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Antidiabetic drugs used in Europe prior to the discovery of insulin

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Many therapeutic agents had been used for the treatment of diabetes mellitus before insulin was discovered and several hundred plants have shown some extent of antidiabetic activity. This study tries to explore which agents were most widely used in Europe in the pre-insulin era. According to the scientific literature and the proprietary drug industry around 1900, more than 100 agents were considered to have hypoglycemic activity. Most of them seem to have been used only occasionally while some others were recommended and marketed to a large extent. Among the medicinal plants, *Syzygium cumini* (syn. *S. jambolanum*, *Eugenia jambolana*), *Vaccinum myrtillus* and *Phaseolus* sp. were most common, and other frequently used agents were opium, opium alkaloids, other alkaloids like quinine or *Belladonna* alkaloids, salicylates, alkaline substances like sodium (bi)carbonate and even strong poisons like arsenic or uranium salts. *Syzygium jambolanum* seed powder seems to be one of the most intensively studied antidiabetic agents of plant origin.

1. Introduction

The discovery of insulin in 1921 clearly marks a turning-point in the history of diabetes mellitus, if not "one of the most remarkable and dramatic events in the history of medicine" (Bliss 1997): For the first time an agent was available which offered a really effective treatment option for patients suffering from diabetes. Despite the underlying hormone deficiency and the involvement of the pancreas having been known for decades previously, technical problems had prevented hormone substitution therapy from being introduced earlier. Oral therapy with pancreatic extracts, which had been attempted in the early 20th century was of course insufficient (Tattersall 1995). But from 1921 onwards, patients suffering from what is now called type-1-diabetes were no longer under a death sentence. The hormone was of course also useful in the treatment of type-2-diabetes, since oral antidiabetics were also not available before the 1920's (Otten 1966) and did not start their successful career until the 1950's (Meyer and Schuhmann 2001; Meyer et al. 2002). Before causal treatment options were available, a vast range of agents were, not surprisingly, recommended as antihyperglycemic drugs. It might be a sign of desperate attempts to cure a basically incurable disease but on the other hand, these treatment options were mostly derived from folk medicine which often reflects some useful experience. Thus, 20th century research found that there are several hundred medicinal plants showing some antihyperglycemic activity (Atta-Ur-Rahman and Zaman 1989; Bailey and Day 1989). Very recently, mechanisms of action have been proposed relying on molecular biology investigations. For example, a variety of plant extracts have been shown to activate the human peroxisome proliferator-activated receptor gamma (Rau et al. 2006a, b) which is involved in human glucose homeostasis and is also activated by the oral antidiabetics of the glitazone family. Investigations like these should certainly rely on a sound knowledge of the kind of agents traditionally used. Additionally, a knowledge of the extent of use and the number of recommendations made may be useful to direct investigations toward those agents most often regarded as active.

Thus, a study was undertaken to explore which agents were most often recommended in the decades before insulin was discovered.

2. Investigations and results

As a first step, textbooks and review articles published in the second half of the 19th and the beginning of the 20th century were screened to see what kind of pharmacotherapy they recommended. Dietary recommendations, organotherapy, physiotherapy, and spa cures were not considered further. Secondly, patent medicines and commercial products marketed as diabetes remedies were investigated with regard to their composition to explore which agents have been used and to what extent.

2.1. Frequency of use

Common 19th century textbooks on diabetes therapy (Watt 1808; Pavy 1864; Düring 1868; Külz 1874, 1899; Schnée 1888; Noorden 1895; Lenné 1898), therapy handbooks (Lengerken 1904; Klemperer and Rost 1929), review articles (Ormerod 1847; Schmitz 1881; Squire 1882; Saundby 1886), reports published in the review journal 'Centralblatt für klinische Medicin' (1882–1900; from 1894 onwards: 'Centralblatt für innere Medizin'), an early historical PhD

thesis (Heuel 1929) and occasional literature reports were evaluated. They deal mainly with dietary recommendations for diabetes patients and most of them do not seriously favour pharmacotherapy with many authors taking a negative view of its efficacy. However, most publications refer to what had been tried and are therefore a useful source for the purpose of this study.

