Supplementation of geranylgeraniol and tocotrienols to high-fat diet shifts the gut microbiome composition and function in type 2 diabetic mice

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Abstract

- **INTRODUCTION** In recent years, characterization of gut microbiota composition and function were linked to the progression of type 2 diabetes mellitus. Recent evidence showed that Geranylgeraniol, an isoprenoid found in fruits, vegetables, and grains, improves glucose homeostasis. Similarly, Tocotrienol, a subfamily of vitamin E, also contains anti-diabetic properties. In this study, we examined the combined effect of geranylgeraniol and tocotrienols on the composition and function of gut microbiome in obese male mice. **METHOD** Forty male C57BL/6J mice were assigned to 4 groups in a factorial design as follows: high-fat diet (HFD) (control group), HFD+geranylgeraniol [400 mg/kg diet] (GG group), HFD+tocotrienol [400 mg/kg diet] (TT group), and HFD+geranylgeraniol+tocotrienol (G+T group) for 14 weeks. 16S rRNA gene sequencing was done from cecal samples and microbiome and data analysis was performed with QIIME2 and PICRUSt2. **RESULTS** Across all groups, the most abundant phyla were Verrucomicrobia, Firmicutes, Bacteroidetes, and Actinobacteria. There was no difference in alpha diversity among different groups. Different treatments influenced the relative abundance of certain bacteria. In the Bacteroidetes phylum, the relative abundance of family S24-7 increased in the TT group only. In the Firmicutes phylum, the relative abundance of family Lachnospiraceae was reduced upon the supplementation of geranylgeraniol or tocotrienols; individually or in combination. In Verrucomicrobia phylum, *Akkermansia muciniphila* relative abundance was reduced in the TT group but increased in the G+T group. The results of functional profiling of the gut microbiome revealed that geranylgeraniol supplementation caused an increase in the proportion of biosynthetic pathways related to purine, pyrimidine, and inosine-5'-phosphate and hexitol fermentation, and a decrease in the proportion of pathways involved in the biosynthesis of isoleucine, valine, histidine, arginine, and chorismate. The G+T group increased pathways related to thiamine diphosphate biosynthesis, and decreased others involved in sulfur oxidation and methylerythritol phosphate. **CONCLUSION** Their beneficial influence on gut microbiome composition and function suggests that geranylgeraniol and tocotrienol have prebiotic potential. **FUNDING** This study was supported by American River Nutrition, LLC, Hadley, MA.

Introduction

- Both obesity and diabetes are associated with insulin resistance and show numerous physiological and metabolic disturbances. Previous studies have linked gut microbiome dysbiosis with diabetes and obesity, and established the beneficial role of probiotics in stabilizing the gut microbiome.
- Geranylgeraniol is an isoprenoid found in fruits, vegetables, and grains that has several health benefits. Tocotrienol, a subfamily of vitamin E, has anti-inflammatory activity among other health benefits. The benefits of geranylgeraniol and tocotrienols on the gut microbiome, however, have yet to be discovered.
- In the present study, we further examined the combined effect of geranylgeraniol and tocotrienol on the gut microbiome of obese male mice. We hypothesized that this combination would have a beneficial effect on the composition and function of the gut microbiome than either geranylgeraniol or tocotrienol individually.

Methods

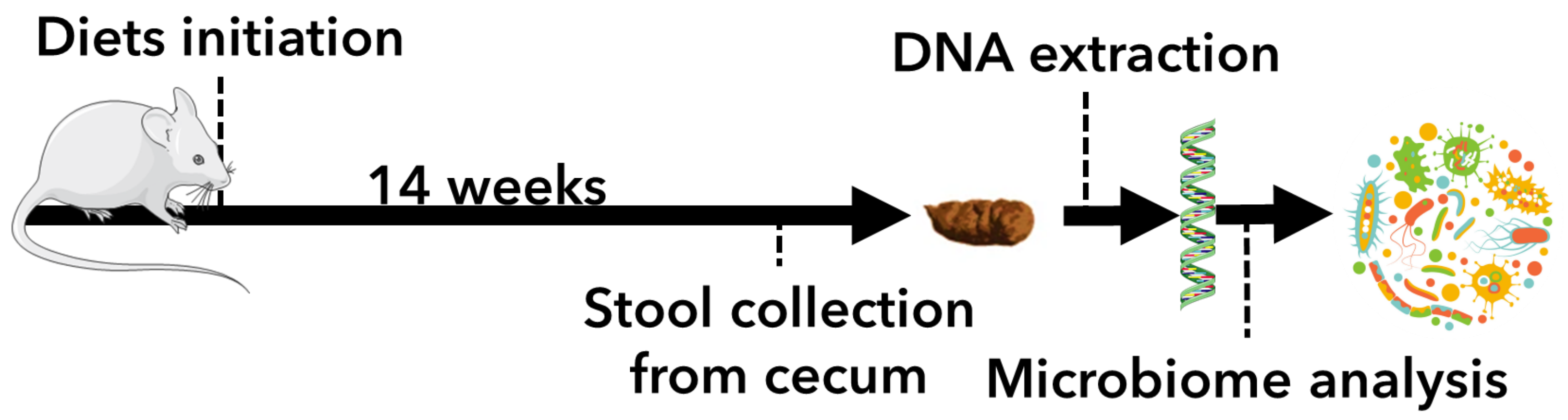

Figure 1. Diagram illustrating the experimental design of the study.

