

Clinical Study of *Morus Alba* Linn. on Glycemic Control and Blood Lipids in Patients with Type 2 Diabetes: A Preliminary Study

Somsak Sinsatienporn, M.D.*, Ubon Boonrood, RN*, Pranee Chavalittumrong, M.Sc.**, Malee Banjob, M.Sc.**,
Kalaya Anulukanapakorn, Ph.D**, Omboon Luanratana, Ph.D***, Phinai Hong Thongdaeng, B.Sc ****, Visanu Thamlikitkul, M.D.*****

*Pathumthani Hospital, Pathumthani 12000, **Medicinal Plant Research Institute, Department of Medical Sciences, Ministry of Public Health, Nonthaburi 11000, ***Faculty of Pharmaceutical Sciences, Faculty of Pharmacy, Mahidol University, Bangkok 10400, ****Seri Culture Institute, Department of Agriculture, Ministry of Agriculture and Co-Operatives, Bangkok, *****Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Effects of *Morus alba*-leaf extracts on glycemic control and blood lipids were carried out in 27 patients with newly diagnosed type 2 diabetes. Water extracts of *Morus alba* leaves at a dosage of 700 mg were given to the patients thrice daily for 8 weeks. The patients did not receive any concomitant medications for diabetes or hyperlipidemia. The mean fasting plasma glucose levels at baseline, week 2, week 4, week 6 and week 8 were 155.1, 179, 173.6, 183.9 and 185.8 mg/dl, respectively ($p=0.04$). The mean glycosylated hemoglobin levels at baseline and week 8 were 7.6% and 8.4%, respectively ($p=0.002$). The mean blood total cholesterol levels at baseline, week 2, week 4, week 6 and week 8 were 229.6, 211.2, 210.2, 204.5 and 199.4 mg/dl, respectively ($p<0.001$). The mean blood triglyceride levels at baseline, week 2, week 4, week 6 and week 8 were 235.4, 191.3, 174.5, 183.5 and 168.2 mg/dl, respectively ($p=0.001$). No patients experienced side effects of the treatment. Laboratory results on CBC, urine, blood electrolytes, renal function and liver function at baseline, week 2, week 4, week 6 and week 8 were not significantly different. *Morus alba*-leaf extracts have no hypoglycemic effect but they may exert lipid lowering effects.

Keywords: Hyperglycemia; hyperlipidemia; *Morus alba*; type 2 diabetes

Siriraj Med J 2006; 58: 1039-1041
E-journal: <http://www.sirirajmedj.com>

The risk of cardiovascular diseases is increased in patients with poorly controlled diabetes mellitus and hyperlipidemia.^{1,2} A number of medicinal herbs were reported to yield hypoglycemic effect.³⁻⁵ *Morus alba* was found to contain hypoglycemic and lipid lowering effects in animals.⁶⁻⁹ A toxicity study of *Morus alba* leaves revealed no remarkable acute and sub-chronic toxicities.¹⁰ Water infusion of *Morus alba* leaves has been widely used in Thailand over the past decades. The claims for promoting consumption of *Morus alba* leaves infusion are its beneficial effects on glycemic control and hyperlipidemia in patients with diabetes.

The objective of this study was to determine whether *Morus alba*-leaf extracts improved blood glucose, glycosylated hemoglobin, total cholesterol and triglyceride levels in patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Com-

mittee of the Department for Development of Thai Traditional and Alternative Medicine, Ministry of Public Health, Thailand. The study site was Pathumthani Hospital, Pathumthani, Thailand. The study was conducted from October 2004 to May 2005.

Patients

The eligible patients were newly diagnosed type 2 diabetes mellitus (fasting plasma glucose between 127 to 200 mg/dl) aged 40 to 70 years. The patient was excluded if he/she had acute complications of diabetes or received anti-diabetics or lipid lowering agents or was allergic to *Morus alba*.

