Fenugreek: a natural prototype oral hypoglycaemic agent used in Malta

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Abstract

Before the discovery of insulin therapy in 1921 and the development of effective oral hypoglycaemic therapy in 1926, pharmacological management of diabetes mellitus was restricted to empirical treatment often based on plant products and relegated to folklore medicine. One therapy reputed in Malta as useful for the management of diabetes mellitus in 1927 was Fenugreek. This has now been shown to have definite pharmacological properties that controls blood glucose levels in diabetic subjects.

Keywords

Diabetes mellitus, phytotherapy, hypoglycaemic agents, therapeutics

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Introduction

The history of diabetes mellitus has its beginning in antiquity, and this disease has apparently plagued man for a very long time, since the writings from the earliest civilisations refer to boils and infections, excessive thirst, loss of weight, and the passing of large quantities of honey-sweet urine which often drew ants and flies. There is a reference to the disease in the Ebers Papyrus dating back to 1500 BC, which recommended that those afflicted with the malady go on a diet of beer, fruits, grains, and honey, which was reputed to stifle the excessive urination. The mainstay of managing the disorder remained primarily dietary based on two schools of thought. One school believed in dietary replacement of the sugar lost in the urine, while the other believed in restriction of carbohydrate so as to reduce the effects which were attributed to an excess of sugar. Adjuvant pharmacological management in the early decades of the nineteenth century remained restricted to regimens utilizing plant products such as opium and scammony, and mineral products such as magnesium hydroxide and sodium phosphate and calomel [mercurous chloride]. These supplemented the use of venesection, emetics and stimulants.[1] The breakthrough in the pharmacological management of diabetes was made in 1921 after F.G. Banting and C.H. Best obtained extracts of insulin and administered the hormone to Leonard Thompson on the 11th January 1922 in the Toronto General Hospital. The first oral biguanide hypoglycaemic, Synthalin, was developed by the drug company Schering in 1926-27. This was eventually modified to Phenformin in 1957. The sulphonylureas were derived from the sulphonamides and marketed after 1955.

Pharmacological treatment of diabetes in Malta

Medical practitioners in Malta were long familiar with diabetes, with the first local case being documented in 1782 by Dr. Giuseppe Demarco who in his manuscript notes described a case of a nun suffering from diabetes and who in the space of ninety-four days voided 3594 chamber-pots of urine. His reference to contemporary medical literature confirms that Dr. Demarco was familiar with the literature.[2] The cause-specific mortality rate from the disease in 1834 amounted to about 4.9 per 100,000 population.[3] Developments in the pharmacological management of diabetes were followed by Maltese practitioners during the subsequent decades of the nineteenth century. The Maltese medical journal *Il Filocamo* on the 1st September 1841 published a summary of a paper previously published in a

foreign medical journal about the pharmaceutical management of diabetes using pills containing iron sulphate, zinc sulphate and extract of gentian. The editor, Prof. Schinas, observed that diabetes "was an illness very often resistant to the most rational and active forms of treatment ..... and because the essential nature of it was still unknown and, therefore, until this is determined one could not devise ways of curing it."[4] In 1890, the Maltese medical journal *La Rivista Medica* reviewed a paper read by Dr. F.W. Pavy at the International Medical Congress held in Berlin in August who advocated the administration of opium, codeine and morphine to further reduce the sugar levels.[5] The subsequent year, *La Rivista Medica* reported the work of Dr. N. Casarelli, published in the *Rivista generale italiana di Clinica medica,* with the use of the hypnotic Sulphonal (Sulfonmethane - $C_7H_{16}O_4S_2$) in diabetes mellitus which had been shown to exert a favourable influence on diabetes.[6] In 1893, the medication known as China anti-diabetica, which consisted of a tonic element extracted from the plant *Cinchona officinalis* (Quinine Bark) and an anti-diabetic basis (redistilled glycerine of great purity) was being advocated and imported for sale in local pharmacies.[7] The pharmacist Francesco Caruana Dingli in 1899 manufactured an anti-diabetic medication Nuovo Liquore Anti-diabetico claimed to be "an infallible and very quick acting remedy against diabetes even in its most resistant form." This had been examined and approved by Prof. V. Micallef, Professor of Chemistry and Government Analyst.[8] In the first decade of the twentieth century, another locally prepared anti-diabetic agent Fermentina was being marketed.[9] The contents of the latter two agents are unknown. Effective pharmacological therapies were introduced by the Professor of Surgery P.P. Debono, who in June 1923 reviewed the use of insulin finding it useful in cases of diabetic coma, the juvenile form of diabetes, diabetics with infections or undergoing surgery, and in those cases who could not be kept on a sugar-free diet. Because of the high cost associated with the medication and its control, insulin therapy was still restricted to those who could afford to buy the medication or were in-patients in the hospital.[10] In 1927, the Professor of Medicine J.E. Debono outlined the principles of diabetic management with the mainstay of treatment remaining a maintenance-diet that contains just enough calories to maintain life and health. Insulin by injection was added to the management if glucosuria persisted after a week of dietary control. He considered all insulin substitutes available at the time to be "absolutely valueless." However Synthalin, then still under investigation, was mentioned as a possible substitute to insulin in mild cases in spite of its toxic effects.[11]

