Editorial

Fenugreek and Insulin Resistance

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Virtually all cultures have, throughout history, used a variety of materials derived from plants for the prevention and treatment of diseases. There are references in Ayurveda and subsequent Indian medical literature on a wide variety of herbs that possess anti-diabetic properties.

Worldwide, over 700 different species of plants have been described as traditional treatments for diabetes mellitus. A wide array of plant-derived active principles (more than 40), representing numerous classes of chemical compounds have been shown to demonstrate activity consistent with their possible use in the treatment of patients with type 2 diabetes mellitus.[1,2] *Trigonella foenum graecum,* commonly known as fenugreek, prominently figures in this list as a widely used medicinal herb for treating many chronic diseases including diabetes mellitus. The name, fenugreek, comes from *foenum-graecum,* meaning Greek hay, the plant being used to scent 'inferior hay'. Although originally from Southeastern Europe and Western Asia, fenugreek grows today in many parts of the world, including India, Northern Africa and the United States. It has been used in India for centuries, both as a medicine and as a condiment in cooking. The seeds of fenugreek comprising mucilaginous fibre (~50% by weight) and steroid saponins (12% by weight) have been claimed to account for many of the beneficial effects of fenugreek. In general, the steroidal saponins are thought to inhibit cholesterol absorption and synthesis while the fibre may help lower blood sugar levels.

Unlike other herbs, it is interesting to note that fenugreek has been subjected to a certain level of rigorous scientific testing. In this issue of the journal, Gupta *et al*[3] report on the effect of *Trigonella foenum-graecum* (Fenugreek) seeds on glycaemic control and insulin resistance in type 2 diabetes. Seeds of fenugreek are considered as a rich source of fibre and believed to have multiple benefits (hypoglycaemic, hypolipidaemic and insulinotrophic) in both experimental and clinical diabetes and these are reviewed in the article by Gupta *et al.*[3] Dietary fibres, especially soluble fibres such as guar gum and pectins, have modest glucose-lowering effects due to interference with intestinal absorption. In fact, delaying the digestion and absorption of dietary carbohydrate in the intestine is one such principle adopted by the pharmaceutical industry out of which inhibitors of intestinal α-glucosidases (e.g., acarbose, miglitol) have evolved as one of the successful classes of oral hypoglycaemic agents. Besides hypoglycaemic effects, fenugreek also appears to have lipid-lowering actions. It is suggested that fenugreek might decrease serum triglyceride levels by influencing the enterohepatic circulation of bile acids and enhancing cholesterol metabolism. The saponin-containing fenugreek fibers could inhibit the intestinal absorption of cholesterol much the same as alfalfa saponins do i.e., by absorbing bile acids, and increasing the loss of bile acids by fecal excretion, which then leads to an increased conversion of cholesterol into bile acid by the liver. The available data on the beneficial effects of fenugreek suggest that it could be used as an adjunct therapy of type 2 diabetes. However, most studies including the one by Gupta *et al*[3] have been performed on small number of patients and several of the outcome result parameters show great inter-individual differences. Therefore, the future for these anti-diabetic plant principles has to rely on high-throughput screening, toxicity testing and large multicentre randomized clinical studies.

Gupta *et al*[3] report that Fenugreek seeds improve insulin resistance. They have used the HOMA (homeostasis model assessment) which is a surrogate method for measuring insulin resistance. The hyperinsulinemic-euglycemic clamp measures insulin resistance (IR) directly and is the gold standard for measurement of IR. However, this procedure is very cumbersome and not practical for routine clinical evaluation. On the other hand, the evaluation of insulin sensitivity by HOMA requires measurement of

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only fasting and insulin concentrations. This mathematical model is based on the theory of a negative feedback loop between the liver and β-cells that regulates both fasting glucose and insulin concentrations and can be used to estimate pancreatic β-cell function and the degree of IR. Therefore, it is considered to be a useful noninvasive tool for clinicians and epidemiologists to diagnose IR in the general population while it may not be very suitable for any given individual. The HOMA IR correlates highly and significantly with whole-body insulin action in nondiabetic and type 2 diabetic individuals.[4] However for HOMA estimates to be accurate, at least two fasting insulin estimations must be done in view of the pulsatile nature of insulin secretion. The authors have presumably measured insulin only once. It is interesting to note from the work of Gupta *et al*[3] that two months treatment with fenugreek has considerably increased insulin sensitivity in type 2 diabetes patients as measured by HOMA. One could argue that the authors should have used a larger sample size. This study[3] however, deserves appreciation as the beneficial effect of fenugreek on blood glucose, insulin metabolism and lipid profile was shown through a double blind placebo controlled study.

Very recently, Sauvaire *et al*[5] and Broca *et al*[6] have demonstrated that 4-hydroxyisoleucine, an amino acid extracted from fenugreek seeds, is a novel potentiator of insulin secretion. The action of 4-hydroxyisoleucine is very specific on β-cells without any interaction with the effects of other insulin secretagogues such as leucine, arginine, tolbutamide and glyceraldehyde. More importantly the insulinotropic activity of 4-hydroxyisoleucine appeared to be strongly dependent upon an increasing concentration of glucose i.e. only under hyperglycaemic conditions. The glucose dependence of the insulin secretory response to 4-hydroxyisoleucine may be of interest *in vivo* in avoiding the risk of hypoglycemia and this compound deserves further research and development. The multiple beneficial effects of fenugreek on glucose and lipid metabolism indicate that it can serve as an effective supportive therapy in the clinical management of diabetes. Since modern diets have become increasingly fibre deficient, a major factor linked to diabetes, there is considerable interest in fenugreek as it is a rich source of soluble dietary fibre and saponin. However, one should be cautioned that fenugreek may react adversely with a variety of medications, including glipizide, heparin, insulin, ticlopidine and warfarin.[7,8] While taking fenugreek as an adjunct in the treatment of type 2 diabetes, medical supervision and blood sugar monitoring is therefore necessary.

There is no doubt that the discovery and development of medicinal plants for therapeutic use is a Himalayan task. Nevertheless, with its immense medicinal bioresources, India's opportunities for developing plant-based drugs are seemingly limitless. It is important to note that a certain level of scientific testing on fenugreek has been already attempted and documented by the scientists from National Institute of Nutrition (NIN) and Indian Council of Medical Research (ICMR).[9,10] A concerted effort of scientists from diverse scientific disciplines will be now required to transform the traditional wisdom on antidiabetic plant materials to a modern therapeutic tool. Today, fenugreek is most widely used in India as a condiment and in the United States as a flavouring agent. But it would become a pharmaceutical delight when its medicinal values are better known and tested more vigourously and scientifically!

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