REVIEW

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Vaccinium myrtillus as an antidiabetic medicinal plant – research through the ages

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Dedicated to Prof. Dr. Hartmut Morck, Marburg, on the occasion of his 65th birthday.

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Bilberry leaves (*Vaccinium myrtillus* L.) were one of the most frequently used antidiabetic remedies of plant origin before the discovery of insulin. During the last century, many animal, clinical and phytochemical studies have been undertaken with this plant and its extracts and are summarized here. Overall, it must be concluded that the results were more or less disappointing and could not support the traditional use of bilberry leaves against diabetes mellitus which is sometimes recommended even up to the present day.

1. Introduction

Prior to the discovery of insulin by Canadian scientists in 1922, medicinal plants together with highly restrictive diets were widely used in the treatment of diabetes mellitus. Although they were of course unable to cure the disease, many of them had actually shown some hypoglycemic activity and today, several hundred antidiabetic plants are known (Atta-Ur-Rahman and Zaman 1989; Baily and Day 1989). For centuries before the 1920 s, opium was the agent of plant origin most widely used in the treatment of diabetes (Helmstädter 2009), but not for its limited glucose lowering effects, but mainly to "make it easier for the hungry diabetic patient to tolerate his misery" (Allan 1972). There are also three medicinal plants which are known to have been used quite regularly and significantly more often than others in diabetes treatment before the discovery of insulin: *Syzygium cumini*, *Phaseolus vulgaris* and *Vaccinium myrtillus* (Helmstädter 2007). The latter is also one of the herbal drugs most often recommended against diabetes by Italian herbalists (Cicero et al. 2004). As there is recent scientific interest in antidiabetic plants, summarizing experiences from folk medicine and older scientific studies might be of value for guiding future research. As historical knowledge about *Syzygium cumini* (Helmstädter 2008) and *Phaseolus vulgaris* (Carai et al. 2009; Helmstädter 2010) has been reviewed elsewhere, the aim of this paper is to summarize investigations of *Vaccinium myrtillus*.

2. Early history of medicinal use

Vaccinium has been used since at least the Middle Ages, "Heydelbeere" is already mentioned by Hildegard of Bingen (1098–1179, Kreitmair 1947). The herbals ("Kräuterbücher") of the Early Modern Period, however, hardly ever mention *Vaccinium myrtillus* and if they do, it is for indications other than diabetes. The use of the fruits (bilberries) was more common than the use of the leaves (Kröger 1951b). Thus Hieronymus Bock (1498–1554) recommended a preparation made of the berries against cough (Bock 1559) and Pietro Andrea Mattioli (1501–1577) believed the juice had a diuretic and diaphoretic effect (Mattioli 1598), as did Adam Lonitzer (1528–1586) (Lonitzer 1962). Gastrointestinal indications also dominate British herbal literature (Sawyer 1903). The early pharmacopoeias rarely list *Vaccinium myrtillus* and concentrate on the fruits. For example, the Pharmacopoea Wirtenbergica (1741) has monographs for Fructus myrtilli and Syrupus myrtillorum but not for Folia myrtilli. Also Zedler's encyclopedia reports only the use of berries, which it describes as being usuful against gastrointestinal diseases (Zedler 1735). During the 19th century, many uses of bilberries were reported (Kröger 1951b), again as a remedy against various gastrointestinal disorders including bacterial infections and parasitoses. Bernstein (1903) focused on the action of bilberries against typhoid fever, and initiated the commercial preparation of a liquid extract by the Allan and Hanbury's company (anon. 1903). Other indications include skin and mucosal irritations, diseases of the urinary tract, fever and gout. From the end of the 19th century, there were reports of the antidiabetic effects of *Vaccinium* leaf extracts, which were said to have their origin in the folk medicine of the Austrian Alps (Mark and Wagner 1925; Allen 1927a; Kreitmair 1947; Kleiner 1959), and these soon found their way into standard textbooks (Madaus 1938). It has not yet been possible to verify a report referring to "Dr. Richard C. Wagoner of Allentown, NJ" as the discoverer of the antidiabetic action of "huckleberries" (Davis 1928).