Phytotherapy

The inadequacy of available pharmacological agents gave rise to folkloric herbal medicine often without a pharmacological basis (Table 1). In 1927, the year when the first biguanide was being investigated, the Professor of Natural History J. Borg in his list of Maltese flora reports that the seeds of the species *Trigonella foenum-graecum* Linn (English: fenugreek, Italian: fienu-greco; Maltese: helba or fienu; Arabic: hulba or hilbeh) as being a supposed cure for diabetes.[12] The plant, a member of the pea family (Family: Fabaceae – Leguminosae), is a native of southern Europe, the Mediterranean region, and Western Asia, but has been extensively cultivated elsewhere. Prof. Borg believed the species to have been introduced and naturalized in Malta through cultivation. He reported it growing in the Girgenti and Siggiewi region. The species has however been known in the Maltese Islands since at least the mid-eighteenth century having been referred to by G.F. Agius de Soldanis in his 1750 manuscript *"Damma tal Kliem Kartaginis mscerred fel fom tal Maltin u Ghaucin",* and also by G. Gulia's 1889-90 *"Prontuario di Storia Naturale."*[13]

Table 1: *Plants believed to be useful for diabetes in Maltese and Moroccan Medical Folklore*

Scientific name	*English vernacular*
Trigonella foenum graecum	Fenugreek, Greek hayseed
Cichorium intybus	Chicory
Cichorium spinosum	
Cynara scolymus	Globe artichoke
Helianthus tuberosus	Jerusalem artichoke
Helianthus annuus	Sunflower
Urtica urens	Nettle, Stinging nettle
Olea europea	Olive

Fenugreek seeds have been used medicinally all through the ages and were held in high repute among the Egyptians, Greeks and Romans for medicinal and culinary purposes. In ancient Egypt, fenugreek was used to ease childbirth and to increase milk flow. Today, it is still taken by Egyptian women for menstrual pain and as "hilba tea" to ease stomach problems of tourists. Therapeutically, in 1905, the seeds of the plant were reportedly employed for the preparation of emollient poultices, enemata, ointments and plasters. They were not recommended for use internally, presumably excluding their use in diabetes.[14] In common with other legumes, fenugreek seeds are high in protein with a 100 g of seeds supplying about 23 g of protein. In the Middle East, boiled fenugreek seeds are served as a high protein main dish. The seeds are also rich in vitamin and minerals. The seeds also contain the vanilla-scented coumarin, making them useful for food flavoring as components of curry powders and chutneys. Its traditional medical properties come for the presence of mucilage, an emollient soothing to the skin. Fenugreek seeds further contain a wide range of components including trigonelline that when heated yields nicotinic acid (100 g of seed yields 1.6 mg of nicotinic acid – about 10% of the recommended requirements); and diosgenin that can be converted to pregnenolone and progesterone. The seeds have traditionally been considered to have expectorant, demulcent, emollient, febrifuge, carminative, nutritive, tonic, mucilaginous, restorative, anti-inflammatory, diuretic, stimulant, laxative, and stomachic functions. The aerial parts were further attributed with antispasmodic properties.[15]

Numerous animal studies and preliminary trials in humans over the last two decades have found that fenugreek can reduce blood sugar and serum cholesterol levels in people with both type 1 and type 2 diabetes.[16,17,18] The mode of action of fenugreek in improving metabolic control in diabetic subject is still not clear. It has been suggested that Fenugreek acts by reducing the rate of gastric emptying thus inhibiting glucose transport and intestinal glucose absorption.[19] Further studies have also attributed the seeds with secretagogue actions, similar to those of glibenclamide, stimulating insulin synthesis and/or secretion from the beta pancreatic cells of Langerhans.[20] An extra-pancreatic mode of action by increasing the sensitivity of tissues to available insulin for the active principle of fenugreek seeds has also been demonstrated[18]. It has been suggested that the active hypoglycemic agent in fenugreek seed may be the amino acide 4-Hydroxyisoleucine. This amino acid has been shown to increase glucose-induced insulin release through a direct effect on isolated islets of Langerhans from both rats and humans. The stimulating effect of 4-hydroxyisoleucine was shown to be biphasic occurring in the absence of any change in pancreatic alpha- and delta-cell activity. The insulin response was dependant on the glucose concentration. The active ingredient did not interact with other agonists of insulin secretion such as leucine, arginine, tolbutamide, and glyceraldehyde.[21]

Conclusions

Many modern medications owe their origins to plant products, the classical examples being morphine extracted from the opium poppy and digitalis originally extracted from the foxglove plant. Some traditional therapeutic measures have been generally abandoned and relegated to medical folklore, particularly with the development of inorganically produced or modified pharmacologic agents. The use of fenugreek for diabetes is one such traditional measure that was superseded after the mid-1950s with the development of the biguanides and the sulphonylureas, which proved to be effective oral hypoglycaemic agents. It is only in recent years, that fenugreek has been scientifically investigated in relation to its anti-diabetogenic properties and found to be effective in reducing blood sugar levels in mild diabetics. While no recommendation can at present be safely made to control diabetic patients with fenugreek, it may be opportune to re-introduce the legume in the local diet particularly in those individuals diagnosed to have impaired glucose tolerance or are at high risk of developing the metabolic syndrome.

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