Diabetologia (1997) 40: 614–617

Diabetologia

For debate

From plant to patient: an ethnomedical approach to the identification of new drugs for the treatment of NIDDM

A. Y. Oubré, T. J. Carlson, S. R. King, G. M. Reaven

Shaman Pharmaceuticals Incorporated, South San Francisco, California, USA

Pharmaceutical research conducted over the past three decades shows that natural products are a potential source of novel molecules for drug development [1, 2]. In this context, evidence has been published [3–6] that a wide array of plant-derived active principles, representing numerous classes of chemical compounds, demonstrate activity consistent with their possible use in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Among the classes of chemical compounds isolated from plants with documented biological activity are alkaloids, glycosides, galactomannan gum, polysaccharides, peptidoglycans, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, amino acids, and inorganic ions. Despite these interesting observations, to date, metformin is the only ethical drug approved for treatment of NIDDM derived from a medicinal plant historically used to treat diabetes. Why is this so, given the fact that higher plants are such a potential source of new drugs? The answer to this rhetorical question may lie in the reliance of most pharmaceutical companies on random, in vitro, mechanism-based, high throughput screening in the initial phases of plant drug research. In this article we will present the case for an alternative pathway to discovery of drugs for the treatment of NIDDM; one based on an ethnomedical approach, involving ethnobotany and traditional medicine.

Corresponding author: G. M. Reaven, MD, Shaman Pharmaceuticals, Inc. 213 East Grand Avenue, South San Francisco, CA 94080-4812 USA

Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus.

NIDDM as a disease of affluence: how could traditional medicine be relevant?

It is often argued that since NIDDM is a disease of Western civilization, there is no reason to believe that a corpus of traditional medicine approaches could have evolved. If there was no disease, how could knowledge of treatment be gained? The simplest answer is to point out that physicians of the ancient world utilized botanical medicines to treat diabetes, a condition mentioned in several medical works of historical significance. The *Ebers Papyrus,* written about 552 B. C., was a comprehensive compendium of drugs and prophylactics derived from animal, plant, and mineral sources. As part of a collection of ancient Egyptian medical textbooks, the *Ebers Papyrus* described the pathology of a clinical condition resembling diabetes [7]. During the classical Brahmanic period (700–200 B.C.) in India, physicians diagnosed diabetes by tasting the patient's urine for sweetness as well as other symptoms observable upon examination. The *Sushruta Samhita,* an Ayurvedic textbook written between the fourth and fifth centuries B.C., describes two types of diabetes. The author of this work distinguished between a genetically based disorder and one resulting from dietary indiscretion [8]. Thus, even 2500 years ago, Ayurvedic physicians recognized and categorized clinical entities corresponding to insulin-dependent-diabetes mellitus and NIDDM. The pharmacopoeia of ancient India listed specific treatments for diabetes, including dietary modifications, medicinal plant remedies, and minerals. Like its Indian counterpart, Chinese medical books written as early as 3000 B.C. spoke of diabetes and therapies for this disease. These historical accounts reveal that NIDDM was well known among the ancients and that medicinal plants have been used for millennia to treat this disease [9]. At least, this information supports the view that there has been ample opportunity for the development of

considerable clinical experience in the treatment of NIDDM, and that the potential use of this knowledge in the drug discovery process should not be rejected out of hand.

Plants used to treat diabetes

Over the last two decades, several comprehensive reviews [3–6] have been written on the evidence that higher plants are of use in the treatment of diabetes, providing discussions of the botany, phytochemistry, pharmacology, and in some cases, toxicology, of the botanical agents. Literally hundreds of extracts of higher plants used in folk medicine for diabetes (or active principles derived from these plants) have been screened for their biologic activity in both in vitro and in vivo assays. The most extensive review [6] evaluated available data on more than 1000 species of plants reported to have been used to either treat diabetes and/or been investigated for antidiabetic activity, and indicated that approximately 80 % of the traditional plants used for the treatment of diabetes demonstrated some antidiabetic activity. In many instances the chemical constituent in the plant responsible for the biological activity has been isolated and identified, and information is also available concerning the mechanism of action. On the other hand, as indicated by Marles and Farnsworth [6], not all of the plants reported to be useful are entirely safe, and they emphasize the need for carefully planned scientific research to identify those hypoglycemic plants with true therapeutic efficacy and safety.

