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Research Article

Comparative Analysis of Hepatoprotective Potential of Coenzyme Q10 as a Preventive and a Therapeutic Agent in Statin-Induced Hepatotoxicity

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Abstract

Statins induce hepatotoxicity via reduced levels of Coenzyme Q10, inflammation, and oxidative stress. Coenzyme Q10 is anti-apoptotic and possesses the antioxidative potential and hence has been studied for its hepatoprotective potential. However, owing to the differing mechanisms of prevention of damage and its reversal, we hypothesize that coenzyme Q10 might not have the same efficacy as a protective versus a therapeutic agent. An experimental study of 3 weeks was conducted on a sample of 35 mice, randomly divided into 7 groups. Group 1 was used as control. Group 2 received 50mg/kg/day of simvastatin intraperitoneally (I/P). Group 3 received I/P 50mg/kg/day rosuvastatin. Group 4 received 50mg/kg/day of simvastatin+10mg/kg of coenzyme Q10. Group 5 received 50mg/kg/day of rosuvastatin+10mg/kg of coenzyme Q10 I/P. In group 6 simvastatin 50mg/kg & 7 rosuvastatin 50mg/kg was given for a week, while 10mg/kg of Coenzyme Q10 was started in the 2nd week and continued for 2 weeks. Hepatic damage was observed in groups 2,3,6 and 7 indicated by raised alanine transaminase levels of 320.4, 179.8, 301.4, and 186.8 and raised aspartate aminotransferase levels of 320, 196, 421.4, and 307.6. Bilirubin stayed within normal limits. This study concludes that Coenzyme Q10 prevents statin-induced liver damage but has no role as a therapeutic agent once the liver damage has occurred.

Keywords: Hepatotoxicity, hepatoprotection, oxidative stress, inflammation.

Introduction

Statins are the first-line therapy for hypercholesterolemia. These drugs block the rate-limiting step in cholesterol synthesis by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, and by this mechanism, these drugs cause marked reductions in LDL-C (National Cholesterol Education Program Expert Panel on Detection and Treatment of High Blood Cholesterol in 2002). As a result, there is enhanced removal of LDL-C from circulation.

Although the risk is low, statins are known to cause hepatotoxicity. Statins cause elevations of aspartate aminotransferase (AST) and alanine transaminase (ALT), cholestatic hepatotoxicity, fulminant hepatitis, autoimmune hepatitis, and cirrhosis. Various mechanisms are hypothesized that are responsible for statin-induced hepatotoxicity (Bhardwaj and Chalasani 2007) (a) Simvastatin (Lipid Lowering Agent) competitively inhibits 3-hydroxy-3 methyl-glutaryl coenzyme A (HMG-Co A) to mevalonate which is a precursor of Coenzyme Q10 (CoQ10). CoQ10 has membrane stabilizing effects and also possess antioxidant property. Statins lower the levels of CoQ10 in the body which can be responsible for hepatotoxicity (Frei, Kim, and Ames 1990; Whirl-Carrillo et al. 2012).

Coenzyme Q is well defined as a crucial component of the oxidative phosphorylation process in mitochondria which converts the

Table 1 Descriptive statistics of the bilirubin, ALT, and AST for each group

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean Lower Bound	95% Confidence Interval for Mean Upper Bound
Bilirubin	1	5	.1340	.01140	.00510	.1198	.1482
	2	5	.1300	.01000	.00447	.1176	.1424
	3	5	.1180	.01095	.00490	.1044	.1316
	4	5	.1180	.00837	.00374	.1076	.1284
	5	5	.1260	.01817	.00812	.1034	.1486
	6	5	.1540	.00548	.00245	.1472	.1608
	Total	30	.1300	.01619	.00296	.1240	.1360
ALT	1	5	24.6000	1.14018	.50990	23.1843	26.0157
	2	5	320.4000	37.85895	16.93104	273.3919	367.4081
	3	5	179.8000	26.02307	11.63787	147.4881	212.1119
	4	5	23.2000	1.78885	.80000	20.9788	25.4212
	5	5	23.0000	1.58114	.70711	21.0368	24.9632
	6	5	301.4000	32.72308	14.63421	260.7689	342.0311
	Total	30	145.4000	133.39224	24.35398	95.5905	195.2095
AST	1	5	80.4000	1.51658	.67823	78.5169	82.2831
	2	5	420.0000	126.86804	56.73711	262.4725	577.5275
	3	5	196.0000	15.79557	7.06399	176.3872	215.6128
	4	5	80.0000	5.61249	2.50998	73.0312	86.9688
	5	5	80.4000	4.82701	2.15870	74.4065	86.3935
	6	5	421.4000	45.85085	20.50512	364.4687	478.3313
	Total	30	213.0333	163.06683	29.77179	152.1432	273.9235

