## REPLY TO THE REVIEWERS

**Reviewer: 00503536**

Conclusion: Minor revision

Classification: Grade B (Very good)

Language Evaluation: Grade B: minor language polishing

The review manuscript written by Hernández-Aquino et al. describes the molecular mechanism of naringenin, a natural product of flavonoids, which has an ability to inhibit oxidative stress and inflammation and has anti-inflammatory and anticancer properties. Those various activities may suggest a therapeutic potential of the product in various liver diseases. The manuscript comprehensively covers the current understanding of the molecular mechanisms that provide a possibility of clinical utilization of the products. The review is well written, but in vivo data from animal or human trials are not well described. In addition, adverse effects that might be observed during the animal experiments or human study should be more mentioned.

**Answer:**

The manuscript was edited by American Journal Experts. Certificate Verification Key: 2B91-C441-6BCB-7C9D-4A06.

Some in vivo data from animals are included; unfortunately, there is very few information in humans. We think that the basic research reported should encourage clinicians to investigate naringenin effects in controlled human trials.

The following paragraph was included in the new version of the manuscript. Please see page 42 of the new version, highlighted text.

**NARINGENIN SAFETY AND TOXICITY**

The first study about the toxicity of naringenin was carried out in 1996, and it was found that in a model system of isolated rat liver nuclei, the flavonoid induced a concentration-dependent peroxidation of nuclear membrane lipids concurrent with DNA strand breaks [218]. It has been reported that the flavonoid can be oxidized to form naringenin phenoxyl radicals [219] and that the medium lethal dose (LD50) is > 5000 mg/kg [220]. Interestingly, embryos exposed to naringenin with hydroxyurea were significantly protected from growth and developmental retardation, and abnormalities induced by hydroxyurea [221]. Only a few studies on the safety, teratogenicity and toxicity of naringenin have been published, therefore use of this flavonoid in the clinical setting should be cautious.

**Reviewer: 00051373**

Conclusion: Accept

Classification: Grade A (Excellent)

Language Evaluation: Grade A: priority publishing

A comprehensive review on the pathways of the hepatic fibrosis and well described the possible benefits of the naringenin on the treatment of different liver diseases in the future. In my opinion, it should be accept for publication without alter.

**Answer:**

Thank you very much for your comments.

**Reviewer: 01555255**

Conclusion: Major revision

Classification: Grade C (Good)

Language Evaluation: Grade A: priority publishing

The paper is intersting, however in the present form is not useful for the reader to detect. I suggest a revision of this paper, with a reduction of the lenght. In this new version is essential to highlight the role of naringenin in liver diseases, and to stress its antioxidant, anti-inflammatory, anti-fibrotic, scaveger and anti-diabetic properties.

**Answer:**

In fact, this review deals with the role of naringenin in liver diseases, stressing its antioxidant, free radical scavenging, anti-heavy metal toxicity, anti-inflammatory, and anti-fibrotic properties. Unfortunately, there is little information available as antidiabetic (now included in the revised version). We think that a reduction in the length of the manuscript will lead to lost of important information available in the scientific literature since, to the best of our knowledge, there are no reviews dealing with the effects of naringenin on liver diseases.

The following paragraph was added to page 42 of the revised version, please see highlighted text.

**ANTIDIABETIC EFFECT OF NARINGENIN**

In addition to its antioxidant, scavenger, anti-inflammatory, antiviral and antifibrotic properties, naringenin possesses antidiabetic effects. It has been reported that, in diabetic rats, the flavonoid reduced diabetic markers through PPARγ and glucose transporter type 4 (GLUT4) and increased their gene and protein expression levels in pancreas [213]. In the liver, naringenin increased glycogen content, decrease activities of glycogen phosphorylase and glucose-6- phosphatase [214] and ameliorated diabetes-induced hepatotoxicity [215, 216]. For more information see Nyane *et al* [217].

**Reviewer: 01805500**

Conclusion: Rejection

Classification: Grade E (Poor)

Language Evaluation: Grade D: rejected

According to the content of article.....World J Gastroenterol. 2017 May 21; 23(19): 3388–3395...authors should bring a note of caution in their work, because evidence is quite exclusively on basic research, lacking randomized trials on humans, by which is evaluated the action but also the safety.

**Answer:**

The manuscript was edited by: American Journal Experts. Certificate Verification Key: 2B91-C441-6BCB-7C9D-4A06.

Some in vivo data from animals are included; unfortunately, there is only limited information in humans. We think that the extensive basic research reported an summarized in this review should encourage clinicians to investigate naringenin effects in controlled human trials.

The following paragraph was included in the new version of the manuscript. Please see page 42 of the new version, highlighted text.

**NARINGENIN SAFETY AND TOXICITY**

The first study about the toxicity of naringenin was carried out in 1996, and it was found that in a model system of isolated rat liver nuclei, the flavonoid induced a concentration-dependent peroxidation of nuclear membrane lipids concurrent with DNA strand breaks [218]. It has been reported that the flavonoid can be oxidized to form naringenin phenoxyl radicals [219] and that the medium lethal dose (LD50) is > 5000 mg/kg [220]. Interestingly, embryos exposed to naringenin with hydroxyurea were significantly protected from growth and developmental retardation, and abnormalities induced by hydroxyurea [221]. Only a few studies on the safety, teratogenicity and toxicity of naringenin have been published, therefore use of this flavonoid in the clinical setting should be cautious.