Ampelopsis grossedentata, addressed as “vine tea”, is distributing in the southwest of China with high polyphenol contents. It is traditionally used as a daily beverage to maintain health by local folks. However, the molecular mechanisms on the biological functions remain unclear. Therefore, the present study aimed to investigate the preventive effects and molecular mechanisms of vine tea polyphenol on metabolic syndrome.

Firstly, the content and antioxidant activity of vine tea polyphenol (VTP) from different origins were evaluated. The results showed that VTP content of different origins had slightly differences, average content were 19.35% on dry weight basis. The principal component of VTP was further identified as dihydromyricetin (DMY), and the average value of DMY in VTP was high as 61%. Both VTP and DMY showed stronger DPPH scavenging activity *in vitro* and Nrf2-mediated antioxidant activity in culture cells.

Secondly, the preventive effects of VTP on non-alcoholic fatty liver disease (NAFLD) mouse was investigated by administration of 0.5%, 1% and 2% VTP in a Western diet (WD, high-fat, high-cholesterol, and high-sugar) mouse model. Results showed 1~2% VTP supplementation decreased serum levels of cholesterol and triglyceride, and reduced accumulation of hepatic lipid droplets induced by WD. 1~2% VTP supplementation enhanced fatty acid oxidation by activating phosphorylation of AMP-activated protein kinase (AMPK) and inhibited hepatic lipogenesis by reducing the level fatty acid synthase (FAS). Furthermore, 1~2% VTP reduced bacterial lipopolysaccharide into blood by protecting intestinal barrier function and ameliorating gut microbiota dysbiosis.

Thirdly, administration of 1% VTP and 0.6% DMY were performed in the same mouse model to identify whether the effect of VTP is due to DMY. The data showed both VTP and DMY supplementation reduced serum and hepatic cholesterol and triglyceride accumulation. Molecular analysis revealed that both VTP and DMY facilitated fatty acid β-oxidation and inhibited endogenous cholesterol synthesis, which were associated with AMPK phosphorylation. Phosphorylated AMPK induced mitochondria biogenesis and resulted in an enhancement of mitochondria fatty acid consumption. Meanwhile, phosphorylated AMPK inhibited the expression of hepatic HMG-CoA reductase to reduce cholesterol biosynthesis. Furthermore, cellular analysis showed that AMPK activated by both DMY and VTP was related to cellular nicotinamide adenine dinucleotide (NAD+) levels, both DMY and VTP increased NAD+ salvage pathway and declined NAD+ consumption enzyme expressions to finally result in a NAD+ boosted effect, which induced AMPK phosphorylation. Therefore, DMY acted as bioactive compound of VTP and targeted AMPK signaling pathway to facilitated fatty acid β-oxidation and inhibited endogenous cholesterol synthesis.

In conclusion, vine tea polyphenol had the preventive effects on WD-induced metabolic syndrome, and the bioactive compound was DMY. DMY targeted AMPK to mediate lipid metabolism, which was associated with cellular proton donor NAD+ and NADH balance. These findings provide new insight for understanding the molecular mechanisms of VTP on the prevention of metabolic syndrome, and suggested that vine tea has the potential as a functional food resource for preventing against metabolic syndrome.