A total of 107 antidiabetic agents could be identified from these sources. Most of them (72 = 67.3%) appear just once or twice which is certainly a sign of only occasional use. Some agents, however, are regularly described and seem therefore to have been used in general practice. The agents most often reported as antidiabetic in scientific literature include opium and opium alkaloids, spa waters, sodium (bi)carbonate, salicylates, arsenic salts, quinine, bromine, *Atropa belladonna* and its alkaloids, and *Syzygium jambolanum* (syn. *Syzygium cumini*, *Eugenia jambolana*) preparations.

From the beginning of the 20th century and even earlier, proprietary or "patent" medicines were marketed against a vast variety of diseases including diabetes. Their composition is not always clear but there are sources where such information can be found. Those include contemporary encyclopedial literature (Hahn and Holfert 1906; BMA 1909; AMA 1917; GEHE 1920, 1933) as well as PhD theses (Konstantinowksy 1912; Otten 1966). In a total of 76 antidiabetic preparations mentioned in these sources, 112 different compounds could be identified. 84 (75%) were only used once or twice, while just a few agents were contained in five preparations or more: *Vaccinium myrtillus*, *Syzygium jambolanum*, *Phaseolus* sp., sodium (bi)carbonate, quinine, salicylates, sodium chloride, *Linum* seeds, and *Gentiana* extract.

Matching both analyses, it is clear that only a few agents were simultaneously mentioned in the scientific literature and recommended as commercial products in the decades before insulin was discovered (Fig.).

2.2. Agents considered active against diabetes

Syzygium jambolanum (syn. *Syzygium cumini*, *Eugenia jambolana*, Jambul) preparations were those most often recommendend in the sources investigated. Parts of the plant were contained in several commercially marketed remedies and were relatively frequently mentioned in scientific literature which otherwise concentrated on dietetic treatment. Carl von Noorden (1858–1944), for instance, considered every kind of drug treatment almost useless. Reported success is said to be due to patient suggestion or to an improvement in nervous irritability, which might lead to reduced glucosuria in consequence. He admitted, however, that *Syzygium* might have some direct effects, despite never having seen positive results himself (Noorden 1895).

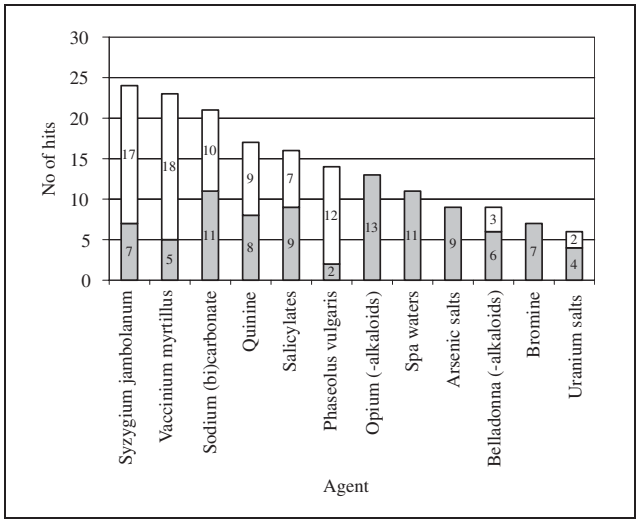

Fig.: Antidiabetic agents mentioned in scientific review literature (grey) and included in antidiabetic proprietary medicines (white) before the discovery of insulin

Syzygium came to Europe from the East Indies and Java in the 1880s and was imported by the British company Thomas Christies (Christy 1887). The drug, in particular the seed powder, had been used against diabetes in the countries of origin and was immediately tested for that purpose in Europe. There are about 50 studies published even before 1900 including four PhD theses (Henrichs 1891; Villy 1891; Benner 1892; Posthumus 1896), mostly describing one or several case studies. Altogether, more than 100 cases with patients receiving *Syzygium* preparations against diabetes were described in scientific literature between 1883 and 1896 besides *in vitro* experiments and animal studies.

