the world; however, acetaminophen overdose causes significant hepatic injury and compromises renal function. This study aimed to evaluate the protective effect of Boswellia serrata resin extract against acetaminophen-induced injury in rats. This was assessed by measuring biochemical and oxidative stress markers, as well as histopathological changes across all groups to provide both direct and indirect evidence of the protective effect of Boswellia serrata against hepatotoxicity and nephrotoxicity caused by acetaminophen. Acetaminophen administration increased serum ALT, AST, ALP, bilirubin, creatinine, and urea levels, elevated malondialdehyde, and reduced levels of glutathione, superoxide dismutase, and catalase levels in liver and kidney tissues. Histopathological examination showed that acetaminophen induced centrilobular hepatic injury and renal tubular injury. Treatment with Boswellia serrata attenuated these biochemical, oxidative, and histopathological alterations in a dose-dependent manner, with the higher dose providing greater protection. These findings indicate that Boswellia serrata resin extract exerts hepatoprotective and reno-protective effects against acetaminophen-induced injury, likely through antioxidant and anti-inflammatory mechanisms.

Keywords: *Boswellia serrata, acetaminophen, hepatotoxicity, nephrotoxicity, oxidative stress.*

التأثير الوقائي لمستخلص راتنج نبات البوسويليا سيراتا ضد إصابة الكبد تحت السريرية الناجمة عن الأسيتامينوفين في الجرذان

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الملخص

إن التأثير المسكن للألم والخافض للحرارة لدواء الأسيتامينوفين جعله واحدًا من أكثر الأدوية استخدامًا على مستوى العالم؛ إلا أن الجرعة الزائدة منه تُسبب أذية كبدية ملحوظة وتؤثر سلبًا في وظائف الكلى. هدفت هذه الدراسة إلى تقييم التأثير الوقائي لمستخلص راتنج Boswellia serrata ضد الأضرار الناجمة عن الأسيتامينوفين في الجرذان. وقد تم ذلك من خلال قياس المؤشرات الكيميائية الحيوية ومؤشرات الإجهاد التأكسدي، بالإضافة إلى التغيرات النسيجية المرضية في جميع المجموعات، لتقديم أدلة مباشرة وغير مباشرة على فعالية Boswellia serrata كعامل وقائي ضد السمية الكبدية والكلوية الناتجة عن الأسيتامينوفين. أدى إعطاء الأسيتامينوفين إلى زيادة مستويات ALT و ASTو ALP والبيليروبين والكرياتينين واليوريا في المصل، كما رفع مستويات المالونداليدهيد، وخفّض مستويات الغلوتاثيون، وإنزيم سوبر أوكسيد ديسميوتاز، والكاتالاز في أنسجة الكبد والكلى. وأظهر الفحص النسيجي المرضي أن الأسيتامينوفين تسبب في أذية كبدية مركزية الفصيص وأذية في النبيبات الكلوية. وقد أدى العلاج بـ Boswellia serrata إلى تقليل هذه التغيرات الكيميائية الحيوية والتأكسدية والبنيوية بشكل يعتمد على الجرعة، حيث وفرت الجرعة الأعلى حماية أكبر. وتشير هذه النتائج إلى أن مستخلص راتنج Boswellia serrata يمتلك تأثيرات واقية للكبد والكلى ضد الأذية الناتجة عن الأسيتامينوفين، ويرجح أن ذلك يتم عبر آليات مضادة للأكسدة ومضادة للالتهاب.

الكلمات المفتاحية: *الأسيتامينوفين، السمية الكبدية، السمية الكلوية، الإجهاد التأكسدي، بوسويليا سيراتا*

1. Introduction

Acetaminophen (paracetamol; APAP) is among the most commonly used analgesic and antipyretic drugs worldwide because of its efficacy, availability, and relative safety at therapeutic doses. However, APAP overdose remains one of the leading causes of drug-induced liver injury and acute liver failure [1]-[7]. APAP-induced hepatotoxicity begins when a fraction of the administered dose is bioactivated by cytochrome P450 enzymes to form the reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). Under physiological conditions, NAPQI is detoxified by conjugation with reduced glutathione (GSH). Following toxic exposure, however, hepatic GSH stores become depleted, permitting covalent binding of NAPQI to cellular proteins, particularly mitochondrial proteins. This process triggers mitochondrial oxidative stress, activation of c-Jun N-terminal kinase, ATP depletion, nuclear DNA fragmentation, and ultimately regulates necrotic death of hepatocytes [8]-[15].

