Hops (*Humulus lupulus*) Content in Beer Modulates Effects of Beer on the Liver After Acute Ingestion in Female Mice

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Abstract

**Aim:** Using a binge-drinking mouse model, we aimed to determine whether hops (*Humulus lupulus*) in beer is involved in the less damaging effects of acute beer consumption on the liver in comparison with ethanol.

**Methods:** Female C57BL/6J mice were either fed one iso-alcoholic and iso-caloric bolus dose of ethanol, beer, beer without hops (6 g ethanol/kg body weight) or an iso-caloric bolus of maltodextrin control solution. Markers of steatosis, intestinal barrier function, activation of toll-like receptor 4 signaling cascades, lipid peroxidation and lipogenesis were determined in liver, small intestine and plasma 2 h and 12 h after acute alcohol ingestion.

**Results:** Alcohol-induced hepatic fat accumulation was significantly attenuated in mice fed beer whereas in those fed beer without hops, hepatic fat accumulation was similar to that found in ethanol-fed mice. While markers of intestinal barrier function e.g. portal endotoxin levels and lipogenesis only differed slightly between groups, hepatic concentrations of myeloid differentiation primary response gene 88, inducible nitric oxide synthase (iNOS) and plasminogen-activator inhibitor 1 protein as well as of 4-hydroxynonenal and 3-nitrotyrosine protein adducts were similarly elevated in livers of mice fed ethanol or beer without hops when compared with controls. Induction of these markers was markedly attenuated in mice fed hops-containing beer.

**Conclusion:** Taken together, our data suggest that hops in beer markedly attenuated acute alcohol-induced liver steatosis in female mice through mechanisms involving a suppression of iNOS induction in the liver.

INTRODUCTION

Alcohol-related liver diseases are among the most frequent diseases associated with high chronic alcohol intake (Rehm et al., 2014). However, epidemiological studies suggest that the consumption of different kinds of alcoholic beverages might have different effects on the liver. For instance, results of others suggest that the consumption of hard spirits may be more harmful to the liver in regards to the risk of developing cirrhosis than the consumption of fermented beverages like wine or beer (Becker et al., 2002; Kerr and Ye, 2011). However, data are still contradictory as results of some studies also...
reported no differences between the consumption of different types of alcoholic beverages and the risk to develop liver cirrhosis in heavy drinkers (Pellietier et al., 2002). Furthermore, mechanisms and cofactors involved in the proposed less harmful effects of a high intake of wine and beer versus that of hard spirits have also not yet been fully clarified (e.g. the role of drinking habits, secondary plant compounds and others).

Beer is one of the most frequent consumed alcoholic beverages worldwide (WHO, 2014). Recently, using a binge-drinking model in female and male mice, we reported that acute intake of beer has less damaging effects on the liver than a comparable intake of plain ethanol (Kanuri et al., 2014; Landmann et al., 2015). In these studies, the less damaging effects of beer were associated with a protection against the induction of toll-like receptor (TLR)-4- and inducible nitric oxide synthase- (iNOS) dependent signaling cascades in the liver. In line with these findings, results obtained in human intervention studies using alcohol-free beer suggest that regular intake of alcohol-free beer can promote anti-oxidative capacity (Franco et al., 2013) and is associated with improved lipid profiles but also lower markers of oxidative stress in elderly women (Martinez Alvarez et al., 2009). Furthermore, consumption of alcohol-free beer protected rats from adriamycin-induced heart and liver toxicity due to a reduction of markers of lipid peroxidation in the liver (Valls-Belles et al., 2008). In vitro and in vivo studies using isolated beer constituents like xanthohumol and iso-accids have been shown to attenuate hepatic inflammation and even fibrosis (Dorn et al., 2012) as well as to suppress lipopolysaccharide (LPS)-induced inflammation (Desai et al., 2009). However, in most of these studies, compounds were applied in doses that cannot be reached with moderate or even high beer intake. Starting from this background, the aim of the present study was to further delineate the role of hops (Humulus lupulus), one of the main ingredients in beer, in the less damaging effects of acute high beer consumption when compared with acute intake of plain ethanol on mouse livers.

