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学位論文審査の要旨

博士の専攻分野の名称　博士（農学）　氏　名 Panchita Phuwamongkolwiwat

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学位論文題名

Promotion of anti-diabetic effects of flavonoid glycosides by nondigestible saccharides
（難消化性糖質によるフラボノイド配糖体の抗糖尿病作用を高める研究）

The thesis is composed of 96 pages, 6 tables, 13 figures, and attached with 2 related papers.

Type 2 Diabetes Mellitus (T2DM), a common metabolic disorder, can be chronic and progressively destructive condition that is characterized by insulin resistance or decreased pancreatic β-cell production of insulin. In addition to implementing lifestyle modifications as a first-line therapy for early stage diabetic patients, management of blood glucose level is predominately done with exogenous insulin or prescription drugs. Many prescription drugs, however, carry undesirable side effects and potential adverse drug interactions. To mitigate the limitations of diabetic medications, researchers have looked at flavonoids, which are in various fruits and vegetables.

An example of a flavonoid is quercetin 3-O-glucoside (Q3G), which is shown to possess anti-diabetic effects (i.e., decrease plasma glucose level). Q3G, however, have poor bioavailability in the system due to poor absorption in the small intestine. Fructooligosaccharide (FOS) is a non-digestible oligosaccharides that reduces the risk of hyperglycemia and dyslipidemia. GLP-1 is an eneroendrocrine-derived peptide, which reduces blood glucose level by stimulating insulin secretion and regulating lipid metabolism (i.e., anti-diabetic effects).

We have previously demonstrated that FOS promotes the bioavailability of Q3G by way of suppressing the degradation in the caecum. The inter-relationship between Q3G, FOS and GLP-1 suggests an important but not yet realized effects on insulin secretion, which in turn has implications for reducing the risk of T2DM as well as hyperglycemia and dyslipidemia.

1) A nondigestible saccharide augments benefits of quercetin-3-*O*-*β*-glucoside on insulin sensitivity and plasma total cholesterol with promotion of flavonoid absorption in sucrose-fed rats.

Our *in vivo* experiment investigated both individual and synergistic effects of Q3G and FOS in rats' diet on visceral (i.e., abdominal) fat deposition, HOMA-IR and oral glucose tolerance test (OGTT). HOMA-IR and OGTT were chosen because they are standard diagnostic tests for insulin resistance. We hypothesized that supplementation of

Q3G+FOS in a sucrose based AIN-93G diet would reduce a) visceral mass, b) OGTTs, c) fasting blood glucose, d) fasting insulin concentration, e) plasma total cholesterol, and f) HOMA-IR when compared to the S diet. We also hypothesized that Q3G+FOS supplementation would improve the plasma concentration of Q3G.

To conduct our *in vivo* experiment, four groups of rats were fed a dextrin-based (D) diet as the normal reference group, or sucrose-based (S) diets with 0.3% Q3G, 5% FOS, or 0.3% Q3G+5% FOS (Q3G+FOS) for 48 days. Oral Glucose Tolerance Tests (OGTTs) were conducted on day 0, 14, 28 and 45, and adipose tissue and aortic blood were collected on day 48. Our *in vivo* experiment yielded significantly lower blood glucose level for the Q3G+FOS group at 60 min in OGTT than S group on day 14, 28 and 45. HOMA-IR value was significantly lower in the Q3G+FOS group than in S group throughout the experimental period (0.25 ± 0.03 vs 0.83 ± 0.12 on day 45, $P < 0.05$). The plasma quercetin derivatives increased for FOS diet group on day 48 (18.37 ± 1.20 with FOS, 2.02 ± 0.30 without FOS, $P < 0.05$). Plasma total cholesterol levels for the Q3G+FOS group (3.10 ± 0.12, $P < 0.05$ on day 45) was suppressed compared to the S (4.03 ± 0.18). GLP-1 secretion was enhanced in Q3G+FOS group than other diet groups.

2) A nondigestible saccharide increase the promotive effect of flavonoids on glucagon-like peptide 1 (GLP-1) secretion

Investigating the anti-diabetic effects of Q3G, FOS and GLP-1 were conducted via *in vivo*, *in situ* and *in vitro* experiments.

Effect of Q3G and FOS on GLP-1 secretion was separately examined from jugular vein after oral gavage (*in vivo* experiment) and portal vein after ileal administration (*in situ* experiment). We hypothesized that test solution of Q3G+FOS orally gavage and injected directly into distal ileum would increase the plasma GLP-1 signaling the β-cells to increase insulin secretion and consequently, reduction in hyperglycemia. Baseline blood samples were obtained via jugular vein for *in vivo* but portal vein for *in situ* rat group with subsequent samples obtained at 15, 30, 60, 90 and 120 minutes to evaluate plasma GLP-1 levels. From our *in situ* experiment, we found that Q3G with FOS significantly enhanced and prolonged plasma GLP-1 concentrations.

In vitro experiment was conducted tested for direct effects of Q3G with- and without FOS on GLP-1 using a murine enteroendocrine cell line, GLUTag (i.e., L-cell model). Application of Q3G on GLUTag cells stimulated GLP-1 secretion and FOS promote the effect of Q3G.

Findings of our study suggests that synergistic effects of Q3G with FOS has the potential for prevention as well as management of T2DM by mediating the GLP-1 secretion and prolongation the high plasma concentration of the antidiabetic hormone with direct stimulation of L-cell.

Therefore, we acknowledge that the author is qualified to be granted the Degree of Doctor of Philosophy in Agriculture from Hokkaido University.