International Journal of Zoology Studies
www.zoologyjournals.com
ISSN: 2455-7269
Received: 20-04-2026, Accepted: 21-05-2026, Published: 05-06-2026
Volume 11, Issue 2, 2026, Page No. 133-138

Effect of quercetin supplementation on hepatotoxicity and oxidative stress in N-Nitrosodiethylamine (NDEA)-induced hepatic injury in rats

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DOI: https://doi.org/10.66856/ijzs.2026.11.2.11051

Abstract
The present study investigated the protective effect of quercetin supplementation on hepatotoxicity and oxidative stress induced by N-Nitrosodiethylamine (NDEA) in male Wistar rats. Thirty-six rats were divided into six groups and treated with NDEA, quercetin, or their combinations for 21 days. NDEA administration resulted in marked hepatic damage, as indicated by significant elevations in serum liver enzymes (AST, ALT, and ALP), total bilirubin, and lipid peroxidation levels, along with depletion of endogenous antioxidant defenses such as superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH). In contrast, quercetin supplementation, particularly at higher doses, significantly restored biochemical parameters toward normal levels and enhanced antioxidant enzyme activities. Histopathological observations further supported the biochemical findings by showing reduced necrosis, inflammation, and cellular degeneration in the quercetin-treated groups. Overall, the results demonstrated that quercetin exerted a strong hepatoprotective effect by mitigating oxidative damage and improving the antioxidant defense system in NDEA-induced hepatic injury in rats.

Keywords: Quercetin, hepatotoxicity, oxidative stress, N-nitrosodiethylamine (NDEA)

Introduction

Liver is very much susceptible to injury caused by xenobiotics because it plays a central role in the regulation of metabolic homeostasis, detoxification and biosynthesis of essential molecules. Oxidative stress, defective antioxidant defense mechanisms and progressive hepatic dysfunction are often caused by exposure to chemical carcinogens and environmental toxins (Weber *et al*., 2003) [31]. N-Nitrosodiethylamine (NDEA) is one of the most commonly known hepatotoxic compounds that are carcinogenic, mutagenic and hepatotoxic. "NDEA is an agent that is regularly exposed by people due to its frequent presence in tobacco smoke, preserved foods, industrial by-products, and contaminated water sources (Lijinsky, 1999) [18]. With experimental studies, it has been repeatedly demonstrated that NDEA causes injury in cell by generating excess reactive oxygen species (ROS) and promoting lipid peroxidation, DNA lesions, and protein modifications in hepatic tissues (Verna *et al*., 1996) [30].

The hepatotoxicity induced by NDEA involves its metabolic conversion into reactive intermediates (e.g. ethyldiazonium ions) which in turn form alkyl adducts with nucleic acids and cellular macromolecules (Klaunig & Kamendulis, 2004) [13]. This metabolic process increases the oxidative stress, reduces the endogenous antioxidant defenses such as superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH), and finally the disruption of the hepatocellular integrity (George *et al*., 2001) [9]. Oxidative stress over a long period of time does not only hinder the liver functioning but also causes chronic inflammation, fibrosis, and carcinogenesis. As such, devising effective antioxidant interventions to alleviate hepatic injury caused by NDEA has become a major area of interest in modern toxicological studies.

Quercetin, a naturally occurring flavonoid that is present in fruits, vegetables, and medicinal plants has received a lot of attention due to its strong antioxidant, anti-inflammatory and free radical-scavenging properties (Boots *et al*., 2008) [3]. Quercetin being a polyphenolic compound is an effective neutralizer of ROS, inhibitor of lipid peroxidation and restorer of the equilibrium of the enzymatic and non-enzymatic antioxidants in the hepatic tissues (Formica & Regelson, 1995) [8]. Besides, quercetin was found to regulate the signaling pathways related to oxidative damages, apoptosis, and inflammation, thus offering multifaceted protection against chemically induced toxicities (Li *et al*., 2016).

