# Study on the anti/hyperglycemic effect and mechanism of non/absorbable polyphenols

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Title : Study on the anti-hyperglycemic effect and mechanism of non-absorbable polyphenols（腸管非吸収性ポリフェノール類の抗糖尿病作用とその機構に関する研究）

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## Thesis Summary

Type II diabetes mellitus (T2DM), a non-insulin dependent diabetes caused by deficient secretion or inappropriate insulin utilization, have been considered as the fasting growing epidemic in both developed and development countries. Healthy lifestyles such as diet, exercise and weight control are the first line strategy managements for T2DM treatment. However, anti-diabetic agents (e.g. sulfonylurea) are required to regulate blood glucose levels in the serious conditions but some side-effect of these drugs such as hypoglycemia, drug-resistance, dropsy, and weight gain must be noted. Thus, there is a growing interest for the alternative-medicinal dietary food compounds especially intestinal non-absorbable phytochemicals that possessing physiological potential in modulating intestinal functions, to prevent diabetes through *e.g.* inhibiting carbohydrate digestion, inhibiting intestinal glucose absorption, or promoting incretin secretion. The present study aimed to get insights of dietary non-absorbable compounds into anti-hyperglycemic effect in terms of intestinal regulation of glucose transporting systems using Caco-2 cells and spontaneously diabetic rats, respectively.

Firstly, the transportability and anti-hyperglycemic potential of tomatoside A, a saponin derived from tomato seed, was investigated using Caco-2 cells. In transport experiments, tomatoside A could not penetrate through Caco-2 cell monolayers. Interesting, it was found that in 10 μM tomatoside A (3 h)-treated cells, a 46.0% reduction of $^{13}C_6$-glucose transport was observed compared to that in intact cells, implying that non-absorbable tomatoside A had a potential to suppress glucose transport in Caco-2 cells. Western blot analyses revealed that tomatoside A significantly suppressed the expression of GLUT2, while no change in the expression of SGLT1 was obtained. In $^{13}C_6$-glucose transport experiments, the reduced glucose transport by tomatoside A was ameliorated by PKC and MRP2 inhibitors. In apical ASBT-knocked down Caco-2 cells, the reduced glucose transport by tomatoside A was significantly recovered. Taken together, it was demonstrated for the first time that the non-transportable tomato seed saponin, tomatoside A, suppressed GLUT2 expression via PKC signaling pathway during the ASBT-influx/MRP2-efflux process in Caco-2 cells.

Secondly, the anti-hyperglycemic potential of theaflavins was investigated in Caco-2 cells. To examine the effect of theaflavins on $^{13}C_6$-glucose transport across Caco-2 cell monolayers, the monolayers were treated with 40 μM theaflavins for 24 h. All the tested theaflavins exerted a significant reduction of $^{13}C_6$-glucose transport, indicated that benzotropolone 7-ring of theaflavins would play an important role for exerting the reduction effect. Theaflavin treatment of Caco-2 cells

caused a significant reduction of GLUT2 expression, whereas no effect on SGLT1 was observed. Theaflavin-induced reduction of $^{13}C_6$-glucose transport was significantly ameliorated by AMPK inhibitor, whereas no recovery of reduced glucose transport to the control level was obtained by PKC inhibitor, indicated that AMPK signaling pathway could play a key role in the inhibitory action of theaflavins on $^{13}C_6$-glucose transport.

Thirdly, *in vivo* the anti-hyperglycemic effect of theaflavins was evaluated in SDT rats. In a long-term administration of theaflavin extract (25 mg/kg/day) for 20 weeks to 8-week-old SDT rats, it was revealed that the daily intake of theaflavins resulted in a significant improvement of impaired glucose tolerance at pre-diabetic stages. At diabetic stages of 28-week-old SDT rats, theaflavin-dosed SDT rats did not reach to the diabetes BGL, demonstrating *in vivo* preventive effect for diabetes. The retardation of progressive impaired glucose tolerance at pre-diabetic and the subsequent diabetic stages by non-absorbable theaflavins was due to the improvement of impaired insulin and incretin secretion.

In conclusion, the present study has demonstrated for the first time that even though phytochemicals have less bioavailability, some could be useful as alternative medicinal treatment to prevent or manage T2DM *e.g.* via suppression of intestinal glucose transport and/or stimulation of insulin secretion.