報告番号	※　　第　　号

主　論　文　の　要　旨

論文題目　**Studies on the prebiotic effect of 1-kestose on the physiology**
（1-ケストース摂取による腸内環境の調節を介した生理作用に関する研究）

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論　文　内　容　の　要　旨

Accumulating studies have indicated links between the gut microbiota and health and diseases. Development of insulin resistance is observed when intestinal barrier-protecting *Bifidobacterium* is reduced, and endotoxin is increased. Low levels of butyrate-producing microbiota are frequently observed in patients' gut and experimental animals with type 2 diabetes. This dissertation aims to determine the prebiotic effects of 1-kestose on health and diseases. Specifically, it investigates whether 1-kestose effects stimulate beneficial bifidobacteria and has the potential to mitigate glucose tolerance in type 2 diabetes and the development of insulin resistance. In this context, the prebiotic effect is defined as stimulating and activating beneficial gut microbiota, which brings host health benefits. Also, insulin resistance is defined as the reduced ability of both cellular glucose uptakes and inhibition of endogenous glucose production to respond to the action of insulin from the bloodstream.

To determine the threshold dose of dietary 1-kestose that increased cecal bifidobacteria levels in rats, rats were fed experimental diets containing 0% to 0.3% 1-kestose for four weeks. Also, to test the hypothesis that dietary 1-kestose leads to beneficial effects on type 2 diabetes metabolic status, type 2 diabetes model rats were fed the 1-kestose supplemented diet for 16 weeks. Lastly, to assess the effect of 1-kestose on plasma insulin level and their association with the gut microbiota composition, diet-induced obesity rats were fed 1-kestose for 19 weeks. The results showed that the genus *Bifidobacterium* levels and total gut bacteria were significantly increased in fecal samples of rats fed the 0.3% 1-kestose diet. The results using type 2 diabetes rats showed that supplementation

with 1-kestose suppressed the development of diabetes, i.e., later onset of insulin resistance and hyperglycemia, and cecal contents of rats fed 1-kestose were high in butyrate and harbored a higher proportion of the butyrate-producing genus *Anaerostipes* compared to rats fed a control diet. The results using obese rats showed that 1-kestose reduced fasting plasma insulin concentrations, and this amelioration was accompanied by changes in mRNA expression of inflammatory cytokines, microbial compositions, and short-chain fatty acid concentrations.

These results suggest prebiotic effects of 1-kestose as follows; first, for stimulation of beneficial bacteria, the minimum dose of dietary 1-kestose to induce significant bifidogenic activity in rats is presumably as low as 0.3% by weight in the diet. Second, the alteration of short-chain fatty acids, specifically butyrate, in the ceca may be responsible for a suppressive effect on glucose intolerance in type 2 diabetes rats. Thirdly, 1-kestose may increase insulin sensitivity in obese rats with normalizing short-chain fatty acid concentrations in the ceca. Both type 2 diabetes and obesity rates may be deeply associated with the gut microbial community's modulation, i.e., increase of butyrate-producing bacteria. On this basis, modulation of the gut microbiota should be taken into account when regaining health from sick associated with gut microbial dysbiosis.

Apart from those studies mentioned above, this dissertation aims to propose a new therapeutic approach that integrates gut microbial interventions with conventional therapy. The resilience of the gut microbiota is a feature of healthy gut microbiota. Since associations between diseases and the gut microbiota have been increasingly recognized in humans, besides lifestyle interventions, microbial interventions to increase the resilience of the gut microbiota, including probiotics, prebiotics, and fecal microbial transplantations, have been utilized clinically. The last part of the dissertation aims to explore the idea of "co-resilience," which emphasizes the importance of the resilience of the gut microbiota and that of the hosts to fitness with outlining the current evidence showing that gut microbial interventions influence host fitness for resilience-building management of the gut microbiota.