Herbal Solutions: Bangladesh

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Summary

Diabetes mellitus is a major health problem worldwide but its therapeutic management still suffers from major limitations.

Plants have been used for the treatment of diabetes for centuries. As a result, their scientific evaluation has been an important responsibility of scientists and also a logical way of searching for new antidiabetic drugs. The World Health Organization (WHO) is now emphasizing the importance of solving the diabetes problem. A systematic study of plant materials used for treating diabetic patients has been undertaken by the Bangladesh Institute of Research and Rehabilitation in Diabetes Endocrine and Metabolic Disorders (BIRDEM). BIRDEM has collaborated with the Department of Chemistry at Dhaka University and other institutions abroad to attack this disease through herbal solutions.

Laboratory trials on diabetic model rats were designed to explore the possible hypoglycemic (abnormally low concentration of sugar in the blood) and antihyperglycemic (prevention of the abnormally high concentration of sugar in the blood) activity of the plant materials. The trials also focused on the possible target tissues involved in the action. This background knowledge was then used to conduct human trials with the identified active principle or one of its upstream products that was found to be therapeutically acceptable as well as economically feasible in the context of the society in which it would be used.

In these trials, the plant commonly known as fenugreek (*Trigonella foenumgraecum*), which is native to southeast Europe and west Asia, was scientifically tested for its well-known ability in traditional medicine to act as a substitute for insulin among diabetic patients. Through extensive investigation on several plants from south and south east Asia for their hypoglycemic and antihyperglycemic effects, fenugreek was shown to be a successful herbal solution to diabetes mellitus. Using the diabetic model rats, fenugreek was found to have a partially mediated activity due to a soluble dietary fiber (galactonmannan) present in the plant. Analysis of the data indicated the possibility of delayed glucose absorption in the gut. This finding was useful given that such an effect is one of the major approaches for antidiabetic drug development.

Additional results showed that the water extract of fenugreek can effectively reduce the rise in plasma glucose during digestion without any elevation in serum insulin levels. Preliminary findings indicate that the antihyperglycemic effect of the fenugreek water extract might be related to the inhibition of disaccharidase activity in the gut. This finding again points to the strength of fenugreek as an antidiabetic drug.

Background studies on human subjects are now being conducted to transform the knowledge and skill derived from animal studies into human use through appropriate trials. A national pharmaceutical company has signed an agreement with BIRDEM and Dhaka University for scientific rationalization of the existing use of the product by the local population.

Lessons Learned

Western-trained medical doctors, pharmacologists and pharmaceutical industries in many developing countries have neglected the rich traditions of herbal medicines far too long. As a result, the ethnomedicinal knowledge and vegetative resources are fast-depleting while the majority of the population still has limited access or no access to modern medicines. Lack of awareness about the effective use of plants as medicines and poor understanding of the philosophy and cultural traditions behind ethnomedicinal uses of plants are some of the reasons why plant uses have not been rationalized on a scientific basis.

One of the main reasons for the limited number of clinical studies in the developing world is a severe shortage of skilled human resources. Such work demands pharmacologists and toxicologists to conduct scientifically valid clinical studies on plant extracts. Without these studies, large-scale development of drugs cannot occur. In countries like Bangladesh, it often is difficult to form interdisciplinary teams of scientists who are required for such studies. With BIRDEM's first set of experiments, however, it is evident that, with consistent effort, it is possible to gather an experienced group of chemists who can successfully conduct the phytochemical analyses at an international standard (see below).

Several lessons were learned during this study. First, traditional knowledge about the use of various plants as an antidiabetic medicine is usually undocumented, sometimes unreliable, inconsistent, sketchy and often based on myths and stories. However, some plants, including fenugreek, have an unbroken tradition of success and, as a result, are ideal candidates for chemical studies. With the partnerships that were forged, BIRDEM was able to take this traditional knowledge and put it through rigorous scientific tests for clinical and phytochemical investigation. The scientific results supported traditional knowledge in using herbal solutions to combat such human diseases as diabetes mellitus. In addition, the tests provided more specific information on how various extractions and dosages of a particular plant could be used to address diabetes mellitus.

Impact

BIRDEM faced many obstacles when conducting these tests. Lack of proper infrastructure and trained researchers, as well as an inadequate scientific culture, caused chronic delays.