Although the liver is the primary target organ of APAP toxicity, the kidney is also vulnerable to injury. APAP-associated nephrotoxicity has been linked to local metabolic activation, oxidative stress, depletion of antioxidant defenses, and direct injury to tubular epithelial cells, particularly within the proximal tubule [16]-[19]. Clinical reports and experimental studies have shown that renal dysfunction may accompany hepatic injury in APAP intoxication and that the renal lesions are consistent with toxic acute tubular injury rather than being solely secondary to hepatic failure [16],[17],[20]. Accordingly, evaluating both organs provides a more comprehensive understanding of APAP-induced systemic toxicity.

A major common feature of APAP-induced hepatic and renal injury is oxidative stress. Increased lipid peroxidation, reflected by elevated malondialdehyde (MDA), together with depletion of GSH and impairment of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), has been consistently documented in experimental model of APAP toxicity [4],[5],[9]-[15],[21],[22]. These biochemical changes are reflected histologically by hepatocellular degeneration, vascular congestion, inflammatory cells infiltration, and necrotic foci in the liver, as well as tubular epithelial swelling, vacuolar degeneration, cast formation, and focal necrosis in the kidney [5],[16]-[22].

Natural products with antioxidant and anti-inflammatory properties have therefore attracted considerable attention as potential protective agents against APAP-induced organ injury. Among these, *Boswellia serrata* is of particular interest. The resin contains bioactive pentacyclic triterpenes known as boswellic acids, which have been associated with inhibition of 5-lipoxygenase and modulation of several inflammatory and redox-sensitive pathways [23]-[29]. Beyond their anti-inflammatory activity, Boswellia serrata and boswellic acid-rich preparations have shown antioxidant, cytoprotective, and organ-protective effects in several experimental models [24]-[29].

Previous studies have shown that Boswellia serrata gum resin can ameliorate toxic liver injury, improve serum aminotransferase levels, reduce oxidative stress, and attenuate histopathological damage [32]. Boswellia-based treatments have also demonstrated nephroprotective and hepatorenal protective effects in kidney-centred injury models through repression of inflammatory mediators and restoration of redox balance [33],[34]. However, direct evaluation of Boswellia serrata resin extract in APAP-induced subclinical hepatorenal injury remains limited. Accordingly, this study was designed to investigate the protective effect of Boswellia serrata resin extract against APAP-induced subclinical hepatic and renal injury in rats through biochemical, oxidative stress, and histopathological assessment.

2. Material and methods

2.1. Animals

Male albino rats weighing 180-220 g were selected to minimize hormonal variability and to facilitate comparison with established rodent models of acetaminophen toxicity. The animals were housed under standard laboratory conditions (22 ± 2°C, 50-60% relative humidity, 12 h light/12 h dark cycle) with free access to food and water. All rats were acclimatized to the laboratory environment for at least 7 days before the experiments began. All experimental procedures were performed in accordance with approved animal care protocols and institutional ethical guidelines.