3. Studies prior to the discovery of insulin

Early, but in fact anecdotal, reports of the antidiabetic effects of *Vaccinium* leaves date from 1892, when a pharmacist from Colberg near Breslau wrote a short notice about a patient whose urine sugar content he regularly monitored. After the patient had started to consume two cups of bilberry leaf tea, sugar excretion could no longer be detected. The pharmacist then started to prepare and sell bilberry leaf extract (Knorr 1892). One of

the first physicians known to be interested in *Vaccinium* therapy of diabetes was Rudolf Weil. Initially he achieved positive results with a decoction of the herb in one case of diabetes and wished to make this medicine available for more patients in a preparation with equivalent doses. He cooperated with the pharmacist Max Jasper, owner of a chemical factory in Bernau near Berlin, who agreed to produce pills later called "Pilulae Myrtilli Jasper" according to Weil's suggestions, including the use of young leaves harvested before the fruits appear (Weil 1892). Each pill contained 0.12 g extractum foliorum myrtillorum. Weil tested these pills in some of his patients and presented the results of 3 cases. After intake of 3 to 15 pills, e.g. 0.36 to 1.8 g extract, urine glucose vanished completely or almost completely within 12 weeks. The patients were described as having improved health status and gaining body weight. Weil stated that these results were similar to those of some of his colleagues. He added that all his patients had to keep strictly to a special diet which was low in carbohydrates and rich in vegetables. The physician recommended this diet for every patient who wanted to take Pilulae Myrtili Jasper.

In 1902, Bruno Steffan from Wädensweil tested the effect of Pilulae Myrtilli Jasper along with many other preparations recommended against diabetes on himself. In his first test Steffan took 16 pills within 12 hours which meant a total dose of 1.92 g aqueous extract. Three hours after an intake of 50 g glucose his urine glucose decreased by about 30% and his urine volume was reduced by about 5% over the following 24 h compared with an intake of glucose only. In a second trial he took 36 pills in 4 days, which meant a total dose of 4.32 g extract. This time urine glucose in the first 3 h after an intake of glucose was reduced by about 40% and urine volume decreased by about 12%. The author concluded that Pilulae Myrtilli Jasper had a noticeable although not very strong effect on glucose excretion (Steffan 1902).

In 1908, the German doctor Martin Kaufmann from Mannheim studied a variety of antidiabetic remedies including *Vaccinium myrtillus* administered as a tea and formulated in Pilulae Myrtilli Jasper. He observed two patients who were on a special diet. First he gave a daily amount of 800 mL tea to a 50 year old man. The man took the tea for 7 to 30 days consecutively with a break of one week. Kaufmann observed a slight but practically irrelevant reduction in urine glucose levels. Several weeks later this patient received 6 Pilulae Myrtilli Jasper daily for one week. Again, Kaufmann did not see a clear effect of the pills and described the therapy as harmless but useless (Kaufmann 1908). A 45 year old patient got the same tea as in test one on 6 consecutive days. In his case also no effect of the tea was noticeable.

4. Studies after the discovery of insulin

It is interesting to note that after insulin had been made available, scientific interest in antidiabetic plants did not disappear but even grew significantly. Most probably, this is due to the fact that the insulin discoverers themselves were convinced of the presence of an "insulin-like" substance in lower organisms and plants. In particular James Bertram Collip (1892–1965) believed in such "plant hormones" called "glukokinin" in a publication edited just one year after the discovery of insulin (Collip 1923). The idea of "vegetable insulinoids" (Labbé 1936) initially triggered a large amount of research including investigations on bilberry leaves.

Robert E. Mark and R. J. Wagner from the physiological department of the University of Vienna carried out several studies with *Vaccinium* preparations. In 1925 they tried a remedy made of the herb in 12 healthy dogs. Aqueous extract from 10 g *Vaccinium myrtillus* was given together with 200 g glucose in 500 mL of water. As a result Mark and Wagner observed that the curve of hyperglycaemia took a lower course compared with that after intake of 200 g glucose alone. The absorption of glucose was apparently not delayed (Mark and Wagner 1925). Studies were continued with a preparation called "Myrthillin" on 6 pancreatectomized dogs. One animal survived for 5 days, another one for 29 days. In dog 1 the preparation reduced blood glucose by about 45% and in dog 10 by about 50%; in this case glucosuria was stopped. According to the authors the extract could keep a depancreatized dog alive as long as it was given. The effect on blood glucose was described as being dependent on the method of application (Eppinger et al. 1925).