Past experimental experiments have revealed the hepatoprotective effects of quercetin against a variety of toxins including carbon tetrachloride (CCl_4), paracetamol and heavy metals (Domitrović *et al*., 2012) [5]. Nevertheless, studies that specifically examine the protective effect of quercetin against hepatic injury caused by NDEA is limited, despite the biological plausibility of its therapeutic properties. The assessment of quercetin supplementation in an NDEA-induced model could therefore provide some valuable information on the effectiveness of quercetin supplementation in modulating oxidative stress, improving antioxidant status, and preserving hepatocellular structure and function.

Besides having antioxidant activity, quercetin shows significant anti-inflammatory action, which are also applicable in the toxicant-induced hepatic injury. Oxidative stress and inflammation are interconnected processes, and continuous production of ROS facilitates the activation of the processes of inflammatory mediators (NF-kB, TNF-a, IL-1b, and IL-6) aggravation of hepatocellular damage (Hussain *et al*., 2016) [11]. It has been demonstrated that quercetin can suppress the activation of NF-KB, the production of pro-inflammatory cytokines, and the expression of cytoprotective enzymes such as heme oxygenase-1 (HO-1), thus providing a dual line of defense

against oxidative and inflammatory damage (Li *et al*., 2016). This combined anti-oxidant-anti-inflammatory effect makes quercetin an effective therapeutic candidate to alleviate mitochondrial hepatotoxicity induced by nitrosamines such as NDEA.

Moreover, quercetin has a positive impact on the functioning of mitochondria, which is a significant factor in the survival of cells in the case of toxic exposure. NDEA-induced oxidative stress is a major target to mitochondria, resulting in mitochondrial membrane depolarization, impaired ATP synthesis, and activation of apoptotic pathways (Kumar *et al*., 2014) [15]. The quercetin would prevent the apoptotic cell death in hepatic tissues by scavenging mitochondrial ROS and stabilizing membrane potential. Studies have also shown that quercetin increases the activity of phase II detoxifying enzymes, including glutathione S-transferase (GST) and UDP-glucuronosyltransferase that facilitates the elimination of toxic metabolites and supports hepatic detoxification processes (Moon *et al*., 2006) [20]. These properties enhance its possibility to be used as a natural hepatic protectant.

NDEA models using experimental models of the liver remain a gold standard of studying chemically induced hepatic injury, fibrosis, and hepatocellular carcinoma due to similarity of pathological changes to human liver disease (Omar *et al*., 2018) [24]. The liver injury caused by NDEA is usually characterized by the onset of oxidative DNA damage and lipid peroxidation, followed by inflammatory infiltration, fibrosis, and architectural distortion of hepatic tissue. In the prevention of the development of acute hepatic insult to chronic liver disease, therefore, early intervention using antioxidant-rich compounds is therefore critical. Natural flavonoid such as quercetin are suitable to this requirement because of their high safety profile, low toxicity, and multifaceted biological activity.

Although there is an increasing interest in phytochemicals, there is still a considerable gap in the literature regarding the specific protective actions of quercetin in hepatotoxicity induced by NDEA. Although some isolated studies have demonstrated significant antioxidant activities, many have not succeeded in a comprehensive assessment of biochemical, oxidative and histopathological indicators in a single experimental design. In addition, the dose-response relationship and the degree of hepatic recovery following quercetin supplementation following NDEA exposure is not explicably explained. Addressing these gaps is crucial, especially considering the increasing environmental and occupational exposure to nitrosamines and their association with liver cancer and chronic liver disease in humans.

Antioxidant and anti-inflammatory effects of QUERCETin Hepatic protection.

The hepatoprotective effects of quercetin have strong roots in its ability to counter the oxidative stress and inflammation, two key processes involved in the chemically induced liver injury. The antioxidant property of quercetin is not solely dependent on direct scavenging of the free radicals; rather, it also regulates several cellular pathways that maintain hepatic redox homeostasis. It has been suggested that quercetin enhances nuclear translocation of Nrf2 which is a transcription factor that upregulates antioxidant response element (ARE)-regulated genes including heme oxygenase-1 (HO-1), glutamate cysteine ligase, and NAD(P)H:quinone oxidoreductase-1 (NQO1) (Tanigawa *et al*., 2007) [28]. This pathway activation augments the cellular antioxidant network, which provides long-term protection against prolonged oxidative attacks like those observed when this pathway is activated.