2.2. Chemicals

Acetaminophen was obtained from Pioneer Pharmaceutical Company (Sulaymaniyah, Iraq) and Boswellia serrata resin was obtained either as authenticated resin or as a standardized commercial

Table 1. Serum liver function biomarkers

Group	ALT (U/L)	AST (U/L)	ALP (U/L)	Total bilirubin (mg/dL)
Control	41.8 ± 4.6	86.4 ± 7.9	112.5 ± 10.8	0.46 ± 0.05
Boswellia only	40.2 ± 4.1	84.9 ± 8.3	109.7 ± 9.6	0.45 ± 0.04
APAP	109.6 ± 12.4*	168.3 ± 15.8*	181.9 ± 16.7*	0.96 ± 0.09*
APAP + Boswellia low dose	73.4 ± 8.2#	128.6 ± 12.7#	146.2 ± 13.8#	0.68 ± 0.07#
APAP + Boswellia high dose	54.9 ± 6.1#	101.8 ± 9.4#	124.6 ± 11.5#	0.53 ± 0.06#

* Significantly different from **Control** ($p < 0.05$), # significantly different from **APAP** ($p < 0.05$)

Table 2. Serum kidney function biomarkers

Group	Creatinine (mg/dL)	Urea (mg/dL)
Control	0.58 ± 0.06	31.7 ± 3.1
Boswellia only	0.57 ± 0.05	30.9 ± 2.8
APAP	1.19 ± 0.11*	59.8 ± 5.7*
APAP + Boswellia low dose	0.87 ± 0.08#	43.5 ± 4.2#
APAP + Boswellia high dose	0.66 ± 0.07#	35.9 ± 3.6#

* Significantly different from **Control** ($p < 0.05$), # significantly different from **APAP** ($p < 0.05$)

extract from Aladdin Scientific (Meridian, USA).

2.3. Experimental design

The rats were randomly allocated into five groups: group I, normal control; group II, Boswellia serrata control; group III, acetaminophen (APAP) only group; group IV, APAP + low-dose *Boswellia serrata*; and group V, APAP + high-dose *Boswellia serrata*. *Boswellia serrata* was administered orally, whereas acetaminophen (APAP) was given at a hepatotoxic/nephrotoxic dose selected based on established rodent models [5],[8],[21],[22]. Twenty-four hours after acetaminophen exposure, the animals were sacrificed, and blood, liver, and kidney samples were collected for analysis.

2.4. Biochemical Testing

ALT, AST, ALP, and total bilirubin levels were evaluated in serum using Biochemical assay kits obtained from Active Bio Lab. MDA, GSH, SOD, and CAT levels were evaluated in liver and kidney tissues using assay kits commercially sourced from Beijing Solarbio Science & Technology Co., Ltd. (China) and used according to manufacturers' protocols.

2.5. Histopathologic Evaluation

Samples from both the liver and kidneys were fixed in formalin (10 per cent), routinely processed, and embedded in paraffin wax, followed by sectioning and staining with haematoxylin. The samples from both the liver and kidney were evaluated microscopically for evidence of cellular damage and changes. A semi-quantitative scoring system was utilized to facilitate intergroup comparisons regarding the severity of lesions [21],[22],[32]-[34].

2.6. Statistical Analysis

Data were expressed as mean ± standard deviation (Mean ± SD). Comparisons among groups for biochemical and oxidative stress variables were performed using one-way analysis of variance (One-way ANOVA) followed by Tukey's post hoc test.

3. Results

3.1 Serum biochemical findings

3.1.1. Liver function biomarkers

One-way ANOVA showed a significant treatment effect on serum ALT, AST, ALP, and total bilirubin ($p < 0.05$ for all variables). Post hoc analysis demonstrated that the APAP group had significantly higher values than the control group ($p < 0.05$). Both Boswellia serrata-treated groups showed significant reductions in these liver injury markers relative to the APAP group ($p < 0.05$), whereas the Boswellia serrata-only group did not differ significantly from the control group ($p > 0.05$). The high-dose Boswellia serrata group showed a stronger corrective effect than the low-dose group, particularly for ALT, AST, and ALP, as shown in Table 1.