MATERIALS AND METHODS

Animals and treatments

All procedures were approved by the local Institutional Animal Care and Use Committee (Jena, 02-061/13). Six- to eight-weeks-old female C57BL/6j mice (n = 6–9 per group, Janvier S.A.S, France) were kept in a standard pathogen-free barrier facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care with free access to standard pellet chow (Sniff, Germany) and tap water at all times. Female mice were used as it had been shown before that female mice but also women are more susceptible to alcohol-induced liver damage (Becker et al., 1996; Wagnerberger et al., 2013). At the day of the experiment, mice received one single dose of either iso-caloric and iso-alcoholic (6 g ethanol/kg body weight (b.w.)) ethanol solution, normal beer with hops or specially brewed beer without hops (EKU Pils, Kulmbacher Brauerei AG, Germany). Controls were fed an iso-caloric maltodextrin solution. Alcoholic and iso-caloric maltodextrin control solutions were prepared as detailed previously (Kanuri et al., 2014). Alcohol doses used did not cause mortality; however, mice were sluggish but conscious and regained normal behavior within ~5–6 h after alcohol feeding. During the first half hour, animals were closely observed and afterwards at least every 30 min until sacrifice. Animals were sacrificed 2 and 12 h after acute treatment, respectively, and tissue was harvested as detailed before (Kanuri et al., 2014).

Liver histology and clinical markers of liver damage as well as plasma endotoxin and alcohol levels

Accumulation of hepatic triglycerides and staining of lipids with Oil Red O were carried out as described in detail previously (Spruss et al., 2012b). Representative pictures of staining were taken at ×200 magnification using a Leica microscope (DM4000 B LED, Leica, Germany). In addition, formalin-fixed liver tissue was sectioned (4 µm) and stained with hematoxylin and eosin (H&E) to evaluate liver histology.

Alcohol and endotoxin levels in portal plasma of mice were measured as described previously (Wagnerberger et al., 2013). Levels of alanine and aspartate aminotransferases (ALT and AST) in portal plasma were measured at the Institute for clinical chemistry and laboratory diagnostics (Architect, Abbott GmbH & Co. KG, Germany) at the University Hospital of Jena.

RNA isolation and real-time RT-PCR

RNA was isolated with Trizol (Peqlab, Germany) and reverse transcribed (cDNA synthesis kit, Promega, Germany). Relative mRNA expression was quantified using a MX QPCR System (Agilent Technologies, Germany) using a SybrGreen Mix and 2-step PCR protocol as recommended by Agilent Technologies. The comparative C_T method was used to determine the amount of target genes, normalized to an endogenous reference (18S) and relative to a calibrator (2−ΔΔC_T). Primers for the detection of acetyl-CoA carboxylase (ACC), carnitine palmityltransferase 1 (CPT-1), fatty acid synthase (FAS), perilipin-2, peroxisome proliferator-activated receptor gamma (PPAR), sterol regulatory element-binding protein (SREBP) 1c, TLR-4 and 18 S were designed using Primer 3 software and synthesized at Eurofins MWG Operon (Eurofins, Germany). Primer sequences are listed in Supplemental Material 1.

Immunostaining of myeloid differentiation factor 88 and iNOS, as well as 4-hydroxynonenal and 3-nitrotyrosin protein adducts in liver tissue and occludin in the small intestine

Using polyclonal primary antibodies (3-nitrotyrosin (3-NT): SantaCruz Biotech, Germany; 4-hydroxynenol (4-HNE): AG Scientific, USA; iNOS: Affinity BioReagents, USA; myeloid differentiation factor 88 (MyD88): Santa-Cruz Biotech, Germany; Occludin: Life Technologies, Germany) immunostainings of MyD88, iNOS and occludin protein as well as 3-NT and 4-HNE protein adducts were performed in liver and small intestinal tissue as previously described (Arteel, 2003; Spruss et al., 2012b; Kanuri et al., 2015). The extent of labeling in liver lobules and small intestine, respectively, was defined as percent of the field area within the default color range determined by a software using an image acquisition and analysis system incorporated in the microscope (DM4000 B LED, Leica, Germany). Data from eight fields of each tissue section (×200 magnification) were used to determine means.