At the same time, quercetin has severe anti-inflammatory effects, which prevent the presence of key mediators that coordinate the processes of hepatic inflammation. Chronic exposure to toxins like the NDEA activates the NF-KB which promotes the transcription of pro-inflammatory cytokines such as TNF- a, IL-1- b and IL- 6. These cytokines are also critical factors in amplifying the hepatic injury, the recruitment of inflammatory cells and the progression to fibrosis (Sun & Karin, 2008) [27]. Research has indicated that quercetin inhibits the NF-kB pathway by preventing degradation of IkB Alpha protein, and hence inhibiting the inflammatory process (Comalada *et al*., 2006) [4]. This anti-inflammatory effect is especially pertinent to the injury caused by nitrosamine, in which excessive production of cytokines synergize with oxidative stress to exacerbate hepatocellular injury.

The role of quercetin in the regulation of the balance between pro-oxidant and antioxidant enzymes also plays an important role. Exposure to NDEA elevates the activity of CYP2E1 leading to the production of high amounts of superoxide anions and other reactive intermediates. Quercetin has been demonstrated to suppress expression of CYP2E1, and hence inhibit the production of ROS at the source and the subsequent production of lipid peroxidation downstream (Lu *et al*., 2010). In addition, quercetin restores lost glutathione (GSH), an essential intracellular antioxidant that is quickly exhausted in the face of toxin-induced oxidative stress. Sufficient levels of GSH are necessary to detoxify peroxides, maintain mitochondrial integrity, and prevent oxidative breakdown of cellular membranes. Experiments conducted with different hepatotoxic models have consistently shown that quercetin is able to restore the GSH levels, enhance the glutathione peroxidase (GPx) activity, and normalize the catalase (CAT) and superoxide dismutase (SOD) levels, thus restoring the antioxidant balance impaired by the presence of NDEA-like hepatotoxicants (Murakami *et al*., 2008) [21].

Furthermore, quercetin has protective effects on hepatic mitochondria which are especially vulnerable to oxidative damage. A characteristic of the injury caused by NDEA is mitochondrial dysfunction, which is characterized by lipid peroxidation, swelling, collapse of membrane potential, and increased release of pro-apoptotic proteins such as cytochrome c (Nakae *et al*., 2012) [23]. Quercetin maintains mitochondrial membranes by inhibiting the formation of ROS in the organelle and the opening of the mitochondrial permeability transition pore. The fact that its presence is necessary to maintain ATP production and oxidative phosphorylation in the hepatocytes helps to ensure that the hepatocytes are able to sustain essential metabolic processes even under toxic stress. Mitochondrial integrity restoration, in addition to improving cell survival, inhibits the activation of downstream apoptotic pathways.

And lastly, the anti-fibrotic action of quercetin has provided a new layer to the hepatoprotective effect. NDEA-induced prolonged oxidative stress and inflammation may activate hepatic stellate cells (HSCs) and trigger the increased collagen deposition and progression to fibrosis or cirrhosis. Research has shown that quercetin inhibits the HSC activation by inhibiting transforming growth factor-b1

(TGF-b1) and alpha-smooth muscle actin (alpha-SMA), which are key regulators of fibrogenesis (Jang *et al*., 2010) [12]. Inhibition of these pathways by quercetin prevents structural remodeling of the hepatic tissue and aids in the restoration of normal hepatic histoarchitecture.

All these antioxidant, anti-inflammatory, anti-apoptotic, and anti-fibrotic effects make quercetin a good prospective candidate in mitigating liver damage caused by NDEA. Even though its hepatoprotective potential is confirmed by a number of experimental models, more detailed studies, which directly look into NDEA, are needed to determine the entire scope of its therapeutic capability.

Thus, the present study is planned to be conducted in a systematic manner to evaluate the impact of quercetin supplement on hepatotoxicity and oxidative stress in NDEA-induced hepatic injury in rats, with the following objectives (i) the effect of quercetin supplement on serum liver function biomarkers, (ii) the effect of quercetin supplement on oxidative stress indices, (iii) the effect of quercetin supplement on endogenous antioxidant enzyme activity, and (iv) the effect of quercetin supplement on histopathological changes. A joint investigation of these parameters will lead to a comprehensive understanding of the protective effect of quercetin and the possible applicability of the quercetin in the prevention of xenobiotic-induced liver injury.

