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Nicotinamide Riboside, an NAD precursor and supplement, reduces liver damage caused by sepsis

La nicotinamida ribósido, un precursor y suplemento de NAD, reduce el daño hepático causado por la sepsis

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ABSTRACT

Sepsis leads to liver failure and eventually death. The supplement nicotinamide riboside is an antioxidant and nicotinamide adenine dinucleotide precursor. This study aimed to evaluate the therapeutic effect effect of nicotinamide riboside on liver injury in a rat sepsis model induced by cecal ligation and perforation. 21 rats were divided into 3 groups: control, sepsis and sepsis+ nicotinamide riboside group. Cecal ligation and perforation applied to sepsis and sepsis + nicotinamide riboside groups. Nicotinamide riboside applied to sepsis + nicotinamide riboside group orally (200 mg·kg^{-1}) 1 hour (h) before and 12 h after cecal ligation and perforation. 24 h after cecal ligation and perforation, rats sacrified. Histopathological and biochemical parameters were analyzed. Nicotinamide riboside treatment resulted in a decrease in high levels of aspartate and alanine aminotransferases, creatine, and ceruloplasmin. Serum albumin, calcium, and amylase levels were decreased in sepsis group and increased in sepsis + nicotinamide riboside group (P<0.05). However, no significant differences of uric acid, sodium, magnesium and chloride levels were seen between the groups. The liver structrure that injured because of sepsis were ameliorated histologically. Superoxide dismutase levels were low in sepsis group but elevated in sepsis + nicotinamide riboside group (P<0.05). Malondialdehyde levels were high in sepsis group but elevated in sepsis + nicotinamide riboside group (P<0.05). Nicotinamide riboside mitigated liver tissue damage in septic rats. It corrected the impaired oxidant-antioxidant balance and some serum parameters. This might be evidence of the ameliorative effect of nicotinamide riboside in liver. Nonetheless, new investigations should be held in the future to understand deeply the mechanism.

Key words: Liver injury; oxidative stress; nicotinamide riboside; sepsis; liver histopathology

RESUMEN

La sepsis conduce a insuficiencia hepática y finalmente, a la muerte. El suplemento ribósido de nicotinamida es un antioxidante y precursor del dinucleótido de nicotinamida y adenina. Este estudio tuvo como objetivo evaluar el efecto el efecto terapéutico del ribósido de nicotinamida sobre la lesión hepática en un modelo de sepsis en ratas inducida por ligadura y perforación cecal. Se dividieron 21 ratas en 3 grupos: control, sepsis y sepsis + ribósido de nicotinamida. Se realizó ligadura y perforación cecal en los grupos sepsis y sepsis + ribósido de nicotinamida. Al grupo sepsis + ribósido de nicotinamida se le administró ribósido de nicotinamida por vía oral (200 mg·kg^{-1}) 1 hora (h) antes y 12 h después de la ligadura y perforación cecal. Veinticuatro horas después de la ligadura y perforación cecal, se sacrificaron las ratas. Se analizaron parámetros histopatológicos y bioquímicos. El tratamiento con ribósido de nicotinamida resultó en una disminución de los niveles elevados de aspartato aminotransferasa, alanina aminotransferasa, creatina y ceruloplasmina. Los niveles séricos de albúmina, calcio y amilasa disminuyeron en el grupo con sepsis y aumentaron en el grupo con sepsis y control (P<0,05). Sin embargo, no se observaron diferencias significativas en los niveles de ácido úrico, sodio, magnesio y cloruro entre los grupos. La estructura hepática dañada por la sepsis mejoró histológicamente. Los niveles de superóxido dismutasa fueron bajos en el grupo con sepsis, pero aumentaron significativamente en el grupo con sepsis y control (P<0,05). Los niveles de malondialdehído fueron altos en el grupo con sepsis, pero aumentaron en el grupo con sepsis y control (P<0,05). El ribósido de nicotinamida mitigó el daño tisular hepático en ratas sépticas. Corrigió el desequilibrio oxidante-antioxidante y algunos parámetros séricos. Esto podría ser evidencia del efecto beneficioso del ribósido de nicotinamida en el hígado. No obstante, se deben realizar nuevas investigaciones para comprender mejor el mecanismo.

