Original article

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COENZYME Q10 ATTENUATES METHOTREXATE-INDUCED LIVER INJURY IN RATS

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Main goal of this research was investigation the protective effects of coenzyme Q10 on methotrexate-induced liver damage. Study was performed on 32 Wistar rats divided in 4 groups, whereas first group received normal saline, second received coenzyme Q10, third received methotrexate alone and fourth group received concomitantly coenzyme Q10 and methotrexate. Morphological and functional changes in liver tissue were performed by biochemical analysis of serum, histopathological analysis of liver tissue sections and determination of parameters of oxidative stress in liver tissue. Administration of methotrexate in rats caused a significant increase of the concentrations of AST, ALT and γ-GT and significant decrease of amount of total proteins in the serum compared with C group of animals. Also, methotrexate significantly increased MDA and AOPP levels in and decreased catalase activity in hepatic tissue. Histopathological analysis showed pronounced liver damage with cellular derangement of hepatic cordons and significant cell swelling, vacuolar degeneration and signs of inflammatory response after methotrexate administration.In group of rats that received coenzyme Q10 8 days after methotrexate administration, injury of liver tissue was significantly decreased with mild disorder of normal radial arrangement of the hepatocytes and only discretely uneven distribution of hepatic glycogen content. In same group, biochemical analysis showed significantly decreased concentrations of serum parameters of liver injury and changes of parameters of oxidative stress were statistically significantly ameliorated compared with results in group that received methotrexate alone. Our results confirmed coenzyme Q10 as a protective agent in methotrexate-induced hepatotoxicity probably due to its antioxidant effects.

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Key words: *methotrexate, coenzyme Q10, hepatotoxicity, oxidative stress*

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Introduction

Methotrexate (MTX) is a folic acid antagonist and it belongs to the group of cytostatics known as antimetabolites. Its use is widespread, considering that it is used as a therapeutic drug in the treatment of various types of cancer, rheumatoid arthritis and other autoimmune diseases (1). Side effects of MTX are numerous, some of which are myelosuppression, various infections, gastrointestinal disorders, and kidney and liver disorders.Considering liver, frequent side effects include an increase in liver enzymes, fatty liver, liver cirrhosis, a decrease in serum albumin, while acute hepatitis and reactivation of chronic hepatitis occur very rarely (2). The mechanisms by which MTX causes liver damage have not yet been fully investigated and clarified, but there are several assumptions about the pathophysiology of these injuries. Among many, the occurrence of oxidative stress in the tissue is the most common (3). Therefore, several antioxidant agents have been used to reduce its side effects (4).

Coenzyme Q10 (CQ10) is an endogenous lipid-soluble substance that is a strong antioxidant. Antioxidant properties of CQ10 are demonstrated trough its ability to scavenge reactive oxygen species (ROS) and prevent the lipid peroxidation in cellular membranes. Also, CQ10 has antiapoptotic and anti-inflammatory effects due to its ability to reduce secretion of proinflammatory cytokines (5). In earlier studies, the administration of CQ10 has shown a significant preventive effect in several models of oxidative and inflammatory damages of renal

or liver tissue induced by cisplatin and acetaminophen (6, 7). Considering that some studies have shown a protective effect of CQ10 in cases of nephrotoxicity and hepatotoxicity, the main goal of this research is to investigate the beneficial effects of CQ10 on methotrexate-induced liver damage.

Materials and methods

In our investigation we used adult male Wistar rats, of an average weight of 270 grams. The rats were kept in a standard conditions with controlled temperature (20 ± 2 ^{O}C) and humidity (60%) and 12 hours light/12 hours dark cycle. The animals had free access to food and water. All experiments were conducted at the Institute of Biomedical Research, Medical Faculty, Niš, Serbia, in accordance with all ethical regulations of European Union (EU Directive of 2010; 2010/63/EU) and principles for the Guide for the Care and Use of Laboratory Animals (8th Edition, 2011), and approved by the Ministry of Environmental Protection of the Republic of Serbia (No. 323-07-00073/2017-05/1).

