More than your average bread spread: plant stanols as therapeutical tool in Niemann-Pick type C1 disease

Niemann-Pick type C1 (NPC1) disease is a lysosomal storage disease that affects nearly 1 in 100,000 live births worldwide. NPC1 disease is caused by mutations in the *NPC1* gene that result in a dysfunctional NPC1 protein, which contributes to the efflux of cholesterol and other lipids from lysosomes to other organelles. In the absence of a fully functioning NPC1 protein, lysosomes gradually accumulate cholesterol, which impairs their function and the cells' ability to use these lipids for their energy and structural needs. Ultimately, lysosomal lipid accumulation leads to cell dysfunction, inflammation and cell death. These pathological processes cumulate in severe neurological, lung, splenic and hepatic damage that greatly limits quality of life and lifespan of NPC1 disease patients. Currently, the range of therapeutical NPC1 disease tools is limited, making further research essential for these patients.

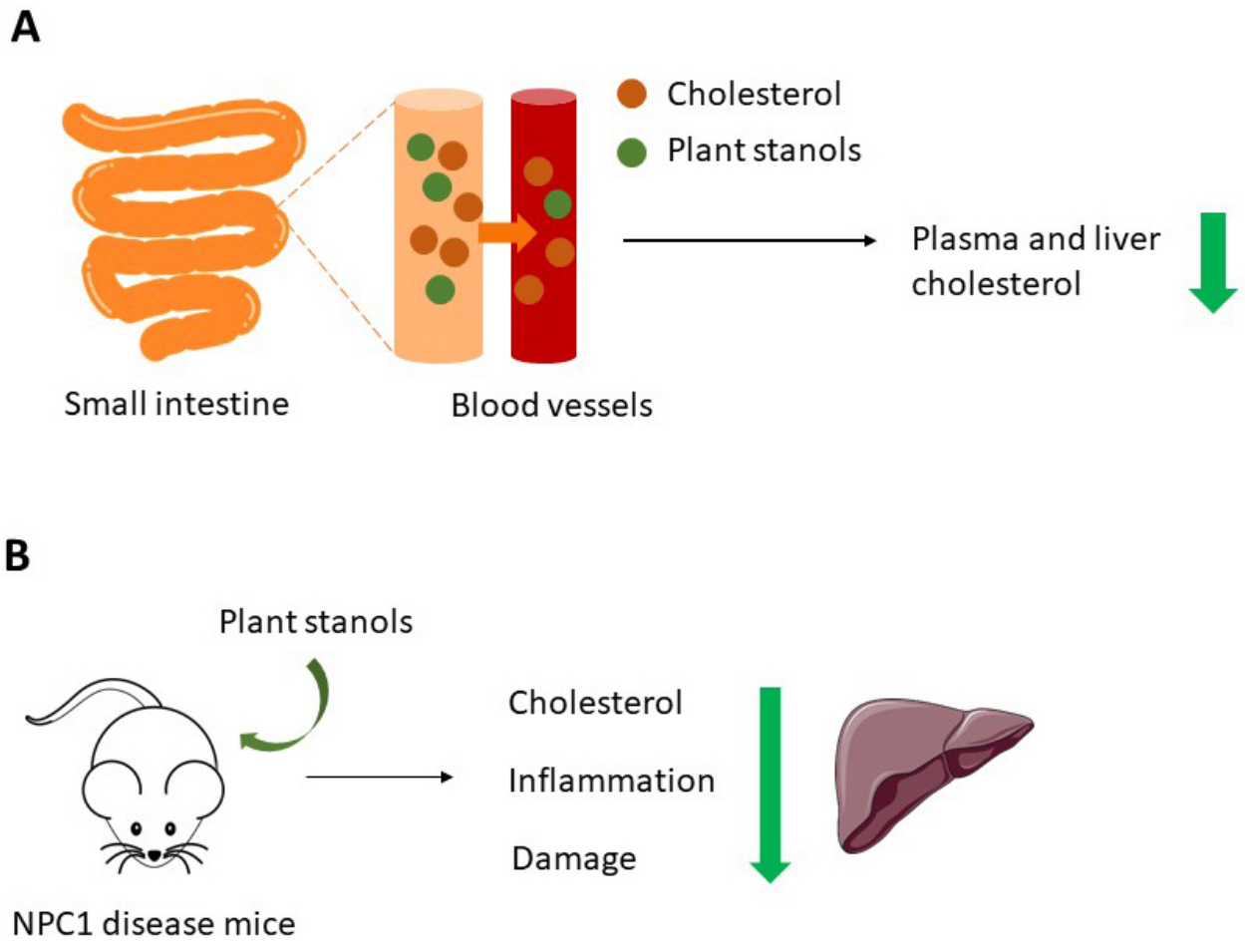

Fig. 1. (A) Once consumed, plant stanols compete with cholesterol for intestinal absorption. As such, ingesting high amounts of plant stanols reduces the amount of cholesterol that is absorbed

by the intestines, which in turn lowers liver and plasma cholesterol levels. (B) Niemann-Pick type C1 (NPC1) disease mice (i.e., mice that mimic human NPC1 disease symptoms) were fed a regular diet supplemented with plant stanols. Plant stanol supplementation, particularly at higher amounts, reduced liver cholesterol levels, inflammation and damage, thereby improving NPC1 disease liver symptoms.

Plant stanols are compounds found in a variety of plants and nuts which are consumed at very low amounts in the average diet. Because of their structural similarity with cholesterol, plant stanols interfere with dietary cholesterol absorption in the intestines. As such, increased consumption of plant stanols, for instance via so-called “functional” margarines, reduces liver and blood cholesterol levels. In the past, our group showed that dietary plant stanol supplementation reduces liver cholesterol levels, inflammation and damage in mouse models of non-alcoholic steatohepatitis, a disease that, similarly to NPC1 disease, features lysosomal lipid accumulation as a key pathological trigger. Given the results of this study, we sought to investigate whether plant stanol supplementation can also improve peripheral symptoms in a mouse model of NPC1 disease.

Our results indicate that plant stanol supplementation reduces liver cholesterol accumulation, inflammation and damage in NPC1 disease. In addition, plant stanol supplementation shifted plasma immune cells towards a more anti-inflammatory profile. These results suggest that plant stanols may be an inexpensive, widely available tool to ameliorate peripheral NPC1 disease symptoms. Future research should investigate whether plant stanols are safe and effective for NPC1 disease patients, particularly in conjunction with other available NPC1 disease therapies.

Inês Magro dos Reis, Tom Houben, Ronit Shiri-Sverdlov
Department of Molecular Genetics, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University Medical Center, Maastricht, The Netherlands

Publication

Dietary plant stanol ester supplementation reduces peripheral symptoms in a mouse model of Niemann-Pick type C1 disease.
Inês Magro dos Reis, Tom Houben, Yvonne Oligschläger, Leoni Bücken, Hellen Steinbusch, David Cassiman, Dieter Lütjohann, Marit Westerterp, Jos Prickaerts, Jogchum Plat and Ronit Shiri-Sverdlov
J Lipid Res. 2020 Jun