Palabras clave: Lesión hepática; estrés oxidativo; ribósido de nicotinamida; sepsis; histopatología hepática

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INTRODUCTION

Liver, the largest gland in humans, has a central role in metabolism and immunological homeostasis. In sepsis toxins, pathogens or inflammatory mediators may cause liver injury. The injury process ranges from hepatocellular dysfunction, damage and to liver failure [1, 2].

In sepsis, firstly the bacteria and their products are caught and cleared by hepatocytes. Meanwhile, the hepatic immunocytes produce pro-inflammatory mediators that can lead to acute liver injury [2]. Sepsis-induced liver damage is a risk factor of multiple organ failure and death [3, 4].

An effective treatment of sepsis is not available, yet. Thus, prevention of liver failure is crucial in sepsis. Acute hepatic injury may directly deteriorate the disease and death in patients with sepsis, conversely the amelioration of liver injury may reduce mortality and increase survival rate .Pathophysiology of acute liver injury in sepsis involves oxidative stress, inflammation, apoptosis, and necrosis [5, 6].

Nicotinamide adenine dinucleotide (NAD^+) is involved in redox reactions that maintain mitochondrial fitness. NAD^+ is an immune modulator. It poorly diffuses across cell membrane [7, 8]. Nicotinamide riboside (NR) is one of the root substrates of NAD^+ biosynthesis. It attenuates inflammation and oxidative stres. NR is found in milk and also it is used as a supplement. If the amount of NR is high, the amount of NAD also increases [9, 10]. NAD^+ is decreased in sepsis [7].

This study aimed to eveluate the effect of NR on sepsis-induced liver injury in rats (*Rattus norvegicus*) by histopathological and biochemical methods.

MATERIALS AND METHODS

Experimental animals and experimental design

This investigation was carried out in compliance with both national and international regulations governing the use of experimental animals. The experimental protocols were evaluated and approved by the animal care and use committee (Burdur Mehmet Akif Ersoy University Local Ethics Committee, the decision number: 1382, date: 13.11.2024).

Twenty one adult female Sprague Dawley rats, weighing 200 – 250 g were used. Rats were housed under hygienic and properly controlled environmental conditions at 22–25°C ambient temperature and adjusted light (14 hours (h))/dark (12 h) rhythm. They were allowed free spontaneous motility and fed with a standard diet. The rats were divided into three groups (n = 7): Control group, Sepsis group, Sepsis + NR group

Sepsis model was established as cecum ligation perforation (CLP) determined based on the method described by an earlier study with minor modifications (2–0 silk, 20-gauge needle; 3–0 silk, 12-gauge needle) [11]. Anesthesia was induced by i.p. administration of ketamine (80 $mg \cdot kg^{-1}$; Ketalar, Pfizer, Newyork, USA) ve xylazine (10 $mg \cdot kg^{-1}$; Rompun, Bayer, Leverkusen, Germany) intraperitoneally. Then the peritoneal cavity was opened. The cecum was ligated with a 3–0 silk ligature. 2 punctures were made with a needle (12-gauge) to the area of ligation, and the cecum was put back to the peritoneal cavity. Then, the abdominal incision was closed with a sterile suture. The wound area was bathed with a 1% lidocaine solution (Sigma-Aldrich Canada Ltd., Oakville, ON, Canada) for analgesia. All rats were injected normal saline (2 $mL \cdot 100\ g^{-1}$ body weight) subcutaneously at the time of surgery and at 6 h postoperatively, for fluid support [11].

A half an hour before and 12 h after the CLP induction, NR (200 $mg \cdot kg^{-1}$) was administered orally to the sepsis + NR group. 24 h after CLP application, the rats were terminated with general anesthesia overdose (thiopental sodium, 50 $mg \cdot kg^{-1}$; Sigma Co., St Louis, MO, USA). In rats, a dose of 200 $mg \cdot kg^{-1}$ NR has been successfully used in previous studies in terms of pharmacological effects and tolerability [12]. Half of the each rat's liver specimens was stored (-80°C) for biochemical analyses and the other half was kept in 10% formalin solution for histopathological analyses.