Experimental protocol

A total of 32 animals were divided into four groups of 8 animals. The methotrexate group of animals or M-group, received MTXEBEWE Pharma (Ges.m.b.H.NFG.KG, Austria) intraperitoneally (i.p.) at a dose of 20 mg/kg on the first day of the experiment. Control group or C-group received 1 ml/kg i.p. of normal saline daily for eight days. Coenzyme Q10 (Q) group of animals received CQ10 Sigma-Aldrich (St. Louis, MO, USA) dissolved in corn oil (10 mg/kg) for 8 days(i.p.). Methotrexate - coenzyme Q10 (MQ) group of animals received MTX (20 mg/kg) on day 1, and CQ10 dissolved in corn oil (10 mg/kg) for 8 days. On the ninth day of the experiment, all animals were anesthetized with ketamine in a dose of 80 mg/kg and sacrificed. We took blood from aorta (separated serum immediately) to perform biochemical analysis, and we removed liver to determine tissue biochemical and histopathological studies.

Serum biochemical analysis

Biochemical analysis of serum included determining the concentrations of alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transferase (γ-GT) and total protein levels. All parameters were determined by Olympus AU680 Chemistry-Immuno Analyzer (A25 Biosystems, Barcelona, Spain).

Histopathological analysis

One part of liver tissue from each animal first was fixed in 10% paraformaldehyde at room temperature for 48 hours, than dehydrated in alcohol and embedded in paraffin. We cut tissue samples at a thickness of 5 mm (model: LKB 2218, LKB-Produkter AB, Bromma, Sweden) and stained using haematoxylin and eosin (HE) and periodic acid-Schiff (PAS) methods and analysed using Olympus BH2 light microscope.

Tissue biochemical analysis

We cut liver tissue samples into small pieces and homogenized in ice cold water by a homogenizer (VELP Scientifca, Italy). We prepared homogenates and separated supernatant using the same method as in our previous research (8). Protein content in the supernatants was determined according to the Lowry's method (9).

Levels of malondialdehyde (MDA) as a marker of lipid peroxidation in liver tissue were determined by method described by Ohkawa (10). After measuring of homogenate absorption, concentration of MDA was calculated and expressed as g/protein.

Determination of the concentration of advanced oxidation protein products (AOPP) in tissue homogenates was described in our previous study (8). The concentrations of AOPP were expressed as mmol/g of proteins.

Determination of the activity of catalase (CAT) was performed by the method described by Goth (11). We measured homogenate absorption at 405 nm and expressed activity of this enzyme as international units (IU) per gram of protein.

Statistical analysis

For statistical analysis we expressed results of examined parameters as the mean value ± standard deviation (SD). To determine statistically significant differences we performed one-way analysis of variance (ANOVA) followed by Tukey's post hoc test (GraphPad Prism version 5.03, San Diego, CA, USA). Probability values (p) ≤ 0.05 were considered to be statistically significant.

Results

Biochemical analysis

Administration of MTX in rats caused a significant increase ($p < 0.001$) in the concentrations of AST, ALT and γ-GT in M group compared to the values of the same parameters in the C group of rats. The amount of total protein in the serum was significantly decreased in the M group compared to the C group of animals ($p < 0.001$) (Figure 1). Rats that received CQ10 combined with MTX showed a significant decrease in AST, ALT andγ-GT compared to that when receiving MTX alone ($p < 0.001$) (Figure 1),while the serum total protein levels were significantly increased in the MQ group compared to the M group ($p < 0.05$) (Figure 1).