Western blot

To analyze phosphorylation status of inhibitor kappa B alpha (IκBα) and protein levels of alcohol dehydrogenase (ADH) as well as cytochrome P450 2 E1 (CYP2E1), western blot analysis was performed as previously described (Kanuri et al., 2014; Engstler et al., 2015). Primary antibodies against IκBα and pIκBα (Cell Signaling Technology, Germany) as well as ADH and CYP2E1 (ADH: Cell Signaling Technology, Irvine, CA, USA; CYP2E1: Enzo Life Science
Inc., Germany) were used. Bands were analyzed densitometrically using a ChemiDoc MP System (BioRad Laboratories, Germany) and in the case of ADH and CYP2E1 normalized to band intensity of β-actin (New England Biolabs, Frankfurt, Germany). All blots were stained with Ponceau Red (Roth, Germany) to ensure equal loading.

Detection of apolipoprotein B, total glutathione, nuclear factor kappa-light-chain-enhancer of activated B cells, plasminogen-activator inhibitor and tumor necrosis factor alpha

Protein levels of apolipoprotein B (ApoB), plasminogen-activator inhibitor (PAI-1) and tumor necrosis factor alpha (TNFα) in total liver lysates were determined via commercially available ELISA (enzyme-linked immunosorbent assay) kits and NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) p65 protein activity as well as total glutathione (GSH) protein were determined following the instructions of the manufacturer (ApoB: Cloud-Clone Corp, USA; GSH: Cayman Chemicals, USA, NFκB: Active Motif, La Hulpe, Belgium, PAI-1: Loxo GmbH, Germany; TNFα: IBL International GmbH, Hamburg).

Statistical analyses

Data are shown as mean ± standard error of mean (SEM) unless indicated otherwise. To determine significant differences, one-way analysis of variances with the post hoc test of Tukey was used (GraphPad Prism Software, USA). A P-value of <0.05 was considered as significantly different. Grubbs test was used to identify outliers (GraphPad Prism Software, USA).

RESULTS

Effect of beer with or without hops on blood alcohol levels and hepatic fat accumulation 2 and 12 h after ingestion

Two hours after acute ingestion of ethanol or beer, plasma ethanol levels of mice fed ethanol or beer were significantly increased (+2.5–2.8-fold) when compared with maltodextrin-treated controls with no significant differences between alcohol-treated groups (see Table 1). Ethanol concentrations in plasma were still slightly elevated 12 h after acute ingestion in all three alcohol-fed groups when compared with controls (+1.4–1.7-fold in comparison with controls, n.s.). Protein levels of ADH and CYP2E1 in liver did not differ between groups (see Table 1 and Supplemental Material 2 for representative pictures). Lipid accumulation as detected by Oil Red O staining, quantification of triglycerides and mRNA expression of perilipin-2 were significantly higher in livers of mice fed plain ethanol when compared with controls but also in comparison with mice fed normal beer (lipids: +4.5–6.5-fold compared with controls and +1.3-fold compared with beer-fed mice; triglycerides: +12.8-fold compared with controls and +2.2-fold compared with beer-fed mice; perilipin-2: +4.7-fold compared with controls and +1.7-fold compared with beer-fed mice, P < 0.05; Fig. 1). However, lipid and triglyceride concentrations as well as perilipin-2 mRNA expressions in livers of beer-fed mice were still markedly higher than in livers of controls (lipids: +4.5–1-fold, P < 0.05; triglycerides: +5.8-fold, P = 0.15; perilipin-2: +2.3-fold, P < 0.05; Fig. 1). In contrast, lipid and triglyceride concentrations but also perilipin-2 mRNA expressions in livers of mice fed beer without hops were similarly elevated than in mice fed plain ethanol. Despite these findings, 12 h after ingestion of ethanol or beer, plasma ALT activities did not differ between groups as data varied considerably in some groups. In contrast, plasma AST activities were significantly higher than those of controls in all three alcohol-fed groups. Furthermore, AST plasma activities of mice fed beer without hops were even higher than those of mice fed beer with hops (Table 1).