Biochemical analysis

For biochemical analysis, liver tissue samples were stored at –80°C. The tissue samples were homogenized by adding cold 0.1 M phosphate buffer (pH: 7.4) at 1:10 ratio, for superoxide dismutase (SOD) and malondialdehyde (MDA) analysis. The homogenates were centrifuged (4000× g, 4°C, 20 min; Sigma Model 3–15, Germany) to obtain supernatants. SOD and MDA levels were measured in the supernatants taken from liver homogenates. SOD activity was determined based on the method described according to the previous study [13]. MDA activity was determined according to the method according to the previous study [13]. For these analyses YLBiont commercial ELISA kits were used (Shanghai, China) based on the sandwich enzyme-linked immunosorbent assay (ELISA) method and using an Epoch Biotek ELISA reader.

Blood samples were collected in hemogram tubes with EDTA and centrifuged (Sigma Model 3–15, Germany) at 3000 rpm for 15 min to separate the serum which was then stored at -80°C. The serum samples were thawed at room temperature to perform analyses. Serum aspartate aminotransferases (AST) and alanine aminotransferases (ALT) and albumin levels were detected using a Beckman Coulter AU5800 clinical chemistry autoanalyzer.

Histopathological examination

Livers were fixed in 10% formaldehyde (Merck KGaA, Darmstadt, Germany). After fixation, they were washed with water, subjected to dehydration by increasing concentrations of ethyl alcohol (from 50 to 100%; Sigma-Aldrich, St. Louis, USA), cleared by Xylol (PanReac AppliChem, Barcelona, Spain) and embedded in paraffin blocks. Then, they were cut by microtome. Specimens of 5 µm thickness were placed in an oven at 60°C overnight. Then, the sections were deparaffinized in xylene, rehydrated with an ethyl alcohol series (decreasing grades from 60 to 100%), stained with hematoxylin (Biopack, Buenos Aires, Argentina) and eosin (PanReac AppliChem, Spain) (H&E).

Liver injury was defined by the evaluation of capsular inflammation (scored from 0 – 3), steatosis (scored from 0 – 3), portal inflammation (scored from 0 – 4), spotty necrosis (scored from 0 – 4), and ballooning degeneration (scored from 0 – 3),

using the Hepatic Injury Severity Scoring system as described in Muftuoglu *et al.* and reported by Zhu *et al.* [14, 15].

- The degree of steatosis was graded and scored as follows: 0 = none; 1 = < 30% hepatocytes containing fat; 2 = 30%– 70% hepatocytes containing fat; 3 = > 70% hepatocytes containing fat.
- Portal inflammation was scaled as follows: 0 = none; 1 = mild, some, or all portal areas; 2 = moderate, some, or all portal areas; 3 = marked, all portal areas.
- Spotty necrosis was graded as follows: 0 = none; 1 = one focus or less per 10× objective; 2 = two to four foci per 10× objective; 3 = five to ten foci per 10× objective; 4 = more than ten foci per 10× objective.
- Ballooning degeneration was graded and scored as follows: 0 = none; 1 = ballooning degeneration in one third of hepatic lobule; 2 = ballooning degeneration in two thirds of hepatic lobule; 3 = ballooning degeneration in all parts of hepatic lobule.
- Capsular inflammation was graded and scored in each 10× area as follows: 0 = none; 1 = capsular inflammation in 1 × 10 magnification area; 2 = capsular inflammation in 2 × 10 magnification areas; 3 = capsular inflammation in 3 × 10 magnification areas.

Statistical analysis

Statistical analyzes were performed using the Statistical Package for the Social Sciences (SPSS), version 25.0. (IBM Corp., Armonk, NY, USA). For serum biochemistry data, distributions of the groups were detected with one-sample Kolmogorov-Smirnov test. The groups with normal distribution were analyzed by one-way analysis of variance (ANOVA) test and multiple comparisons were carried out with Tukey test. Groups that did not follow normal distribution were compared with Kruskal-Wallis and multiple comparisons were carried out with Mann Whitney U analysis (95% confidence interval, 5% margin of error, 50% expected prevalence). Correlations were calculated with Pearson or Spearman tests. The results are presented as mean ± SEM. The distribution type of histopathological scoring data was evaluated through the Shapiro-Wilk test. It did not have a normal distribution so they were analyzed using the independent samples Kruskal Wallis 1 – Way Anova (k samples) test, and the determination of significant differences between groups using the Dunn test. The data were presented as percentages. Statistical difference with values of $P<0.05$ considered statistically significant.