energy in carbohydrates and fatty acids into ATP to drive cellular machinery and synthesis. In mitochondria and lysosomes, coenzyme Q undergoes reduction/oxidation cycles during which it transfers protons across the membrane to form a proton gradient (Ricaurte et al. 2006; Kennedy et al. 2020). The presence of coenzyme Q stimulates cell growth, inhibits apoptosis, controls thiol groups, forms hydrogen peroxide, and controls membrane channels. All of this is evidence of the anti-oxidative potential of coenzyme Q (Tawfik 2015; Pompella et al. 2003). In addition, it is capable of preventing and reversing the hepatotoxicity induced by statins.

It has been a long-believed fact that via all the above-mentioned mechanisms, CoQ10, seems to be one of the ideal drugs for the prevention and treatment of liver damage induced by statins, but the question arises here, does CoQ10 has equal efficacy in preventing as well as treating the statin or for that matter any hepatotoxic drug-induced damage to the liver (Kyrklund et al. 2000;

Mohamed et al. 2019). The literature shows separately conducted studies on the prevention of hepatic damage and treatment but comparative data is not available. Preventing the damage by blocking mechanisms and reversing it, require different mechanisms so we may hypothesize in this regard, that CoQ10 may have a varying response when used as a preventive agent as compared to its utility as a therapeutic choice for treatment of drug-induced liver damage.

Table 2 Multiple comparisons between different groups for bilirubin. *p<0.05

			Mean			95% Confidence Interval	
Dependent Variable	(I) Group	(J) Group	Difference (I-J)	Std. Error	Sig.	Lower Bound	Upper Bound
Bilirubin	1	2	.00400	.00721	.993	-.0183	.0263
		3	.01600	.00721	.266	-.0063	.0383
		4	.01600	.00721	.266	-.0063	.0383
		5	.00800	.00721	.873	-.0143	.0303
		6	-.02000	.00721	.097	-.0423	.0023
	2	1	-.00400	.00721	.993	-.0263	.0183
		3	.01200	.00721	.567	-.0103	.0343
		4	.01200	.00721	.567	-.0103	.0343
		5	.00400	.00721	.993	-.0183	.0263
		6	-.02400*	.00721	.030*	-.0463	-.0017
	3	1	-.01600	.00721	.266	-.0383	.0063
		2	-.01200	.00721	.567	-.0343	.0103
		4	.00000	.00721	1.000	-.0223	.0223
		5	-.00800	.00721	.873	-.0303	.0143
		6	-.03600*	.00721	.001*	-.0583	-.0137
	4	1	-.01600	.00721	.266	-.0383	.0063
		2	-.01200	.00721	.567	-.0343	.0103
		3	.00000	.00721	1.000	-.0223	.0223
		5	-.00800	.00721	.873	-.0303	.0143
		6	-.03600*	.00721	.001*	-.0583	-.0137
	5	1	-.00800	.00721	.873	-.0303	.0143
		2	-.00400	.00721	.993	-.0263	.0183
		3	.00800	.00721	.873	-.0143	.0303
		4	.00800	.00721	.873	-.0143	.0303
		6	-.02800*	.00721	.008	-.0503	-.0057
	6	1	.02000	.00721	.097	-.0023	.0423
		2	.02400*	.00721	.030*	.0017	.0463
		3	.03600*	.00721	.001*	.0137	.0583
		4	.03600*	.00721	.001*	.0137	.0583
		5	.02800*	.00721	.008	.0057	.0503

This study aimed to assess and compare the hepatoprotective efficacy of coenzyme 10 in preventing liver damage as well as reversing it in statin-induced hepatotoxicity.