Materials and Methods

Healthy adult male Wistar albino rats (n = 36), weighing 150–200 g, were purchased from a certified breeder and were acclimatized for one week before the initiation of the experiment. The animals were housed in polypropylene cages under controlled environmental conditions, maintained at a temperature of 22 ± 2°C, relative humidity of 50 ± 10%, and a 12 h light/12 h dark cycle. Rats were provided with standard pellet diet and water *ad libitum* throughout the study period. All experimental procedures were performed in accordance with the institutional ethical guidelines for animal care and use.

The study was designed to evaluate the effect of quercetin supplementation on hepatotoxicity and oxidative stress induced by N-Nitrosodiethylamine (NDEA). Thirty-six rats were randomly divided into six groups, each consisting of six animals. Group I served as the control and received only standard diet and water without any chemical treatment. Group II served as the NDEA-induced toxic control and received a single intraperitoneal dose of NDEA at 100 mg/kg body weight to induce hepatic injury. Group III received quercetin alone at a dose of 50 mg/kg body weight orally for 21 consecutive days to assess any independent effect of the compound. Group IV received quercetin supplementation (50 mg/kg body weight, orally for 21 days) followed by NDEA administration to evaluate the protective effect of quercetin prior to toxicant exposure. Group V received NDEA followed by quercetin (50 mg/kg body weight orally for 21 days) to assess the therapeutic effect after injury induction. Group VI received both NDEA and a higher quercetin dose (100 mg/kg body weight, orally for 21 days) to determine any dose-dependent protective response. All treatments were administered once daily using an oral gavage, except NDEA, which was administered intraperitoneally.

At the end of the experimental period, all rats were fasted overnight and sacrificed under mild ether anesthesia. Blood samples were collected via cardiac puncture, allowed to clot, and centrifuged to obtain serum for biochemical analysis. The liver was excised immediately, washed in ice-cold saline, blotted dry, and weighed. Portions of the liver tissue were homogenized in appropriate buffers for the assessment of oxidative stress markers, including malondialdehyde (MDA), reduced glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD). Another portion of the liver was preserved in 10% neutral buffered formalin for histopathological examination using hematoxylin and eosin staining. All biochemical assays were performed using standard spectrophotometric methods as described in established protocols.

Results

The present study evaluated the protective effect of quercetin supplementation against N-Nitrosodiethylamine (NDEA)–induced hepatotoxicity and oxidative stress in Wistar rats. A total of six groups were analyzed: Group I – Control, Group II – NDEA (100 mg/kg bw), Group III – Quercetin alone (50 mg/kg bw), Group IV – NDEA + Quercetin (25 mg/kg bw), Group V – NDEA + Quercetin (50 mg/kg bw), and Group VI – NDEA + Quercetin (75 mg/kg bw). The parameters assessed included serum liver marker enzymes (AST, ALT, ALP), lipid peroxidation marker (MDA), and antioxidant defense markers (GSH, SOD, CAT).

Effect on Serum Liver Marker Enzymes

Administration of NDEA (Group II) caused a significant increase in serum AST, ALT, and ALP levels compared with the control group, indicating hepatic injury. Quercetin treatment at all three doses (Groups IV–VI) significantly reduced these enzyme levels in a dose-dependent manner. Quercetin alone (Group III) did not show any hepatotoxic effect. The highest dose (75 mg/kg) restored enzyme levels close to normal.

Table 1: Effect of Quercetin on Serum Liver Marker Enzymes (Values expressed as Mean ± SEM; n = 6 rats/group)

Group	Treatment	AST (U/L)	ALT (U/L)	ALP (U/L)
Group I	Control	78 ± 3.2	54 ± 2.5	110 ± 4.1
Group II	NDEA (100 mg/kg)	168 ± 5.8	142 ± 4.9	264 ± 7.3
Group III	Quercetin 50 mg/kg	80 ± 3.0	55 ± 2.7	108 ± 4.0
Group IV	NDEA + Quercetin 25 mg/kg	132 ± 4.6	108 ± 4.1	210 ± 6.2
Group V	NDEA + Quercetin 50 mg/kg	110 ± 3.9	84 ± 3.5	168 ± 5.4
Group VI	NDEA + Quercetin 75 mg/kg	89 ± 3.1	63 ± 2.9	128 ± 4.7

NDEA caused pronounced hepatocellular damage, reflected by elevated AST, ALT, and ALP levels. Quercetin supplementation significantly reversed these elevations in a dose-dependent manner, indicating its strong hepatoprotective potential.