3.1.2. Kidney function biomarkers

One-way ANOVA demonstrated a significant treatment effect on serum creatinine and urea ($p < 0.05$). Compared with the control group, APAP administration significantly increased both renal function markers ($p < 0.05$). Low-dose and high-dose Boswellia serrata significantly reduced creatinine and urea relative to the APAP group ($p < 0.05$), while the Boswellia serrata-only group remained statistically comparable to the control

Table 3. Hepatic oxidative stress markers

Group	MDA (nmol/mg protein)	GSH (µmol/g tissue)	SOD (U/mg protein)	CAT (U/mg protein)
Control	2.38 ± 0.22	7.84 ± 0.63	12.6 ± 1.1	53.7 ± 4.8
Boswellia only	2.29 ± 0.20	8.01 ± 0.59	12.9 ± 1.0	55.1 ± 4.5
APAP	5.91 ± 0.48*	4.12 ± 0.39*	7.04 ± 0.66*	31.8 ± 3.2*
APAP + Boswellia low dose	4.08 ± 0.34#	5.88 ± 0.47#	9.63 ± 0.84#	41.9 ± 3.9#
APAP + Boswellia high dose	2.96 ± 0.27#	7.01 ± 0.56#	11.4 ± 0.93#	49.2 ± 4.1#

* Significantly different from **Control** ($p < 0.05$), # significantly different from **APAP** ($p < 0.05$)

Table 4. Renal oxidative stress markers

Group	MDA (nmol/mg protein)	GSH (µmol/g tissue)	SOD (U/mg protein)	CAT (U/mg protein)
Control	2.11 ± 0.19	6.91 ± 0.54	11.7 ± 0.9	47.5 ± 4.2
Boswellia only	2.05 ± 0.17	7.03 ± 0.51	11.9 ± 0.8	48.1 ± 4.0
APAP	5.06 ± 0.43*	3.69 ± 0.32*	6.81 ± 0.61*	28.9 ± 2.8*
APAP + Boswellia low dose	3.62 ± 0.31#	5.21 ± 0.44#	8.92 ± 0.77#	37.8 ± 3.5#
APAP + Boswellia high dose	2.58 ± 0.24#	6.34 ± 0.50#	10.8 ± 0.86#	44.1 ± 3.8#

* Significantly different from **Control** ($p < 0.05$), # significantly different from **APAP** ($p < 0.05$)

Table 5. Semi-quantitative histopathological scores

Group	Liver injury score	Kidney injury score
Control	0.33 ± 0.21	0.25 ± 0.18
Boswellia only	0.29 ± 0.19	0.21 ± 0.17
APAP	2.71 ± 0.26*	2.46 ± 0.31*
APAP + Boswellia low dose	1.63 ± 0.24#	1.52 ± 0.27#
APAP + Boswellia high dose	0.79 ± 0.22#	0.67 ± 0.20#

* Significantly different from **Control** ($p < 0.05$), # significantly different from **APAP** ($p < 0.05$)

group ($p > 0.05$). The high-dose group showed greater improvement than the low-dose group and approached near-control values, as shown in Table 2.

3.2. Tissue oxidative stress finding

3.2.1. Hepatorenal oxidative stress markers

One-way ANOVA showed significant overall differences among groups in hepatic Table 3 and renal Table 4 MDA, GSH, SOD, and CAT levels ($p < 0.05$). In

both organs, APAP significantly increased MDA and significantly decreased GSH, SOD, and CAT compared with the control group ($p < 0.05$). Treatment with Boswellia serrata significantly reversed these changes relative to the APAP group ($p < 0.05$), and the high-dose regimen produced a more complete restoration of redox balance than the low-dose regimen. The Boswellia serrata-alone group showed no significant differences compared with the control group ($p > 0.05$).

3.3. Histopathological evaluation

3.3.1. Semi-quantitative injury scores

Semi-quantitative scoring demonstrated a significant overall difference among groups for both liver and kidney injury scores ($p < 0.05$). The APAP group showed significantly higher injury scores than the control group ($p < 0.05$), whereas both Boswellia serrata-treated groups showed significant reductions versus the APAP group ($p < 0.05$). The high-dose Boswellia serrata group had lower injury scores than the low-dose group, indicating a stronger histological protective effect.