Materials and Methods

This experimental study was conducted at the Pharmacology Dept, Animal house Northwest School of Medicine Hayatabad Peshawar for 3 weeks. BALB/C male mice, weighing between (25 to 30 gm), aged 5-7 weeks were used for this study. Mice were randomly divided into 7 groups of 5 mice each for 3 weeks. In the normal control group (*n=5* mice), 5 mice were given 1 ml of saline intraperitoneally daily. In the simvastatin group (n=5 mice) 50mg/kg of simvastatin was administered intraperitoneally in saline daily. In the rosuvastatin group (n=5 mice) 50mg/kg of rosuvastatin was administered I/P in saline daily. In group 4 (n=5 mice) 50mg/kg of simvastatin+10mg/kg of CoQ10 was administered I/P in saline daily. Group 5 (n=5 mice) received 50mg/kg of rosuvastatin+10mg/kg of CoQ10 I/P in saline daily. In group 6 simvastatin 50mg/kg was given for a week, and 10mg/kg of CoQ10 was started in the 2nd week and continued for 2 weeks. In group 7, rosuvastatin 50mg/kg was given for a week, and 10mg/kg of CoQ10 was started in the 2nd week and continued for 2 weeks.

At the end of the experiments after 3 weeks mice were sacrificed in the pharmacology department, Northwest School of Medicine. Assessment of the bilirubin, enzymes including alkaline phosphatase, aspartate transaminase enzyme, and alanine aminotransferase enzyme was performed from the blood samples collected. Data were analyzed through social sciences (SPSS) version 23. The arithmetic means of the observed values were calculated. Results were expressed as mean ± S.E.M.

Results

Table 1 shows the descriptive statistics of bilirubin, ALT, and AST for each animal group. For group 1 which received I/P normal saline daily for 3 weeks, liver function parameters remained within normal limits Mean serum ALT level was 24.6 ± 1.14 U/L, AST had a mean value of 80.4 ± 1.51 U/L, and Bilirubin showed a mean value of 0.13 ± 0.01 mg/dL.

The average weight of the mice in group 2 reduced from 30g initially to 21g by the end of 3 weeks. Mean serum ALT levels significantly raised to a mean value of 320.4 ± 37.85 U/L. The levels of AST showed a raised mean value of 320 ± 126.86 U/L, while the rise in Bilirubin was within normal limits with a mean value of 0.12± 0.01mg/dL.

The initial average of 30g was reduced to an average of 26g in group 3. The average weight of the mice in group 3 reduced from 30g initially to 21g by the end of 3 weeks. Mean serum ALT levels significantly raised to a mean value of 179.8 ± 26.02 U/L. The levels of AST showed a raised mean value of 196 ± 15.79 U/L, while the rise in Bilirubin was within normal limits with a mean value of 0.12± 0.01mg/dL.

Group 4 simvastatin along with CoQ10 for 3 weeks. Liver function parameters remained within normal limits Mean serum ALT level was 23.2± 1.78 U/L, AST had a mean value of 80 ± 5.61U/L and Bilirubin showed a mean value of 0.11 ± 0.00 mg/dL.

Group 5 received rosuvastatin along with CoQ10. Liver function parameters remained within normal limits Mean serum ALT level was 23 ± 1.58 U/L, AST had a mean value of 80.4 ± 4.82U/L, and Bilirubin showed a mean value of 0.12 ± 0.01.

Group 6 received Simvastatin for 1 week then followed by CoQ10 daily intraperitoneally for 2 weeks, mice were noted to be extremely lethargic and the weight was reduced from an initial 30g average to 19g average. The liver function test parameters of ALT and AST were elevated higher as compared to the group that

