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## PEER-REVIEW REPORT

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

**Manuscript NO:** 33793

**Title:** Hwangryunhaedok-tang induces the depolarization of pacemaker potentials through 5-HT3 and 5-HT4 receptors in cultured murine small intestine interstitial cells of Cajal

**Reviewer's code:** 01436006

**Reviewer's country:** China

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-03-04

**Date reviewed:** 2017-03-05

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

### COMMENTS TO AUTHORS

The authors investigated the effects of HHT (a traditional herbal medicine) on the pacemaker potentials of mouse interstitial cells of Cajal (ICCs), the results of study suggest that HHT dose-dependently depolarizes ICC pacemaker potentials through 5-HT3 and 5-HT4 receptors via external and internal Ca<sup>2+</sup> regulation and via G protein-, and MLCK-dependent pathways. These data are somewhat interesting. Minor comments: 1.The authors wrote that HHT dose-dependently depolarizes ICC pacemaker potentials via MLCK-dependent and PKC- and Rho kinase-independent pathways, but the results showed HHT-induced pacemaker potential depolarizations were inhibited by ML-7 (88.5% inhibition) , but not by calphostin or Y27632. So I am confused. 2.The discussion paragraph should be rewritten, arrangement is not clear. 3.There are some grammar mistakes in the manuscript.



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## PEER-REVIEW REPORT

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

**Manuscript NO:** 33793

**Title:** Hwangryunhaedok-tang induces the depolarization of pacemaker potentials through 5-HT3 and 5-HT4 receptors in cultured murine small intestine interstitial cells of Cajal

**Reviewer's code:** 03476131

**Reviewer's country:** United States

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-03-04

**Date reviewed:** 2017-03-14

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

### COMMENTS TO AUTHORS

Hwangryunhaedok-tang induces the depolarization of pacemaker potentials through 5-HT3 and 5-HT4 receptors in cultured murine small intestine interstitial cells of Cajal. The manuscript has important value to the interstitial cells field and the idea of exploring a traditional herbal medicine to treat gastrointestinal (GI) disorders. The authors examined the effects of the potential herbal drug Hwangryunhaedok-tang (HHT) on pacemaker potentials generated by ICCs. HHT depolarized ICC pacemaker potentials and the authors stated that this depolarization was due to activation of 5-HT3 and 5-HT4 receptors in ICC. It seems that G-protein coupled receptors, calcium influx and release mechanisms and MLCK are involved in mediating the HHT effects on ICC.

Major comments: This hypothesis and conclusions are lacking evidence in the current form of the paper, as the authors did not establish clearly the link of how HHT active elements (Coptidis Rhizoma and Gardeniae Fructus) can bind to 5-HT receptors on ICC.



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Furthermore, the data lacks the effects of HHT identified compounds ( geniposide, berberine chloride, baicalin, and wogonin) on ICCs. A surprising results that HHTE-induced pacemaker potential depolarizations were inhibited by ML-7. These results are confusing as native ICCs are non-contractile and do not express MLCK. Therefore, the results obtained maybe due direct effects on smooth muscle cells contaminated with ICC cultures or there is potential change in ICC phenotype in culture. A more careful approach should be used to assess the data and interpretations. The authors demonstrated that the actions of HHTE is linked to G-protein coupled receptor mechanisms. Although 5HT3 receptors are cation channels that can be activated without G- protein mechanisms. No explanation was discussed to explain results of 5HT3 antagonist effects in relation to GDP–S effects. Minor comments: -Please indicate if patched ICC were immunopostive for kit. - “Confirmation of HHTE receptor subtypes in ICCs”. Please consider revising the sentence. For example HHTE mechanisms of action on ICC. -The conclusions that HHTE affects ICC may be through 5-HT3 and 5-HT4 receptors by the authors is weak and supported by data or discussed. Questions what and how exactly HHTE components binds to 5HT receptor are lacking. -Frequency of ICC pacemaker potentials should be analyzed for all drugs used to assess the effects of HHTE on pacemaker currents and provide valuable information on how these drugs affects motility. -The authors should explain and discuss the link between calcium signaling and 5HT receptor (5HT 3 and 4) activation and provide a model of the role of calcium influx and release mechanisms in mediating HHTE effects. -Abstract: please include the drug action rather than drug name alone. For example the A 5-HT3 receptor antagonist (Y25130). - Please include the full name. For example HPLC (high performance liquid chromatography) - What is the definition of “standard compounds” ? Should be included throughout the MS - Patch clamp temperature should be included in results section

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

**Manuscript NO:** 33793

**Title:** Hwangryunhaedok-tang induces the depolarization of pacemaker potentials through 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors in cultured murine small intestine interstitial cells of Cajal

**Reviewer's code:** 02440844

**Reviewer's country:** China

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-03-04

**Date reviewed:** 2017-03-15

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> [ Y] Accept
<input type="checkbox"/> [ Y] Grade B: Very good	<input type="checkbox"/> [ Y] Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> [ ] High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> [ ] Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> [ ] Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> [ Y] No	<input type="checkbox"/> [ ] Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> [ Y] No	

### COMMENTS TO AUTHORS

The manuscript (NO: 33793) entitled Hwangryunhaedok-tang induces the depolarization of pacemaker potentials through 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors in cultured murine small intestine interstitial cells of Cajal was investigated the effect of HHTE which is a traditional herbal medicine used to treat gastrointestinal (GI) disorders on ICC pacemaking potential. The author suggested that HHTE dose-dependently depolarizes ICC pacemaker potentials through 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors via external and internal Ca<sup>2+</sup> regulation and via G protein-, and MLCK-dependent and PKC- and Rho kinase-independent pathways. The work is concerned with traditional herbal medicine and its effect of promoting gastrointestinal motility via 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors of ICC. This work is very interesting and has potential clinical application value. Comments 1. The effect of HHTE on ICC pacemaking potential is very dramatically, so I think to know if the effect of HHTE on smooth muscle contraction is



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matched to the effect of HHTE on ICC. 2. Does the author think HHTE may activates 5-HT3 and 5-HT4 receptors? 3. It is well known that ICC pacemaking currents elicited by ANO1 channel, so test the effect of ANO1 blocker on ICC pacemaking potential is very important.