Myricetin alleviates Western diet induced obesity through modulating gut microbiota and activating the Wnt-signaling in mice.

Min Ju Kim¹, Seol Hee Song¹, Jeong Ha Park¹, Su A Kim¹, Jeong Min Kim¹, Mi Ran Choi¹, Su Jin Lee¹, Ki Tae Suk¹

Institute for Liver and Digestive Diseases, Hallym University, Chuncheon, Republic of Korea

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a global health problem that can lead to the development of severe liver disease. Myricetin, a member of the flavonoid class contained in spinach, berries, tea and red wine, has numerous pharmacological properties such as anti-oxidative, anti-inflammatory, anti-fibrotic, antiobesity, and anti-diabetic effects.

<u>AIM</u>

Myricetin has not been revealed yet whether myricetin is associated with gut microbiota modulation and Wnt-signaling activation that regulates lipogenesis. We aimed to evaluate the effect of myricetin on lipid accumulation inhibition in MASLD.



METHOD

To investigate clinical characteristics of gut microbiota associated with liver disease, network pharmacology analysis and 16S rRNA analysis of human stool samples (30 healthy controls and 40 MASLD patients) were conducted. For animal experiment to prove the efficacy of myricetin, the mice were randomly divided into a normal control (n = 5), a normal diet with myricetin treatment (150 mg/kg, n =7), a Western diet (n = 6), a Western diet with myricetin treatment (150 mg/kg, n = 5). We used Western diet-induced MASLD, and myricetin was fed to the mice by oral gavage five times a week for 14 weeks. We performed oral glucose tolerance test, mice were fasted for 16 hours before the oral gavage with glucose (2 g/kg). MASLD severity was determined based on liver/body weight, pathological makers. We conducted qPCR analysis for Wnt-signaling pathway target genes

RESULTS

In human data, *Escherichia* (23.07 %) and *Bifidobacterium* (1.34 %) levels were increased in MASLD patients. On the contrary, the levels of *Bacteroides* decreased (75.74 % \rightarrow 62.91 %). In the network pharmacology analysis, myricitrin is metabolized to myricetin by *Escherichia* species. In the MASLD model, myricetin treatment group significantly improved liver/body weight ratio, with lower steatosis,



ballooning grade and NAS score (p < 0.0001) compared to the Western diet group. Myricetin supplementation improved glucose tolerance and significantly increased the expression of PGC1a (p = 0.0016) and C/EBPa (p = 0.0228) mRNA levels associated with lipid metabolism. Additionally, in Wnt-signaling target genes, Lrp6 (p = 0.0005) and Fzd5 (p = 0.0056) were up-regulated by normalizing RNA sequencing data. Clustering showed that *Proteobacteria* (*phylum*) (2.34 % \rightarrow 5.39 %), *Escherichia*, and *Bifidobacterium* were enriched in the myricetin group (more than 1 %). Additionally, administration of myricetin showed an increase in Proteobacteria compared to the control group.





from Healthy controls, MASLD patients, and MASH patients.

Fig 1. Body, liver, eWAT weight and L/B ratio respectively from 0-14 weeks.





We suggest that myricetin ameliorates lipid accumulation through activating the Wnt-signaling pathway and modulating gut microbiota composition. We assess the potential of myricetin to alleviate MASLD.

ACKNOWLEDGEMENTS

We would like to thank Professor Ki-Tae Suk (K.T.S.) for providing this wonderful research opportunity. Funded by National Research Foundation of Korea (NRF-2019R1I1A3A01060447, NRF-2020R1A6A1A03043026, P0020622, and MOTIE-20018494)