Table 3 Multiple comparisons between different groups for ALT. *p<0.05

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
ALT	1	2	-295.80000*	14.57921	.000*	-340.8779	-250.7221
		3	-155.20000*	14.57921	.000*	-200.2779	-110.1221
		4	1.40000	14.57921	1.000	-43.6779	46.4779
		5	1.60000	14.57921	1.000	-43.4779	46.6779
		6	-276.80000*	14.57921	.000	-321.8779	-231.7221
	2	1	295.80000*	14.57921	.000*	250.7221	340.8779
		3	140.60000*	14.57921	.000*	95.5221	185.6779
		4	297.20000*	14.57921	.000*	252.1221	342.2779
		5	297.40000*	14.57921	.000*	252.3221	342.4779
		6	19.00000	14.57921	.780	-26.0779	64.0779
	3	1	155.20000*	14.57921	.000*	110.1221	200.2779
		2	-140.60000*	14.57921	.000*	-185.6779	-95.5221
		4	156.60000*	14.57921	.000*	111.5221	201.6779
		5	156.80000*	14.57921	.000*	111.7221	201.8779
		6	-121.60000*	14.57921	.000*	-166.6779	-76.5221
	4	1	-1.40000	14.57921	1.000	-46.4779	43.6779
		2	-297.20000*	14.57921	.000*	-342.2779	-252.1221
		3	-156.60000*	14.57921	.000*	-201.6779	-111.5221
		5	.20000	14.57921	1.000	-44.8779	45.2779
		6	-278.20000*	14.57921	.000*	-323.2779	-233.1221
	5	1	-1.60000	14.57921	1.000	-46.6779	43.4779
		2	-297.40000*	14.57921	.000*	-342.4779	-252.3221
		3	-156.80000*	14.57921	.000*	-201.8779	-111.7221
		4	-.20000	14.57921	1.000	-45.2779	44.8779
		6	-278.40000*	14.57921	.000*	-323.4779	-233.3221
	6	1	276.80000*	14.57921	.000*	231.7221	321.8779
		2	-19.00000	14.57921	.780	-64.0779	26.0779
		3	121.60000*	14.57921	.000*	76.5221	166.6779
		4	278.20000*	14.57921	.000*	233.1221	323.2779
		5	278.40000*	14.57921	.000*	233.3221	323.4779

received only Simvastatin. Mean serum ALT was 301.4 ± 32.72 U/L; AST had a mean value of 421.4 ± 45.85 U/L and Bilirubin was 0.15± 0.00 mg/dL.

Group 7 was given Rosuvastatin for 1 week followed by CoQ10 daily intraperitoneally for 2 weeks, mice were noted to be extremely lethargic and the weight reduced from an initial 30g average to 18g average. The liver function test parameters of ALT and AST were elevated higher as compared to the group that received only Simvastatin. Mean serum ALT was 186.8± 17.62 U/L; AST had a mean value of 307.6± 34.37 U/L and Bilirubin was 0.14 ± 0.00 mg/dL.

Table 2 shows multiple comparisons between different groups for bilirubin after post hoc test-Tukey's Honest Significant Difference (HSD). These results show statistically significant differences between groups 2 & 6, 3 & 6, and 4 & 6. Similarly, table 3 shows multiple comparisons between different groups for ALT after post hoc tests-Tukey's HSD. These results show statistically significant differences between groups 1 & 2, 1 & 3, 2 & 3, 2 & 4, 2 & 5, 3 & 4, 3 & 5, 3 &6, 4 & 6 and 5 & 6. Similarly, table 4 shows multiple comparisons between different groups for AST after post hoc tests-Tukey's HSD. These results show statistically significant differences between groups 1 & 2, 1 & 3, 1 & 6, 2 & 3, 3 & 4, 2 & 5, 3 & 4, 3 & 5, 3 & 6, 4 & 6, and 5 & 6.

Discussion

Treatment with statins, especially for prolonged periods and at higher doses produces hepatic cell death and damage to the DNA hence reducing the synthesis of ATP. CoQ10 is one of the major antioxidants in the body. The reduction in the levels of the CoQ10 is directly related to the increasing doses of the HMG-CoA reductase inhibitors. Various studies have postulated the protective effects of CoQ10 supplementation in statin-induced liver cell damage, causing a reduction in hepatocyte damage, reducing oxidative stress that was causing damage to the DNA, and improvement in the production of ATP. CoQ10 also stabilizes the cell membranes and is one of the mandatory requirements for mitochondrial respiration, hence producing energy for different body functions.

