

Reviewer #1:

Specific Comments to Authors: The article with the title "Promotive action of 2-acetylaminofluorene on hepatic precancerous lesions initiated by diethylnitrosamine in rats; molecular study" is in generally well done, but I would offer these comments to the investigators:

1) Several words throughout the manuscript appear to be merged. Please correct it.

- Thanks v much for your valuable comments. As suggested by the reviewer, The whole Ms was revised and merged words were sperated

2) Some minor grammatical errors occur. The manuscript contains significant language-related issues. Please correct these types of grammatical errors throughout the paper.

- Thanks v much for your valuable comments. As suggested by the reviewer, The whole Ms was revises by native English speaker to correct linguistic and grammatical errors

3) The references are quite old. Please add or replace some of the current references with more recent articles.

- As suggested by the reviewer, all the old references has been updated by recent one

e.g.

- Old..... Mohammadian M, MahdaviFar N, Mohammadian-Hafshejani A, Salehiniya H. Iver Cancer in the world: epidemiology, incidence, mortality and risk factors. World Cancer Research Journal WCRJ 2018; 5 (2): e1082.
- RecentBray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424. doi: 10.3322/caac.21492. Epub 2018 Sep 12. Erratum in: CA Cancer J Clin. 2020 Jul;70(4):313. PMID: 30207593
- Old... wang et al.,2000
- Recent ... Teng YC, Shen ZQ, Kao CH, Tsai TF. Hepatocellular carcinoma mouse models: Hepatitis B virus-associated hepatocarcinogenesis and haploinsufficient tumor suppressor genes. World J Gastroenterol. 2016 Jan 7;22(1):300-25. doi: 10.3748/wjg.v22.i1.300. PMID: 26755878; PMCID: PMC4698494.
- Old Kowen et al.,1983

- Recent... Newell P, Villanueva A, Friedman SL, Koike K, Llovet JM. Experimental models of hepatocellular carcinoma. *J Hepatol.* 2008;48(5):858-879. doi:10.1016/j.jhep.2008.01.008
- Old... Tsujiuchi et al.,1999
- Recent....Calvisi DF, Conner EA, Ladu S, Lemmer ER, Factor VM, Thorgeirsson SS. Activation of the canonical Wnt/beta-catenin pathway confers growth advantages in c-Myc/E2F1 transgenic mouse model of liver cancer. *J Hepatol.* 2005 Jun;42(6):842-9. doi: 10.1016/j.jhep.2005.01.029. Epub 2005 Apr 8. PMID: 15885355.
- Old.. Chen et al.,1993
- Recent.... Omerovic J, Laude AJ, Prior IA. Ras proteins: paradigms for compartmentalised and isoform-specific signalling. *Cell Mol Life Sci.* 2007;64(19-20):2575-2589. doi:10.1007/s00018-007-7133-8
- Old.. Farber et al.,1977
- Recent... Espandiari P, Robertson LW, Srinivasan C, Glauert HP. Comparison of different initiation protocols in the resistant hepatocyte model. *Toxicology.* 2005 Jan 31;206(3):373-81. doi: 10.1016/j.tox.2004.07.014. PMID: 15588927.
- Old... Aström et al.,1986
- Recent... Bagnyukova TV, Tryndyak VP, Montgomery B, Churchwell MI, Karpf AR, James SR, Muskhelishvili L, Beland FA, Pogribny IP. Genetic and epigenetic changes in rat preneoplastic liver tissue induced by 2-acetylaminofluorene. *Carcinogenesis.* 2008 Mar;29(3):638-46. doi: 10.1093/carcin/bgm303. Epub 2008 Jan 19. PMID: 18204080.
- Old... Neumann et al.,1997
- Recent... Klöhn PC, Soriano ME, Irwin W, Penzo D, Scorrano L, Bitsch A, Neumann HG, Bernardi P. Early resistance to cell death and to onset of the mitochondrial permeability transition during hepatocarcinogenesis with 2-acetylaminofluorene. *Proc Natl Acad Sci U S A.* 2003 Aug 19;100(17):10014-9. doi: 10.1073/pnas.1633614100. Epub 2003 Aug 7. PMID: 12907702; PMCID: PMC187745.
- Old reference... Maddison et al.,2005
- Recent.... Xin B, Cui Y, Wang Y, Wang L, Yin J, Zhang L, Pang H, Zhang H, Wang RA. Combined use of alcohol in conventional chemical-induced mouse liver cancer model improves the simulation of clinical characteristics of human hepatocellular