Plant extractions, preparations and administration

Mulberry leaves (*Morus alba*, Nakornratchasima 50) were obtained from the Department of Agriculture, Ministry of Agriculture and Co-Operatives in Plant Genetics Conservation Project. The sample was prepared by boiling 60 kg of *Morus alba* leaves in powder form with water at the ratio of 1:5, and evaporated to dryness using spray-dried apparatus. The percentage yield of the water extract was 18% w/w. The *Morus alba*-leaf extracts used in the

Correspondence to: Visanu Thamlikitkul
E-mail: sivth@mahidol.ac.th

TABLE 1. Effects of *Morus alba*-leaf extracts on glucose, glycosylated hemoglobin (HbA1c), total cholesterol and triglyceride levels in blood of 27 diabetic patients.

	Mean $\pm$ S.E.M.			
	Glucose (mg/dl)	Total Cholesterol (mg/dl)	Triglyceride (mg/dl)	HbA1c (%)
Baseline	155.11 $\pm$ 4.15	229.58 $\pm$ 11.24	235.38 $\pm$ 20.63	7.57 $\pm$ 0.22
Week 2	179.04 $\pm$ 9.26	211.24 $\pm$ 9.37	191.28 $\pm$ 15.96	
Week 4	173.62 $\pm$ 8.76	210.16 $\pm$ 9.92	174.52 $\pm$ 18.39	
Week 6	183.88 $\pm$ 9.50	204.48 $\pm$ 9.88	183.52 $\pm$ 21.58	
Week 8	185.84 $\pm$ 10.23	199.36 $\pm$ 10.10	168.24 $\pm$ 18.52	8.43 $\pm$ 0.23
P-value	0.004	<0.001	0.001	0.002

study were composed of 90% herb extracts and 10% maltodextrin. Each capsule of the study medication contained 350 mg of *Morus alba*-leaf extracts. The patient was instructed to take *Morus alba*-leaf extracts two capsules (700 mg) orally thrice daily before meals for eight weeks. Concomitant medications for diabetes or hyperlipidemia were not allowed during the study period.

Outcome measures

The patients were followed every two weeks for four visits. For each visit, the patient was asked for symptoms, examined by the investigators and had blood tests for complete blood count (CBC), fasting plasma glucose, total cholesterol, triglyceride, electrolytes, renal function, liver function as well as urine examination. Glycosylated hemoglobin assay was done at baseline and at the end of the study.

Statistical analysis

Data were expressed as mean $\pm$ standard error of mean (SEM). Statistical comparisons between different values were done using paired student-t-test or repeated measured one-way analysis of variance (ANOVA). Significance was accepted at $P < 0.05$.

RESULTS

Twenty-seven patients with newly diagnosed type 2 diabetes were included. Twenty-two patients were females. The mean age of the patients was 53.4 years. The patients' compliance to the study medication was satisfactory. The changes in fasting plasma glucose, glycosylated hemoglobin, blood total cholesterol and triglyceride are shown in Table 1. The mean fasting plasma glucose levels at baseline, week 2, week 4, week 6 and week 8 were 155.1, 179, 173.6, 183.9 and 185.8 mg/dl, respectively ($p=0.04$). The mean glycosylated hemoglobin levels at baseline and week 8 were 7.6% and 8.4%, respectively ($p=0.002$). The mean blood total cholesterol levels at baseline, week 2, week 4, week 6 and week 8 were 229.6, 211.2, 210.2, 204.5 and 199.4 mg/dl, respectively ($p<0.001$). The mean blood triglyceride levels at baseline, week 2, week 4, week 6 and week 8 were 235.4, 191.3, 174.5, 183.5 and 168.2 mg/dl, respectively ($p=0.001$). No patients experienced side effects of the treatment. Laboratory results on CBC, urine, blood electrolytes, renal function and liver function at baseline, week 2, week 4, week 6 and week 8 were not significantly different.

DISCUSSION

Our study was unable to detect hypoglycemic effect of *Morus alba*-leaf extracts at a dosage of 2.1 g per day

for 8 weeks. Although *Morus alba* was found to have hypoglycemic effect in several animal studies,⁶⁻⁸ one of these studies used *Morus alba* root bark extract.⁸ Another animal study did not observe any hypoglycemic effect of *Morus alba*.¹¹ The hypoglycemic effect of higher dose of *Morus alba*-leaf extracts or the extracts from its root bark in patients with diabetes was unknown and needed further clinical study. It should be mentioned that the levels of fasting plasma glucose and glycosylated hemoglobin at the end of treatment were significantly higher than those at baseline. The reason for this observation was unclear. The study medication

was composed of maltodextrin but this substance was not related to glucose. The amount of glucose in *Morus alba*-leaf extracts was minimal and this should not explain the increase in fasting plasma glucose at the end of treatment.

