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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56546

Title: Aramchol improves liver glucose and lipid homeostasis in nonalcoholic steatohepatitis via AMPK and mTOR regulation

Reviewer's code: 03075520
Position: Peer Reviewer
Academic degree: MD
Professional title: Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Spain

Manuscript submission date: 2020-05-19
Reviewer chosen by: AI Technique
Reviewer accepted review: 2020-05-19 07:57
Reviewer performed review: 2020-05-26 08:43
Review time: 7 Days

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Reviewers' comments Reference No: 56546

Title:Aramchol improves liver glucose and lipid homeostasis in NASH via AMPK and mTOR regulation Comments: Arachidyl amido cholanoic acid (Aramchol) is a potent downregulator of hepatic SCD1 protein expression that reduces liver triglycerides (TG) and fibrosis in animal models of steatohepatitis. In a phase IIb clinical trial, Aramchol reduced blood levels of glycated hemoglobin (HbA1c), which reflects how well glucose is controlled, after 52 weeks of treatment in non-alcoholic steatohepatitis (NASH) patients. To asseslipid and glucose metabolism in mouse hepatocytes and in a NASH mouse model(0.1MCD) after treatment with Aramchol. Isolated primary mouse hepatocytes were incubated with 20 μM Aramchol or vehicle for 48 hours. After this, it was performed an analysis including Western blot, proteomics by mass spectrometry, and fluxomic analysis with13C-uniformly labeled glucose. For the in vivo part of the study, male C57BL/6J mice were randomly fed a control or 0.1% methionine and choline deficient diet (0.1MCD) for 4 weeks and received 1 or 5 mg/kg/day Aramchol or vehicle by intragastric gavage for the last 2 weeks. Liver metabolomics were assessed using an ultrahigh performance liquid chromatography (UHPLC)-Time of Flight-MS for the determination of glucose metabolism-related metabolites. Results showed that Combination of proteomics and Western blot analysis showed increased AMP activated protein kinase (AMPK) activity while the activity of nutrient sensor mammalian target of rapamycin complex 1 (mTORC1) was in vitro decreased by Aramchol treatment in hepatocytes. This translated into changes in the content of their downstream targets including proteins involved in fatty acid (FA) synthesis and oxidation (P-ACCα/β(S79), SCD1, CPT1a/b, HADHA and HADHB), oxidative phosphorylation (NDUFA9, NDUFB11, NDUFS1, NDUFV1, ETFDH and

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UQCRC2), tricarboxylic acid (TCA) cycle (MDH2, SUCLA2 and SUCLG2), and ribosome (P-p70S6K(T389) and P-S6(S235/S236)). Flux experiments with 13C-uniformely labeled glucose showed that TCA cycle cataplerosis was reduced by Aramchol in hepatocytes, as indicated by the increase in the number of rounds malate remains in the TCA cycle. Finally, liver metabolic analysis showed that glucose homeostasis was improved by Aramchol in 0.1MCD fed mice in a dose-dependent manner, showing normalization of glucose, G6P, F6P, UDP-glucose and Rbl5P/Xyl5P. The data above suggeats that aramchol exerts its effect on glucose and lipid metabolism in NASH through activation of AMPK and inhibition of mTORC1, which in turn activate FA β- oxidation and oxidative phosphorylation. It is a topic of interest to the researchers in the related areas but the paper needs large improvements before acceptance for publication.My detailed comments are as follows: 1.the introduction ,materials and methods in the paper work very well ,especially Western blot analysis,Proteomic analysis,Fluxomic analysis and Metabolomic analysis. 2. Results are good,and the figures are clear but the results got in the experiments should be described objectively,not conclusions were made;In addition, the part of dicussion is not well discussed combined with results and references and should make some modifications. 3.The references are not up-to-date,references of the last 10 years should be cited. 4.The language is not fluent ,sguugesing that the paper should be language-edited by native english-speaker editors. Pelase make large revisions, espically in the parts of results, dicussion,references and language-editing. After making large revisions,the paper may be considered for publication

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56546

Title: Aramchol improves liver glucose and lipid homeostasis in nonalcoholic steatohepatitis via AMPK and mTOR regulation

Reviewer's code: 03075520
Position: Peer Reviewer
Academic degree: MD
Professional title: Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Spain
Manuscript submission date: 2020-05-19
Reviewer chosen by: Han Zhang
Reviewer accepted review: 2020-07-23 12:03
Reviewer performed review: 2020-07-27 02:59
Review time: 3 Days and 14 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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It is a topic of interest to the researchers in the related areas ,my detailed comments are as follows: 1.the introduction ,materials and methods in the paper work very well ,especially Primary mouse hepatocytes isolation and culture,Western blot analysis,Proteomic analysis and Fluxomic analysis. 2.Results are good,and the figures are clear 3.The language is fluent 4.The references are almost up-to-data,except reference27,30,34,references of the last 10 years should be cited. Pelase make minor revisions, espically in the parts of references. After making minor revisions,the paper may be considered for publication.