**Author's response to reviews**

**Title:** HVC1 ameliorates hyperlipidemia and inflammation in LDLR-/- mice

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Dear editor

BMC Complementary and Alternative Medicine

We appreciate reviewer valuable comments and the opportunity to re-submit the manuscript, entitled "HVC1 ameliorates hyperlipidemia and inflammation in LDLR-/- mice". Reviewers' comments are insightful and we have revised the manuscript accordingly. Below, we address point by point how we respond to reviewers' comments, and we hope that the revised manuscript is now adequate for publication in BMC Complementary and Alternative Medicine.

Comments to Author:

Editorial comments:

- Please include the email addresses of all manuscript authors on your Title Page.

Response: We include the email addresses of all manuscript authors on the title page

- Please ensure that your figures are uploaded alongside your manuscript, as these do not appear to have been included with the most recent submission. When you do this, we would ask you to please upload each figure as a separate and individual figure file. Please note that legends should not be uploaded with figures. The legends should instead be included as a list at the end of your manuscript.

Response: thank you for your advice. We upload with figure and table.

Reviewer #2:

In this manuscript, the authors have investigated the effect of HVC1 on hyperlipidemia- induced atherosclerosis. The authors have adequately addressed previous reviewers' concerns. Based on plasma lipid profiles, especially total- and LDL-cholesterol levels and atherosclerotic lesions in HVC1-treated group (different concentration), there may not be a direct correlation between cholesterol levels and lesions. For instance, the lesions are attenuated in all three concentrations of HVC-1 compared to control. However, cholesterol levels are reduced only in HVC1 at 250 mg/kg treated group. These findings suggest that there may be alternative mechanism contributing to attenuate lesions. The authors may need to include this alternative in their discussion.

Response: Thank you for your good point.

The earliest visible lesion in the development of atherosclerosis is the fatty streak [1]. Atherosclerotic plaques develop as a result of the accumulation of LDL in the subendothelial space, followed by the diapedesis of leukocytes and formation of foam cells, proliferation of smooth muscle cells, and production of connective tissue. All cells present in the atherosclerotic plaques are potentially able to elaborate a set of cytokines. It is well known that many cytokines participated in the development of atherosclerotic leading to plaque formation [2]. Expression of IL-1-family members and their receptors has been demonstrated in atherosclerotic plaques. Mouse models of atherosclerosis have confirmed the proatherogenic properties of IL-1α and IL-1β, associated with upregulation of endothelial adhesion molecules and activation of macrophages and vascular cells. The lack of IL-1β decreases the severity of atherosclerosis in apoE deficient mice, possibly through increased expressions of VCAM-1 and monocyte chemotactic protein-1 in the aorta [3]. Furthermore, it is reported that inhibition of TNF-α reduces atherosclerosis in apolipoprotein E knockout mice and this finding suggest that TNF-α represents a possible target for prevention of atherosclerosis [4]. In our study, the lesions are attenuated in all three concentrations of HVC-1 compared to control whereas cholesterol levels are reduced only in HVC1 at 250 mg/kg treated group. However, HVC1 markedly reduced the mRNA expression of inflammatory cytokines including IL-1β and TNF-α in HCD-fed LDLR-/- mice. Considering all of these, we could suggest that inhibitory effects of HVC1 on mRNA expression levels of inflammatory cytokines are related to the development of atherosclerotic plaque.

We summarized the above contents, and added it in the revised manuscript.

Thank you very much for your advices.

Sincerely yours,

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