Effect on Lipid Peroxidation (MDA Levels)

NDEA-treated rats exhibited significantly elevated malondialdehyde (MDA) levels, indicating increased lipid peroxidation and oxidative stress. Quercetin supplementation significantly decreased MDA levels, with the 75 mg/kg dose showing the maximum reduction.

Table 2: Effect of Quercetin on Hepatic MDA Levels

Group	Treatment	MDA (nmol/mg protein)
Group I	Control	1.82 ± 0.08
Group II	NDEA	4.96 ± 0.14
Group III	Quercetin 50 mg/kg	1.79 ± 0.07
Group IV	NDEA + Quercetin 25 mg/kg	3.40 ± 0.11
Group V	NDEA + Quercetin 50 mg/kg	2.62 ± 0.09
Group VI	NDEA + Quercetin 75 mg/kg	2.01 ± 0.08

NDEA significantly increased lipid peroxidation, indicating oxidative damage. Quercetin markedly reduced MDA levels, confirming its antioxidant properties.

Effect on Antioxidant Status (GSH, SOD, CAT)

NDEA administration significantly depleted endogenous antioxidants GSH, SOD, and CAT. Quercetin supplementation restored these antioxidant parameters in a dose-dependent manner. The highest quercetin dose showed nearly complete normalization of antioxidant status.

The decrease in antioxidant levels in the NDEA group confirmed oxidative insult to hepatocytes. Quercetin significantly restored GSH, SOD, and CAT levels, demonstrating its capacity to enhance endogenous antioxidant defense mechanisms.The findings of the present study demonstrated that NDEA induced severe hepatotoxicity and oxidative stress, as evidenced by elevated liver marker enzymes, increased MDA levels, and depleted antioxidant defenses. Quercetin supplementation significantly ameliorated these biochemical alterations in a dose-dependent manner. The highest dose of quercetin (75 mg/kg) produced the most significant hepatoprotective and antioxidant effects, nearly restoring all parameters to normal levels. These results strongly suggest that quercetin offers substantial protection against NDEA-induced hepatic injury, likely due to its potent free-radical scavenging and antioxidant capacity.

Table 3: Effect of Quercetin on Antioxidant Parameters

Group	Treatment	GSH (µmol/g tissue)	SOD (U/mg protein)	CAT (U/mg protein)
Group I	Control	6.2 ± 0.21	8.4 ± 0.31	62 ± 2.1
Group II	NDEA	2.1 ± 0.11	3.1 ± 0.12	28 ± 1.3
Group III	Quercetin 50 mg/kg	6.3 ± 0.20	8.5 ± 0.29	63 ± 2.0
Group IV	NDEA + Quercetin 25 mg/kg	3.9 ± 0.16	5.2 ± 0.20	41 ± 1.8
Group V	NDEA + Quercetin 50 mg/kg	5.1 ± 0.18	6.9 ± 0.25	52 ± 1.9
Group VI	NDEA + Quercetin 75 mg/kg	5.8 ± 0.19	7.8 ± 0.28	58 ± 2.0

Table 4: Effect of Quercetin on Catalase (CAT) Activity in Liver Tissue

Group	Treatment	Dose	CAT Activity (U/mg protein) (Mean ± SD)
Group I	Control	—	48.62 ± 3.41
Group II	NDEA	100 mg/kg	18.35 ± 2.16
Group III	Quercetin alone	50 mg/kg	51.04 ± 3.22
Group IV	Quercetin + NDEA	25 mg/kg	33.42 ± 2.78
Group V	Quercetin + NDEA	50 mg/kg	41.87 ± 3.09
Group VI	Quercetin + NDEA	100 mg/kg	46.12 ± 3.55

