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RESEARCH ARTICLE OPEN ACCESS

Resveratrol attenuates ANIT-induced cholestasis in rats via modulation of bilirubin, ALP, and IL-1β

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Abstract
Objective: The study aimed to evaluate the protective and therapeutic effects of resveratrol on experimentally induced cholestasis and to provide new insights into the dual hepatoprotective and anti-inflammatory mechanisms of resveratrol in cholestasis.
Method: Thirty male Wistar albino rats (270–330 g) obtained from the College of Science at Babylon University were housed in standard plastic cages (five per cage) under controlled conditions (12-hour light/dark cycles, 50% humidity, and 22–25°C temperature, with free access to water). After two weeks of acclimatisation, rats were randomly divided into three groups (n=10 per group). Group A served as the negative control, Group B received ANIT (α-naphthylisothiocyanate) (positive control), and Group C received Resveratrol treatment following ANIT exposure. After the treatment period, all rats were sacrificed, and blood samples were collected for biochemical and inflammatory marker analysis.
Results: Total bilirubin (TBIL) levels were significantly reduced in the resveratrol-treated group (1.09 ± 0.18 µmol/L) compared to the cholestasis group (1.98 ± 0.48 µmol/L) (TBIL: p=0.05). Serum IL-1β levels also showed a significant decrease (16.99 ± 2.41 pg/mL vs. 26.07 ± 3.52 pg/mL) (IL-1β: p=0.03). Additionally, ALP levels were significantly reduced in the resveratrol group (16.24 ± 2.81 IU/L) compared to the cholestasis group (50.14 ± 3.16 IU/L) (ALP: p=0.001). These findings demonstrate that resveratrol exerts both anti-inflammatory and hepatoprotective effects.
Conclusion: Resveratrol effectively attenuates ANIT-induced cholestasis in rats, likely through the reduction of ALP and bilirubin levels, and modulation of the inflammatory response via IL-1β inhibition.

Keywords: Cholestasis, Resveratrol, α-naphthylisothiocyanate

Plain English Summary

Cholestasis is a liver condition where the normal flow of bile is reduced or blocked. In this study, cholestasis was induced in rats using a chemical called ANIT (a liver-damaging chemical). This condition typically leads to a rise in certain blood markers that reflect liver damage and inflammation, such as ALP, total bilirubin, and IL-1β. The researchers investigated whether resveratrol, a natural compound, could improve this condition. After treatment with resveratrol, these elevated markers significantly decreased. This suggests that resveratrol may help protect the liver and reduce the damage caused by cholestasis.