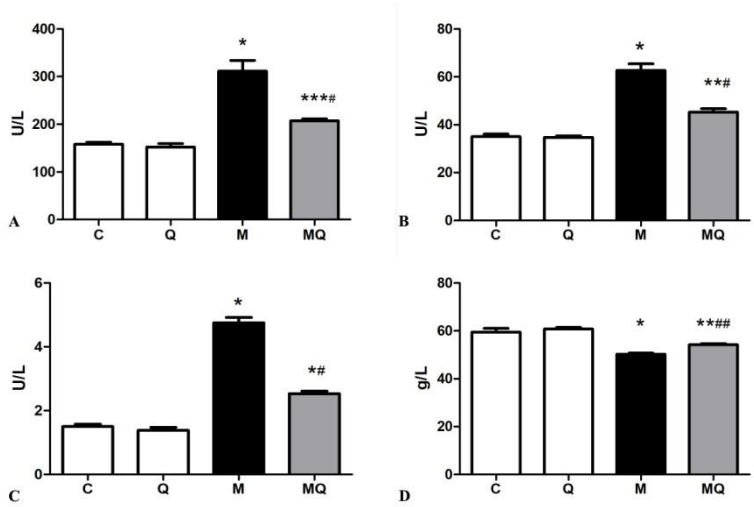

Figure 1. The concentrations of AST (A), ALT (B), γ-GT (C) and total protein (D) in serum of experimental animals. Data are given as mean ± SD, ANOVA followed by Tukey post hoc test.
*p < 0.001 vs. C group; **p < 0.01 vs. C group; ***p < 0.05 vs. C group;
#p < 0.001 vs. M group; ## p < 0.05 vs. M group

Histopathological analysis

Liver sections from the control group showed the normal morphology of hepatic lobules. Features of a regular tissue structure, including adequate localization of central veins, normal composition of portal tracts and streaming of blood sinusoids are presented in Figure 2A. Orderly distribution of hepatocytes in hepatic plates is also retained in the Q group, where no significant changes in histologic architecture were observed (Figure 2B). Sections from the methotrexate-treated group demonstrated liver injury associated with cellular derangement of hepatic cordons and significant cell swelling. Hepatotoxic damage reflected in the reversible and irreversible cellular alterations ranged from vacuolar degeneration, nuclear reactive changes, to apoptosis of hepatocytes. Individual hepatocytes or cell clusters showed cytoplasmic hypereosinophillia and condensation, and nuclear hyperchromasia and pyknosis.

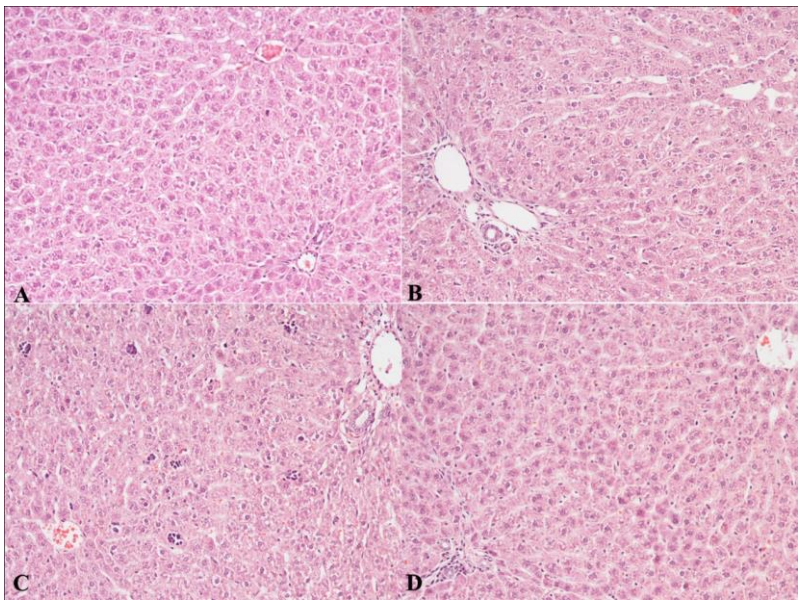

Figure 2. Photomicrographs of hematoxylin and eosin (H&E)-stained liver sections of:
A) C group, B) Q group, C) M group and D) CQ group of animals (Original magnification 200x)

