

Anti-diabetic Activities of Ashitaba (*Angelica keiskei*): Induction of Adipocyte Differentiation and Enhancement of Glucose Uptake in Adipocyte

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SUMMARY

The number of diabetic patients is increasing especially in Asia according to change of life habits (1). In mild case of diabetes, many patients are left without medical treatments and the long period of none treatment causes serious complications that impair the quality of life of the patients (2). Diabetes is a chronic disease that is characterized by hyperglycemia caused by insufficiency of the insulin action (3). So, we considered that edible ingredients which can complement insulin action are useful to prevent and cure diabetes and complications associated with the disease.

We tried to find the insulin mimic compounds from edible plants. We investigated the two insulin mimic activities of edible plant materials; (a) adipocyte differentiation activity and (b) enhancement activity of glucose uptake, using pre-adipocyte cell line 3T3-L1 (4,5). As a result, we found that ethanol extract of *Angelica keiskei*, a dropwort indigenous to Japan and called "Ashitaba", has both activities (6). We tried to isolate active compounds from the extract, and we found that two major chalcones peculiar to *Angelica keiskei*, xanthoangelol (XA) and 4-hydroxyderricin (4HD) have both activities (a) and (b). Regarding adipocyte differentiation, XA and 4HD have the similar level of activities. On the other hand, regarding enhancement of glucose uptake, the activity of 4HD is several times as high as that of XA. Furthermore, the combination of XA and 4HD could complement insulin action (induction of adipocyte differentiation and enhancement of glucose uptake) in *in vitro* assay.

Taking the results of *in vitro* assay into consideration, we investigated each anti-diabetic activity of XA and 4HD using KKAY mice that develop diabetes and shows hyperglycemia by aging (7). To investigate the preventive activity against diabetes, we administered oral dose of XA or 4HD for several weeks to KKAY mice that had not showed symptoms of diabetes. As a results, both oral dose of XA and 4HD suppressed the increase of blood sugar. Namely, oral dose of XA and 4HD suppressed the development of diabetes. To investigate the curing activity of XA and 4HD against diabetes, we administered oral dose of XA or 4HD for several days to KKAY mice that had showed hyperglycemia, and observed oral dose of XA and 4HD decreased the blood sugar respectively. These results suggested that XA and 4HD have anti-diabetic activities.

On the other hand, we had already found that some coumarins and a chroman contained in Ashitaba can induce nerve growth factor (NGF) that has preventive and curing activity of peripheral nerve disease caused by diabetic hyperglycemia. Also founded is that many chalcones contained in Ashitaba have aldose reductase inhibition activity that is effective to prevent complications caused by diabetic hyperglycemia.

Our research results mentioned above strongly suggest that daily ingestion of Ashitaba may be able to prevent and cure diabetes and complications by synergistic effect of each biological activity of Ashitaba.

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