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Background

Cholestasis is a pathological condition characterised by poor bile synthesis, production, and excretion, preventing bile from facilitating normal liver-intestinal circulation. Variations in bile production or excretion can lead to several effects. When bile builds up beyond what the liver can normally process, it damages the liver parenchyma cells, induces toxicity in the biliary system, and eventually blocks the bile ducts (1). Pruritus is often the first sign of an episode, followed by jaundice a few weeks later. Patients with cholestasis may exhibit systemic symptoms such as general malaise, anorexia, nausea, vomiting, steatorrhea, impaired nutrient absorption, and consequent weight loss. Laboratory findings typically reveal an elevation in serum alkaline phosphatase (ALP) levels following the onset of pruritus. This is subsequently accompanied by increased levels of conjugated (direct) bilirubin in the blood. In contrast, serum levels of gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) often remain within normal limits or show only mild elevations (2). Both congenital and acquired cholestasis can result from a wide variety of injuries. The relative incidence depends on the population being studied. In children, biliary atresia and genetic cholestasis disorders (such as PFIC syndromes and Alagille syndrome) cause considerable pathology. A wide variety of causes can lead to cholestasis in adults. Rare forms of genetic cholestasis include benign recurrent cholestasis and biliary illness caused by harmful variations in the MDR3 gene. On the other hand, biliary obstruction—whether internal or external to the biliary tree—can be either benign or malignant; drug-induced liver damage and pregnancy (obstetric cholestasis) are common causes of acute cholestasis. Sepsis is another common cause. Autoimmune biliary diseases, such as primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), or immunoglobulin G4 (IgG4) disease, are common causes of chronic and persistent damage (3). Conversely, resveratrol (3,5,4′-trihydroxystilbene), a phytoalexin belonging to the natural polyphenol family, is widely distributed among various plant sources, including peanuts, blueberries, cranberries, legumes, rhubarb, grapes, eucalyptus, and several species of grasses (4). Among its various bioactivities are those of antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, anti-obesity, neuroprotective, and anti-ageing ones (5). The antioxidant properties of resveratrol can be attributed to its dual mechanism of action: directly scavenging reactive oxygen species (ROS) and indirectly promoting the expression of cellular defence mechanisms and antioxidant-related genes. Notably, resveratrol demonstrates high efficacy in neutralising various oxidants, including peroxynitrite, superoxide anion, hydrogen peroxide, hydroxyl radical, nitric oxide, and singlet oxygen. Resveratrol (RES) promotes the activity of key endogenous antioxidant enzymes, including catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD), which together form the core of the enzymatic defence system against oxidative stress. Central to the regulation of this antioxidant response is the nuclear factor erythroid 2-related factor 2 (Nrf2), which governs the expression of genes containing antioxidant response elements (ARE) essential for maintaining cellular redox balance. In human lung, hepatic, intestinal, and endothelial cells, resveratrol has been shown to mitigate oxidative stress through the activation and modulation of the Nrf2 signalling pathway (6). Resveratrol's anti-inflammatory potential is primarily attributed to its ability to suppress the production of pro-inflammatory mediators. Oxidative stress, resulting from the excessive accumulation of reactive oxygen species (ROS), plays a central role in triggering inflammatory responses across a wide spectrum of pathological conditions. Resveratrol mitigates inflammation by modulating the generation of ROS and nitric oxide (NO), primarily through its influence on several critical signalling pathways, including activator protein-1 (AP-1), mitogen-activated protein kinase (MAPK), arachidonic acid (AA), and nuclear factor kappa B (NF-κB) (7).

Materials and methods

This research involved 30 mature male Wistar albino rats, weighing between 270 and 330 grams, acquired from the animal house of the College of Science at Babylon University. The rats were accommodated in normal plastic cages (five per cage) for two weeks before the commencement of the investigation to acclimatise to laboratory settings. In a typical laboratory setup, rats were given water, a pellet feed, and a 12-hour light/dark cycle in addition to regular ventilation, temperature (22–25°C), and humidity (50 per cent). The labs of the University of Babylon's College of Medicine housed the animals used in this study. The thirty rats were randomly and manually assigned into three groups, n=10 per group (Based on prior studies with similar effect sizes, n=10/group was deemed sufficient) using a simple randomisation method to ensure unbiased group allocation. Group A is the negative control group (normal

group), given distilled water orally for twelve days and corn oil (1 ml/kg) once a day, 48 hours ahead of sacrifice. Group B is the positive control group, given distilled water orally for twelve days and a single dosage of ANIT at 100 mg/kg, dissolved in corn oil, 48h before sacrifice. Group C is the treated group, given resveratrol at a dosage of 30 mg/kg orally for twelve days, along with a single dose of alpha-naphthylisothiocyanate (ANIT) at 100 mg/kg, dissolved in corn oil, 48h before sacrifice. The selected Resveratrol dose (30 mg/kg) was based on previous studies, which demonstrated its hepatoprotective and anti-inflammatory effects at this concentration in rat models (8). On day 12 of the trial, the rats were killed compassionately with xylazine (10 mg/kg) and ketamine (75 mg/kg). The abdomen was dissected, and blood samples were collected from all rats that underwent laparotomy, while experimental parameters were assessed. Blinding was applied during both treatment administration and sample analysis. The personnel involved in administering treatments and analysing samples were unaware of the group allocations to minimise bias. The researchers performing the biochemical and histological analyses were blinded to the group assignments to minimise potential assessment bias. A sample size of 10 rats per group was chosen in alignment with previously validated studies investigating the effects of resveratrol or similar agents in ANIT-induced cholestasis models. Although no formal power calculation was conducted before the experiment, this sample size was deemed sufficient to observe statistically and biologically significant changes in key parameters such as ALP, total bilirubin, and IL-1β levels, based on expected effect sizes and variability reported in the literature. This approach also complies with the principle of minimising the number of animals used while ensuring scientific validity.