In this context, the discovery process that led to the use of metformin is worthy of summary. Goat's rue *(Galega officinalis),* also known as French lilac, was used as a treatment for diabetes in medieval Europe. Early laboratory investigations revealed that *Galega officinalis* contains a high concentration of guanidine. In 1918, Watanabe [10] demonstrated that injections of guanidine could produce hypoglycaemia in parathyroidectomized test animals. Though this compound proved too toxic for clinical use, alkyl diguanides were synthesized from it in the 1920s. In 1957, two independent research teams discovered that biguanidines, a third generation of guanidine derivatives, were efficacious as a new class of antidiabetic agents [11, 12]. Derived from a prototypic molecule found in a plant with a long history of medicinal use, metformin exemplifies an efficacious drug the development of which was based on a use of a plant to treat diabetes.

Antidiabetic plants: random high-throughput screening

One approach to drug discovery involves random in vitro assays, permitting a high throughput of plant extracts and compounds to be tested at a rapid rate. 'Hits' can then be evaluated further in relevant in vitro and in vivo models. The cost-benfit of random screens depends to a considerable extent on the therapeutic area under investigation. In vitro techniques may offer an efficient tool for identifying potential therapeutic agents to treat infectious diseases, including conditions caused by viral, bacterial, mycobacterial, and parasitic organisms. However, the practical merit of these techniques for evaluating potential therapeutic agents for complex metabolic disorders is less clear. In the case of NIDDM, the choice of a target is problematic. What should the target be? A few years ago it was shown that muscle glycogen synthase activity was decreased in patients with NIDDM, as well as in their first degree relatives [13, 14]. More recently, evidence has been presented that this change is likely to be secondary to a more proximal defect in glucose transport [15]. What would have been the advantage of using random, high-throughput, in vitro screens for compounds that modulate glycogen synthase activity? In his Banting Lecture, Kahn [16], presented an elegant overview of the insulin signal transduction system. Given the complexity he pictured, what molecular step should be targeted in order to discover new drugs for the treatment of NIDDM? IRS-I? tyrosine kinase? The potential pitfalls of this approach seem to be self-evident. Efficacious new drugs for the treatment of NIDDM may be discovered in this manner, but, as elegant as this approach may seem to the molecular biologist, we believe that its utility as the means to discover compounds for the treatment of NIDDM can be questioned.

The ethnomedical approach

An alternative process used to identify and prioritize plants for drug development entails ethnomedical and ethnobotanical field work. This combined approach involves the study of plants used in traditional societies. Over the past several decades, medical ethnobotany has emerged as a new, or more appropriately revived, interdisciplinary approach to drug discovery, involving collaboration between a Western trained, physician-ethnobotanist team and indigenous healers [17–20]. The establishment of such a team permits the physician to interact with the native healers in evaluation of the clinical diagnosis, while at the same time the ethnobotanist can identify the plants being used as medicines [20]. The result is to greatly enhance the quality of the field research data. For medicinal plant research to operate in an optimal manner, it is extremely helpful if the field researchers possess interdisciplinary training [20].

In order to identify and prioritize plants that warrant phytochemical and pharmacological analysis it is necessary for the Western trained field research team to collect detailed information on the botany and

traditional medicinal uses of the target plant(s) utilized by traditional healers to treat specific diseases [21]. Cross-cultural data on the medicinal uses of the same or related species from geographically diverse areas, primarily tropical regions, can be compared [22] to help eliminate plants will probably prove efficacious because of placebo effects rather than bioactivity. If culturally sensitive interviewing techniques are used, the physician-ethnobotanist field research team should be able to assess the clinical diagnosis of the disease being treated with a given plant. In addition, they can gather data on the plant part(s) used in the traditional healer's remedy, the mode and frequency of administration of the indigenous (ethnomedical) preparation, the course of treatment outcome expected by the healer, and other pertinent botanical and ethnomedical information [20–23].

The ethnomedical approach provides an interface between modern clinical medicine and the empirical facets of traditional herbal medicine. Because both Western allopathic doctors and traditional healers diagnose diseases on the basis of observable signs and symptoms, there is a considerable degree of overlap between these two types of medical systems in their recognition of clinical entities. In other words, regardless of the cultural or geographical background of healers, all of them are concerned principally with alleviating the physical suffering of their patients. Since the pathophysiology of NIDDM appears to be similar across cultures, Western physicians and non-Western traditional healers alike can use clinical signs and symptoms in order to communicate in a common, universal language. An important component of the ethnomedical field research approach is to discuss with traditional healers case presentations of patients with NIDDM. By so doing, it is possible to stimulate traditional healers to share their knowledge of NIDDM with the ethnobotanist team. An example of a prototypic case presentation is as follows: the patient is a middle-aged man with complaints of increased urination, fatigue, general weakness, numbness in his feet, and a foot sore that will not heal. In addition, a photograph of a diabetic foot ulcer is shown to the healer. The brief description of case history consistent with the diagnosis of NIDDM, and the photograph of a diabetic foot ulcer, dissolve cultural and linguistic differences and facilitate communication in a common language about the disease. If the healer recognizes this clinical syndrome, they are then asked to describe their experience with it. As this dialogue continues, the traditional healer will often give a detailed description of the natural history of the disease that includes additional clinical details that were not included in the case presentation. The more congruent the traditional healers' description is to the clinical course of NIDDM, the stronger the degree of confidence that the two healers, Western and traditional, are referring to the same disease.