Effect of beer with and without hops on markers of lipogenesis, PAI-1 protein and lipid export in the liver 12 h after ingestion

In line with our previous findings, 12 h after acute alcohol ingestion, expression of SREBP-1c mRNA was significantly lower in livers of all three alcohol-fed groups regardless of the type of beverage consumed when compared with maltodextrin controls (Kanuri et al., 2014). Expression of FAS mRNA was also lower in livers of mice fed plain ethanol or the beers 12 h after ingestion; however, as data varied considerably only the differences between mice fed plain ethanol and controls reached the level of significance. Neither mRNA expression of ACC nor CPT-1 or PPARγ in the liver differed between groups 12 h after acute alcohol ingestion. Furthermore, 12 h after ingestion of ethanol or the beers, PAI-1 protein concentration was significantly higher in livers of mice fed plain ethanol (P < 0.01 when compared with controls, P < 0.001 when compared with beer-fed animals). A similar effect was not found in livers of animals fed beer without hops when compared with controls; however, PAI-1 protein levels in livers of these mice were significantly higher than in beer-fed mice (P < 0.05; Table 2). In contrast, protein levels of ApoB were slightly but not significantly higher in livers of mice fed plain ethanol and the different beers, respectively, when compared with control animals (Table 2).

### Table 1. Ethanol concentration as well as ALT and AST levels in plasma and markers of ethanol metabolism in liver of mice fed ethanol, beer with and without hops, respectively, or maltodextrin

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ethanol</th>
<th>Beer + hops</th>
<th>Beer − hops</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol after 2 h (µmol/µl plasma)</td>
<td>69 ± 5</td>
<td>176 ± 16*</td>
<td>193 ± 20*</td>
<td>179 ± 24*</td>
</tr>
<tr>
<td>Ethanol after 12 h (µmol/µl plasma)</td>
<td>51 ± 4</td>
<td>78 ± 13</td>
<td>91 ± 16</td>
<td>72 ± 15</td>
</tr>
<tr>
<td>ALT levels (IU)</td>
<td>40 ± 6</td>
<td>65 ± 7</td>
<td>45 ± 4</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>AST levels (IU)</td>
<td>48 ± 3</td>
<td>102 ± 5*</td>
<td>81 ± 2*</td>
<td>108 ± 9*</td>
</tr>
<tr>
<td>ADH/β-actin</td>
<td>0.74 ± 0.09</td>
<td>0.96 ± 0.25</td>
<td>0.94 ± 0.23</td>
<td>1.29 ± 0.46</td>
</tr>
<tr>
<td>CYP2E1/β-actin</td>
<td>0.31 ± 0.04</td>
<td>0.30 ± 0.07</td>
<td>0.32 ± 0.11</td>
<td>0.38 ± 0.09</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SEM. Representative pictures of Western blots for β-Actin, ADH-1 and CYP2E1 are shown in Supplemental Material 2.

*P < 0.05 when compared with control animals fed maltose dextrin. **P < 0.05 when compared with the respective animals fed beer with hops.
Effect of beer with and without hops on markers of intestinal barrier function, hepatic Kupffer cell activation, lipid peroxidation as well as NFκB activation 2 and 12 h after ingestion

Two hours after acute ingestion of ethanol or beer with and without hops, respectively, occludin protein concentration in the small intestine was only significantly lower in duodenum of mice fed beer with hops and by trend in ethanol-fed animals (P = 0.08) when compared with controls (Table 3 and Supplemental Material 3 for representative pictures). In contrast, endotoxin levels in portal plasma were significantly increased in animals fed beer without hops in comparison with all other groups (Table 3). Protein concentrations of MyD88 were significantly higher in livers of mice fed plain ethanol and beer without hops when compared with controls and for the latter also in comparison with mice fed beer with hops. In contrast, MyD88 protein levels did not significantly differ between mice fed beer with hops and controls. In line with these findings, iNOS protein levels and concentrations of 3-NT and 4-HNE protein adducts were all significantly higher in livers of mice fed plain ethanol and beer without hops in comparison with controls and in case of 4-HNE protein adducts also in comparison with mice fed normal beer. Furthermore, neither hepatic concentration of iNOS protein nor 3-NT and 4-HNE protein adducts were significantly induced in mice fed normal beer when compared with controls (Fig. 2 and Supplemental Material 4 for representative pictures). Concentration of total GSH was significantly lower in livers of mice fed plain ethanol and beer without hops when compared with controls and for the latter also in comparison with mice fed beer with hops. In contrast, MyD88 protein levels did not significantly differ between mice fed beer with hops and controls. In line with these findings, iNOS protein levels and concentrations of 3-NT and 4-HNE protein adducts were all significantly higher in livers of mice fed plain ethanol and beer without hops in comparison with controls and in case of 4-HNE protein adducts also in comparison with mice fed normal beer. Furthermore, neither hepatic concentration of iNOS protein nor 3-NT and 4-HNE protein adducts were significantly induced in mice fed normal beer when compared with controls (Fig. 2 and Supplemental Material 4 for representative pictures). Concentration of total GSH was significantly lower in livers of mice fed plain ethanol.
ethanol or beer without hops when compared with mice fed beer with hops or controls, while total GSH concentration in liver did not differ between controls and mice fed beer with hops. However, ingestion of ethanol and beer with or without hops had no marked effects on nuclear NFXB p65 activity, the phosphorylation status of IκBα or TNFα protein concentration in the liver of mice 12 h after acute ingestion (see Table 3 and Supplementary Material 2 for representative pictures of the western blot).

