



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46607

**Title:** Human umbilical cord mesenchymal stem cells ameliorate liver fibrosis in vitro and in vivo

**Reviewer’s code:** 00532996

**Reviewer’s country:** India

**Science editor:** Fang-Fang Ji

**Reviewer accepted review:** 2019-03-12 10:25

**Reviewer performed review:** 2019-03-20 07:06

**Review time:** 7 Days and 20 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer’s expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

Liver fibrosis and cirrhosis form liver chronic disease which is considered as a great healthcare burden across the world. Liver transplantation is the preferred effective treatment, however shortage of donor organs is a serious problem contributing to the



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increasing mortality rate of patients as wait list is long. Efforts are being focused on developing antifibrotic drugs and therapies. On this background, stem cell-based therapy is gaining interest as promising therapeutic alternative. Current review addresses characterization and application of umbilical cord MSC as therapy for Liver fibrosis. Topic is of importance in related field, however review needs to be strengthened based on following points. 1. Introduction should include disease epidemiology in detail in terms of predisposing conditions, causative factors, incidence, prevalence, frequency etc. 2. It should include a table on currently ongoing clinical trials using UC-MSC. 3. Section on ethical issues, regulatory guidelines to be followed, limitations and concerns should be included. 4. Few latest relevant references to be included; Fiore et al 2018 (World J Gastroenterol. 24(23): 2427-2440); Kwak et al 2018 (Canadian Journal of Gastroenterology and Hepatology, Article ID 4197857); Zhao et al 2018 (Stem Cell Res Ther. 9: 72) and Lee et al 2018, (Gastroenterology 154:46-56) It can be accepted for publication after necessary minor revision.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

- The same title
- Duplicate publication
- Plagiarism
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##### ***BPG Search:***

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[ Y ] No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46607

**Title:** Human umbilical cord mesenchymal stem cells ameliorate liver fibrosis in vitro and in vivo

**Reviewer's code:** 02728252

**Reviewer's country:** Egypt

**Science editor:** Fang-Fang Ji

**Reviewer accepted review:** 2019-04-15 03:14

**Reviewer performed review:** 2019-04-15 12:35

**Review time:** 9 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

It is a narrative review that should be shortened to a greater degree to be consistent with the title (amelioration of liver fibrosis by hUC-MSCs). The second major concern is how the authors take they decision that human umbilical cord mesenchymal stem cells



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ameliorate liver fibrosis in vitro and in vivo. If this is case, this decision should depend on a systematic method of review followed by meta-analysis. In addition there are minor concerns about the abbreviation used in the study that should be clarified when they used for the first time in the text and minor English language editing is advisable.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

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##### ***BPG Search:***

- The same title
- Duplicate publication
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**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46607

**Title:** Human umbilical cord mesenchymal stem cells ameliorate liver fibrosis in vitro and in vivo

**Reviewer's code:** 02446223

**Reviewer's country:** Italy

**Science editor:** Fang-Fang Ji

**Reviewer accepted review:** 2019-04-15 09:02

**Reviewer performed review:** 2019-04-16 12:20

**Review time:** 1 Day and 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

The present review is interesting and extremely detailed, all the most important points have been covered and discussed, with explanatory figures. My only suggestion is to try to reduce, at least a little, the paper length, besides the correction of some few spelling



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mistakes.

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**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46607

**Title:** Human umbilical cord mesenchymal stem cells ameliorate liver fibrosis in vitro and in vivo

**Reviewer's code:** 03471268

**Reviewer's country:** Japan

**Science editor:** Fang-Fang Ji

**Reviewer accepted review:** 2019-04-15 02:18

**Reviewer performed review:** 2019-04-18 11:23

**Review time:** 3 Days and 9 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input checked="" type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

Author tried to summarize the progress of human UC-MSCs, described a promising therapeutic strategy, based mainly on the paracrine effects, transdifferentiation capacity, and immunomodulatory function of the cells. However, until today, although some



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small scale clinical trials are performed, there is still much unclear points to understand the mechanism. So, we should take care to conclude and avoid from mis-understanding. Inconsistent work and non-systematic summary might not result in correct conclusion. I pick up partial points to make your attention as followings. I suggest authors to arrange the reasonable and logic story comprehensively. 1. The structure of human umbilical cord and hUC-MSCs isolation as well as the culture conditions are common knowledge, there is no direct relation with this topic. 2. There is no meaning to compare with the molecular markers of ESCs such as OCT4, SOX2, and NANOG. MSCs are distinctly different from ESCs. 3. Trans-differentiation of hUC-MSCs into hepatocyte-like cells in vitro is one kind of experiment performed from two decades ago, the conversed cells could not be comparable with real hepatocytes, and also could not imply they will make function in vivo to inhibit hepatic fibrosis. 4. Also the authors understand that hUC-MSCs-derived hepatocyte-like cells are insufficient to express hepatocyte function, so introduced gene editing to enhance. Here, the concept of this review is changed dramatically far from the topic.