RESULTS AND DISCUSSION

This study reveals that NR ameliorates liver injury in an experimental sepsis rat model. We successfully established an acute sepsis animal model and found that sepsis rats showed liver damage. This findings indicate that SOD levels were low in sepsis and NR increase liver tissue SOD levels which are indicators of oxidative stress. Malondialdehyde concentration were high in sepsis group and it was detected to be low in sepsis + NR group. Liver histology, also, supports these findings.

In the control rat livers, hepatic cords and sinusoids are arranged orderly and the portal areas have healthy appearance. Hepatocytes have polyhedral shape with acidophilic cytoplasm. All structures were observed normal.

In sepsis group, inflammatory cell infiltration especially around the portal triad were observed. In some areas, there were apoptotic hepatocytes, while some areas had ballooning hepatocytes. Besides, there were necrotic hepatocytes results of ballooning degeneration. Also, intracellular vacuolization was seen in some hepatocytes. There was an accumulation of small fat droplets in the tissue (steatosis). In addition, sinusoidal congestion and sinusoidal dilation were available. Vessel walls exhibited degeneration.

In sepsis+NR group, inflammatory cell infiltration was observed, too. Although ballooning hepatocytes were more numerous in the sepsis group compared to the “sepsis + NR” group, the differences were not statistically significant in the analysis (P=0.687) (TABLE I). Nonetheless, other hepatocytes seemed better and apoptotic hepatocytes were decreased comparing to sepsis group. There was no vacuolization or edema. Steatosis and necrosis were very little (Hepatic Injury Severity Score was statistically significant, rspectively $P<0.002$ and $P<0.004$). Sinusoidal congestion and sinusoidal dilation were decreased. Besides, vessel wall degeneration was decreased (FIG. 1).

TABLE I
Hepatic Injury Severity Score

	Control group Median (min-max)	Sepsis group Median (min-max)	Sepsis + NR group Median (min-max)	*P***	Post hoc *P*
Capsular inflamation	0 (0–1)	3 (2–3)	2 (1–2)	< 0.001	Sepsis – control = 0.001 Sepsis + NR–Sepsis = 0.542
Steatosis	0 (0–1)	3 (2–3)	1 (1–2)	< 0.002	Sepsis – control = 0.002 Sepsis + NR–Sepsis = 0.04
Portal inflamation	1 (0–2)	3 (2–4)	3 (2–3)	< 0.004	Sepsis – control = 0.009 Sepsis + NR–Sepsis = 1
Spotty necrosis	0 (0–1)	3 (2–3)	1 (0–1)	< 0.004	Sepsis – control = 0.006 Sepsis + NR–Sepsis = 0.035
Ballooning degeneration	0 (0–1)	2 (1–3)	3 (3–3)	< 0.004	Sepsis – control = 0.45 Sepsis + NR–control = 0.001 Sepsis – Sepsis + NR = 0.687

The increased scores of sepsis group is observed to reflect the progressive severity of capsular inflammation, steatosis, portal inflamation, spotty necrosis and ballooning degeneration. The decreased scores of sepsis + NR group reflect reduction of the liver injury caused by sepsis. Ordinal measures were expressed as median and quartiles. *P***: Significance level $P<0.05$ by Kruskal-Wallis test