However our study showed that blood total cholesterol and triglyceride levels at the end of therapy were significantly reduced from those at baseline. The magnitude of the reductions was meaningful, i.e., blood total cholesterol level was reduced by 13% whereas blood triglyceride was reduced by 28.5%, and the mean blood levels of both total cholesterol and triglyceride at the end of therapy were less than 200 mg/dl. Our observation on lipid lowering effect of *Morus alba*-leaf extracts in the patients supported the findings from animal experiments.⁹ Enkhmaa, et al. studied the effects of dietary consumption of *Morus alba* leaves and their major flavonol glycoside on the development of atherosclerotic lesions in LDL receptor-deficient mice. The mice fed with dried *Morus alba*-leaf powder or *Morus alba* leaves' major flavonol glycoside in addition to an atherogenic-diet for 8 weeks had significantly lower total cholesterol and triglyceride levels in the sera when compared with the control mice. Atherosclerotic lesion areas in *Morus alba*-treated mice were significantly reduced by 52% compared with that of the controls. Although a lipid lowering effect of *Morus alba*-leaf extracts in patients with type 2 diabetes observed in our study was very promising, the study was open-labeled without concurrent controls hence the effect could partly due to co-interventions. Although diet control instructions were not officially provided to the patients by the investigators during the study period, the patients might modify their eating habits due to a concern of having diabetes and this could lead to a reduction in blood lipids. Therefore, further clinical trials on treatment of patients with hyperlipidemia comparing *Morus alba*-leaf extracts to placebo or conventional lipid lowering agents are warranted.

CONCLUSION

The present study suggested that *Morus alba*-leaf extracts taken orally at a dosage of 700 mg thrice daily had no hypoglycemic effect but they exerted lipid lowering effect. Further clinical trials on treatment of patients with hyperlipidemia comparing *Morus alba*-leaf extracts to placebo or conventional lipid lowering agents are warranted.

ACKNOWLEDGEMENTS

We thank the Department of Medical Sciences, Ministry of Public Health, Thailand and The Thailand Research Fund for supporting the study.

REFERENCES

1. Raza A, Movahed A. Current concepts of cardiovascular diseases in diabetes mellitus. *Int J Cardiol* 2003; 89: 123-34.
2. Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in persons with and without diabetes. The atherosclerosis risk in communities study. *Arch Intern Med* 2005; 165: 1910-6.
3. Shapiro K, Gong WC. Natural products used for diabetes. *J Am Pharm Assoc* 2002; 42: 217-26.
4. Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. *Diabetes Care* 2003; 26: 3215-8.
5. Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS. Systematic review of herbs and dietary supplements for glycemic control in diabetes. *Diabetes Care* 2003; 26: 1277-94.
6. Broadhurst CL, Polansky MM, Anderson RA. Insulin like biological activity of culinary and medicinal plant aqueous extracts in vitro. *J Agric Food Chem* 2000; 48: 849-52.
7. Littlert P, Tiangda C, Phornchirasilp S, Luanratana O. Effect of Mulberry (*Morus Alba* Linn.) leaves extracts on plasma glucose level in streptozotocin-induced diabetic rat. *Thai J Pharmacol* 2004; 26: 63.
8. Singab AN, El-Beshbishy HA, Yonekawa M, Nomura T, Fukai T. Hypoglycemic effect of Egyptian *Morus alba* root bark extract: Effect on diabetes and lipid peroxidation of streptozotocin-induced diabetic rats. *J Ethnopharmacol* 2005; 100: 333-8.
9. Enkhmaa B, Shiwaku K, Katsube T, Kitajima K, Annuurad E, Yamasaki M, Yamane Y. Mulberry (*Morus alba* L.) leaves and their major flavonol quercetin 3-(6 malonylglucoside) attenuate atherosclerotic lesion development in LDL receptor-deficient mice. *J Nutrition* 2005; 135: 729-34.
10. Subsung A, Phornchirasilp S, Luanratana O, Sirikulchayanonta V, Tiengda C. A toxicity of *Morus alba* Linn. leaves. *Thai J Pharmacol* 2004; 26: 70.
11. Hussain Z, Waheed A, Qureshi RA, Burdi DK, Verspohl EJ, Khan N, Hasan M. The effect of medicinal plants of Islamabad and Murree region of Pakistan on insulin secretion from INS-1 cells. *Phytother Res* 2004; 18: 73-7.

