Antioxidants added to preservative solutions protect the liver from ischemia-reperfusion damage

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- **Background:** Delayed liver function after transplantation (or lack of liver function) is caused by ischemia-reperfusion injury. Damage occurs during graft storage before transplantation at reduced temperature (4°C) and during warm reperfusion, i.e., resumption of blood perfusion. Oxygen free radicals are particularly destructive. The use of antioxidants can minimize the effects of oxidative stress. Antioxidants added to organ perfusion and preservation solution can neutralize reactive oxygen species. The purpose of this analysis was to evaluate the effectiveness of antioxidants in protecting the liver before transplantation based on a review of the literature.
- **Method:** Medline/PubMed, Embase, Cochrane Library, and Google Scholar databases were searched. Only peer-reviewed articles were included in the study. Synonym indexing of MeSH (Medical Subject Heading) and EMTREE (Elsevier's Life Science Thesaurus) was used. Key words used were: transplantation, liver, solution preservation, free radicals, ischemia-reperfusion injury, antioxidants. Articles published between January 2000 and October 2021 were included in the analysis.

Strategies based on modifications of preservation solutions.

Author, year of publication	Antioxidant	Species	Preservation solution modification / cold ischemia	Outcome measures, (intervention, I / control, C)	Antioxidant dose	Effects of antioxidant
Hide et al. 2014 [1]	rMnSOD	Human tissue, Rat tissue	Celsior 16h, 4°C; SCS	I: Celsior + rMnSOD C1: no SCS	rMnSOD: 0,15 µM	↓ Oxidative stress ↑ NO
Kato et al. 2020 [2]	quercetin	Rat	UW 24h; 4°C	I: UW + quercetin C1: UW	Quercetin: 0.33; 33,1 µM/L Optimum: 33,1 µM/L Sucrose: 0,1M/L	↓ ALT, AST Mild vascular degradation Improvement of histological changes
Coskun et al. 2007 [3]	l-carnitine	Wistar Albino rat	UW 2h, 24h, 36h, 48h; 4°C	I: UW + l-carnitine C1: UW	5 mM/L	↓ ALT, ACP ↓ MDA
Gdara et al. 2018 [4].	phycocyanin	Rat	Krebs Henseleit 12h, 24h; 4°C	I: KH + Pc C1:KH	0.1; 0.2 mg $ml^{-1}g^{-1}$ of liver	↓ ALT, AST, ALP ↓ MDA ↓ GST, GPx
Ben et al. 2006 [5]	trimetazidine	Zucker rats	UW 24h; 4°C	I: UW + trimetazidine C1: UW	10^{-6} mol/L	Protects against mitochondrial damage Preserves more ATP Decreases oxidative stress Higheres bile production
Zaouali et al. 2010 [6]	trimetazidine	Zucker rats	IGL-1 24h; 4°C	I: IGL-1 + trimetazidine C1: IGL-1	10^{-6} mol/L	Increases HO-1 expression Increases NO production HIF-1α accumulation Higheres bile production
Cherkashina et al. 2011 [7]	SkQ1	Rat	Sucrose-saline 24h; 4°C	I: Sucrose-saline + SkQ1 C1: Sucrose-saline	1 µM	↓ Hepatic injury and oxidative stress ↑ Mitochondrial function

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ACP, acid phosphatase; ALP, alkaline phosphatase; GPx, glutathione peroxidase; GST, glutathione S-transferase; MDA, malondialdehyde; NO, nitric oxide; ATP, adenosine triphosphate; HO-1, heme oxygenase-1; HIF-1α, hypoxia-inducible factor; SkQ1, 10-(6'-plastoquinonyl)decyltriphenylphosphonium; rMnSOD, manganese superoxide dismutase, UW: University of Wisconsin; EC, Euro-Collins; KH, Krebs Henseleit

- **Results:** We found a relationship between the efficacy of the preservative solution and its composition. The addition of antioxidant (quercetin, l-carnitine, phycocyanin, trimetazidine, SkQ1 (10-(6'-plastoquinonyl)decyltriphenylphosphonium), rMnSOD (manganese superoxide dismutase)) protects hepatocytes from oxidative stress and stabilizes mitochondrial structures.
- **Conclusion:** Antioxidants added to preservative solution minimize ischemia-reperfusion injury to hepatocytes.

[1] **Hide** D, Ortega-Ribera M, Fernández-Iglesias A, Fondevila C, Salvadó MJ, Arola L, García-Pagán JC, Mancini A, Bosch J, Gracia-Sancho J. A novel form of the human manganese superoxide dismutase protects rat and human livers undergoing ischaemia and reperfusion injury. Clin Sci (Lond). 2014;127(8):527-37.

[2] **Kato** F, Gochi M, Kawagoe T, et al. The protective effects of quercetin and sucrose on cold preservation injury in vitro and in vivo. Organ Biology. 2020;27:207–215.

[3] **Coskun** A, Gunal O, Sahin I, Aslaner A, Yildirim U, Yavuz O. Does l-carnitine have any effect on cold preservation injury of non-fatty liver in the University of Wisconsin solution? Hepatol Res. 2007;37(8):656-60.

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[6] **Zaouali** MA, Ben Mosbah I, Boncompagni E. Hypoxia inducible factor-1alpha accumulation in steatotic liver preservation: role of nitric oxide. World J. Gastroenterol.2020;16: 3499-3509.

[7] **Cherkashina** DV, Sosimchik IA, Semenchenko OA, Volina VV, Petrenko AY. Mitochondria-targeted plastoquinone derivative SkQ(1) decreases ischemia-reperfusion injury during liver hypothermic storage for transplantation. Biochemistry (Mosc). 2011;76(9):1022-9.