The deficiency of the CoQ10 produced following statin administration has the potential to trigger hepatic cellular apoptosis and cirrhosis. The entire cascade of the protective mechanism controlled by Q10 is disturbed. Not only the scavenging action of the free radicals is lost but in addition, but the membrane stabilizing effect is also disturbed, hence causing severe cellular damage. Although these mechanisms undoubtedly play a very significant role in hepatotoxicity induced by statins and its valid to conclude the protective effect of CoQ10, however, its preventive role is not clear. CoQ10 does may have a preventive role but there are not a lot of investigations that studied the preventive role of CoQ10 in statin-induced hepatotoxicity. Previous literature talks about the role of coenzyme in hepatic protection but fails to demarcate the differences in its preventive and protective effects.

The current study was designed based on the above-mentioned debate and we experimented on the preventive and therapeutic supplementation of the co-enzyme Q10 in statin-induced hepatotoxicity. Two groups received coenzyme from the very beginning of the therapy along with simvastatin and rosuvastatin while two groups were given CoQ10 after impending liver damage has occurred, which was confirmed via liver function parameters of 2 mice from each group. The CoQ10 was started after the hepatotoxicity had already ensued. The groups receiving only simvastatin and rosuvastatin showed raised

Table 4 Multiple comparisons between different groups for AST. *p<0.05

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
AST	1	2	-339.60000*	35.12302	.000*	-448.1980	-231.0020
		3	-115.60000*	35.12302	.032*	-224.1980	-7.0020
		4	.40000	35.12302	1.000	-108.1980	108.9980
		5	.00000	35.12302	1.000	-108.5980	108.5980
		6	-341.00000*	35.12302	.000*	-449.5980	-232.4020
	2	1	339.60000*	35.12302	.000*	231.0020	448.1980
		3	224.00000*	35.12302	.000*	115.4020	332.5980
		4	340.00000*	35.12302	.000*	231.4020	448.5980
		5	339.60000*	35.12302	.000*	231.0020	448.1980
		6	-1.40000	35.12302	1.000	-109.9980	107.1980
	3	1	115.60000*	35.12302	.032*	7.0020	224.1980
		2	-224.00000*	35.12302	.000*	-332.5980	-115.4020
		4	116.00000*	35.12302	.031*	7.4020	224.5980
		5	115.60000*	35.12302	.032*	7.0020	224.1980
		6	-225.40000*	35.12302	.000*	-333.9980	-116.8020
	4	1	-.40000	35.12302	1.000	-108.9980	108.1980
		2	-340.00000*	35.12302	.000*	-448.5980	-231.4020
		3	-116.00000*	35.12302	.031*	-224.5980	-7.4020
		5	-.40000	35.12302	1.000	-108.9980	108.1980
		6	-341.40000*	35.12302	.000*	-449.9980	-232.8020
	5	1	.00000	35.12302	1.000	-108.5980	108.5980
		2	-339.60000*	35.12302	.000*	-448.1980	-231.0020
		3	-115.60000*	35.12302	.032*	-224.1980	-7.0020
		4	.40000	35.12302	1.000	-108.1980	108.9980
		6	-341.00000*	35.12302	.000*	-449.5980	-232.4020
	6	1	341.00000*	35.12302	.000*	232.4020	449.5980
		2	1.40000	35.12302	1.000	-107.1980	109.9980
		3	225.40000*	35.12302	.000*	116.8020	333.9980
		4	341.40000*	35.12302	.000*	232.8020	449.9980
		5	341.00000*	35.12302	.000*	232.4020	449.5980

liver function tests indicating the toxic potential of the preparation being used. These results are comparable with previous studies that identified the hepatotoxic potential of simvastatin (Velickova, Nateva, and Stojanovska 2019) as well as rosuvastatin (Thotakura et al. 2018). and hypothesized various mechanisms involved (Lee and Kim 2019; Farrag et al. 2018).

Groups 4 and 5 were given preventive CoQ10. These two groups had normal liver parameters, indicating a preventive effect of coenzyme Q. These results are consolidated by several studies experimenting on the protective effect of CoQ10 in statin-induced liver damage (Eghbal, Abdoli, and Azarmi 2014). The drug-induced liver damage starts with the damage to the cellular mitochondria, whose processes are normally regulated by CoQ10 (Marques et al. 2018; Eftekhari et al. 2018). The depletion of the CoQ10 disturbs the entire mitochondrial respiratory chain which then leads to cellular apoptosis and damage (Zhong et al. 2017). The results in our study are suggestive of the fact that the mechanisms triggered by the disturbance of the respiratory chain cannot be stopped or controlled by CoQ10 once they have been triggered, hence leading to progressive cellular damage even in the presence of CoQ10 supplementation.