The ethnobotanical and ethnomedical information gleaned from field research provides the potential to identify which plants are most likely to be useful in the treatment of NIDDM. Furthermore, the continued use of plants by traditional healers offers a reasonable degree of certainty that the plant in question is active when taken by mouth and can be ingested by humans without apparent toxicity. Thus, at the time the drug development process begins an enormous amount of critical information is available that can be employed to guide laboratory preparations of crude extracts, to devise dosing regimens in test animals, and in certain cases, to develop formulations of drugs for preclinical bioassays when active principles are identified. Though the ethnobotanical approach cannot generate the high volume of plant extracts that can be studied in random in vitro screens, it has the potential to be remarkably efficient as an initial phase of plant drug discovery and development.

Glucose monitoring studies: a tool in the ethnomedical approach

Historically, the ethnomedical approach has relied almost entirely on the clinical insights and experience of the traditional healer. However, this no longer need be the only criteria. With the availability of urine and blood glucose monitoring devices, it is now possible to increase the precision of the ethnomedical evaluation of plants that might be useful in the treatment of NIDDM. For example, plants that have traditionally been administered orally for treatment of vaginal candidiasis in middle-aged women can be evaluated for their effect on blood glucose concentrations in hyperglycaemic patients. Plants that were thought to be highly effective by traditional healers, but do not appear to be antihyperglycaemic when tested in relevant in vitro or in vivo assay systems, can be re-evaluated in the field for their effect on blood glucose concentrations in patients with NIDDM. Obviously, the decision to discontinue pre-clinical evaluation of a given plant as the source of a compound to treat NIDDM would be less likely if it was shown to be efficacious in patients with the disease. Some idea of pharmacokinetics can also be gained by evaluating blood glucose changes when the plants are administered by traditional healers. Indeed, there are innumerable examples of how such field information would be useful in identifying and prioritizing potential plant candidates. Of equal, if not greater, importance is that the results of these studies can benefit patient populations in Third World host countries where botanical medicines are commonly used and where blood glucose monitoring studies can be easily conducted in an economical and ethical manner. By exchanging modern medical data and indigenous healing information, ethnobotanists can discover

pharmaceutical leads and traditional healers can learn more information about efficacy and dosing.

Eager to continually refine and ameliorate their own traditional methods, many indigenous healers in Africa, Asia, and Latin America have expressed keen interest in knowing whether or not their remedies are efficacious for specific diseases according to Western scientific criteria. Some healers want to be informed even if a botanical treatment does not prove to be effective in pharmacological screens. Given the escalating prevalence and incidence of NIDDM, especially in many of the countries of the Southern hemisphere, as well as the lack of access to modern medicine in these regions, traditional medicine represents the primary, and, in some cases, the only source of health care available in much of the developing world.

Conclusions

The previous discussion indicates that NIDDM has existed for at least 2000 years and has been treated historically with the use of plants. One medicinal plant, *Galega officinalis,* led to the discovery and synthesis of metformin. Today, of an estimated 250000 higher plants, less than 1% have been screened in depth for phytochemistry or pharmacology. Given a reasonable likelihood that medicinal plants with a long history of human use will ultimately yield novel drug prototypes, systematic and intensive searches for new drugs to treat NIDDM seem to be a great utility. Because it provides a way to capture, document, and rapidly assess data about medicinal plants used in traditional cultures, the ethnomedical approach to plant drug discovery is practical, cost-effective, and logical. This approach seems likely to increase the chances for discovering new drugs for the treatment of NIDDM, while simultaneously enhancing the quality and integrity of affordable traditional medicine available in the developing world.

