

**The Effects of Wolfberry Consumption on the Human Plasma Lipidome and Its Potential Role in Cardiovascular Disease Risk Modulation: A Randomized Controlled Trial**

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**Objectives:** The adverse effects of dyslipidemia on cardiovascular health are well-documented. Conventionally assayed by blood lipids/lipoproteins, these classical indicators alone yield an oversimplified view of the human plasma lipidome. We previously observed an attenuation of cardiovascular disease (CVD) risk after regular wolfberry consumption for 16 weeks, with a prominent reduction in oxidative stress. To complement these findings, the objective of this study was to characterize the alterations to the plasma lipidome and explore its potential correlations to CVD risk.

**Methods:** In this parallel randomized controlled trial, middle-aged and older adults ( $55 \pm 4$  y) from Singapore were counselled to follow a healthy dietary pattern, either with or without consuming 15 g cooked whole wolfberry daily (WB;  $n = 21$ , CON;  $n = 17$ ). Following lipid extraction of weeks 0 and 16 plasma samples, the

lipidome was assayed by high-performance liquid chromatography-tandem mass spectrometry and quantified with internal standards (427 lipid species). Pearson's correlations between the fold changes (FCs) of lipid species from baseline, with corresponding changes to CVD risk-related outcomes including blood lipids/lipoproteins, blood pressure as well as vascular health and oxidative stress-related indicators were further evaluated.

**Results:** A comparison between the groups identified 7 distinct lipid species between WB and CON ( $FC > 1.2$ ;  $P < 0.05$ ). Notably, sphingomyelin 38:1, which had a markedly higher FC in WB compared to CON ( $FC_{WB}: 1.2$ ,  $FC_{CON}: 1.0$ ), was also significantly raised compared to baseline. Phosphatidylcholine (PC) 35:2, which increased by 1.8-fold in WB only ( $P < 0.05$ ), additionally depicted an inverse linear correlation with the FC of plasma 8-isoprostanes (Pearson's correlation coefficient:  $-0.45$ ,  $P < 0.05$ ). Across both groups, FCs from baseline were also significant for species of triglycerides (TG; 42 species), PC (4 species), ether-TG, ether-PC, plasmalogen-PC and cholesteryl ester (1 species each) albeit independent of wolfberry intake and with no clear associations to the other CVD risk-related outcomes.

**Conclusions:** Characteristic alterations to the plasma lipidome observed with wolfberry consumption may potentially modulate its underlying antioxidant effect.

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