Reviewer's report

Title: Attenuation of early liver fibrosis by herbal compound "Diwu Yanggan" through modulating the balance between epithelial-to-mesenchymal transition and mesenchymal-to-epithelial transition

Version: 3 Date: 21 July 2014

Reviewer: Ruiqiong Ran

Reviewer's report:

Comments to Authors:

General Comments

The Authors reported that a herbal prescription “DWYG” significantly prevents the hepatic fibrosis and cirrhosis experimentally induced by CCl4. Moreover, they demonstrated that the imbalance between the mesenchymal-to-epithelial transition (MET) and the epithelial-to-mesenchymal transition (EMT) is vital and contributes to the formation of hepatic fibrogenesis. They also found that TGF-β1/BMP-7 and Hedgehog (Hh) signaling pathways play important roles in the regulation of the balance between the mesenchymal-to-epithelial transition (MET) and the epithelial-to-mesenchymal transition (EMT). DWYG could reverse CCl4-induced imbalance between MET and EMT by simultaneously regulating TGF-β1/BMP-7 and Hedgehog (Hh) cell signaling pathways. For example, these findings show that DWYG simultaneously enhances BMP-7 but inhibits TGF-β1 and Hedgehog (Hh) cell signaling pathways in injured liver tissues and maintain MET homeostasis, and subsequently prevents and reverses hepatic fibrosis. This study highlights that TGF-β1/BMP-7 and Hedgehog (Hh) are potential targets for anti-fibrotic strategies in liver fibrosis therapy. The methodological quality of the study is sufficiently high and the results are convincing. The manuscript reads well, with minor suggestions for improvements.

Specific suggestion:

1. Conclusion is well written but needs to be a bit shorter by eliminating unnecessary sentences. My concern is that the conclusion is a bit too long and you'll lose the reader.

2. The last paragraph of background needs to be revised. You should add the main results to this paragraph. In addition, “in order to decipher the clinical efficacy and make better application of DWYG” needs to be rewritten.

3. I rewrote or corrected the following sentences or words (see blue color)

Page 3, line 71: severe morbidity and significant mortality; considerable morbidity and mortality

Page 3, line 77 Please delete “as even advance fibrosis is reversible”

Page 3, line 88: be paramount for normal embryonic development; be paramount
importance for normal embryonic development

Page 4, line 91: Various in vitro and in vivo studies; In vitro and in vivo studies

Page 4, line 103-104: Through obviously decreasing the serum levels of ALT and AST; as evidenced by the results of an obvious decrease in serum ALT and AST levels.

Page 4, line 112: it has been shown to provide good clinical application; provide clear therapeutic benefit

Page 4 line 115: Based on above; Based on the above mentioned information

Page 5 line 133: recovered ethanol by reduced pressure; removed ethanol by reduced pressure

Page 6 line 158: Serum AST/ALT determination; Determination of serum ALT and AST activities

Page 8 line 216: treatment with DWYG; DWYG treatment

Page 8 line 221: inhibited the increases of serum ALT and AST; inhibited the increase in serum levels of AST and ALT.

Page 8 line 234-235: was drastically decreased to 4.41±1.02% # was drastically decreased from 8.10±0.92% to 4.41±1.02% #

Page 8 line 237-239: indicating that DWYG had an inhibition effect #indicating that DWYG has an inhibitory effect.

Page 8, line 239: induced a disastrous elevation of hydroxyproline at 6 weeks; induced a considerable elevation in the level of hydroxyproline at 6 weeks.

Page 9 line 243: inhibition effect; inhibitory effect

Page 9 line 260: induction; treatment

Page 9 line 268: accompanied by repression of the protein; accompanied by diminished protein

Page 10 line 282: stimulating a mean 1.5-fold increase in transcript expression levels; stimulating 1.5-fold increase in transcript expression levels

Page 10 line 284: a mean 3-fold decrease; 3-fold decrease

Page 10 line 286: expression ratio TGF-#1/BMP-7; expression ratio of TGF-#1/BMP-7

Page 10 line 291-292: liver fibrosis in CCl4-induced rats; CCl4-induced liver fibrosis in rats

Page 10 line 297: has been implicated in EMT induction #has been implicated in the regulation of EMT

Page 11 line 305-306: compared to CCl4-induced model group; compared to that of rats treated with CCl4 alone

Page 11 line 309: the robust mRNA and protein expressions of Smo exhibited in untreated CCl4-induced fibrotic rats were considerably diminished; robust increases of Smo mRNA and protein expression in untreated CCl4-induced fibrotic rats were considerably diminished.
Page11 line 311: correspondingly weakened; was correspondingly diminished
Page11 line 312: inhibited; inhibit
Page11 line 321-322: chronic CCl4-injury rat liver: CCl4-induced chronic liver injury
Page11 line 323: provoked the reverse of EMT to MET; could result in reversal of EMT to MET
Page11 line 324-325: up-regulation expression of E-cadherin and down-regulation expression of Vimentin; up-regulation of E-cadherin expression and down-regulation of Vimentin expression
Page11 line 326: anti-fibrotic efficacy; anti-fibrotic mechanism
Page12 line 333: have been ascendant due to its effects of; are in the ascendant due to their effects on
Page12 line 348: As evidenced in our data, As evidenced by our data,
Page13 line 365-366: As was shown in our study; Our study showed that chronic exposure
Page13 line 368: liver fibrogenesis by CCl4 induction; CCl4-induced liver fibrogenesis
Page13 line 369: were paralleled to the elevation; were paralleled by the elevation
Page13 line 377: contributed to alleviate the degree of; contributed to alleviating the degree of
Page17 line 508: Anti-#-actin blotting was used to control for equal protein loading; Anti-#-actin blotting was used as control for equal protein loading.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests