

## ANSWERING REVIEWERS

August 5, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12144-review.doc).

**Title:** Effects of the traditional herbal medicine San-Huang-Xie-Xin-Tang on gastrointestinal motility

**Author:** Min Woo Hwang, Tae Seok Ahn, Noo Ri Hong, Han-Sol Jeong, Myeong Ho Jung, Byung Joo Kim

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 12144

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) This study clarified the effect of SHXXT on gastrointestinal motility. But the way to evaluate the gastrointestinal motility was only one method and it was unclear which the effect of SHXXT was stronger or weaker than other drugs which were reported to change the gastrointestinal motility. Major Comment (1) The power of effect of SHXXT on gastrointestinal motility was unclear. The authors should compare the effect of SHXXT with other prokinetic drugs which had been reported to change the gastrointestinal motility.

Answer) For the comparison of the prokinetic activity among the test drugs in this study, we used an aqueous extract from the dried immature fruit of *Poncirus trifoliata* Raf. (PF-W) [26]. PF-W is one of the most popular traditional folk medicines in Korea originated from Rutaceae fruits and is known to have unique and potent prokinetic activity in both normal and GI motility dysfunctions rodents [26,29]. When we applied PF-W in normal and GI motility dysfunctions mice, the effects of SHXXT on GI motility was the same as those of PF-W (Fig. 1, 2 and 3). Also, in case of CR and RR, the effects of SHXXT on GI motility was the same as those of PF-W (Fig. 4 and 5). However, in case of SR, though the effects of PF-W on GI motility was good as a prokinetic activity, SR had no effects on GI motility (Fig. 6).

(2) Dear authors, I would recommend to expand on your discussion. Well done for the rest of your work which I found interesting.

Answer) We added this part in Discussion.

GI tract consists of enteric neurons, interstitial cells, immune cells and smooth muscle cells. Interstitial cells include ICC and platelet-derived growth factor receptor alpha-positive (PDGFR $\alpha^+$ ) and generate pacemaker activity throughout the GI tract and also transduce enteric nerve signals to adjacent smooth muscle cells<sup>[38]</sup>. Though we experimented the effects of SHXXT on only ICC, SHXXT depolarized the pacemaker activity in ICC and increased the ITR on GI motility. Therefore, we think that SHXXT may have a potential role in regulation of GI motility through the modulation of ICC. In future, we will experiment the effects of SHXXT on enteric neurons and smooth muscle cells. Additionally, it has been shown that the pacemaker activities of ICC in the murine small intestine are mainly due to periodic activations of nonselective cation channels (NSCCs)<sup>[25,39]</sup> or Cl<sup>-</sup> channels<sup>[40]</sup>. Kim et al. (2005)<sup>[25]</sup> suggested that transient receptor potential melastatin (TRPM) 7 is required for ICC pacemaker activity in the murine small intestine, and Hwang et al. (2009)<sup>[41]</sup> suggested that a Ca<sup>2+</sup>-activated Cl<sup>-</sup> channel (CaCC, Tmem16A, anoctamin 1 (ANO1)) is involved in slow wave generation in ICC. Therefore, it has been proposed that TRPM7 and ANO1 may be important targets for the pharmacological treatment of GI motility disorders. In future, because the TRPM7 or ANO1 channels are involved in pacemaker activity in ICC, we will investigate which ion channel is involved in SHXXT action.

3 Revision has been made according to the suggestions of the editor

#### (1) COMMENTS

##### **Background**

San-Huang-Xie-Xin-Tang (SHXXT) (composed of *Coptidis Rhizoma* (*Coptis chinensis* Franch), *Rhei Rhizoma* (*Rheum officinale* Baill), and *Scutellariae Radix* (*Scutellaria baicalensis* Georgi), a traditional Chinese medicinal formula, is widely used in Eastern Asia, to ameliorate the symptoms of gastrointestinal (GI) disorders. However, despite the considerable use made of SHXXT to treat GI dysfunction, little is known of its *in vivo* regulatory effects on GI motility.

##### **Research frontiers**

SHXXT is a good candidate for the development of a gastroprokinetic agent.

##### **Innovations and breakthroughs**

In normal mice, intestinal transit rate (ITRs) were significantly and dose-dependently increased by SHXXT (0.1–1 g/kg). GMD was induced by injecting acetic acid (AA) or streptozotocin (STZ) intraperitoneally. ITRs of GMD mice were significantly lesser than in normal mice, and these decreases were significantly and dose-dependently inhibited by SHXXT (0.1–1 g/kg).

##### **Applications**

SHXXT may be a new target or a novel candidate prokinetic agent for pharmacological treatment of GI motility disorders.

##### **Terminology**

Gastrointestinal (GI) motility : the movements of the digestive system, and the transit of the contents within it.

Intestinal transit rates (ITRs) : Passage of food (sometimes in the form of a test meal) through the GI tract as measured in minutes or hours

Interstitial cells of Cajal (ICCs) : The pacemaker cells of the GI tract.

*Peer review*

(2) For the figures, decomposable figures are required. It means that the fonts and lines can be edited or moved. It can be made by ppt.

Answer) We made decomposable figures again.

(3) Indicate the number and character of observations and subjects. Identify statistical significance by superscripts in front of the probabilities ( $P$ ), e.g.  $^aP < 0.05$ ,  $^bP < 0.01$  vs A;  $^cP < 0.05$ ,  $^dP < 0.01$  vs B; etc.

Answer) We changed.

4 We corrected this manuscript 12144 by American Journal Experts.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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