The group focused on overcoming these problems by developing increased institutional support through expanding awareness about the scientific evaluation and potential value of plant materials among policy makers. BIRDEM broadened the national and international collaborations through experimental work. The link between academic and commercial organizations should become both stronger and broader through the additional experimentation that has been planned.

Future Plans

As a result of the educational program of BIRDEM, plans have been made to educate communities that the folkloric reputation of plants does not always match the real potency of the plant. This is a fact that was revealed by BIRDEM results on a large number of plant materials. Once the clinical trial is completed, the task will be to popularize the practice of administering accurate timing and dosage of fenugreek among its users.

As the project grows, BIRDEM hopes to devise herbal solutions to control diseases safely and economically. Such efforts would involve the inclusion of other plants, improvement of the capability of the animal house, laboratories and experimental facilities for clinical pharmacology, and more in-depth studies of plant material both chemically and biologically. To make this economically feasible, BIRDEM will pursue additional agreements with other private enterprises and strengthen ties with other national and international organizations.

Background and Justification

As the ancient archives of Egypt reveal, diabetes mellitus has been a disease known to humans since 1500 BC. Today it is one of the major chronic diseases affecting people all over the world. It is a condition where the body fails to appropriately metabolize glucose. The cause of this disease may be due to any one of many genetic mutations. Failure can occur anywhere in the pathway, from the synthesis and release of insulin in response to a glucose signal to the complete oxidation of glucose by the target cells.

Diabetes mellitus thus can result from a number of errors in the genetic code of any one of the proteins involved in a variety of processes. The myriad of disorders that have the clinical symptoms of diabetes mellitus constitutes the largest group of genetic disorders found in humans.

Due to the lack of organized health care systems in such developing countries as Bangladesh, people with chronic diseases like diabetes are among the worst sufferers in their communities today. Recent WHO and International Diabetic Federation (IDF) reports show that the incidence of diabetes is

increasing at an epidemic rate, especially in developing countries, probably due to rapidly changing lifestyles, eating habits and environmental conditions. It is now well established that diabetes mellitus is a symptom of a range of abnormalities rather than the manifestation of a single disease. Put another way, there are a number of symptomatic abnormalities in diverse tissues that characterize diabetes. Thus no single group of compounds probably will be effective in all types of diabetes. Consequently, medical researchers are now focusing on developing distinct molecules with targeted action on specific problems for treatment of the disease.

Plants have been used for centuries in the treatment of diabetes mellitus. Certain plants have a vast potential to serve as antidiabetic agents or to provide source materials for such products. Fenugreek seed powder is one of the most widely used plant materials used in the subcontinent for the treatment of diabetes. It has been shown to possess hypoglycemic properties in both animal and human subjects. However, opinions vary regarding the nature of the active compounds and their mechanisms of action. Moreover, the therapeutic details of the extract (timing, dosage, *etc*.) have not been determined through scientific experimentation. In addition, the animal models used for the experiments have not simulated Type 2 diabetes (the most abundant type) and, consequently, were not entirely suitable for additional scientific study in the majority of diabetic subjects. The pungent smell and gastric upset in higher doses also adversely affected the widespread use of the product.

Through BIRDEM's work during the past few years, several extracts and fractions of plant materials that mimic insulin action in some peripheral tissues have been discovered. During the course of these experiments, fenugreek seed powder and its various extracts were found to exert antihyperglycemic action in rats, particularly when given with food.

Hyperglycemia after meals is a special problem in diabetes millitus patients. In the later stages of the disease, when the pancreatic beta cells (which are defective in diabetic patients) cannot cope with the acute demand of insulin after food intake, the relative deficiency of insulin leads to overt Type 2 diabetes. Based on this understanding, delaying glucose absorption from the gut, with the resultant lowering of acute demand on insulin after a meal, is now one of the major approaches for antidiabetic drug development. In addition to diabetic patients, this approach also helps patients with hypertension, dyslipidemia and other disorders. Based on the data of animal experiments, BIRDEM scientists explored the chemistry and biological effects of fenugreek that seem to exert hypoglycemic activity through this mechanism.