บทคัดย่อ

ประสิทธิผลและความปลอดภัยของใบหม่อน (*Morus alba*) ในการลดระดับน้ำตาลและไขมันในเลือดในผู้ป่วยเบาหวานชนิดไม่พึ่งอินซูลิน : การศึกษาเบื้องต้น

สมศักดิ์ สีนเสถียรพร พ.บ.*, อุบล บุญรอด พย.บ.*, ปราณี ชวลิตธำรง ก.ม.**, มาลี บรรจบ ก.ม.**, กัลยา อุบลักษณ์ปกรณ์ ปส.ด.**, ออมบุญ ล้วนรัตน์ ปส.ด.***, พนีย์ ทองทองแดง วท.บ.****, วิษณุ ธรรมลิขิตกุล พ.บ.*****

*โรงพยาบาลปทุมธานี, **กระทรวงสาธารณสุข, ***กรมวิทยาศาสตร์การแพทย์, กระทรวงสาธารณสุข, ****คณะเภสัชศาสตร์, มหาวิทยาลัยมหิดล, *****สถาบันวิจัยสมุนไพร, กรมวิชาการเกษตร, กระทรวงเกษตรและสหกรณ์, *****ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กทม.10700, ประเทศไทย.

คณะผู้วิจัยได้ศึกษาประสิทธิผลเบื้องต้นของสารสกัดใบหม่อนในการลดระดับน้ำตาลและไขมันในเลือดในผู้ป่วยเบาหวานชนิดไม่พึ่งอินซูลินรายใหม่จำนวน 27 คนที่ได้รับสารสกัดใบหม่อนด้วยน้ำขนาด 350 มิลลิกรัมบรรจุในแคปซูล รับประทานครั้งละ 2 แคปซูล วันละ 3 ครั้งก่อนอาหาร ติดต่อกันนาน 8 สัปดาห์ ผู้ป่วยทุกรายไม่ได้รับยารักษาเบาหวานหรือยาลดไขมันร่วมด้วย ระดับน้ำตาลในเลือดเฉลี่ยก่อนการรักษาและสัปดาห์ที่ 2, 4, 6 และ 8 ภายหลังการรักษามีค่า 155.1, 179, 173.6, 183.9 and 185.8 มก/ดล. ตามลำดับ ($p=0.004$) ระดับ glycosylated hemoglobin เฉลี่ยก่อนการรักษาและสัปดาห์ที่ 8 ภายหลังการรักษามีค่า 7.6% และ 8.4% ตามลำดับ ($p=0.002$) ระดับ total cholesterol เฉลี่ยก่อนการรักษาและสัปดาห์ที่ 2, 4, 6 และ 8 ภายหลังการรักษามีค่า 229.6, 211.2, 210.2, 204.5 และ 199.4 มก/ดล. ตามลำดับ ($p<0.001$) ระดับ triglyceride เฉลี่ยก่อนการรักษาและสัปดาห์ที่ 2, 4, 6 และ 8 ภายหลังการรักษามีค่า 235.4, 191.3, 174.5, 183.5 และ 168.2 มก/ดล. ตามลำดับ ($p=0.001$) ผู้ป่วยทุกรายไม่มีการข้างเคียงจากการรักษา สารสกัดใบหม่อน 2.1 กรัมต่อวันไม่สามารถลดระดับน้ำตาลในเลือดของผู้ป่วยเบาหวานได้ แต่อาจลดระดับไขมันในเลือดได้