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PII: S0955-2863(17)30212-7
DOI: doi: 10.1016/j.jnutbio.2017.09.012
Reference: JNB 7848

To appear in: *The Journal of Nutritional Biochemistry*

Received date: 3 March 2017
Revised date: 7 August 2017
Accepted date: 12 September 2017

Please cite this article as: Li Yihui, Qin Ranran, Yan Hongdan, Wang Feng, Huang Shanying, Zhang Yun, Zhong Ming, Zhang Wei, Wang Zhihao, Inhibition of vascular smooth muscle cells premature senescence with rutin attenuates and stabilizes diabetic atherosclerosis, *The Journal of Nutritional Biochemistry* (2017), doi: 10.1016/j.jnutbio.2017.09.012

Inhibition of vascular smooth muscle cells premature senescence with rutin attenuates and stabilizes diabetic atherosclerosis

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Running title： Rutin attenuates plaque via inhibiting premature senescence

Funding: This work was supported by the research grants from the National Natural Science Foundation of China (81471036, 81470560, 81570400, 81600633, 81670411, 81300168, 81270352, 81270287, 81100605, 81530014, 81530014 and 91439201), the National Basic Research Program of China (973 Program, Grant No. 2013CB530703), Key research and development program of Shandong Province(2015GSF118062), the Natural Science Foundation of Shandong Province (ZR2014HQ037) and the Specialized Research Fund for the Doctoral Program of Higher Education (SRFDP 20130131120065).

Key words： Rutin, Diabetes, Plaque, Premature senescence, Vascular smooth muscle cell

Abstract

Atherosclerosis is an age-associated disease, however, diabetic atherosclerosis has higher severity beyond age range for accumulative premature senescent cells in diabetes. Recent findings suggest that rutin, a flavonoid, has potential benefits for diabetic individuals. This study was designed to evaluate the effects of rutin on premature senescence and atherosclerosis. Apolipoprotein E knockout mice exhibiting insulin resistance after 6 weeks high-fat diet were administered with a low dose of streptozotocin (STZ) to induce diabetes. After 8 weeks of STZ administration, rutin (40 mg/kg/d) was supplemented by gavage for the last 6 weeks. We evaluated the prosperity of the plaque and diabetes using serial echocardiography, histopathologic and metabolite analysis. Premature senescence induced by hydrogen peroxide in primary vascular smooth muscle cells was used to analyse the underlying mechanism. Mice with diabetes showed a more severe plaque burden on aortic arteries and less smooth muscle cells but a larger senescent cell ratio in plaque compared with mice with control diets. Rutin significantly improves glucose and lipid metabolic disturbance in diabetes. Moreover, rutin decreased the atherosclerotic burden and senescent cell number and increased the vascular smooth muscle cells (VSMCs) ratio in aortic root plaque. In vitro, we demonstrated that rutin ameliorated premature