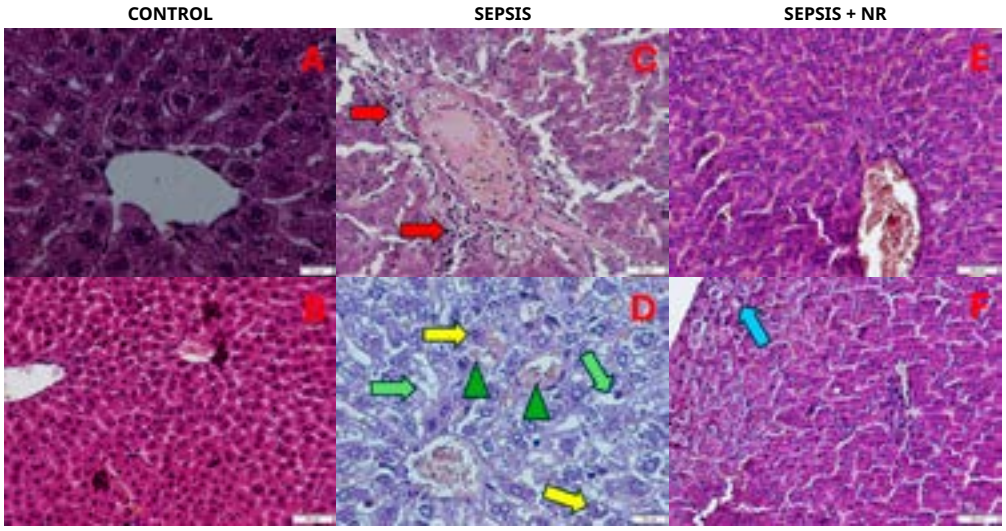

FIGURE 1. Representative liver histology of the rats (H&E). (A 40× – B 10×) Livers of control rats show normal architecture. (C 10× – D 40×) Livers of sepsis rats exhibit inflammatory cell infiltration (red arrows), sinusoidal congestion (triangles) and sinusoidal dilation (green arrows), apoptotic hepatocytes (yellow arrows). (E 10× – F 10×) Livers of NR treated rats show better liver architecture. They show reduction in cellular hypertrophy, sinusoidal space and inflammatory cell infiltration. Ballooning cells are seen in this group (blue arrows)

According to hepatic injury severity scoring capsular inlamation, steatosis, portal inflamation, spotty necrosis and ballooning degeneration increased in sepsis group. Steatosis and spotty necrosis decreased by the help of NR treatment (P<0.05). There were no statistical difference in capsular and portal inflamation (P=0.542, P = 1). Ballooning degeneration was available in sepsis group. It raised in NR treatment according to the percentiles but it did not have a statistical difference (P=0.687) (TABLE I).

In comparison with the control animals, the sepsis animals had an increase in the histopathological score. However, NR treatment decreased the pathological score in some aspects. Capsular inflamation and portal inflamation did not decreased with NR treatment. Because, the rats were not treated for sepsis and did not recieve any antibiotics. They were only treated for liver injury especially for oxidative stress. This is the reason of inflamatory cell infiltration absence in NR treated group (TABLE II and FIG.1). In Cerrah's research, the sepsis group exhibited occasional apoptotic hepatocytes, congestion and inflammatory cells, similar to this findings [16]. Histopathological changes in septic livers parallel to finding of this study were revealed by other studies, also [1, 16, 17].

Peng *et al*. [18] also found karyolysis and karyorrhexis in some nuclei of hepatocytes, inflammatory cells, fibrosis with cellular infiltration around blood vessels, and dilatation with congestion of blood vessels, parallel to these findings]. Although there was no statistically significant difference (P=0.687), ballooning disorder was slightly higher in the NR-treated group than in the sepsis group in percentiles (TABLE I).

NR treatment increased hepatocyte ballooning, on the other hand it decreased apoptotic cells. If ballooning degeneration is severe enough, cell death occurs [19]. In these study, NR may have compensated for apoptosis by ballooning degeneration. To date, human studies have not demonstrated an association between nicotinamide riboside supplementation and serious toxicity, and no serious adverse events have been reported [20].

Reduction of SOD levels are seen in tissues in sepsis [1]. In the present investigation, SOD and MDA levels were measured to determine oxidant and antioxidant activity as presented in TABLES II and III. When comparing the oxidative status of the liver tissues, SOD activity was lower in sepsis rats than those in the sepsis + NR and control groups (P<0.05) (TABLE II). Meanwhile, MDA levels, an end product of lipid peroxidation, were significantly higher in the sepsis group compared to the control group (P<0.05), whereas NR treatment reduced MDA levels compared to the sepsis group (P<0.05) (TABLE III). The elevated levels of MDA, indicates that NR reduces lipid peroxidation and therefore assists the maintenance of cellular integrity. High MDA levels in sepsis were reported in the previous studies [1, 7, 15, 17]. Hong *et al.* [7] reported that NR decreases high MDA levels of lung tissue in septic rats.