Description

With a combination of *in vivo* and *in vitro* techniques, Type 2 diabetic model rats were used to explore the effects of the test material on the release of insulin, gastro-intestinal tract motility, and disaccaridase-inhibiting activity. This result has laid the foundation for a clinical trial that will soon be conducted.

The first study in this project focused on the characterization of the hypoglycemic effects and the nature of the active compounds of fenugreek by using a systematic experimental methodology recently reported by the BIRDEM research group. The fenugreek powder, its methanol extract, and the residue remaining after methanol extraction had significant hypoglycemic effects on the Type 2 diabetic rats when fed simultaneously with glucose ($p<0.05$).

The soluble dietary fiber (SDF) fraction showed no effect on the fasting blood glucose levels of non-diabetic model rats; however, when fed simultaneously with glucose to the diabetic rats, it showed a significant hypoglycemic effect. Chemical analysis revealed that the major constituent of the SDF is a galactomannan. The results confirmed the involvement of SDF in the hypoglycemic effect of fenugreek seeds. In addition, analysis showed that compounds other than SDF also were involved in the hypoglycemic activity.

A second study was designed to evaluate the effect of the hot water extract of fenugreek on carbohydrate digestion and absorption and serum insulin in normal and Type 2 diabetic rats. Rats not given food for 20 hours and sucrose solution were fed to the fasting rats with or without the fenugreek extract.

Significant findings were found in the blood glucose level, sucrose level and serum insulin level of diabetic model rats. The blood glucose level and the amount of glucose liberated from residual sucrose in the gastrointestinal tract were measured by glucose-oxides method. Then the gastrointestinal sucrose

content was calculated from the amount of liberated glucose. The blood samples taken from the rats found serum insulin in both normal and diabetic model rats in chronic stages of the disease.

After the sucrose loading with simultaneous administration of fenugreek extract, about 30 percent of the sucrose remained in the stomach after 30 minutes, which was a much higher level than that of the control group (about 8 percent). At 60 minutes, the remaining sucrose level in the whole gut, except for the cecum and the large intestine, were significantly higher than the control group ($p<0.05$). At 240 minutes, the sucrose content was almost nil in the control group; however, in the treated group, the sucrose level increased throughout the gut but more prominently in the middle and lower intestine as well as the cecum. The serum insulin levels were unchanged both in acute and chronic studies and both in normal and Type 2 model rats.

Thus hot water extract of fenugreek was found to effectively reduce the rise in plasma glucose after diabetic rats were given food. The fenugreek extract was discovered to retard the digestion and absorption of carbohydrate from the gut by agents present in the hot water fraction. The experiment revealed that there was no load on the beta cell of the islet of Langerhans (which in non-diabetics produces the hormone insulin) because no elevation in serum insulin level was observed. The exact chemical nature and mechanism of action of the plant agent(s) remain to be investigated.

Researchers conducted a third study on rat disaccharidase activity under the influence of hot water extract of fenugreek. The purpose was to observe the effect of the extract on non-diabetic and Type 2 model rats. Results suggest that a certain dosage of the fenugreek extract is effective in Type 2 model rats with a simultaneous glucose load.

Through the various animal experiments, and based on the lengthy experience of human use of this edible plant throughout history, BIRDEM then decided to conduct background trials on human subjects with a specially prepared extract of the powder. The components of the powder, which in the past had produced a pungent smell and also gastric upset in larger doses, were removed while preserving their antihyperglycemic benefits. Clinical trials currently are taking place to identify the proper timing and dosage based on information generated from the rat experiments. With the completion of these trials, the results may then be utilized for a more rational use of fenugreek in diabetic patients.

Patenting and Commercialization

Human Drug Laboratories Ltd., a local pharmaceutical company, has signed a formal agreement with BIRDEM and Dhaka University for a possible commercialization of the fenugreek product.

Partnerships

Several academic partnerships have been developed with BIRDEM. The Department of Chemistry at the University of Dhaka, Bangladesh, has assisted in the project's overall development. Scientific assistance in the form of training and advice was available from the scientists of the Department of Medical Cell Biology at Uppsala University, Sweden, and the Department of Chemistry at Mahidol University of Bangkok, Thailand. Financial support was obtained from the International Program in the Chemical Sciences (IPICS) and International Foundation for Science (IFS).

Implementing Institution

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