Histologic signs of inflammatory response were prominent in this group. An infiltrate composed of mononuclear cells, predominantly lymphocytes, and, in lesser extent, polymorphonuclear leukocytes, was observed within the portal tract, surrounding the billiary ducts and portal vein branches. Moreover, the aggregates of the immune cells had a quite conspicuous intralobular distribution. Portal veins and sinusoid capillaries showed marked congestion (Figure 2C). In the group MQ, where animals received CQ10 8 days after the administration of methotrexate, the extent of tissue damage was visibly less striking than in the M group. Liver sections showed a disturbance of the hepatic lobule and a mild congestion of the portal area associated with scarce inflammatory infiltration. There has been some cellular edema and degeneration resulting in mild architectural distortion, but irreversible injury with cell loss was not noted (Figure 2D). Inflammatory infiltrate was restricted to portal tracts, with no significant intralobular activity. Control groups sections showed a normal hepatic architecture and cell cytoplasm rich with PAS-positive glycogen granules (Figure 3 A and B). The abundance of glycogen content significantly deteriorated in methotrexate treated animals. In addition to massive hepatic degeneration, depletion of PAS-positive intracellular content was striking. Hepatocytes appeared empty and displayed clear, transparent cytoplasm, while residual glycogen granules where shifted against the cell membrane. Generally, the distribution of PAS-positive granules was uneven and varied between areas of hepatic tissue (Figure 3C). In the CQ group changes were associated with moderate amelioration of hepatocyte degeneration with apparently near normal distribution of PAS-positive granules (Figure 3D).

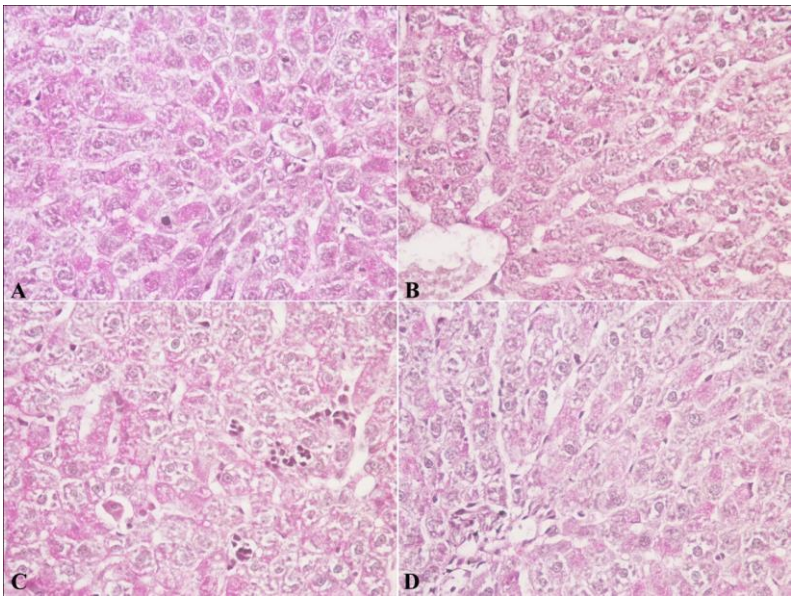

Figure 3. Photomicrographs of PAS - Periodic acid–Schiff-stained rat liver sections of:
A) C group, B) Q group, C) M group and D) CQ group of animals (Original magnification 400x)

Tissue biochemical analysis

The statistical analysis showed a significant increase in MDA and AOPP levels in tissue homogenates in the M group when compared with the C-group ($p < 0.001$), while the CAT activity in liver tissue was significantly decreased ($p < 0.001$) in the M-group of animals in comparison with the C-group (Table 1). Concomitant administration of CQ10 with MTX in the MQ group attenuated oxidative stress induced by MTX, so in this group levels of MDA and AOPP in liver tissue were significantly decreased compared to the M group of animals ($p < 0.05$), while CAT activity was significantly increased compared to the M group ($p < 0.01$).

Table 1. Parameters of oxidative stress in liver tissue

Group/Parameter	**AOPP** (mmol/g proteins)	**MDA** (mmol/g proteins)	**CAT** (IU/g proteins)
C	17.44 ±3.540	5.002 ± 1.766	26.71 ± 3.376
Q	17.45 ±4.645	4.672 ± 1.524	26.72 ± 4.083
M	30.15 ±1.422*	10.45 ± 1.110*	10.40 ± 4.236*
MQ	23.92 ±3.680***#	7.998 ± 0.4312**#	19.12 ± 1.821**##

Data are given as mean ± SD, ANOVA followed by Tukey post hoc test
*p< 0.001 vs. C group; **p< 0.01 vs. C group; ***p< 0.05 vs. C group
#p< 0.05 vs. M group; ##p< 0.01 vs. M group

