Polyhydroxylated alkaloids from mulberry leaves and their biological activities

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In 1991 we started the search for glycosidase inhibiting alkaloids from plant materials. Japanese agrochemists have found the occurrence of 1-deoxynojirimycin (DNJ) in *Morus* (mulberry) plant in 1974. I had long been engaged in isolation work of aminosugar antibiotics and had known that antibiotic producing organims usually coproduce many closely related compounds as a complex. So I thought that *Morus* plant must produce many related compounds other than DNJ. We isolated seven water soluble alkaloids from the leaves of *Morus bombycis*[1]. They are DNJ, N-methyl-DNJ, DNJ-2-*O*-α-D-galactoside, 1,4-dideoxy-1,4-amino-D-arabinitol (DAB), DAB-2-*O*-β-D-glucoside, and calystegine B_2. Furthermore, we isolated eighteen water soluble alkaloids including these seven alkaloids from the roots of *Morus alba*[2]. Inhibition of gut glycosidases by inhibitors could regulate the absorption of carbohydrate[3,4].

Mulberry leaves have traditionally been used to cure "Xiao-ke" (diabetes) in traditional Chinese medicine. The original isolation of DNJ was prompted by the knowledge that extracts of mulberry were able to suppress the rise in blood glucose that follows eating and that this component might be beneficial to diabetes. DNJ, N-methyl-DNJ, and DNJ-2-*O*-α-D-galactoside are very potent inhibitors of gut α-glucosidases and applicable to the therapy of diabetes as well as acarbose (GLUCOBAY™) and voglibose (BASEN™), which have already been introduced onto the market for the treatment of diabetes.

Interestingly, the i.p. injection of mulberry leaf extract has been found to show anti-hyperglycemic effect in streptozotocin(STZ)-diabetic mice[5]. So we measured the anti-hyperglycemic effect of these seven components. Among these components, DNJ-α-galactoside and fagomine

showed a strong anti-hyperglycemic effect in time-and dose-dependent manners. Furthermore, fagomine enhanced glucose-induced immunoreactive insulin release from perfused pancreas of normal rat, while DNJ-α-galactoside had no effect on the immunoreactive insulin release. Thus, mulberry leaves contain potent α-glucosidase inhibitors such as DNJ, N-methyl-DNJ and DNJ-α-galactoside, and effective anti-hyperglycemic agents such as fagomine and DNJ-α-galactoside with a different action mechanism.

References

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