**DISCUSSION**

Results of several epidemiological studies suggest that chronic consumption of fermented alcoholic drinks like beer in comparison with spirits is associated with lower liver disease-associated mortality (Becker et al., 2002; Kerr and Ye, 2011). However, data determining the effect of whole beer and beer lacking certain ingredients (e.g. hops) on the development of liver damage under controlled conditions are limited. Therefore, we aimed to delineate the effects of hops content in beer on the liver using a binge-drinking mouse model. Neither signs of drunkenness and plasma alcohol levels nor hepatic ADH and CYP2E1 protein or plasma transaminase activity differed between alcohol-fed groups. However, in line with our previous findings (Kanuri et al., 2014), fat accumulation in the liver of beer-fed mice was markedly lower than in those of ethanol-fed animals. In contrast, in livers of mice fed beer without hops steatosis was similarly to that found in mice fed plain ethanol. Taken together, our data suggest that hops content in beer is at least in part responsible for the less damaging effects of beer on the liver in settings of acute elevated consumption of alcohol in mice.

In line with previous studies (Kanuri et al., 2014) expressions of SREBP-1c and FAS mRNA were lower in livers of all alcohol-fed groups. Furthermore, expression of ACC, CPT-1 and PPARγ, all being involved in regulating triglyceride synthesis and lipogenesis in the liver (Rogue et al., 2010; Zardi et al., 2013), was similar between groups, too. Differences between our results and those of others might have resulted from differences in the models used (in vitro studies (You et al., 2002) vs. in vivo studies in the present study) and the experimental setup. Indeed, it has been shown before in male mice that the induction of SREBP-1c but also FAS in the presence of ethanol underlies a time-dependent regulation and may be influenced by bioavailability of fatty acids (Wada et al., 2008). Therefore, in the present study, the induction of SREBP-1c and PPARγ but also other markers of lipogenesis and fatty acids synthesis might have been missed. Taken together, our data suggest that the less harmful effects of the ingestion of beer containing hops on the liver after acute ingestion did not primarily stem from hops-induced alterations of hepatic SREBP-1c- and PPARγ-mediated lipogenesis.

In the present study, protein levels of the tight-junction protein occludin, suggested before to be critical in alcohol-induced intestinal barrier dysfunction (Elamin et al., 2012), were similar between groups. Two hours after alcohol ingestion, portal endotoxin levels of mice fed plain ethanol and beer with or without hops were markedly higher than those of controls, with alcohol- and beer with hops-fed groups not differing. These data suggest that the less harmful effects of beer with hops on the liver might not have resulted in the less harmful effects of beer with hops on the liver.
from changes at the levels of intestinal barrier function. However, as we only studied protein levels of the tight-junction protein occludin and endotoxin plasma levels 2 h after acute intake of alcohol we might have missed the point of time when marked changes in these markers occurred. Indeed, results of others suggest that translocation of bacterial endotoxin in rats appeared rather quickly e.g. ~30 min after acute ingestion of alcohol while erosions of intestinal barrier were only observed ~4 h after ingestion (Tamai et al., 2000).

