

## Comparative analysis of anti-diabetic effects of citrus flavonoids on pancreatic $\beta$ -cell function

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The chronic hyperglycemia that occurs in type 2 diabetes causes deterioration of pancreatic  $\beta$ -cell dysfunction which involves a decrease in insulin secretory response and a decrease in  $\beta$ -cell mass. Thus, to promote  $\beta$ -cell function and survival would provide therapeutic approaches to prevent the onset and development of type 2 diabetes. Citrus flavonoids are known to have health benefits, especially those related to improvement of type 2 diabetes. However, little is known about the effects of these flavonoids on pancreatic  $\beta$ -cell functions. We have previously demonstrated that nobiletin has anti-diabetic effects on  $\beta$ -cell functions. Tangeretin and sudachitin are polymethoxy flavonoids (PMF) contained in citrus peel and have a similar structure to nobiletin. In the present study, we investigated the effects of the PMFs on glucose-induced insulin secretion (GSIS) and  $\beta$ -cell apoptosis in the  $\beta$ -cell line INS-1 and compared these effects with those of nobiletin. Tangeretin significantly increased GSIS at 10  $\mu$ M and inhibited thapsigargin-induced apoptosis. Sudachitin also significantly increased GSIS at 100  $\mu$ M but did not affect  $\beta$ -cell apoptosis. The anti-diabetic effects of tangeretin on  $\beta$ -cell functions were more potent than those of sudachitin, but they were less potent than those of nobiletin. These results suggest that nobiletin has more remarkable anti-diabetic effects on  $\beta$ -cells, i.e., more potent insulinotropic and anti-apoptotic effects, than tangeretin and sudachitin.