In the US, Frederick Madison Allen (1876–1964, for life and work see Medvei 1993) from Morristown, NJ, tried an extract of *Vaccinium myrtillus* called myrtillin in fully and partially depancreatized dogs and in patients. A daily dose of 1 g of an alcoholic extract (for preparation see Allen 1927a), was given at least one hour before mealtime. Allen found that the preparation could considerably prolong the survival time of fully depancreatized dogs and that it tended to stabilize blood sugar. In partially depancreatized dogs the extract kept the dogs in good condition with sugar-free urine and normal blood glucose. Clinical trials with 81 patients (in fact only 60 patients after Allen had excluded 21, mainly for "insufficient length of observation") showed that the extract was not a reliable remedy as it failed in 24 cases. In 36 cases there was some benefit, which led to an insulin dose reduction ranging from 6 to 28 units. In 6 patients insulin therapy could be entirely stopped. In Allen's tests the therapy achieved best results in the mildest cases, poorest in children and best in the middle aged or elderly. Even the largest doses of 20 grams per day proved in Allen's experiments to be nontoxic. He claimed a "possible vitamin nature" of the substance isolated (Allen 1927a, b). Eventually, Allen lost a lot of money in the development of a myrtillin preparation which ended up in severe personal disappointment (Medvei 1993).

The same year, Leonard Benjamin Shpiner from the University of Chicago repeated and extended Allen's studies. He used an extract of *Vaccinium myrtillus* named myrtillin which was not further characterised for experiments in dogs which were partially or totally pancreatectomised. Some of the dogs were tested during experimental hyperthyroidism. Three to 6 tablets á 5 grain of the supposedly active agent were given daily to dogs on a standard diet. The intake of the preparation resulted in a reduction of the hyperglycaemia and urine sugar in the totally depancreatized dogs, so that these animals survived longer. In partially depancreatized dogs relying on only 1/20 of the organ no diabetes symptoms developed. Here no glycosuria appeared and normal blood sugar levels were noted during experimental hyperthyroidism (Shpiner 1928).

Blair Holcomb (born 1894) from Portland, Oregon, also referred to Allen when he tested a preparation which he called myrtomel. He tested it in 18 patients aged 6 to 64 of whom 4 patients stopped taking it. Eight patients were described as "severe" cases by the author and 12 were on insulin. According to Holcomb his remedy led to a reduction of insulin dose in 7 of 12 patients and 2 patients could completely stop insulin injections. He described the action of the active sugar lowering principle as being slower in patients without insulin than in patients taking both insulin and his preparation (Holcomb 1928).

E. M. Watson from the Department of Medicine of the University of Western Ontario in London treated patients with tablets containing 0.3 g of *Vaccinium myrtillus* extract each. His study group consisted of 16 people, 3 of them being children aged 16 and 12. Four patients were described as "severe" cases and 13 were on insulin. The tablets were given one hour before a meal. Watson said that the intake of tablets reduced the doses of

insulin in 6 cases and also reduced the blood glucose level. In 7 cases the tablets increased carbohydrate tolerance. According to the author the best results were obtained in the milder cases and in middle-aged or elderly patients whereas the effects of the remedy were lost in the presence of even a slight infection (Watson 1928).

Elmer Louis Sevringhaus (born 1894), a famous endocrinologist from the Department of Medicine of the University of Wisconsin (Madison) discussed the effect of two antidiabetic preparations: synthalin and myrtomel. The preparation of *Vaccinium myrtillus* made by the Squibb Research Laboratory was described as being less promising than synthalin, a guanidine derivative (Sevringhaus 1928, see also Wilder and Allan 1928). However, details about the studies with myrtomel are not reported.

The French scientists M. F. Rathery and L. Levina tried an alcoholic preparation of fresh *Vaccinium myrtillus* leaves in normal and depancreatized dogs as well as in six human diabetics. In three of the patients the preparation reduced blood glucose and in two patients a reduction of blood glucose was observed after doubling the dose. In two patients urine glucose vanished. The scientists remarked that no immediate effect was to be expected, but nevertheless there was undoubtedly an effect of some kind (Rathery and Levina 1928).

Braun and Rees (1935) treated hyperglycemia induced in normal fasting rabbits by giving 10 g glucose per kg body weight with 1 g/kg myrtillin, defined as "the hypoglycemic fraction of an alcoholic hydrochloric acid extract of the dried green leaves of the whortleberry or the blueberry". They found some effect, but stated that the hyperglycemia was "depressed distinctly but very variably".

In a Ph.D. thesis published in 1936, a *Vaccinium* containing combination product, Norisdiabet, was tested (Pomp 1936). In addition to bilberry leave extract, the preparation contained a variety of salts derived from Spa waters, alkalizing agents like sodium hydrogen carbonate und Syzygium cumini extract. 'Norisdiabet", which was marketed by a pharmacy in Nuremberg, Germany, was tested in 7 patients without any benefit.

