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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 42384

Title: Integrated metabolomic profiling of the antilipidemic effects of Polygonatum kingianum extract on dyslipidemia in rats

Reviewer's code: 00506276

Reviewer's country: Poland

Science editor: Ruo-Yu Ma

Date sent for review: 2018-09-25

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Review time: 9 Days

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[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced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

SPECIFIC COMMENTS TO AUTHORS

The aim of this study was to examine the effect of Polygonatum kingianum rhizome extract (PK) on lipid and metabolomic profiles in high fat diet-fed rats. Rats were fed regular or high-fat diet for 14 weeks; separate groups received simultaneously

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simvastatin or PK extract intragastrically. It is demonstrated that high fat diet increased serum total cholesterol but not triglycerides whereas both cholesterol and triglycerides increased in the liver. PK corrected these abnormalities similarly to simvastatin. In addition, serum, liver and urine samples were subjected to HPLC-MS based untargeted metabolomics profiling in both positive and negative ionization modes. The results indicate that all samples clearly differ between normal and HFD groups. Both PK and simvastatin significantly affected metabolomics profiles with PK generally restoring it more closely to normal groups. Potential biomarkers of the PK activity were identified. In the positive ionization mode, 15, 17 and 18 biomarker candidates were identified in serum, urine and liver samples, respectively, whereas in the negative ionization mode 4, 7 and 22 biomarker candidates were identified in these samples, respectively. Metabolic pathways altered by HFD and PK were identified by KEGG database. The results suggest that PK may be useful in the treatment of dyslipidemia. The topic and the findings are of interest. Sample preparation, HPLC-MS metabolomics profiling and data analysis were performed by modern sophisticated methods and are described in detail. However, there are also some important concerns to be addressed. 1) Caloric composition of both diets (% of calories provided from carbohydrates, proteins and fat) should be presented. 2) Due to fundamental differences in plasma lipoprotein metabolism between rats and humans, the rat is not an optimal model to study the effects of lipid-lowering medications. This issue should be discussed. 3) Only very basic lipid parameters were measured in serum (total cholesterol and triglycerides). It would be of interest to present lipoprotein fractions (HDL, LDL) as well as major apolipoproteins (B, A-I). 4) Triglyceride and cholesterol concentrations in the liver should be better presented per mg protein rather than per ml of homogenate. 5) To get more insight into the mechanism of PK activity, it would be of interest to include the additional group of rats fed the normal diet and receiving PK. 6) It would be of interest

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to present data such as body weight, serum glucose and insulin concentrations as well as markers of insulin sensitivity/resistance such as HOMA-IR. Did PK have any effect on food intake and body weight or improved lipid metabolism irrespectively of body weight? 7) Some of the altered metabolic pathways are associated with branched-chain aminoacid (BCA) metabolism. The role of BCA in cardiometabolic diseases such as obesity, metabolic syndrome and dyslipidemia has been extensively studies. The results should be discussed in this context. 8) What molecular mechanism of PK activity could be suggested? 9) The dose of PK extract vs. simvastatin was relatively high. Thus, the conclusion that PK restored metabolomics profiles more closely to normal than simvastatin is the over-interpretation of the data. In addition, how relevant could be this dose regarding humans? 10) Tables 1 and 2/statistical analysis: high fat group should be first compared to normal group and then treated groups to high fat untreated group. Using high fat group as a reference is not appropriate because normally fed group represents the control in this experiment. 11) Line 72: the sentence that "statins stimulate GI tract" needs clarification. 12) Methods: it is stated that rats were kept in in metabolic cages for 3 weeks (line 168). Is it correct? Why so long? 13) Line 355: the conclusion about effects of PK on starch and sucrose metabolism is confusing; starch and sucrose are hydrolyzed in the GI tract and strictly speaking are not components of metabolic pathways in humans. This sentence represents the misinterpretation of KEGG including all metabolic pathways irrespectively of species.

INITIAL REVIEW OF THE MANUSCRIPT

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