Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-22-886

Reviewer A

Comment 1: The organization of the article is difficult to follow. For example, the first section on alveolar epithelial cell and IPF is presumably an introduction to why the alveolar epithelial cell senescence is being discussed; this should be made even more clear with transition statements, and perhaps titled "introduction" to separate it from the body of the text regarding pathways and associated therapeutics.
Reply 1: As Reviewer suggested that we've moved this section to the introduction.
Changes in the text: Please see on Page 4, lines 69-86.

Comment 2: Section 3 ("aging of alveolar epithelial cells and IPF") is a description of the cellular mechanisms known to lead to cellular senescence and the association of these mechanisms with aging and IPF. At times it is difficult to follow whether the author is talking about aging, IPF, or cellular senescence as the outcome of interest. Consider using more paragraphs (for example paragraph break at line 163, complete paragraph 181-196) with summary statements to guide the reader's attention through this dense information.
Reply 2: Thank you for underlining this deficiency. This part is a description of the mechanisms linking alveolar epithelial cell senescence to IPF. Here we focus on alveolar epithelial cell senescence involved in IPF formation through mitochondrial dysfunction and metabolic reprogramming, as shown in Figure 1. Apologies for the confusion created, we've redefined the paragraphs as suggested.
Changes in the text: Please see on Page 8-10, lines 165-219.

Comment 3: Sections 4-7 highlight specific pathways and therapeutic targets. This is the body of the author's discuss. These sections have their own conclusion (line 454-470) and warrant a similarly-dedicated introduction/explanation of relation to the previous sections.
Reply 3: We have re-written this part according to the Reviewer's suggestion. For this section on signaling pathways, I have reassigned graded headings. Introduced one by one, first made a brief introduction of the specific signaling pathway, followed by the relationship between this signaling pathway and alveolar epithelial cell senescence, and finally discussed whether this signaling pathway can be used as a target.
Changes in the text: We have modified our text (see Page 11-23, lines 221-494)

Comment 4: Line 473. Nintedanib is mentioned by name for the first and only time in the conclusion of the paper (and pirfenidone only briefly brought up). Should current therapeutics be introduced and emphasized earlier in the article as the reason for exploring this topic? In which case their therapeutic targets should be further

explained. Else do not emphasize these medications in the conclusion.
Reply 4: Thanks for pointing this out. We have inserted in the introduction the main current treatment measures and added the relevant supporting literature.
Changes in the text: Please check them on Page 5, lines 88-96.

Reviewer B

Comment 5: Could the authors comment on evidence or lack thereof for antisenescence/ telomere preserving agents that are popularly used: e.g. ubiquinol/coenzymeQA, glutathione, L-carnosine, TA-65, attenuated androgens/oestrogen
Reply 5: Considering the Reviewer's suggestion, we searched the literature on antisenescence/ telomere preserving agents and found that most of these drugs are used to treat other age-related diseases such as Alzheimer's disease. Currently no research has confirmed that these agents can be used to cure IPF.
Changes in the text: We have modified our text as advised (see Page 6, line 114-118).

Comment 6: Methods- please indicate how papers were selected for detailed review Justify exclusion of pre 2020 literature
Reply 6: We have sorry for our incorrect writing. We started our search in 2020, but we retrieved literature from 2000-2022.
Changes in the text: We have added conditions for selecting papers for detailed review and reasons for excluding literature prior to 2000 (see Page 6, lines 110-114).

Comment 7: P7 L 262- please give more information regarding (potential) active ingredient(s) of citrus alkaline extract?
Reply 7: It is really true as Reviewer suggested that we added active ingredients of citrus alkaline extract. 75% ethanol extract and flavonoids are the active compounds of CAE, but it is mainly 75% ethanol extract that can alleviate IPF by reducing alveolar epithelial senescence.
Changes in the text: Please see Page 14, lines 302-304.

Comment 8: P7 L277 please write out PI3K & AKT in full the first time these are mentioned.
Reply 8: We have made correction according to the Reviewer's comments.
Changes in the text: Please check them on Page 15, lines 317-318.

Comment 9: P9 L 331 please mention survival benefit (if any) and primary trial outcome result. 'Thus proving their high efficiency" should be deleted unless evidence is provided to this effect.
Reply 9: Special thanks to you for your good comments. We have added primary trial outcome result.

Changes in the text: Please see Page 18, lines 375-376.

Comment 10: P11 L 448 & 450 please indicate which species/ which cirrhosis model this refers to.
Reply 10: We are very sorry for our negligence of species of experimental animals. Mice were used in the literature to construct cirrhosis models
Changes in the text: We have added species (see Page 23, line 489).

Comment 11: P2 L 468 “Quercetin can alleviate IPF by reducing the number of alveolar epithelial cells and fibroblast senescence.”This sentence does not make sense to me- please revise.
Reply 11: We sincerely apologize for confusing you owing to our inappropriate expressions.
Changes in the text: We have modified our text(see Page 24, lines 510-511).