The groups that received CoQ10 as a therapeutic approach after the toxicity has been induced showed a significant increase in the liver function tests and indicated liver damage. The rise in the liver parameters was as high as they were in groups that solely received simvastatin and rosuvastatin. These findings direct us toward the hypothesis that CoQ10 is a preventive agent but has no role in the reversal of liver damage after it has already occurred. In addition, the CoQ10 also does not seem to reduce the progression of an already imposed liver damage as the parameters were the same as the ones that only received hepatotoxic drugs without any protective agents.

This finding may be attributed to the fact that once the liver damage has started and the levels of CoQ10 have been reduced, the cascade of apoptotic reactions is started that most probably is not reversible with the substitution of CoQ10. However, we can also hypothesize that if CoQ10 levels are maintained then the triggers for liver damage are blocked, so CoQ10 plays a role in preventing and blocking the liver damage followed by statin administration but is not capable of repairing and reversing the damage or to stop further damage progression.

Conclusions

CoQ10 possesses a preventive effect on the hepatotoxicity induced by HMG-CoA reductase inhibitors via scavenging oxidative radicals and prevention of mitochondrial damage. However, our study postulates that once the hepatic damage has already started, CoQ10 fails to reverse the hepatic damage or limit the progression. It is most likely due to the inability of the CoQ10 to control the cascade of reactions triggered by the disturbance of the mitochondrial electron transport chain. Hence CoQ10 is not a curative therapy for statin-induced liver damage.

Further studies need to be conducted to not only find more evidence on the hypothesis but also to search out the mechanisms of damage that can be prevented but not reversed by the use of CoQ10.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

Yes. The study was approved by the Institutional Review Board & Ethics Committee of the Northwest School of Medicine.

Consent Forms

NA.

Authors Contribution

SJ and SAK conceptualized the study, and wrote the final manuscript, AS, IUR, OF, and AA helped in the analysis and writing the first draft, SJ and IUR did the experimental analysis and helped in the initial manuscript writing, SJ, and AA supervised the whole project and wrote the final manuscript.

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References

Bhardwaj, S. S., and N. Chalasani. 2007. "Lipid-lowering agents that cause drug-induced hepatotoxicity." *Clin Liver Dis* 11 (3): 597-613, vii. https://doi.org/10.1016/j.cld.2007.06.010.

Eftekhari, A., E. Ahmadian, A. Azami, M. Johari-Ahar, and M. A. Eghbal. 2018. "Protective effects of coenzyme Q10 nanoparticles on dichlorvos-induced hepatotoxicity and mitochondrial/lysosomal injury." *Environ Toxicol* 33 (2): 167-177. https://doi.org/10.1002/tox.22505.

Eghbal, Mohammad Ali, Narges Abdoli, and Yadollah Azarmi. 2014. "Efficiency of hepatocyte pretreatment with coenzyme Q10 against statin toxicity." *Arhiv za higijenu rada i toksikologiju* 65 (1): 101-107.

Farrag, S. M., M. A. Hamzawy, M. F. El-Yamany, M. A. Saad, and N. N. Nassar. 2018. "Atorvastatin in nano-particulate formulation abates muscle and liver affliction when coalesced with coenzyme Q10 and/or vitamin E in hyperlipidemic rats." *Life Sci* 203: 129-140. https://doi.org/10.1016/j.lfs.2018.04.034.

Frei, B., M. C. Kim, and B. N. Ames. 1990. "Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations." *Proc Natl Acad Sci U S A* 87 (12): 4879-83. https://doi.org/10.1073/pnas.87.12.4879.

Kennedy, C., P. Okanya, J. N. Nyariki, P. Amwayi, N. Jillani, and A. O. Isaac. 2020. "Coenzyme Q(10) nullified khat-induced hepatotoxicity, nephrotoxicity, and inflammation in a mouse model." *Heliyon* 6 (9): e04917. https://doi.org/10.1016/j.heliyon.2020.e04917.