However, despite no marked changes in occludin protein levels, protein concentrations of MyD88 and iNOS as well as of 4-HNE and 3-NT were markedly induced in animals receiving either plain ethanol or beer without hops. In line with previous in vivo and in vitro results (Kanuri et al., 2014), in livers of normal beer-fed animals the induction of both markers was markedly attenuated, suggesting that hops in beer at least in part may attenuate the induction of hepatic MyD88 and iNOS expression in mice. In line with these findings and those of others (Cao et al., 2015; Dong et al., 2016), concentration of total GSH was markedly lower in livers of mice fed plain ethanol and beer without hops, respectively. However, neither activity of NFkB, phosphorylation status of IκBα nor protein concentration of TNFα was altered between groups. This effect on TNFα expression is in line with previous studies (Wagnerberger et al., 2013; Kanuri et al., 2014) and might have resulted from the time-dependent regulatory release of TNFα shown before in in vitro experiments (Spencer et al., 2013; Maraslioglu et al., 2014). However, the induction of PAI-1 protein shown before to be regulated through iNOS- and TNFα-dependent signaling pathways (Bergheim et al., 2006; Spruss et al., 2012a) was also markedly attenuated in livers of mice fed normal beer whereas in livers of mice fed beer without hops this effect on PAI-1 expression was not quite as pronounced. However, ApoB protein levels shown to be regulated through PAI-1- and c-Met-dependent signaling pathways (Bergheim et al., 2006) were almost similar between groups. The lack of responsiveness of ApoB protein in the present study when compared with earlier studies might have resulted from gender differences, the detection time point or methods used (Bergheim et al., 2006; Landmann et al., 2015). Taken together, our data suggest that hops in beer attenuated the induction of MyD88 and iNOS in alcohol-fed mice.

**Fig. 2.** Effect of acute ingestion of beer with or without hops on markers of Kupffer cell activation and lipid peroxidation in the liver 12 h after acute alcohol intake. Densitometric analysis of the staining of (a) MyD88 and (b) iNOS protein as well as (c) 4-HNE and 3-NT protein adducts in the liver. Data are shown as mean ± SEM and are expressed as % per microscopic field. ★P < 0.05 when compared with the respective control animals fed maltose dextrin (=C). ◆P < 0.05 when compared with the respective animals fed beer with hops (=B+), B–, mice fed beer without hops; EtOH, ethanol-fed mice.
an acute setting of alcohol ingestion thereby leading to a lower formation of reactive oxygen species and induction of iNOS and subsequently suppressed acute alcohol-induced liver damage.

CONCLUSION

Results of our study lend further support to the hypothesis that consumption of fermented alcoholic beverages like beer may be less harmful for the liver than consumption of hard spirits. Furthermore, our results suggest that hops in beer may at least in part suppress the induction of iNOS and lipid peroxidation in the liver. However, which compound(s) in hops is/are responsible for the less damaging effects of hops-containing beer found in the present study and which molecular mechanisms are involved but also whether these effects are found in chronic settings and humans, too, will have to be determined in future studies.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Alcohol and Alcoholism online.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

3-NIT, 3-nitrotyrosine; 4-HNE, 4-hydroxynonenal; ACC, acetyl-CoA carboxylase; ADH, alcohol dehydrogenase; ALT, alanine aminotransferase; ApoB, apolipoprotein B; AST, aspartate aminotransferase; b.w., body weight; c-Met, hepatocyte growth factor receptor; CPT-1, carnitine palmitoyltransferase I; ELISA, enzyme-linked immunosorbent assay; EU, endotoxin unit; FAS, fatty acid synthase; GSH, glutathione; H&E hematoxylin and eosin; (p)IκBα, (phospho) inhibitor kappa B alpha; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MyD88, myeloid differentiation (phospho) inhibitor kappa B alpha; iNOS, inducible nitric oxide synthase; NFκB, nuclear factor kappaB, and responsiveness to endotoxin in murine Kupffer cells and circulating inflammatory mediators, activation of nuclear factor-kappaB, and responsiveness to endotoxin in murine Kupffer cells and circulating leukocytes. Cell Membr Free Rad Res 5:232–5.


Valls-Belles V, Torres MC, Boix L, et al. (2008) alpha-Tocopherol, MDA-HNE and 8-OHdG levels in liver and heart mitochondria of


