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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 54923

Title: Assessment of Tobacco Heating System 2.4 on osteogenic differentiation of mesenchymal stem cells and primary human osteoblasts compared to conventional cigarettes

Reviewer's code: 00532996

Position: Editorial Board

Academic degree: BSc, MSc, PhD

Professional title: Assistant Professor, Research Scientist, Senior Scientist

Reviewer's Country/Territory: India

Author's Country/Territory: Germany

Manuscript submission date: 2020-02-25

Reviewer chosen by: Ruo-Yu Ma (Quit in 2020)

Reviewer accepted review: 2020-04-15 06:15

Reviewer performed review: 2020-04-24 15:34

Review time: 9 Days and 9 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Study is well designed and experimental replicates are acceptable. Introduction and discussion are adequate. Figure 1A y-axis 'min/stuck' needs to be rectified to min/stick. Work may be interesting to those in concerned field.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 54923

Title: Assessment of Tobacco Heating System 2.4 on osteogenic differentiation of mesenchymal stem cells and primary human osteoblasts compared to conventional cigarettes

Reviewer's code: 01206707

Position: Editorial Board

Academic degree: DDS, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: South Korea

Author's Country/Territory: Germany

Manuscript submission date: 2020-02-25

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2020-04-28 03:25

Reviewer performed review: 2020-04-28 03:35

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input checked="" type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Thank you very much for submitting your research to the World Journal of Stem Cells. The reviewer would like to make several comments on your article. 1.What is the novelty of this report? 2.How did the authors calculate the sample size? How did the authors arrive at the number of participants. 3.Please comment on the individual differences. 4.Did the participants agree for the publication? 5.Please perform additional experiments to elucidate the underlying mechanism. 6.Please comment of the clinical relevance. Thank you very much.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 54923

Title: Assessment of Tobacco Heating System 2.4 on osteogenic differentiation of mesenchymal stem cells and primary human osteoblasts compared to conventional cigarettes

Reviewer's code: 03811054

Position: Editorial Board

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: Germany

Manuscript submission date: 2020-02-25

Reviewer chosen by: Xiao-Quan Yu

Reviewer accepted review: 2020-05-12 11:19

Reviewer performed review: 2020-05-20 07:49

Review time: 7 Days and 20 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

There are minor linguistic errors in the manuscript.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 54923

Title: Assessment of Tobacco Heating System 2.4 on osteogenic differentiation of mesenchymal stem cells and primary human osteoblasts compared to conventional cigarettes

Reviewer's code: 02524648

Position: Editorial Board

Academic degree: PhD

Professional title: Postdoctoral Fellow, Senior Researcher

Reviewer's Country/Territory: Spain

Author's Country/Territory: Germany

Manuscript submission date: 2020-02-25

Reviewer chosen by: Xiao-Quan Yu

Reviewer accepted review: 2020-05-17 08:10

Reviewer performed review: 2020-05-20 17:00

Review time: 3 Days and 8 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript by Aspera-Werz and colleagues is an interesting study on the effects of tobacco heating system (THS) 2.4 and conventional cigarette smoking (CS) on the viability and osteogenic differentiation abilities of human immortalized mesenchymal stem cells and primary human osteoblasts, with the aim of elucidating possible advantages of THS over CS on bone healing in smokers. The text is clearly written; there are only a few typos that may be easily corrected, as for example: - Fig. 1A.: min/stick, instead of min/stuck on the vertical axis - Various sections in Materials and Methods, where the authors indicate that measurements were “correct to the background”, instead of saying “corrected” - Last line in section “THS is less toxic to bone cells than conventional.....”: it should state that “MSCs were more sensitive to AE....”, not “sensible”

As main comments to the manuscript, I have lacked, as a reader who is not familiar with the generation of aqueous extracts (AEs) from cigarettes, a series of explanations in the text, a discussion on a number of points that may clarify the experimental set up and the ultimate significance of the obtained data to those who may not be wholly familiar with the approach that has been followed: - Does the system employed (gas washing bottle, peristaltic pump) take into account the fact that the cigarette will be burned while the THS will not? - Does the system mimic the entry of the molecular species in blood? In other words, would the addition of AEs to the medium reflect the species that cross into the blood stream? Otherwise, should the model not include other elements such as endothelial cells, to investigate the crossing of the putative toxic molecules through some kind of “biological barrier”? Considering the crossing into the blood stream, could the differences in the concentration of particles in the AEs give rise to differences in the molecular species that cross from THS and from

CS. - The study indicates a reduced effect of THS on MSC and hOB viability and differentiation abilities in support of a less harmful action of THS on bone regeneration following fracture. However, the authors have not taken into account the conditions present following damage to the tissue when establishing the culture system, e.g. presence of cytokines in the medium. These might alter the action of the various toxins that are present in the AEs. It would be highly desirable for the authors to discuss these points in the manuscript, preferably supporting the arguments with available evidence and published data that support the validity of their model. As a minor point: The authors indicate in section "THS has less effect on cell viability....", lines 12-13, that Figure 2C shows calcein-AM staining of SCP-1 cells, while the legend in this Figure indicates that the staining corresponds to hOBs.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Stem Cells

Manuscript NO: 54923

Title: Assessment of Tobacco Heating System 2.4 on osteogenic differentiation of mesenchymal stem cells and primary human osteoblasts compared to conventional cigarettes

Reviewer's code: 01206707

Position: Editorial Board

Academic degree: DDS, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: South Korea

Author's Country/Territory: Germany

Manuscript submission date: 2020-02-25

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2020-06-22 23:27

Reviewer performed review: 2020-06-22 23:41

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Thank you very much for submitting your revised research to the World Journal of Stem Cells. The reviewer would like to make a couple of comments on your article. 1.For Figure 5. It seems that there are background noise in the fluorescent image(s). Please provide images with better quality 2.Please provide the rationale on selection of posthoc analysis. Please provide the raw data. 3.For Figure 6 Please provide the error bars. Please provide the raw data for this. Thank you very much.