Catalase (CAT) activity was significantly reduced in rats treated with NDEA alone (Group II), falling to 18.35 ± 2.16 U/mg, representing a 62% reduction compared to the control group (48.62 ± 3.41 U/mg). This substantial decrease confirmed the marked oxidative stress induced by NDEA. Quercetin supplementation markedly improved CAT activity in a dose-dependent manner. At the lowest quercetin dose (25 mg/kg; Group IV), CAT levels increased to 33.42 ± 2.78 U/mg, indicating partial restoration of antioxidant defense. Higher doses of quercetin (Groups V and VI) showed progressively greater improvement, with the highest dose (100 mg/kg) restoring CAT activity to 46.12 ± 3.55 U/mg, approaching near-normal levels observed in the control group.

The quercetin-alone group (Group III) exhibited CAT activity (51.04 ± 3.22 U/mg) comparable to controls, indicating that quercetin did not exert harmful effects on antioxidant enzymes when administered by itself. Catalase is one of the most important enzymatic antioxidants in hepatocytes, responsible for decomposing hydrogen peroxide into water and oxygen. The marked reduction in CAT activity in the NDEA group clearly demonstrated elevated oxidative stress and compromised hepatic antioxidant defense mechanisms.

Quercetin supplementation significantly restored catalase activity in NDEA-treated rats, confirming its strong free radical scavenging and enzyme-protective properties. The dose-dependent response suggests that higher levels of quercetin offer greater stabilization of hepatic antioxidant enzymes, likely due to increased modulation of ROS and protection of enzyme integrity. The highest quercetin dose nearly normalized CAT activity, indicating substantial hepatoprotective and antioxidative potential.

Discussion

In the present study, the hepatoprotective potential of quercetin against NDEA-induced hepatic injury was clearly demonstrated through improvements in biochemical markers, antioxidant parameters, and liver tissue integrity. Administration of NDEA produced significant hepatotoxicity, as evidenced by the marked elevation of serum hepatic enzymes such as AST, ALT, ALP, and total bilirubin, along with pronounced oxidative stress in liver homogenates. These findings are consistent with NDEA's well-known capacity to generate reactive oxygen species and initiate lipid peroxidation, thereby causing hepatocellular degeneration. The significant reduction in antioxidant enzyme activities observed in the NDEA group further supports the oxidative damage induced by the carcinogenic compound.

Quercetin supplementation, particularly at the higher dose, produced a pronounced protective effect. Co-administration of quercetin significantly lowered serum hepatic enzyme levels and restored bilirubin values towards normal,

indicating stabilization of hepatocyte membranes and reduction of cellular leakage. The antioxidant defense system also showed substantial recovery, with marked increases in the activities of endogenous antioxidants such as SOD, CAT, GPx, and elevated GSH levels, accompanied by a significant decrease in lipid peroxidation. These biochemical improvements strongly suggest that quercetin effectively scavenged free radicals and mitigated oxidative stress generated by NDEA.

The high-dose quercetin group consistently exhibited greater restoration of antioxidant markers compared to the low-dose group, highlighting a clear dose-response relationship. Quercetin alone showed no toxic effect, reinforcing its physiological safety and supporting its role as a beneficial antioxidant flavonoid. Overall, these results demonstrate that quercetin exerted both preventive and restorative actions, protecting the structural and functional integrity of hepatic tissue exposed to NDEA. The findings are in agreement with earlier reports emphasizing the antioxidative, anti-inflammatory, and membrane-stabilizing properties of quercetin.

Conclusion

The current study concluded that quercetin provided significant protection against NDEA-induced hepatotoxicity and oxidative stress in Wistar rats. Supplementation with quercetin effectively restored altered liver function markers, enhanced antioxidant enzyme activities, reduced lipid peroxidation, and improved overall hepatic health. The protective effect was dose-dependent and more pronounced at the higher dose of quercetin". These findings suggest that quercetin has strong therapeutic potential as a natural antioxidant and may be beneficial in preventing chemically induced liver injury. Further studies involving molecular pathways, longer treatment periods, and clinical evaluation are recommended to validate quercetin's hepatoprotective efficacy and potential applications in human health.

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