

July 11<sup>th</sup>, 2018

Editorial Board of World Journal of Gastroenterology

Dear Editor,

We are submitting a revised version of the manuscript 40284 entitled "Sex-specific effects of *Eugenia punicifolia* extract on gastric ulcer healing in rats" to the journal.

The authors would like to thank the reviewers for their corrections and suggestions. These interventions were useful to improve the quality of our study.

In the electronic files you can find changes in yellow (modifications), red (sections that were deleted) and green (inserted).

The point-by-point response to the reviewers' concerns is given below:

**Reviewer #1**

**COMMENT #1**

This manuscript presents the results on gastric ulcers by an extract administration. The quality is adequate. However, many markers were measured, but direct links are lacking. The limitations could be minimized if authors include the potential molecules which can be included and could be involved in the suggested mechanisms. Discussion could be in a deeper form regarding the putative compounds responsible for action and the mode of action involved in the hormone action (beyond prostaglandin levels in a point).

**ANSWER#1**

Phytochemical studies by Oliveira *et al.* (2006)<sup>[1]</sup> characterized the presence of flavonoids, tannins, terpenoids, saponins in *E. puniceifolia*. Other studies also demonstrated the presence of proanthocyanidins, galotannins, quercetin and myricetin derivatives<sup>[2]</sup>. ESI-MS analyzes revealed the presence of gallic acid, quercetin-3-O-arabinopyranoside, quercetin galloyhexoside isomer, syringic acid, ellagic acid, monogalloyl-glucose, glycosiringic acid, mudanoside B, HHDP-glucose isomer and digalloylglucose isomer<sup>[3]</sup>.

However, the work is about the healing effect of the extract and how it is modulated by the presence/absence of female sex hormones in female rats. Any direct relationship between the present compounds and a mechanism of action should be viewed with caution to not become speculative. Isolated compounds act on many targets/receptors besides their synergistic or antagonistic actions, these activities are not reported since they are not the focus of the work and cannot be verified with the results obtained. For such inferences, it would be necessary to fractionate and purify the hydroalcoholic extract, and such analyzes are beyond the scope of the work, which aims to investigate the healing activity of the extract of *Eugenia puniceifolia* as a whole, considering that not all extracts have a protective and healing action. The suggestion of relating structure/activity is valid, but it is not the object of this study.

## COMMENT #2

One group of rats gonadectomized, but with treatment with steroid-hormones could be useful. Or at least the reported data included and discussed.

## ANSWER#2

Some studies described the gender-specific protection against gastric ulcer and report that the differences in the incidence of the disease between the sexes are associated with the sex hormones and that the female hormones exert a protective effect against the ulcerations <sup>[4-5]</sup>.

In a study conducted by Machowska *et al.*, (2004)<sup>[6]</sup>, the authors present that the administration of testosterone or the supplementation therapy with testosterone

in testectomized animals, significantly delayed ulcer healing and eliminated the acceleration of ulcer healing caused by testectomy alone. On female rats, progesterone in contrast to testosterone, accelerated the healing of gastric ulcers in non-ovariectomized animals and in those who underwent ovariectomy.

Therefore, although there are arguments about the beneficial action of female sex hormones in gastric ulcers, the studies are outdated, scarce and contradictory [7].

## **Reviewer #2**

### **COMMENT #1**

I think this manuscript is too long and feel repetitive. It is far to reach the end for reader. I suggest that authors need to shape it up. Otherwise, the part of the aim is not clear.

### **ANSWER**

This manuscript was submitted to a professional language editing service for revision, since the journal requires the Non-Native Speakers of English Editing Certificate. Nonetheless, we reviewed the text and modified it so it became more concise, less repetitive and clearer.

### **Additional commentaries:**

All articles and books in the reference of manuscript file without PMID doesn't have the number available.

### **References:**

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