In 1938 the pharmacologist Hans Dietering from Berlin tested a daily oral dose of 0.15 to 18 g/kg body weight of an aqueous extract in more than 50 cats and rabbits. The extracts were commercially produced by the pharmaceutical company Krause-Medico according to their "dispert" procedure. The animals received up to 1.5 g bilberry leaf extract per kg body weight. Referring to Weil (1892) he tested extracts from young leaves and those derived from older ones, both in different doses. However, he could not find a reduction in blood glucose with any of these preparations and called the preparation therapeutically useless. He even feared toxicity due to the reported hydroquinone content of the leaves (Dietering 1938). Oettel (1936) had already pointed out that *Vaccinium* species might be toxic due to their high contents of hydroquinone, a substance which was said to elevate blood glucose levels and to interact with urine glucose determination methods. However, today it is doubted if *Vaccinium myrtillus* contains hydroquinone in relevant concentrations at all (Hänsel et al. 1996). As early as 1929, Shpiner suggested that commercial blueberry leave extracts are "nontoxic to [...] dogs when administered orally in what may be considered excessive doses" (i.e., up to 3.9 g extract which was said to be "two to four times the dosage necessary for its therapeutic effect in man"; Shpiner 1929).

5. Studies after World War II

In contrast to other antidiabetic plants known from traditional medicine, *Vaccinium myrtillus* was only rarely investigated after World War II.

In mice made diabetic with alloxan, a reduction in blood glucose levels by about 10% was reported in the early 1990s, but unfortunately, these experiments are not documented in detail (Hänsel et al. 1996).

Cignarella et al. (1996) tested a dried hydroalcoholic extract of *Vaccinium myrtillus* in streptozotocin-diabetic rats (3.0 g extract per kg body weight). The plasma glucose levels dropped by about 26% within three weeks of treatment, an effect considered as "statistically, though not biologically significant". The authors also report a significant fall in triglyceride levels and therefore found that the traditional plant treatment "could deserve attention for its activity on certain lipid metabolism disorders."

Petlevski et al. (2001) tested a multiingredient preparation composed of Myrtilli folium and nine other plant extracts, patented as an antidiabetic remedy in Croatia. In alloxan-induced non-obese diabetic mice, they found a decrease in blood glucose and fructosamine levels.

Vaccinium was also included in screening programs aimed at identifying alpha-amylase inhibitors and activators of the human peroxisome proliferator-activated receptor gamma and results indicated that bilberry leaf extracts have some activity in both models (Melzig and Funke 2007; Rau et al. 2006). From that point of view, some antidiabetic activity seems possible.

6. The search for an active principle

Along with the studies of the antidiabetic activity of *Vaccinium* extracts the search for an active principle went on. This was dominated by Allen's proposal of a compound named "myrtillin" which was said to be present not only in Vaccinium but in all green plants, yeasts and bacteria. It was said to have been obtained twice "in traces from dog livers" (Allen 1927a) and seems to represent the "glukokinin" initially suggested by Collip. Allen (1927a) gave a detailed description of its preparation by extraction with acidified alcohol (50%). After removal of proteins by addition of alcohol (95%) an aqueous solution of ammonium sulphate (20%) is added which yields a "flocculent precipiate" containing myrtillin. It is said to be "a greyish or brownish amorphous substance, not chemically pure" (Allen 1927a, for the preparation method see also Merck 1925). The supernatant should contain the "sugar-raising principle" which was also suggested to be present in *Vaccinium* leaves.

In principle, this definition of "myrtillin" was also given by Braun and Rees (1935) and still accepted by Kreitmair (1947). He points out that myrtillin (or myrthillin) is glucosidic in nature and must not be confused with the anthocyane dye extracted from bilberries and already named myrtillin by Willstätter and Zollinger (1915). Avoiding confusion might have been the reason why the antidiabetic principle was later called "myrtomel" (Holcomb 1928; Jorgensen and Lynn 1935). In the 1930s Edgars (1934) and Galimard (1939) proposed a methoxy galloyl glucoside "neomyrtillin" as a chemical entity with the molecular formula $C_{24}H_{36}O_{18}$. In contrast, Edgars described Allen's extract as "a group of active principles which have been roughly grouped under the pseudonym of myrtillin". He is highly enthusiastic about the therapeutic use of neomyrtillin, whose existence, however, could not be verified in the extensive investigations done by Kröger (1951a). Quite surprisingly, Hänsel et al. (1996) are still convinced of the "glukokinin neomyrtillin" in the aerial parts of the plant and suggest it to be a methoxylated glycoside of gallic acid. Hydroquinone (Oettel 1936; Kreitmair 1947) and arbutin (Kröger 1951a) are no longer regarded as being contained in considerable amounts. According to Zareba et al. (2005), anthocyanidins are responsible for the proposed "long-term hypoglycemic effect" of extracts from