3.3.2. Liver Histopathology

Histological scores Table 5 and liver sections from the control and Boswellia serrata control groups showed preserved hepatic architecture (Figure 1A, B). In contrast, the APAP group showed the greatest degree of hepatic injury, characterized by hepatocellular degeneration in the centrilobular region, cytoplasmic vacuolar degeneration, congestion of the hepatic sinusoids and central veins, inflammatory cell infiltration, and focal necrotic changes (Figure 1C). The APAP + low-dose Boswellia serrata group showed attenuation of hepatic lesions without complete resolution, with partial restoration of architecture and reduced severity of congestion and degeneration (Figure 1D). In contrast, the APAP + high-dose Boswellia serrata group showed near-normal architecture, with only mild residual changes (Figure 1E).

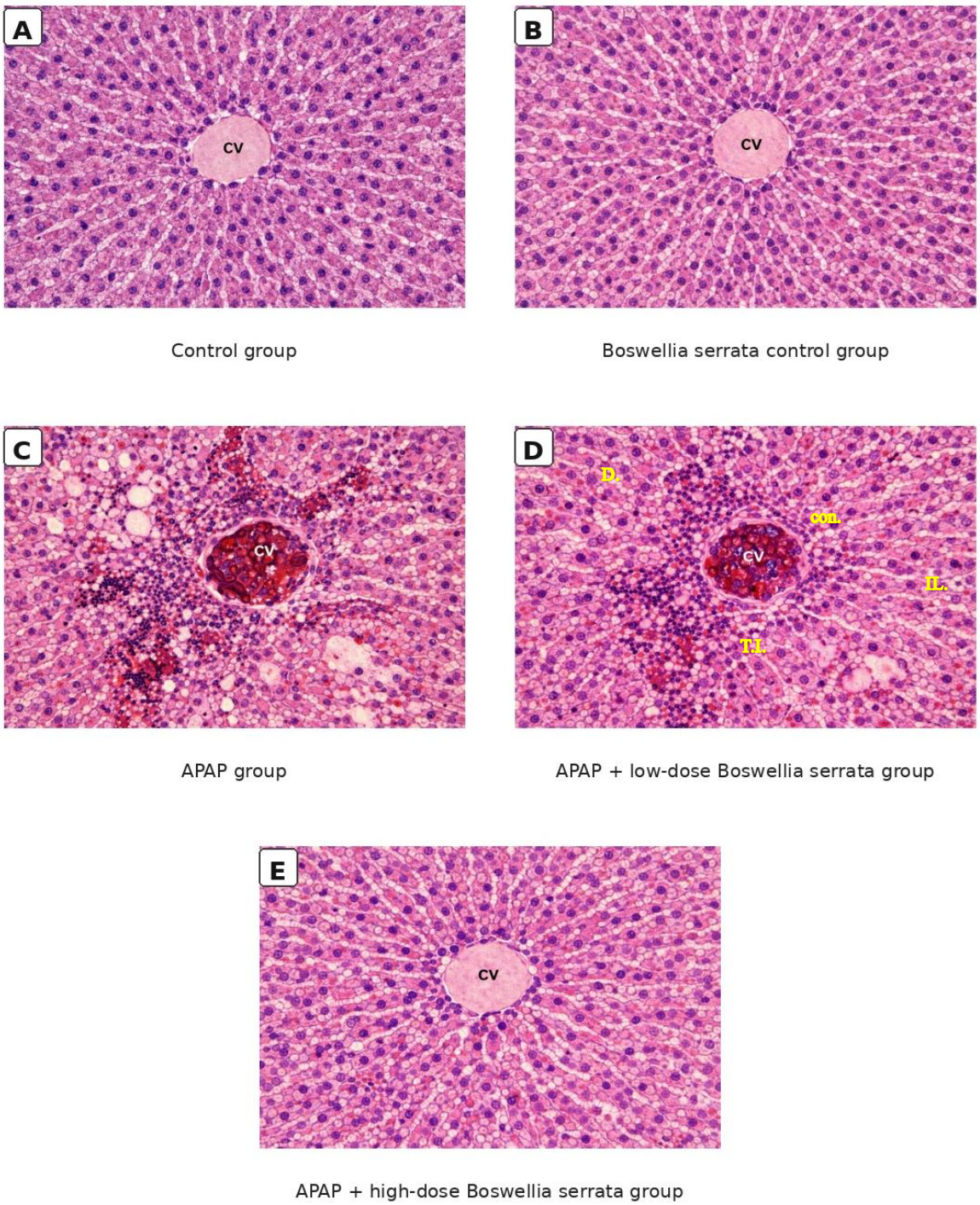

Figure 1. H&E-stained liver sections from the experimental groups. (A) Control group showing preserved hepatic architecture. (B) Boswellia serrata control group showing near-normal hepatic architecture. (C) APAP group showing marked centrilobular injury with congestion(con.), degeneration (D.), vacuolation(V), fibrosis (F) and inflammatory infiltration (IL.). (D) APAP + low-dose Boswellia serata group showing partial improvement. (E) APAP + high-dose Boswellia serrata group showing near-restoration of hepatic architecture. CV: central vein.

3.3.3. Kidney Histopathology

Histopathological scores Table 5 of Kidney sections from the control and Boswellia serrata control groups showed normal renal corpuscles, preserved Bowman's space, and intact proximal. and distal tubules (Figure 2A, B). The APAP group exhibited the most severe renal injury, characterized by tubular epithelial swelling, vacuolar degeneration, tubular dilatation, intraluminal casts, vascular congestion, and focal tubular necrosis (Figure 2C). The APAP +

