Prof. Lian-Sheng Ma,
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Vitoria, December 4th, 2013

Dear Professor Lian-Sheng Ma,

Please find enclosed our revised version of the review entitled "Effects of resveratrol and other polyphenols in hepatic steatosis", by L. Aguirre, M.P. Portillo, E. Hijona and L. Bujanda which manuscript number is **6598**

We think that all suggestions have been taken into account and the emendation introduced as suggested by the reviewer 2. Changes are highlighted in red. As the changes have considerably improved the manuscript, we would like to acknowledge the reviewer for these comments.

We hope that everything will be in order for publication in World Journal of Gastroenterology.

Sincerely yours,

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Reviewer 2

- Page 4: NAFLD definition excludes alcohol consumption. Alcohol consumption gives rise to AFLD. NAFLD and AFLD are distinct clinical entities, although histologically similar. Re-phrase.
The reviewer is right. The sentence "Weekly ethanol consumption of >140 g in women and >210 g in men" has been deleted in this new version (page 4, line 12).

- Pages 4-5: the "two-hit" hypothesis of Chris Day is old and now completely outdated, since the discovery that the major trigger for NAFLD to NASH development is played by the gut microbiota and inflammatory infiltrates annexed (see for short summary Podrini C et al. Curr Pharm Des 2013). Re-write this part.
As suggested by the reviewer this part has been re-written (page 4, lines 16):

"The exact pathogenic mechanisms of liver steatosis are not yet fully known. Steatosis, liver inflammation and fibrosis has been associated with an excessive triglyceride accumulation in the liver, insulin resistance and increases in visceral adipose tissue, mediated by increased free radical formation and free oxygen radical species, and modulated by genetic susceptibility [11, 12]. There is evidence supporting the theory that these genetic factors account for considerable variability in susceptibility to NAFLD. Since the introduction of genome-wide association studies (GWASs) to investigate genomic variations, there have been significant advances in our understanding of human genome and its clinical effects over a range of diseases. A large number of single nucleotide polymorphisms (SNPs) related to NAFLD has been documented by candidate gene studies. The SNPs may increase or decrease the function of the target genes and their encoding proteins. Genes such as patatin-like phospholipase domain-containing protein 3 (PNPLA3), neurocan core protein (NCAN), glucokinase regulatory protein (GCKR) and lysophospholipase-like protein 1 (LYPLAL1) have been implicated in an increased risk of NAFLD[13]. Lipid peroxidation and free oxygen radical species can deplete antioxidant enzymes (glutathione, vitamin E, beta-carotene and vitamin C) and activate proinflammatory citokines, inflammatory mediators and activation of natural killer cells among others. Others factors as iron, leptin, adiponectin and resistin may contribute to the NAFLD. In the last years intestinal microbes have been implicated as a potential source of hepatotoxic oxidative injury. Intestinal bacterial overgrowth and increased intestinal permeability were observed in patients with NAFLD[14]. Mechanisms by which intestinal bacteria may contribute to hepatocellular injury include endotoxin production, deconjugation of bile salts and inactivation of hepatic lipotropes, such as choline.

- Page 5: genetic factors contributing to NAFLD are starting to be understood (PNPLA3 etc) and could be briefly discussed (see Anstee QM, Nat Rev Gastroenterol Hepatol 2013)

A new paragraph as well as the reference suggested by the reviewer related to genetic factors (Anstee QM, Day CP. The genetics of NAFLD. Nat Rev Gastroenterol Hepatol. 10:645-55. 2013) have been included in this revised version. (page 4 , line 20):

There is evidence supporting the theory that these genetic factors account for considerable variability in susceptibility to NAFLD. Since the introduction of genome-wide association studies (GWASs) to investigate genomic variations, there have been significant advances in our understanding of human genome and its clinical effects over a range of diseases. A large number of single nucleotide polymorphisms (SNPs) related to NAFLD has been documented by candidate gene studies. The SNPs may increase or decrease the function of the target genes and their encoding proteins. Genes such as patatin-like phospholipase domain-containing protein 3 (PNPLA3), neurocan core protein (NCAN), glucokinase regulatory protein (GCKR) and lysophospholipase-like protein 1 (LYPLAL1) have been implicated in an increased risk of NAFLD.

- On page 7 a classification of polyphenols is offered in details. On page 8, resveratrol is presented simply as a phytoalexin and this category does not fall among the ones presented in page 7.

The reviewer is right. Phytoalexin did not appear in the classification. Thus, resveratrol has been classified as a stilbene, a type of polyphenol which does appear in the classification.

- Tables: it would be useful, together with reporting the first author of the studies also the reference number. It easies the reading.

The reference numbers have been included in this revised version.

- Throughout the manuscript, several studies are described in which resveratrol activates SIRT1 and/or AMPK. Activation does not mean that SIRT1/AMPK mediate the effect of resveratrol. Mediating the effects means that if you block/inhibit SIRT1 and/or AMPK resveratrol does not have an anti-lipidogenic effect in the liver. I don't have time to do this for the authors, but they should go through each study they cite on this and state things correctly according to what has been done experimentally. Activation does not mean mechanism in biology/medicine.

This issue has been revised, and we have modified the writing of paragraphs related to the potential involvement of SIRT1 and AMPK in the mechanism of action of resveratrol:

Page 9, lines 16 and 22
Page 10, lines 5-7
Page 13, lines 19-20
Page 16, lines 8-10

In those cases where the authors in the original papers used terms such as “mediated throughout” “through” we have not modified this original writing:

Page 15, lines 18-20
Page 23, line 20
Page 29, line 13

- Page 13: "clearly lower" repeated twice.

The repetition has been deleted in this new version.

- Rafa de Cabo has done much deal of study on the effect of resveratrol on rhesus monkeys. Authors should check these publications to describe if liver effects were reported therein.

Following the suggestion of the reviewer, we have looked for the studies reported by Dr. De Cabo in rhesus monkeys. We have found just a paper in Pubmed "Resveratrol improves adipose insulin signaling and reduces the inflammatory response in adipose tissue of rhesus monkeys on high-fat, high-sugar diet". After reading it we have realized that the study focuses on adipose tissue, and no determinations have been performed in liver. Consequently, we have not included this reference in our manuscript.

- Human studies on resveratrol: authors must also report negative data: "Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance." Yoshino J, Cell Metab 2012

We have revised the study published by Yoshino et al. and we have realized that no data concerning liver triacylglycerols or genes related to lipid metabolism in liver are included. The paper focuses on glucose tolerance, and thus results such as plasma triacylglcyerols, basal plasma glucose, hepatic insulin sensitivity index and insulin-mediated suppression of glucose rate of appearance were presented. Taking into account that the aim of the present review is liver steatosis, we consider that this study is out of our scope.

- Delipidating is a very odd term. Better to use anti-lipidogenic?

The suggestion has been taking into account and the term "delipidating" has been changed.