Results were contradictory but, overall, a trend towards a positive effect of the drug can be observed with regard to a reduction in diuresis and glucosuria, the most commonly used diagnostic criteria at that time. The drug was used either in the form of powdered seeds (2–60 g/day; Benner 1892; Gerlach 1892; Posthumus 1896) or, less frequently, as an aqueous fluid extract made from *Syzygium* cortex (Benner 1892; Posthumus 1896). Pre-1900 *Syzygium* studies are going to be investigated in detail and will be the subject of a further publication. The most famous German patent medicines containing *Syzygium* (Bauers Antidiabeticum, Djoeat) were marketed by the Bauer-Company in Kötzschenbroda near Dresden (Bauer 1905; Hahn and Holfert 1906; Kontantonowski 1912; AMA 1917).

Vaccinium myrtillus was the most frequent ingredient of commercial antidiabetic preparations marketed in the early 20th century. Most literature sources do not specify the part of the plant the extract was made from, but leaves might have been used most often. A very common preparation was the "Pilulae Myrtilli Jasper", each containing 0.12 g leaf extract (Konstaninowsky 1912). However, the drug was only occasionally mentioned in scientific treatises only occasionally and just a few particular investigations could be found, which is also the case for *Phaseolus* preparations which were used as a tea or as tablets covered by cacao mass (Otten 1966). Diabetes expert Albert Lenné, physician in the German spa town Bad Neuenahr, explicitly considered the Jasper pills to be completely useless (Lenné 1894).

Alkaloids, namely *quinine* and *opium* compounds played a major role in the early drug treatment of diabetes as well. Opium was certainly not freely available but seems to have been the most highly reputed drug in scientific diabetes treatment around 1900. In 1898, Lenné considered opium the most suitable agent against diabetes while remaining sceptical in general: "Trotzdem halte ich das Opium für das brauchbarste Arzneimittel. Obwohl es durchaus nicht das leistet, was ihm nachgesagt wird" (Lenné 1898, similarly Külz 1899 and Schnée 1888). It was used to symptomatically reduce diabetes symptoms, mainly thirst sensations – in daily doses between 0.1 and 15 g [!] (Balfour 1870; Lenné 1898; Heuel 1929). Opium had been used at least since 1675 and Elias Joslin stated in the same year as Lenné that opium was the only drug

which has been persistently used in the treatment. However, it was well known that this was only a symptomatic treatment: "One suspects that opium was employed because it would make it easier for the hungry diabetic patient to tolerate his misery, but certainly it was never efficacious in actually overcoming the objective effects of the disease" (Allan 1972). Villemin (1887) reported that opium in combination with *Belladonna* extract also reduced the quantity and sugar content of patient's urine as did Saundby (1886), who stated: "Opium is the oldest [remedy] and still retains the first place, next comes its alkaloid, codeine, then salicylic acid or its salts, and lastly the arsenite of bromine".

Indeed, among the remarkably toxic agents recommended against diabetes were *arsenic* (Qiunquaud 1892) and *uranium salts*. Otten (1966) reported that the hepatotoxic arsenic, which was administered orally and subcutaneously (Heuel 1929) was somewhat successful due to decreased hepatic gluconeogenesis. Most remarkably, an uranium containing Bordeaux wine was marketed to the general public in the first decade of the 20th century (Vin Urané Pesqui; BMA 1909).

Salicylates and other early synthetic analgesics like Antipyrin were indeed widely recommended to treat diabetes mellitus. Sodium salicylate was given in very high doses, i.e. 5–10 g per day or even more (Ebstein 1876; Sympson 1891; Otten 1966). Ebstein (1876) saw some success in some cases of diabetes and tried to further characterize the responders to therapy while not beeing too enthusiastic: "Jedenfalls scheint die Thatsache gesichert, dass der Gebrauch des salicylsauren Natron ev. der Salicylsäure in einzelnen Fällen von Diabetes mellitus einen Einfluss auf die diabetischen Symptome hat, welche, wie mein erster Fall lehrt, dabei vollkommen verschwinden können. Freilich dürfen wir [...] auch von diesem, wie von allen anderen bisher bekannt gewordenen antidiabetischen Mitteln, nur einen vorübergehenden Erfolg hoffen."