Results

Table 1. Taxa with a significant difference in their relative abundance among diet groups.

Taxon	Tukey's multiple comparisons test	Mean difference	Adjusted *P*-value
Family-level			
S24-7	Control vs. TT	-2.444	0.0137
Lachnospiracea	Control vs. GG Control vs. TT Control vs. G+T	2.464 1.955 2.783	0.013 0.0487 0.005
Verrucomicrobiaceae	Control vs. G+T	-2.758	0.0054
Species-level			
Akkermansia muciniphila	Control vs. TT Control vs. G+T	2.83 -2.481	0.0043 0.0124

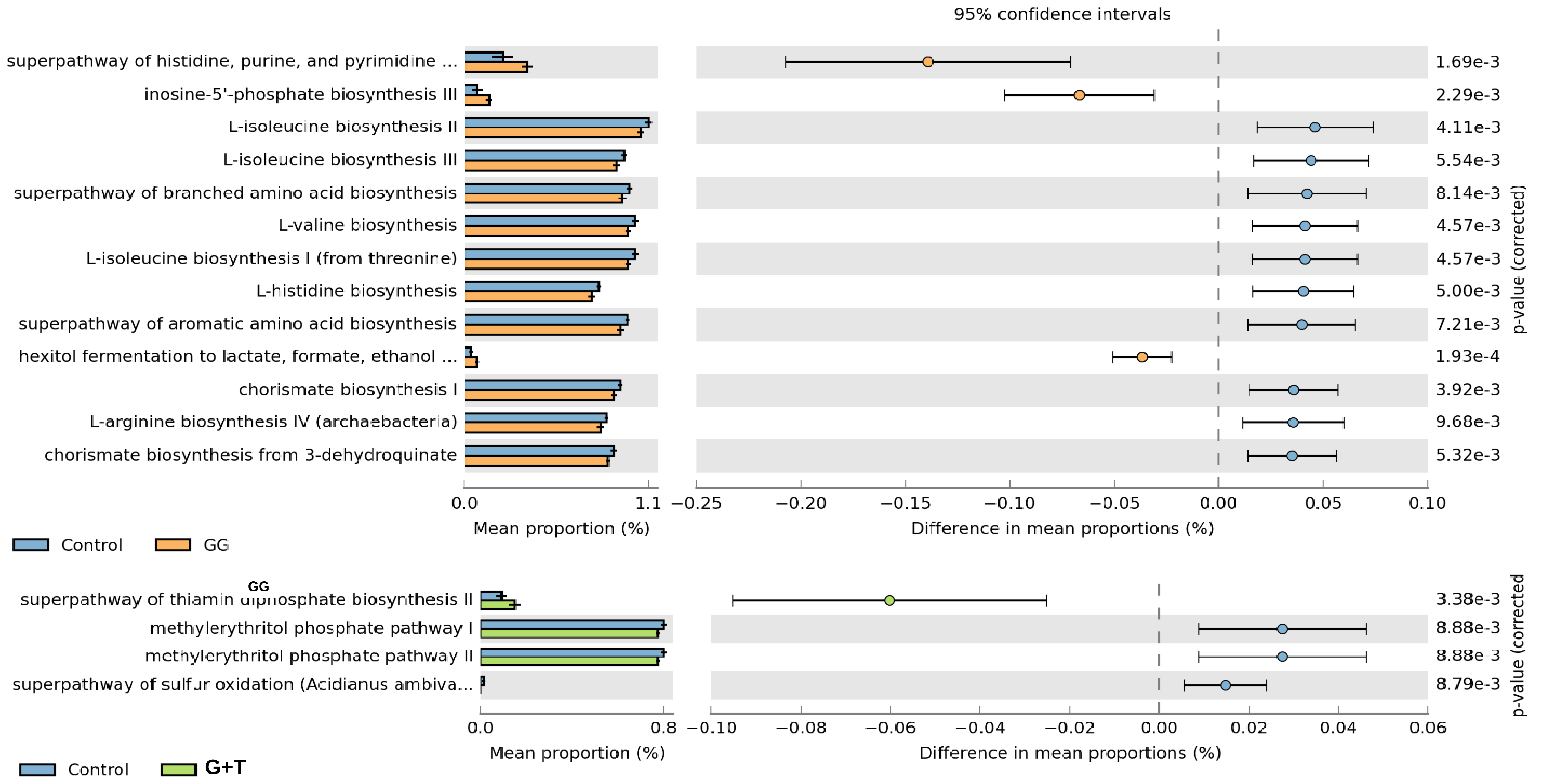

Figure 2. Functional analysis of gut microbiome.

Conclusions

- Our results suggest that geranylgeraniol and tocotrienol affect the gut microbiome composition and its function by being utilized as substrates in their functional metabolism. This implies the potential of geranylgeraniol and tocotrienol to be prebiotics.

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