Kyrklund, C., J. T. Backman, K. T. Kivistö, M. Neuvonen, J. Laitila, and P. J. Neuvonen. 2000. "Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations." *Clin Pharmacol Ther* 68 (6): 592-7. https://doi.org/10.1067/mcp.2000.111414.

Lee, Wang-Soo, and Jaetaek Kim. 2019. "Statin-induced liver and muscle toxicities." *Molecular & Cellular Toxicology* 15 (1): 9-17. https://doi.org/10.1007/s13273-019-0002-3. https://doi.org/10.1007/s13273-019-0002-3.

Marques, Ana C, Estela NB Busanello, Diogo N De Oliveira, Rodrigo R Catharino, Helena CF Oliveira, and Anibal E Vercesi. 2018. "Coenzyme Q10 or creatine counteract pravastatin-induced liver redox changes in hypercholesterolemic mice." *Frontiers in pharmacology* 9: 685.

Mohamed, Mohamed, Ahmed Elshatory, Hanaa Elzahed, George Morcos, Ehab Ibrahim, and Walaa Awad. 2019. "Statin-Induced Hepatotoxicity In Albino Rats: A Comparative Study Between Atorvastatin

And Simvastatin." *The Egyptian Journal of Forensic Sciences and Applied Toxicology* 19 (2): 1-11.

National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Adults Treatment of High Blood Cholesterol in. 2002. "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report." *Circulation* 106 (25): 3143-3421. https://doi.org/10.1161/circ.106.25.3143. http://europepmc.org/abstract/MED/12485966

http://intl-circ.ahajournals.org/cgi/content/abstract/106/25/3143

http://intl-circ.ahajournals.org/cgi/content/full/106/25/3143

https://doi.org/10.1161/circ.106.25.3143.

Pompella, A., A. Visvikis, A. Paolicchi, V. De Tata, and A. F. Casini. 2003. "The changing faces of glutathione, a cellular protagonist." *Biochem Pharmacol* 66 (8): 1499-503. https://doi.org/10.1016/s0006-2952(03)00504-5.

Ricaurte, B., A. Guirguis, H. C. Taylor, and D. Zabriskie. 2006. "Simvastatin-amiodarone interaction resulting in rhabdomyolysis, azotemia, and possible hepatotoxicity." *Ann Pharmacother* 40 (4): 753-7. https://doi.org/10.1345/aph.1G462.

Tawfik, M. K. 2015. "Combination of coenzyme Q10 with methotrexate suppresses Freund's complete adjuvant-induced synovial inflammation with reduced hepatotoxicity in rats: Effect on oxidative stress and inflammation." *Int Immunopharmacol* 24 (1): 80-7. https://doi.org/10.1016/j.intimp.2014.11.018.

Thotakura, Sahithi, Ajit Singh, Kanav Khera, Sheetal Chauhan, and Tom Devasia. 2018. "Atorvastatin-induced hepatotoxicity, increased by clopidogrel stress on CYP450 enzyme: understanding the mechanism through a case." *Journal of Applied Pharmaceutical Science* 8 (4): 168-170.

Velickova, Nevenka, Marina Nateva, and Slagana Stojanovska. 2019. "Liver Enzymes as Biomarkers for Hepatotoxicity of Statins in Patients with Dyslipidemia." International Conference on Medical and Biological Engineering.

Whirl-Carrillo, M., E. M. McDonagh, J. M. Hebert, L. Gong, K. Sangkuhl, C. F. Thorn, R. B. Altman, and T. E. Klein. 2012. "Pharmacogenomics knowledge for personalized medicine." *Clin Pharmacol Ther* 92 (4): 414-7. https://doi.org/10.1038/clpt.2012.96.

Zhong, Xiali, Xing Yi, Rita De Cássia Da Silveira e Sá, Yujing Zhang, Kaihua Liu, Fang Xiao, and Caigao Zhong. 2017. "CoQ10 deficiency may indicate mitochondrial dysfunction in Cr (VI) toxicity." *International Journal of Molecular Sciences* 18 (4): 816.