Alkaline substances were common in the treatment of diabetes as well, mainly in the form of mineral waters from Karlsbad, Bad Neuenahr, Vichy or other spa towns where patients were often sent for recuperation. Lenné, who was, incidentally, in charge of the spa at Bad Neuenahr, considered alkaline mineral waters by far the best remedy against diabetes (Lenné 1893). Sodium (bi)carbonate was mostly used to treat the obvious diabetic acidosis rather than glucosuria in particular (Külz 1899). It was also used intravenously in diabetic coma. Other minerals tried in diabetes patients included calcium sulphate, and egg- or oyster shells.

3. Discussion

There are a number of instances where traditional knowledge has helped to explain the current use of medicines or even to reconsider historical treatment options (Heinrich and Lee Theo 2004; Buenz et al. 2006). Many examples show that traditional "folk" knowledge may indeed give at least hints for further studies and guide pharmacological research to some extent. This is also the case with agents against diabetes mellitus, in particular medicinal plants and their preparations. It is, however, not surprising that many plant extracts have some potential to decrease blood glucose levels; the 'Lehrbuch der biologischen Heilmittel' (Madaus 1935) already listed 46 plant species as recommended against diabetes and systematic reviews have identified several hundreds (Atta-Ur-Rahman and Zaman 1989; Bailey and Day 1989). Thus, we face a vast amount of similar ethnopharmacological reports and study results and in pursuit of a better overview it may be useful to make a rough quantitative estimate of which agents have been most frequently recommended in the past. This is why this study was undertaken.

The results clearly show that the majority of agents have only been used occasionally while others were mentioned more or less regularly. Among those there are several which would no longer be seriously considered because of intolerable side effects, like opium, arsenic salts or high-dose salicylates. Thus, describing their traditional use is mainly of anecdotal value although it is not impossible that research may reveal some rationale behind the treatment: For example, it has recently been found that salicylates inhibit the transcription factor NF-κB which is a potential mediator of insulin resistance (Shoelson 2002; Hundal et al. 2002). Its proposed effect might also have involved a reduction in kidney perfusion leading to a reduction in urine volume, one of the primary diagnostic criteria for diabetes control around 1900.

As regards medicinal plants, however, there is growing interest in their use as adjuvant agents in the treatment of type-2 diabetes or metabolic syndrome. In this context, cinnamon has recently gained great popularity in Germany after successful studies were published (among others Verspohl et al. 2005; Mang et al. 2006). While cinnamon is not once mentioned in the sources investigated here, three medicinal plants seem to have been used more regularly than others: *Syzygium cumini* (syn. *jambolanum*), *Vaccinium myrtillus* and *Phaseolus* sp. In this context, it seems particularly interesting that *Syzygium cumini*, a plant unknown in Europe until the 1880s, immediately became well-known here such that many textbooks on diabetes treatment before 1900 discussed the plant's efficacy, a lot of research was done including four PhD theses and it soon became an ingredient of several proprietary medicines. Furthermore, the plant is one of the medicinal plants frequently investigated against diabetes up to the present day; a recent PubMed search revealed 32 diabetes studies with the plant, 16 of these dating from 2000 or younger. In comparison, only 6 dealt with *Vaccinium myrtillus* and 18 with *Phaseolus* sp. Thus, a further study of the pre-1900 publications about the antidiabetic acticity of *Syzygium* may provide useful information for present day research and is underway.

Very recently, it has been found that several of the plants historically recommended for diabetes treatment are activators of the human peroxisome proliferator-activated receptor gamma and thus act similar to insulin sensitizers like glitazones (Rau et al. 2006a, b). It is interesting to note that *Syzygium cumini* and *Vaccinium myrtillus* are active in this respect while *Phaseolus vulgaris* is not (Rau et al. 2006b).

However, it should be clearly understood that the database of this present study is quite small compared to the number of diabetes treatment recommendations made before (and even after) the discovery of insulin. Thus, a more comprehensive survey may have the potential to reveal somewhat different results, in particular if not only European sources are included as it has been shown that the popularity of natural antidiabetic products varies among people of different ethnicities (Shapiro and Gong 2002).

It must, of course, be kept in mind that the mere appearance of an agent in the scientific literature is only proof of interest in its use and not of its efficacy. This is even more the case for the proprietary medicines whose ingredients were screened, as it is well known that they were often

marketed without any scientific basis and some of them were quite simply fraudulent. However, this study, which is probably the first approach to a quantitative assessment of historical diabetes treatment options may give some clues for further research.

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