carcinoma. *Oncol Lett.* 2017 Oct;14(4):4722-4728. doi: 10.3892/ol.2017.6800. Epub 2017 Aug 23. PMID: 29085472; PMCID: PMC5649534

- Old Imai et al.,1997
- Recent... Muramatsu M, Sakai M. Mechanisms of a tumor marker, glutathione transferase P, expression during hepatocarcinogenesis of the rat. *Proc Jpn Acad Ser B Phys Biol Sci.* 2006;82(9):339-352. doi:10.2183/pjab.82.339
- Old....(Greenwell et al.,1991)
- Recent.... Strzalka W, Ziemienowicz A. Proliferating cell nuclear antigen (PCNA): a key factor in DNA replication and cell cycle regulation. *Ann Bot.* 2011;107(7):1127-1140. doi:10.1093/aob/mcq243
- Old... Bellacosa et al.,1995
- Recent... Testa JR, Bellacosa A. AKT plays a central role in tumorigenesis. *Proc Natl Acad Sci U S A.* 2001;98(20):10983-10985. doi:10.1073/pnas.211430998
- Old.. Wu et al.,2016
- Recent... Duda P, Akula SM, Abrams SL, et al. Targeting GSK3 and Associated Signaling Pathways Involved in Cancer. *Cells.* 2020;9(5):1110. Published 2020 Apr 30. doi:10.3390/cells9051110

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

- As suggested by the editor, a native-English speaker had edited the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability

5 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

- (1) Science editor:** 1 Scientific quality: The manuscript describes a basic study of the promotive action of 2-acetylaminofluorene on hepatic precancerous lesions initiated by diethylnitrosamine in rats. The topic is within the scope of the WJGO. (1) Classification: Grade C; (2) Summary of the

Peer-Review Report: The article is in generally well done. However, words in the manuscript need to be corrected, grammatical errors corrected, and old references need to be replaced. The questions raised by the reviewers should be answered; and (3) Format: There are 3 tables and 5 figures. A total of 42 references are cited, including 5 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade B. A language editing certificate was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form, the Institutional Animal Care and Use Committee Approval Form or Document and the ARRIVE Guidelines.

- The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.

As suggested by the editor, signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. Have been submitted.

No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an invited manuscript. The topic has not previously been published in the WJGO. The corresponding author has not published articles in the BPG.

5 Issues raised:

(1) I found no "Author list" section. Please provide the author list;

- As suggested by the editor, "Author list" section has been added

(2) I found no "Author institutions" section. Please provide the author institutions;

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(3) I found no "Author contribution" section. Please provide the author contributions

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(4) I found no "Corresponding author" section. Please provide the corresponding author

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(5) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

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(5) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

- PMID and DOI in the reference list. As suggested by the editor, PMID and DOI in the reference list have been added to all references

(7) I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text.

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(8) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces; and

- As suggested by the editor, the references in Arabic numerals according to the citation order in the text has been modified and updated for old references

(9) please don't include any *, #, †, §, ‡, ¥, @....in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as aP < 0.05, bP < 0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, cP < 0.05 and dP < 0.01 are used, and a third series of P values is expressed as eP < 0.05 and fP < 0.01. 6 Re-Review: Not required. 7

- As suggested by the editor, *, #, †, §, ‡, ¥, @....in the manuscript has been replaced by superscript numbers for illustration; and for statistical significance