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[ Y ] No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46607

**Title:** Human umbilical cord mesenchymal stem cells ameliorate liver fibrosis in vitro and in vivo

**Reviewer's code:** 02446277

**Reviewer's country:** Romania

**Science editor:** Fang-Fang Ji

**Reviewer accepted review:** 2019-04-18 07:17

**Reviewer performed review:** 2019-04-19 10:55

**Review time:** 1 Day and 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

The manuscript submitted by Fei Yin et al., brings interesting and up to date information about the use of human umbilical cord mesenchymal stem cells in the treatment of liver fibrosis. The potential of MSC to revers liver fibrosis and to improve liver function is



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sustained by bioactive factors and cytokines released from hUC-MSCs such as: TGF- $\beta$ 1 and Smad3, Milk Fat Globule-EGF Factor 8. Several in vivo experiments are presented to sustain the conclusions. The manuscript is not well structured in the sense that the introductory parts dedicated to MSC culture and their differentiation into hepatocytes are far too extensive, and consequently the emphasis does not fall on the stated purpose of the manuscript, namely the use of MSC in the treatment of hepatic fibrosis. So, I suggest concentrating the information, perhaps in the form of tables, so that this introductory part does not exceed 5 pages. Several aspects to be considered: 1. I suggest changing the abbreviation for stellated hepatic cells (HSC) to another because HSC is mainly known as the abbreviation for hematopoietic stem cells. 2. Figure 1- since hepatic stellate cells (aHSCs) “promote the development of liver fibrosis through paracrine and autocrine modes” and is “critical for the formation of liver fibrosis”, the arrow from figure 1 should not be pointed out to liver fibrosis? 3. Pag 4: “endodontic pul” to be corrected: endodontic pulp 4. Pag 15: “Gene edition” in hUC-MSCs is not a proper term here. Gene editing technology imply modification of miRNA sequences. Here, is about controlling / regulation of gene expression. 5. For the CLINICAL TRIALS section, the trial number for referred studies must be entered. If not available, I think changing the section name must be considered. There are, however, many clinical trials that use MSC in the treatment of hepatic fibrosis, some of whom use the umbilical cord (eg. NCT01728727, NCT01342250, NCT01220492) as the source of the MSC. I think they should be referred in this section of the manuscript.

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Plagiarism

No

***BPG Search:***

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No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46607

**Title:** Human umbilical cord mesenchymal stem cells ameliorate liver fibrosis in vitro and in vivo

**Reviewer’s code:** 02524648

**Reviewer’s country:** Spain

**Science editor:** Fang-Fang Ji

**Reviewer accepted review:** 2019-04-15 13:20

**Reviewer performed review:** 2019-04-21 19:07

**Review time:** 6 Days and 5 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

In their review titled “Human umbilical cord mesenchymal stem cells ameliorate liver fibrosis in vitro and in vivo”, the authors have conducted an extensive study on the approaches that have been followed to date in search of a promising therapy for liver



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fibrosis. The text is well structured, presented in an easy-to-follow order, the bibliography extensive, and each section ends with a short paragraph that summarises what has been discussed above. However, and as major comments to the manuscript: - It would greatly benefit from a thorough editing of the English language, since many of the sentences are not correctly written. - One also misses a final paragraph in section 4 (Conclusion and FUTURE PROSPECTS) where the authors, rather than hypothesizing that the number of challenges still to be faced by the use of hUC-MSCs to ameliorate liver fibrosis will be resolved, should at least indicate what lines of research are being currently explored (or should, in their opinion, be conducted) in order to solve such problems; it is a pity that a review that pinpoints many of the current shortcomings to the use of hUC-MSCs as a therapy for liver fibrosis ends so poorly, with just an enumeration of facts and without a proper discussion on possible ways to reach the final goal of this research. Other comments are: - A legend accompanying each of the figures would be desired, in order to clarify their meaning (especially figure 3!). - hUC-MSCs have been sometimes indicated as HUC-MSCs (e.g. section 1 and section 2 headings). - The preservation of genetic stability in hUC-MSCs, mentioned in the final sentence in section 1.3, has not been discussed above, in the corresponding section. - Reference (62): Weiss(h) and colleagues(62) - Section 1.7.4: o First line in page 16: hUC-MSCs infected? Clarify approach: infected with viruses? o Last paragraph: safety and ethical issues are mentioned; it would be convenient that these were briefly discussed above. - Section 2.1, second paragraph: “....Smad3, which can transfer signals from the cytoplasm to the nucleus, thereby promoting onset of liver fibrosis.”: An explanatory note would be wished for as to the mechanism(s) for Smad 3 to promote liver fibrosis. - Section 2.1.2, last paragraph: Please indicate what 8-OHdG stands for. - Section 3, 2nd paragraph: TBIL (what TBIL stands for should be indicated) - Section 4, Sixth point discussed in the second paragraph (page 27): Again, the problems inherent to



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gene editing in hUC-MSCs have not been discussed, neither the transfection problems nor any safety issues. Please comment on this point in this paragraph, as well as in section 1.7.4.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

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- No

##### ***BPG Search:***

- The same title
- Duplicate publication
- Plagiarism
- No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46607

**Title:** Human umbilical cord mesenchymal stem cells ameliorate liver fibrosis in vitro and in vivo

**Reviewer’s code:** 03814168

**Reviewer’s country:** Pakistan

**Science editor:** Fang-Fang Ji

**Reviewer accepted review:** 2019-04-15 03:27

**Reviewer performed review:** 2019-04-22 03:36

**Review time:** 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

The review article on “Human umbilical cord mesenchymal stem cells ameliorate liver fibrosis in vitro and in vivo”, is good quality article, covering all the aspects of Mesenchymal stem cells isolation, and propagation , the signaling pathways involved in



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the differentiation of stem cells toward hepatocytes are very well describe. One point is if the author could add some literature about Wnt and Notch pathway as they are involved in the hepatic differentiation.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

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- No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46607

**Title:** Human umbilical cord mesenchymal stem cells ameliorate liver fibrosis in vitro and in vivo

**Reviewer's code:** 02495033

**Reviewer's country:** South Korea

**Science editor:** Fang-Fang Ji

**Reviewer accepted review:** 2019-04-18 09:02

**Reviewer performed review:** 2019-04-28 02:52

**Review time:** 9 Days and 17 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input checked="" type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

The review on the beneficial effects of human umbilical cord mesenchymal stem cells on the amelioration of liver fibrosis is very extensive and sound. So, I recommend the manuscript should be published in WJSC.



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