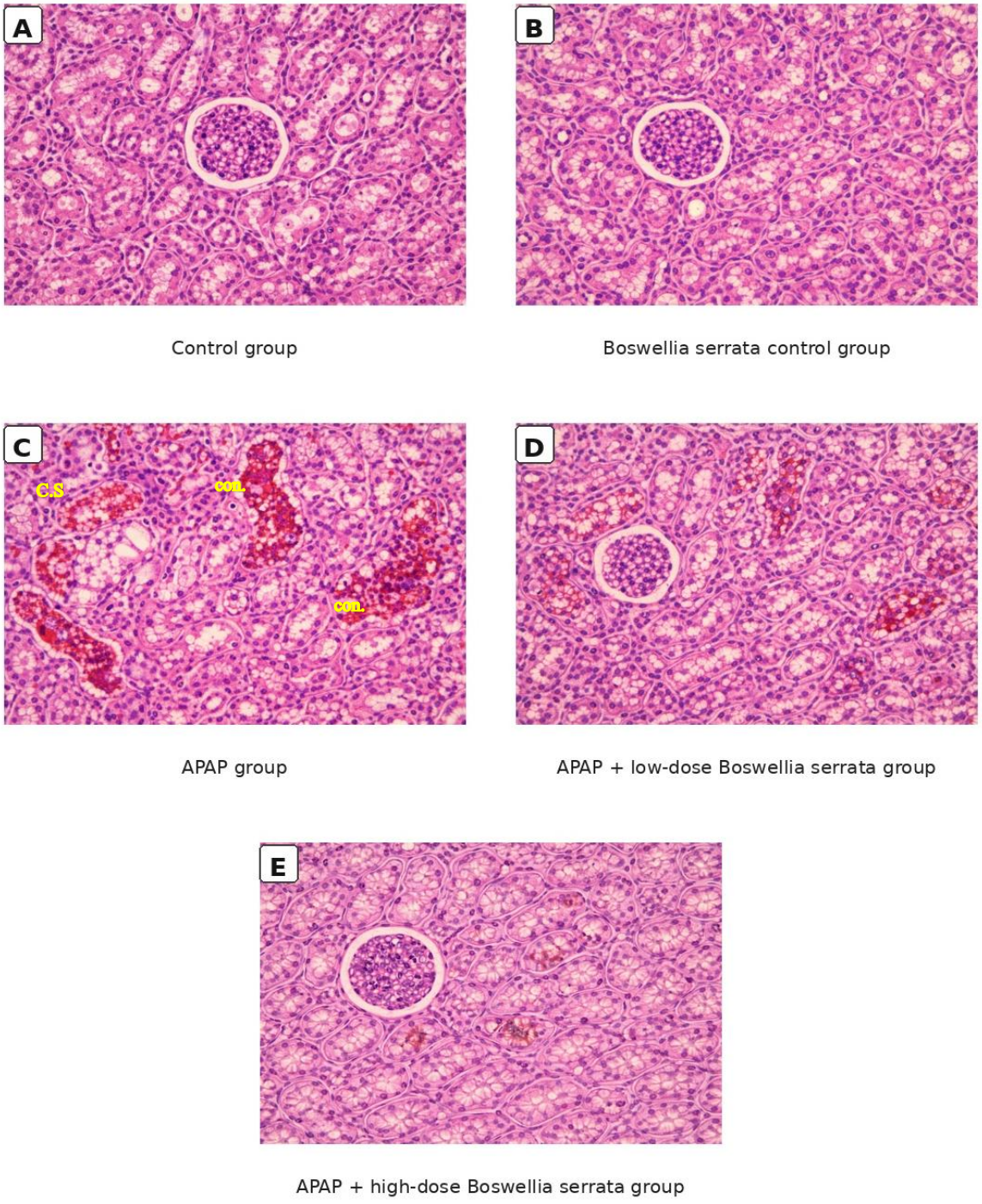

Figure 2. H&E-stained kidney sections from the experimental groups. (A) Control group showing normal glomeruli and tubules. (B) Boswellia serrata control group showing preserved renal architecture. (C) APAP group showing prominent tubular injury (T.I.), degeneration (D), inflammatory cells infeltaration (IL.) and vascular congestion (Con.). (D) APAP + low-dose Boswellia serrata group showing moderate attenuation of renal injury. (E) APAP + high-dose Boswellia serrata group showing marked preservation of renal structure.

low-dose Boswellia serrata group showed moderate improvement, with fewer degenerative tubules and less congestion (Figure 2D). In contrast, the APAP + high-dose Boswellia serrata group showed marked preservation of renal architecture and only minimal residual injury (Figure 2E).

4. Discussion

The present study showed that acetaminophen induced subclinical hepatorenal injury in rats, as evidenced by disturbed liver and kidney function markers, increased oxidative stress, depletion of

endogenous antioxidant defenses, and clear histopathological alterations in both organs. The marked protective effect of Boswellia serrata resin extract, particularly at the higher dose, indicates that the extract attenuated the biochemical and structural consequences of acetaminophen exposure. This overall pattern is consistent with the well-established toxicodynamic profile of acetaminophen and supports the interpretation that Boswellia serrata exerted a biologically meaningful organ-protective effect [1]-[5],[7]-[17],[21],[22].

The increase in serum ALT, AST, ALP, and total bilirubin in the acetaminophen group is consistent with the classical biochemical profile of hepatocellular injury. Acetaminophen hepatotoxicity begins when the metabolite NAPQI depletes glutathione and forms protein adducts, particularly within mitochondria, thereby triggering mitochondrial oxidative stress, JNK activation, bioenergetic failure, and ultimately hepatocellular necrosis [2]-[15]. Accordingly, elevated aminotransferases reflect membrane injury and leakage of intracellular enzymes, whereas increased bilirubin indicates impaired hepatic functional integrity [1],[3],[7],[13],[15]. Improvement in these parameters after Boswellia serrata treatment suggests stabilization of hepatocyte membranes and attenuation of toxic hepatic injury.

The renal function findings confirm that acetaminophen causes damage to the kidneys.

Creatinine and urea are elevated along with degeneration and necrosis of the epithelial cells in the tubules of the kidneys, and these findings are consistent with renal injury caused by acetaminophen. There are studies that demonstrate that acetaminophen can damage the tubular cells in the kidneys by causing oxidative stress, by depleting glutathione, and by directly damaging the tubular epithelial cells, all of which primarily occur in the proximal tubules of the kidneys [15]-[19].