Chemicals

Alpha-naphthylisothiocyanate (ANIT) was obtained from Sigma Aldrich in St. Louis, the United States; Resveratrol was obtained from Now in the United States; ketamine was obtained from Alphatan in the Netherlands; and Xylazine was obtained from Alphatan in the Netherlands.

Statistical analysis

Data are presented as mean ± SEM, and the statistical significance of group differences was assessed using one-way analysis of variance (ANOVA). Differences were deemed statistically significant with a P-value of less than 0.05 and highly significant with a P-value of less than 0.001.

Results

Total bilirubin biomarker

Results (n=10) are presented as the mean (± SD). Figure 1 and Table 1 illustrate a markedly significant elevation in total bilirubin concentration in group B relative to group A and a considerable reduction in group C compared to group B.

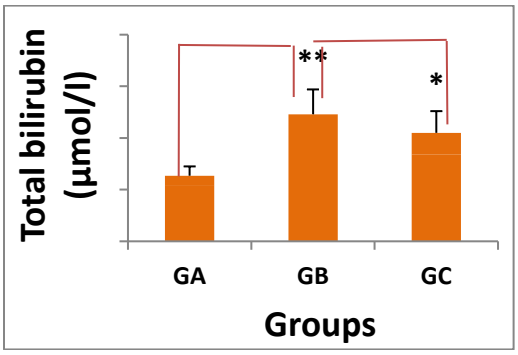

Figure 1: Comparison between different groups regarding total bilirubin in serum

GA is controlled negative; GB is controlled positive; GC is the treated group (resveratrol). Data are presented as mean ± SD. (**p < 0.001) (*p < 0.05)

Table 1: Comparison between the effect of Resveratrol on Total Bilirubin concentration in groups A and B

Dependent Variable	Group	Study group	No.	Mean ± SD	P- value
	Group C	Group A	10	1.09 ± 0.18	0.001
		Group B	10	1.98± 0.48	0.05

p < 0.05 considered significant; p < 0.001 considered highly significant

IL-1β biomarker

Results (n=10) are presented as the mean (± SD). Figure 2 and Table 2 illustrate a markedly significant elevation in IL-1β levels in group B relative to group A. The IL-1β level dramatically decreased in group C compared to group B.

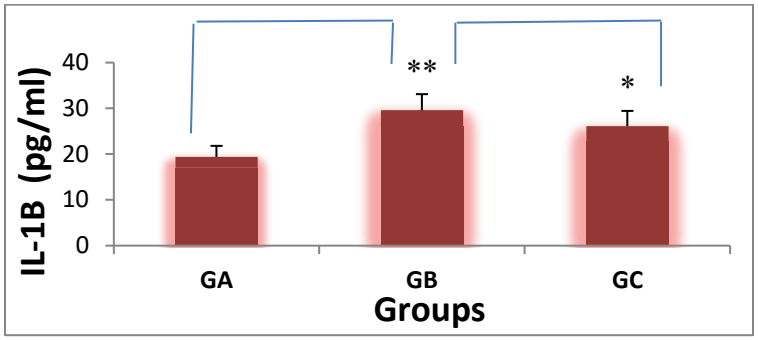

Figure 2: Comparison between different groups regarding IL-1 Beta in serum

GA is controlled negative; GB is controlled positive; GC is the treated group (resveratrol). Data are presented as mean ± SD. (**p < 0.001) (*p < 0.05)

Table 2: Comparison between the effect of Resveratrol on IL-1β level in groups A and B

Dependent Variable	Group	Study group	No.	Mean ±SD	P- value
	Group C	Group A	10	16.99 ± 2.41	0.001
		Group B	10	26.07 ±3.52	0.03

p < 0.05 is considered significant; p < 0.001 is considered highly significant.

Alkaline phosphatase biomarker

The results (n=10) are shown as the mean (± SD). This figure illustrates a markedly significant elevation in ALP activity in group B relative to group A. Group C had a markedly significant reduction in ALP activity in comparison to group B.