Discussion

The antineoplastic drug MTX is a very effective drug in the treatment of various types of cancers and other diseases such as rheumatoid arthritis (12, 13). However, its use leads to side effects that include myelosuppression, gastrointestinal disorders, kidney damage, acute injury of liver, hepatic fibrosis and cirrhosis (14). In order to reduce the side effects, the administration of some non-toxic natural substances could significantly ameliorate the damages caused by MTX with the preservation of its chemotherapeutic efficacy. In our research, we performed histopathological and biochemical analyses of liver tissue to determine structural and functional alterations induced by MTX in the liver and to determine potential protective effects of CQ10 on MTX-induced liver injury. In our research, we found that a single dose of MTX caused a significant increase in AST, ALT and γ-GT levels and a decrease in the total protein ($p < 0.001$) compared to the control group. Similar effects of MTX were shown in study published by Kelleni et al. (14). We showed that administration of CQ10 (10 mg/kg), 8 days after a single dose of MTX had protective effect on liver treated with MTX. This protective effect was evidenced by significantly reduced levels of AST, ALT and γ-GT and decreased levels of total protein in the MQ group in comparison with the group of animals that received only MTX (Figure 1).

A histopathological analysis was performed in order to determine morphological injuries. We showed that MTX-treated group showed pronounced liver damage with cellular derangement of hepatic cordons and significant cell swelling, vacuolar degeneration and signs of an inflammatory response. Portal veins and sinusoid capillaries showed congestion. Small foci of lobular inflammation could also be found (Figure 2C). Also, on PAS stained liver tissue sections there was significant abundance of glycogen content and hepatocytes appeared empty and displayed clear, transparent cytoplasm (Figure 3C).

Our biochemical and histopathological analysis showed that MTX induced damage of liver tissue. Rats treated with CQ10 and MTX revealed an amelioration of histopathological alterations. In the MQ group comprised a mild congestion of the portal area with scarce inflammatory infiltration was observed. Irreversible injury with cell loss was not noted. In PAS stained tissue sections the distribution of PAS positive granules was near normal (Figures 2D and 3D). These results were in accordance with the previous findings that showed that CQ10 has protective effects against cisplatin, fructose and acetaminophen-induced kidney and liver injury (7, 15, 16).

Despite numerous studies with MTX, the main mechanism of MTX-induced liver injury has not yet been clarified fully yet. Coleshowers et al. (4) and Goudarzi et al. (17) suggested that one of the most important mechanisms in MTX-induced liver injury is the generation of the ROS and reduction of the antioxidant defence system. In order to determine if MTX causes oxidative stress, and if CQ10 is able to attenuate possible disturbances of oxidative stress parameters, we examined levels of MDA and AOPP as well as catalase activity in liver tissue homogenates. Our results showed that levels of MDA and AOPP were significantly increased while catalase activity was significantly decreased in the liver tissue after only one single dose of MTX (Table 1). Dalaklioglu et al (18) suggested that MTX induces generation of ROS such as superoxide anion and hydroxyl radicals and also strongly stimulates occurrence of lipid peroxidation in liver tissue. Lipid peroxidation is an autocatalytic process that most often ends with irreversible damage of the function and structure of the cell membrane. Lipid peroxidation products, especially MDA, can damage the membranes of lysosomes, which leads to the release of hydrolytic enzymes, as well as the damage of the mitochondrial membranes, which causes the release of Ca ions and the activation of enzymes dependent on this ion (19). Increased levels of AOPP in the liver tissue in the M group indicate that oxidative protein modification has occurred. Oxidative modification of proteins leads to structural alterations in the primary, secondary and tertiary structure of proteins due to changes in amino acid residue molecules, as well as a functional inactivation of many enzymes (20). Our results were consistent with the assumptions that part of the mechanism of MTX hepatotoxicity is related to the depletion of the antioxidant system (21, 22). Catalase activity in the M group was statistically significantly reduced compared with theCgroup (Table 1). Catalase is one of the endogenous antioxidant enzymes that play a key role in

reducing the oxidative modification of lipids and the propagation of lipid peroxidation (4).