References

1. Farnsworth NR (1994) Ethnopharmacology and drug development. In: Chadwick DJ, Marsh J (eds) Ethnobotany and the search for new drugs Ciba Foundation Symposium 185. John Wiley and Sons, Chichester New York, pp 42–51
2. Farnsworth NR (1990) The role of ethnopharmacology in drug development. In: Chadwick DJ, Marsh J (eds) Bioactive compounds from plants. Ciba Foundation Symposium 154. John Wiley and Sons, Chichester New York, pp 2–11
3. Oliver Bever B, Zahnd GR (1979) Plants with oral hypoglycemic action. Quarterly Journal of crude Drug Research 17: 139–196
4. Bailey CJ, Day C (1989) Traditional plant medicines as treatments for diabetes. Diabetes Care 12: 553–564
5. Ivorra MD, Paya M, Villar A (1989) A review of natural products and plants as potential antidiabetic drugs. Journal of Ethnopharmacology. 27: 243–275
6.. Marles RJ, Farnsworth NR (1995) Antidiabetic plants and their active constituents. Phytomedicine. 2: 137–189
7. Massengill SE (1943) A sketch of medicine and pharmacy. S. E. Massengill company, Bristol, Tennesse
8. Dahanikar S, Thatte U (1989) Ayurveda revisited. Popular Prakashan Bombay
9. Ackerknecht EH (1982) A short history of medicine (Revised edition) Johns Hopkins University Press, Baltimore/ London
10. Watanabe CK (1981) Studies in the metabolic changes induced by administration of guanidine basis. I. Influence of injected guanidine hydrochloride upon blood sugar content. J Biol Chem 33: 253–265
11. Sterne J (1957) Du nouveau dans les antidiabetiques, la NN dimethylamino guanyl guanidine (NNDG). Maroc Med. 36: 1295–1296
12. Ungar G (1957) Pharmacological studies of a new oral hypoglycemic drug. Proc Soc Exp Biol Med. 95: 190–192
13. Thorburn AW, Gumbiner B, Bulacan F, Brechtel G, Henry RR (1991) Multiple defects in muscle glycogen synthase activity contribute to reduced glycogen synthesis in non-insulin-dependent diabetes mellitus. J Clin Invest 87: 489–495
14. Schalin-Jäntti CS, Härkönen M, Groop LC (1992) Impaired activation of glycogen synthase in people at increased risk for developing NIDDM. Diabetes 41: 598–604
15. Rothman DL, Shulman RG, Schulman GI (1992) ^{31}P nuclear magnetic resonance measurements of muscle glucose-6-phosphate. Evidence for reduced insulin-dependent muscle glucose transport or phosphorylation activity in non-insulin-dependent diabetes mellitus. J Clin Invest 89: 1069–1075
16. Kahn CR (1994) Insulin action, diabetogenes, and the cause of type II diabetes. Diabetes 43: 1066–1084
17. King SR, Tempesta MS (1994) From shaman to human clinical trials: the role of industry in ethnobotany, conservation and community reciprocity. In Chadwick DJ, Marsh J (eds) Ethnobotany and the search for new drugs. Ciba Foundation Symposium 185. John Wiley and Sons Chichester/ New York pp. 197–213
18. Cox PA (1994) The ethnobotanical approach to drug discovery: strength and limitations. In: Chadwick DJ, Marsh J (eds) Ethnobotany and the search for new drugs. Ciba Foundation Symposium 185. John Wiley and Sons Chichester New York pp. 25–36
19. Cox PA, Balick MJ (1994) The ethnobotanical approach to drug discovery. Scientific American June, pp. 82–87
20. King S, Carlson T (1995) Biocultural diversity, biomedicine and ethnobotany: the experience of Shaman Pharmaceuticals. Interciencia, Revista de Ciencia y Tecnologia de America [Journal of Science and Technology of the Americas]. 20: 134–139
21. Daly DC, Limbach CG (1996) The contribution of the physician to medicinal plant research. In: Balick MJ, Elisabetsky E, Laird SA (eds) Medicinal resources of the tropical forest: biodiversity and its importance to human health. Columbia University Press New York
22. Conte LA (1996) Shaman Pharmaceuticals' approach to drug development. In: Balick MJ, Elisabetsky E, Laird SA (eds) Medicinal resources of the tropical forest: biodiversity and its importance to human health. Columbia University Press New York
23. King SR, Tempesta MS (1994) From shaman to human clinical trials: the role of industry in ethnobotany, conservation and community reciprocity. In: Chadwick DJ, Marsh J (eds) Ethnobotany and the search for new drugs Ciba Foundation Symposium 185. John Wiley and Sons, Chichester/ New York pp. 197–213