Acetaminophen initiated an increase in MDA and a decrease in GSH, SOD, and CAT levels in both the liver and kidney tissues, indicating that there is both an increase in lipid peroxidation and a decrease in the body's natural (endogenous) processes designed to protect the body from oxidative stress. The loss of the normal balance between oxidants and antioxidants is critical to understanding how acetaminophen damages the liver and kidney (primarily through mitochondrial dysfunction) and increases oxidative injury [4],[8]-[14]. Restoration of all of these parameters by Boswellia serrata supports the hypothesis that part of the protective effect of Boswellia serrata is due to a reduction of oxidative injury and preservation of antioxidant capacity.

The structural side effects of acetaminophen (APAP) are confirmed with histopathologic findings. All APAP-associated hepatic injury findings, such as centrilobular degeneration, congestion, inflammatory cell infiltrate, and focal necrosis, are characteristic lesions observed in the liver (APAP hepatotoxicity) and also correspond to the zonal nature of cytochrome P-450-mediated bioactivation of APAP.[5],[8],[11]-[15] Likewise, the renal pathology of degenerative renal tubular epithelium, dilated renal tubules with casts, congested renal tubules, and focal necrosis corresponds to the characteristics associated with renal tubular toxicity.[16]-[22] Furthermore, the attenuation of histopathologic lesions in Boswellia serrata-treated groups further indicates that Boswellia stimulants can maintain the structural integrity in both the liver and kidneys.

The protective effect of Boswellia serrata can be interpreted in light of the known pharmacological properties of boswellic acids. These compounds are recognized as 5-lipoxygenase inhibitors and are also associated with broader anti-inflammatory and antioxidant activities [23]-[29]. In experimental models of toxic liver injury, Boswellia serrata gum resin has been shown to improve aminotransferases, bilirubin, antioxidant status, and histopathological features while reducing TNF-α, NF-κB, IL-6, TGF-β, and COX-2 [32]. In models of renal and hepatorenal injury, Boswellia-based treatment has likewise been shown to improve creatinine, urea, MDA, and GSH and to reduce inflammatory mediators, in parallel with clear histological recovery [33],[34]. These previous findings strongly support the mechanistic interpretation of the present results.

The dose-dependent pattern observed in this study further supports a genuine pharmacological effect. Compared with the low-dose group, the high-dose Boswellia serrata group showed greater normalization of serum markers, more substantial restoration of antioxidant defenses, and better preservation of tissue architecture. This pattern argues against a nonspecific effect and instead indicates that efficacy was related to adequate biological exposure. From a molecular and physiological perspective, the findings support the view that Boswellia serrata influences not only

downstream markers of injury but also upstream pathogenic mechanisms, including oxidative stress and the amplification of inflammation [25]-[29],[32]-[34].

A major strength of this investigation is its focus on subclinical injury. The mild-to-moderate model of hepatorenal injury is particularly useful because it allows assessment of protective efficacy before irreversible organ failure develops. In addition, the observed improvements in serum markers, tissue redox balance, and microscopic architecture suggest that Boswellia serrata may have greater value as a preventive intervention than as a rescue therapy for advanced toxicity.

Aside from that, mechanistic conclusions must still exercise caution due to scientific limits since findings suggest a strong association between antioxidant and anti-inflammatory mechanisms, but need additional testing to confirm these mechanisms directly, like tests that measure CYP2E1, quantify proteins, assess JNK signaling pathways, and analyze responses from Nrf2/HO-1, and cytokine profiling or immunohistochemistry [8]-[15]. Additionally, using standardized boswellic acid content in future studies would help to improve translational interpretation [25],[30],[31].

5. Conclusion

The resin extract of Boswellia serrata has shown a clear benefit to the liver and kidneys of rats subjected to an acetaminophen-induced subclinical hepatorenal injury. That benefit was manifested by improved liver and kidney biochemical parameters, decreased lipid peroxidation, increased levels of antioxidants in those tissues, and reduced histopathological changes in both the liver and kidney. These results support the potential use of Boswellia serrata as a natural hepato-protectant and nephron-protectant through antioxidant and anti-inflammatory mechanisms.

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