CQ10 is an endogenous liposoluble benzoquinone that contains 10 isoprene side chains and it functions as a transporter of electrons in the mitochondrial respiratory chain where it plays a key role in aerobic cellular respiration to produce ATP. In addition to participating in the elimination of free radicals, it also prevents the initiation of lipid peroxidation, i.e. lipid damage in cell membranes under the influence of free radicals (23). In our study, the levels of MDA and AOPP in liver homogenates of the MQ group of rats were significantly decreased compared to the same in M group (Table 1). Administration of CQ10 significantly increased catalase activity in liver homogenates in the MQ group compared to catalase activity in group of animals that received MTX only once. Our results showed that CQ10 ameliorated liver injuries caused by MTX probably through its antioxidative effects. We can indicate the key role of CQ10 in the scavenging of free radicals produced by the MTX, as well as in the protection of lipids and proteins from oxidative modification, and a significant role in preserving the activity of antioxidant enzymes. These effects of CQ10 certainly greatly contribute to the protection from structural liver damage caused by the MTX, which we confirmed by histopathological and biochemical analysis in our study.In recent studies, it has been confirmed that CQ10 has protective effects on proteins, DNA and lipids in membranes from oxidative damage, primarily by strong inhibition of oxidative stress (24). These effects of CQ10 might be the result of its redox activity in mitochondrial respiratory chain. Earlier studies showed that CQ10 primarily acts in the mitochondria, where it is able to transfer electrons in mitochondrial respiration. When CQ10 is acting as an antioxidant in the mitochondria it is able to neutralize both, free radicals in the cytoplasm and ROS produced in the mitochondria (23).

Conclusion

Our results confirm that MTX damages lipids of the cell membrane and proteins due to increased production of ROS. Probably, lipid peroxidation and damaging of structure of proteins contribute further to DNA damage and apoptosis of cells. According to our results, administration of CQ10 significantly ameliorates oxidative and histological injury of liver tissue caused by MTX. These results indicate that CQ10 can be very useful in the prevention of structural and functional liver injury caused by MTX. Considering the widespread use of MTX in the treatment of a several pathological conditions, the use of CQ10 should be further study in order to standardize its application.

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KOENZIM Q10 UBLAŽAVA OŠTEĆENJE JETRE IZAZVANO METOTREKSATOM KOD PACOVA

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Glavni cilj ovog istraživanja bio je ispitivanje zaštitnih efekata koenzima Q10 na oštećenje jetre izazvano metotreksatom. Studija je obavljena na 32 pacova Vistar podeljenih u 4 grupe, pri čemu je prva grupa primala normalni fiziološki rastvor, druga koenzim Q10, treća samo metotreksat i četvrta grupa istovremeno koenzim Q10 i metotreksat. Morfološke i funkcionalne promene u tkivu jetre urađene su biohemijskom analizom seruma, histopatološkom analizom preseka tkiva jetre i određivanjem parametara oksidativnog stresa u tkivu jetre. Primena metotreksata kod pacova izazvala je značajno povećanje koncentracija AST, ALT i g-GT i značajno smanjenje količine ukupnih proteina u serumu u poređenju sa C grupom životinja. Takođe, metotreksat je značajno povećao nivoe MDA i AOPP i smanjio aktivnost katalaze u tkivu jetre. Histopatološka analiza je pokazala izraženo oštećenje jetre sa ćelijskim poremećajem jetrenih kordona i značajnim oticanjem ćelija, vakuolnom degeneracijom i znacima inflamatornog odgovora nakon primene metotreksata. U grupi pacova koji su primali koenzim Q10 8 dana nakon primene metotreksata, značajno je smanjena povreda tkiva jetre. Blagi poremećaj normalnog radijalnog rasporeda hepatocita i samo diskretno neravnomerna raspodela sadržaja hepatičnog glikogena. U istoj grupi, biohemijska analiza je pokazala značajno smanjene koncentracije serumskih parametara oštećenja jetre, a promene parametara oksidativnog stresa su statistički značajno poboljšane u poređenju sa rezultatima u grupi koja je primala samo metotreksat. Naši rezultati su potvrdili da je koenzim Q10 zaštitni agens kod hepatotoksičnosti izazvane metotreksatom, verovatno zbog njegovih antioksidativnih efekata.

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Ključne reči: *metotreksat, koenzim Q10, hepatotoksičnost, oksidativni stres*