Serum ALT and AST activity showed an increase in sepsis group (P<0.05). This effect was reversed by NR treatment (P<0.05,

TABLE II
SOD enzyme activity in liver tissues after NR treatment

		Mean ± SD	*P*	Post-hoc *P*
SOD	Control	6.16580 ± 1.220821	0.013	Control – Sepsis 0.006928 Control – Sepsis + NR 0.745849
	Sepsis	3.15760 ± 0.972289*	0.013	Sepsis – Control 0.006928 Sepsis – Sepsis + NR 0.012828
	Sepsis + NR	5.85900 ± 1.995278**	0.013	Sepsis + NR – Control 0.745849 Sepsis + NR – Sepsis 0.012828

SOD enzyme decreased in sepsis group and increased in sepsis + NR group. Data are presented as mean ± SD (n = 8). Significant differences were found: *P<0.05 compared with control group, **P<0.05 compared with sepsis group. Kruskal Wallis 1 – Way Anova (k samples) test was performed. SOD: superoxide dismutase

TABLE III
MDA enzyme activity in liver tissues after NR treatment

		Mean ± SD	*P*	Post-hoc *P*
MDA	Control	2.491800 ± 0.811813	0.001	Control – Sepsis 0.002772 Control – Sepsis + NR 0.184509
	Sepsis	4.196800 ± 0.796453*	0.001	Sepsis – Control 0.002772 Sepsis – Sepsis + NR 0.000238
	Sepsis + NR	1.851600 ± 0.507143**	0.001	Sepsis + NR – Control 0.184509 Sepsis + NR – Sepsis 0.000238

MDA enzyme increased in sepsis group and decreased in sepsis + NR group. Data are presented as mean ± SD (n = 8). Significant differences were found: *P<0.05 compared with control group, **P<0.05 compared with sepsis group. Kruskal Wallis 1 – Way Anova (k samples) test was performed. MDA: Malondialdehyde

TABLE IV). Creatinine, creatine kinase and ceruloplasmin levels were also high in sepsis rats compared to the control rats and these parameters decreased in NR treated rats (P<0.05, TABLE IV). Serum albumin and phosphate levels were decreased in sepsis group and increased in sepsis + NR group (P<0.05, TABLE IV). Serum calcium levels decreased in both sepsis and sepsis + NR group (P<0.05, TABLE III). However, no significant differences of sodium, amylase, magnesium, and chloride levels were seen between the groups (P<0.05, TABLE IV).

TABLE IV
Effect of sepsis and/or Nicotinamide Riboside on serum parameters

	Control	Sepsis	Sepsis + NR	
AST	180.75 ± 21.62^{b}	453.00 ± 24.67^{a}	198.33 ± 3.71^{b}	U·L^{-1}
ALT	13.38 ± 2.80^{b}	22.40 ± 2.87^{a}	14.16 ± 4.79^{b}	U·L^{-1}
Amylase	14.85 ± 2.03	21.80 ± 9.51	17.07 ± 1.88	U·L^{-1}
Creatinine	0.43 ± 0.02^{b}	0.62 ± 0.21^{a}	0.37 ± 0.03^{b}	mg·dL^{-1}
Creatine kinase	237.00 ± 79.53^{b}	648.00 ± 120.70^{a}	370.08 ± 103.13^{b}	mg·dl^{-1}
Ceruloplasmin	29.15 ± 2.75^{b}	38.39 ± 9.63^{a}	26.73 ± 1.10^{b}	mg·dL^{-1}
Sodium	135.00 ± 2.28	129.80 ± 6.85	128.77 ± 7.17	mmol·L^{-1}
Chloride	94.25 ± 1.47	97.00 ± 3.41	94.67 ± 3.12	mmol·L^{-1}
Magnesium	2.38 ± 0.12	2.49 ± 0.31	2.19 ± 0.38	mg·dL^{-1}
Phosphate	6.75 ± 0.42^{a}	5.40 ± 0.43^{b}	6.40 ± 0.21^{a}	mg·dL^{-1}
Calcium	10.03 ± 0.45^{a}	9.02 ± 0.80^{b}	9.00 ± 0.28^{b}	mmol·L^{-1}
Albumin	35.83 ± 1.29^{a}	30.27 ± 2.65^{b}	33.74 ± 1.84^{a}	g·l^{-1}