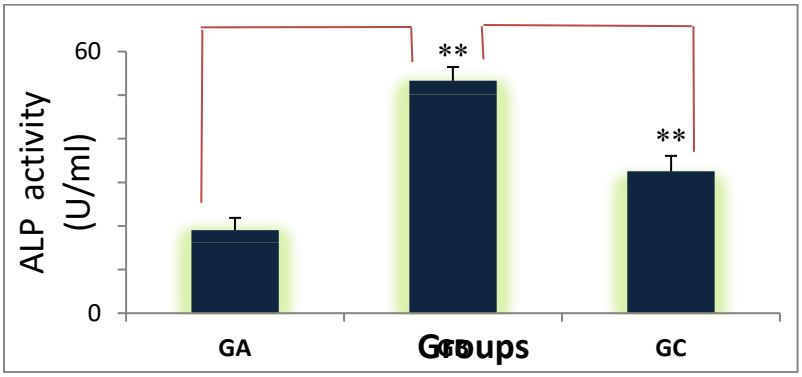

Figure 3: Comparison between different groups regarding ALP in serum

GA is controlled negative; GB is controlled positive; GC is the treated group (resveratrol). Data are presented as mean ± SD. (**p < 0.001) (*p < 0.05)

Table 3: Comparison between the effect of Resveratrol on ALP activity in groups A and B

Dependent Variable	Group	Study group	No.	Mean ± SD	P- value
	Group C	Group A	10	16.24±2.81	0.001
		Group B	10	50.14±3.16	0.001

p < 0.05 considered significant; p < 0.001 considered highly significant

Discussion

This study employs total bilirubin (TBIL), interleukin-1 beta (IL-1β), and alkaline phosphatase (ALP) as biochemical markers to assess and elucidate the effects of resveratrol on cholestasis induced by alpha-naphthyl

isothiocyanate (ANIT) in male rats. These markers are clinically relevant indicators of hepatobiliary function and inflammation, and alterations in their levels have diagnostic and prognostic value in liver disorders, including cholestasis.

Bilirubin has lipophilic characteristics, resulting in its insolubility, which negatively impacts its excretion. The glucuronidation of bilirubin enhances its solubility, facilitating its elimination via bile and urine. The conjugation of bilirubin with glucuronic acid is facilitated by UGT1A1 (9). RES causes activation of the Nrf2 signalling pathways (10), and the overexpression of Nrf2 increased the steady-state levels of UGT1A1 gene transcripts, so there was an increase in bilirubin excretion (11). These results may be due to the upregulation of Mrp2 by RES (12). According to Figure 1 and Table 2, the current investigation found that TBIL levels were significantly lower in Group C, which received pretreatment with 30 mg/kg of RES, than in Group B. These findings are consistent with a previous study (13), which demonstrated that resveratrol significantly decreased serum TBIL levels in a rat model of cholestasis, suggesting consistency in the hepatoprotective role of RES.

Group (C) treated with RES+ANIT results in highly significantly lower ALP levels than group (B), as demonstrated in Figure (3) and Table (4). The elevated ALP levels observed in Group (B) underscore the presence of cholestatic injury and biliary dysfunction (14), which were notably mitigated in Group (C) following resveratrol treatment. These findings are consistent with those reported in study (15), which observed a similar decrease in ALP levels following resveratrol treatment in a cholestasis model. ALP is released into the bloodstream when the bile ducts become blocked (16). The increase in ALP level may result from the retention of bile salts that compromise the membrane, thereby facilitating the release of the ALP enzyme into circulation. Resveratrol exhibits protective benefits against ANIT-induced cholestasis via FXR activation. FXR safeguards against excessive bile acid accumulation by inhibiting CYP7A1 and CYP8B1, thereby diminishing intrahepatic bile acid production. It also augments UGT1A1 activity for bile acid metabolism, elevates BSEP, Mrp2, and organic solute and steroid transporter beta (OSTß) expression to promote bile acid secretion, and ultimately modulates phase II metabolism enzymes such as SULT2A1, these mechanisms are in agreement with studies reporting the modulation of bile acid transporters by RES as part of its hepatoprotective profile (17, 18).

The proinflammatory cytokine IL-1β modulates the immune response during inflammation (19), and its elevation is regarded as a biomarker for inflammation in cases of cholestasis (20). The current investigation demonstrates that ANIT in group (B) highly significantly elevates IL-1β levels compared to group (A), as illustrated in Figure 2, Table 3, corroborating findings from the prior study (21). IL-1β is predominantly triggered and secreted by the overexpression of NF-κB. Pretreatment with Resveratrol in Group (C) results in a considerable decrease in IL-1β levels compared to Group (B), as illustrated in Figure 2 and Table 3, demonstrating the anti-inflammatory impact of resveratrol. These results align with those reported in previous investigations (22), where resveratrol significantly reduced IL-1β levels in a rat model of cholestasis, further strengthening the evidence that RES exerts anti-inflammatory actions in hepatic inflammation.

Furthermore, the observed effects are comparable to those achieved by the current standard treatment for cholestasis, Ursodeoxycholic acid (UDCA), as supported by similar outcomes reported in multiple studies (23, 24, 25).

Resveratrol's modulation of the Nrf2 and FXR signalling pathways plays a crucial role in the observed biochemical improvements in cholestasis. Activation of the FXR pathway by resveratrol enhances the expression of bile acid transporters such as BSEP and OSTβ, while simultaneously downregulating bile acid synthesis enzymes including CYP7A1 and CYP8B1. This mechanism reduces intrahepatic bile acid accumulation and contributes to the significant decline in serum bilirubin and ALP levels observed in this study. Moreover, through activation of the Nrf2 pathway, resveratrol increases the transcription of antioxidant enzymes such as HO-1, NQO1, and SOD2, while suppressing oxidative stress and lipid peroxidation. These effects collectively reduce hepatic inflammation, which is reflected by the marked decrease in IL-1β levels. Therefore, the hepatoprotective and anti-inflammatory actions of resveratrol are mechanistically supported by its regulatory effects on the FXR and Nrf2 pathways, aligning with the biochemical outcomes reported in this study (17).

These findings suggest resveratrol as a promising candidate for adjunct therapy in cholestasis, owing to its multi-targeted action, including antioxidant, anti-inflammatory, and bile flow-regulating effects. However, translational application requires further validation through human clinical studies to confirm efficacy, optimal dosage, and safety.

This study is not without limitations. First, a histopathological evaluation of liver tissues was not

conducted. While biochemical markers such as ALP, TBIL, and IL-1β offer valuable insights, liver histology would have provided direct visual confirmation of tissue-level damage and repair. Future investigations should include microscopic assessment to validate these biochemical findings. Second, the study employed a single fixed dose of resveratrol (30 mg/kg). Although this dose showed effectiveness, a dose-response analysis is necessary to determine the optimal therapeutic window and evaluate potential toxicity or diminishing returns BFuture studies should measure bile acids to further validate resveratrol's choleretic effects.

Conclusion

The current study highlights the notable hepatoprotective effects of resveratrol in a model of cholestasis induced by alpha-naphthyl isothiocyanate (ANIT). Administration of resveratrol resulted in a marked reduction in serum alkaline phosphatase (ALP) and total bilirubin levels, suggesting enhanced liver function and improved bile excretion. Additionally, resveratrol effectively reduced the inflammatory cytokine IL-1β, highlighting its anti-inflammatory potential. These biochemical changes suggest that resveratrol may attenuate both liver injury and inflammation associated with cholestasis.

List of Abbreviations

ALP: Alkaline phosphatase
ANIT: Alpha-naphthylisothiocyanate
IL-1B: Interleukin-1-beta
Nrf2: Nuclear factor erythroid 2–related factor 2
NF-$_K$B: Nuclear factor kappa B
RES: Resveratrol
TBIL: Total bilirubin
UDCA: Ursodeoxycholic acid

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Publication Ethics Committee of the Faculty of Medicine, Babylon University, Iraq. The research protocol was reviewed and authorised by the institutional ethics committee under Document No. 4-34, dated April 6, 2025.

Consent for publication

All the authors gave consent for the publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Data Availability

The data and materials related to this research are available from the corresponding author upon reasonable request.

Competing interests

Nil.

Funding

This research received no external funding

Author Contributions

AEM was responsible for the conceptualisation, methodology, data collection, and drafting of the original manuscript. He played a key role in the experimental design and conducted the primary data analysis.

MKA supervised the overall research project, provided critical feedback, and contributed to the validation and interpretation of the findings. He also reviewed and edited the final version of the manuscript for intellectual content and clarity.

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