Parameters that showed significant difference (P<0.05) are indicated with different superscript (^{a,b,c}). Values without superscripts are not statistically significant. The values are expressed as mean ± SD. Aspartate transaminase: (AST), Alanine transaminase: (ALT), Sepsis + NR (Sepsis+Nicotinamide Riboside)

Serum ALT and AST activity increased in sepsis group (P<0.05), indicating liver tissue damage. Liu *et al.* [17] also showed high AST and ALT levels in sepsis. NR administration may decreased the hepatic damage, so it lowered high AST and ALT levels in this study. Creatine can be taken up from the diet and also produced endogenously by liver, pancreas and kidney before transferring to the skeletal muscles for storing energy. Then, it is phosphorylated in the muscles, converted to creatinine, finially transferred back into the bloodstream [21] . Creatine is delivered through the blood and it is taken up by cells those have high energy demands [22]. The transfer of phosphoryl group from phosphocreatine to ADP (adenosine 5'-diphosphate) is catalyzed by creatine kinase, hence adenosine triphosphate (ATP) is reproduced [21].

The rate of creatinine production is reduced in patients with liver disease [23]. Nonetheless, we found high creatinine levels in septic rats which have injured livers. It probably depends on kidney injury associated with sepsis. In this study, NR treatment reduced creatinine levels. This situation may depends on two mechanisms. First, reduced kidney damage due to NR treatment may decreased creatinine levels. Second, sepsis causes mitochondrial damage, reduced NAD^+ levels and ATP production [22]. If ATP levels decreases, cells use phosphocreatine to produce ATP. So creatine kinase and creatinine levels rise [21, 24]. NR is a precursor in the synthesis of NAD^+ and increase NAD^+ levels and ameliorate mitochondrial dysfunction [25, 26, 27]. NAD^+ is required for energy production and high levels of NAD^+ improve mitochondrial function and increase ATP production [28].

In this study, creatinine and creatine kinase levels were decreased in NR treatment group. In sepsis patients, serum amylase and chloride levels are usually elevated, while magnesium levels are conversely low [29, 30, 31]. Both low and high sodium levels can be observed in septic patients [32]. Amylase, magnesium, chloride, and sodium levels of NR group did not undergo any differentiation compare to sepsis group. There may not have been a significant change in these parameters because this research was an acute study or because the pathways in this disease do not affect these parameters through NR.

Hypocalcemia occurs in sepsis [33]. NR treatment increased ballooning hepatocytes in liver and serum calcium levels were low in this group. In ballooning degeneration, intracellular calcium raises [19]. This may contribute decreases serum calsium levels.

Inflammation, increased vascular permeability, and capillary leakage occur, in sepsis. In this situation, plasma proteins such as albumin can leak out of the vessels, and serum levels of these proteins may decrease. Furthermore, factors such as suppressed liver synthesis, increased destruction, and renal loss also play a role in the decrease in albumin [34, 35] . This study also found decreased albumin levels, in sepsis group. This parameter raised in NR + sepsis group. NR may raised albumin levels by reducing inflamation in kidney and liver.

Ceruloplasmin has some roles such as copper transport, detoxification and homeostasis, ferroxidase activity, antioxidant and antiinflammatory activities [36, 37, 38] . In sepsis, high ceruloplasmin levels are considered to be part of acute phase response [36, 37, 38] . This study also found high ceruloplasmin levels. However, NR treatment decreased ceruloplasmin levels. Antioxidant properties of NR may affect it.

Sepsis lead to liver injury which may be caused by inflammatory response or other mechanisms not understood in this investigation.

These study has several limitations. First, the rats were not treated for sepsis, and the experiment lasted only 24 h. To observe the hepatoprotective effects of NR, another group could have received both sepsis treatment and NR supplementation.

Differences in survival rates in response to sepsis were not monitored. Second, many antioxidants have been tested on sepsis-related liver damage. Some of these can be applied simultaneously in the same experiment to determine which is more effective.

CONCLUSION

This study evaluated the effects of NR on liver injury in a rat model of sepsis. The biochemical and histopathological findings suggest that NR administration may have a protective effect against sepsis-induced liver damage. These results indicate a potential role for NR in modulating hepatic injury during sepsis; however, further studies with larger sample sizes are required to confirm these findings and clarify the underlying mechanisms.

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Conflict of interest

The authors declare no conflicts of interest.

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