Table: Studies with *Vaccinium* extracts as an antidiabetic agent

Author (year)	Patients/animals	Vacc. prep. and dose	Results	Author's conclusions	Remarks
Weil (1892)	3 Patients	0.36–1.8 g aE (3–15 PMJ) daily	Urine glucose completely vanished within 12 weeks	Good results, comparable to those of "colleagues." Should be used in combination with diet	Increase in body weight Improved health status
Steffan (1902)	1 healthy volunteer after 50 g glucose intake	1.92 g aE (16 PMJ) in 12 h	Urine glucose (3 h) -ca. 30% Urine volume in 24 h - ca. 5%	Small effect on glucose excretion	Refers to Kétly (details unknown) who could not find any effect with PMJ.
		4.32 g aE (36 PMJ) in 4 d	Urine glucose (3h) - ca. 40% Urine volume - ca. 12%		
Kaufmann (1908)	2 patients: 1. 50 years of age 2. 45 years of age Both patients got a special diet	800 ccm tea of Mt or 6 PMJ per day	Patient 1: on 800 ccm tea, first observation: slight, practically irrelevant reduction in urine glucose levels Patient 2: 800 ccm tea showed no effect Patient 1: second observation: no clear effect of the PMJ	Mt a harmless therapy without any therapeutic effect	No unpleasant events ocurred
Mark and Wagner (1925)	12 healthy dogs after intake of 200 g glucose	500 ccm aE (10 g Vacc. myrt.) with 200 g glucose	Lower curve of the course of hyperglycaemia		No clear definition of the type of extract used
Eppinger et al. (1925)	6 dogs without pancreas	Mt	2 dogs survived 5 and 29 days Dog 1: Mt reduced blood glucose from 357 mg-% to 192 mg-% Dog 10: reduction in blood glucose from 416 mg-% to 211 mg-%, glucosuria stopped	Mt 1) reduces or removes urine glucose 2) keeps the Minkowski-quotient small 3) keeps alive a depancreatized dog as long as Mt is given	Effect on blood glucose depends on way of application
Allen (1927)	Dogs 81 Patients	1 g eE (Mt) daily for up to 2 years	Considerably prolongs survival time of depancreatized dogs In 24/60 human cases Mt failed In 36/60 cases some benefit, insulin reduction –6–28 units 6/60 patients could stop insulin therapy		Even the largest doses (20 g/day) non toxic "possible vitamin nature" of myrtillin no effect on rats and rabbits 21/81 patients excluded from study

Table: (*Continued*)

Author (year)	Patients/animals	Vacc. prep. and dose	Results	Author's conclusions	Remarks
Holcomb (1928)	18 Patients (6 children, 12 adults) 8 "severe" cases, 12 under insulin	Preparation called "myrtomel" given 1–9 months	Reduction of insulin dose in 7/12 patients, stopping of insulin intake in 2/12 patients	Action of Mm in patients without insulin somewhat slower than in patients taking insulin and myrtomel together	References to Allen
Watson (1928)	16 Patients (3 children, aged 16 and 12, 13 adults, aged 23–77), 4 "severe" cases, 13 under insulin	Tablets of 0,3 gE Mm given one hour before a meal	Reduction of insulin dose in 6 cases and reduction in blood glucose levels, in 7 cases increased carbohydrate tolerance	Best results obtained in the milder cases and in middle-aged or elderly patients	Effects of remedy were lost in the presence of even a slight infection
Severinghaus (1928)	Patients	Synthalin, Mm		Synthalin more promising than myrtomel	Case reports on the use of myrtomel not presented
Shpiner (1928)	Dogs: 1. 2 totally pancreatectomized 2. partially pancreatectomized (loss of 19/20) 3. partially pancreatectomized (loss of 7/8) dogs during experimental hyperthyroidism	3–6 tablets of Mt (5 grain per tablet) were given daily to dogs on a daily standard diet	- Mt reduces the hyperglycemia and the glucosuria in totally pancreatectomized dogs, longer survival - no diabetes developed in partially pancreatectomized dogs (1/20 left) - urine sugar free and blood sugar on normal level when Mt is given to partially pancreatectomized (loss of 7/8) dogs during experimental hyperthyroidism		
Rathery / Levina (1928)	Normal and pancreatectomized dogs, 6 patients	eE	In 3 patients reduction of blood glucose and in 2 patients after dose doubling, vanishing of urine glucose	No immediate effect but a certain effect after prolonged use	Diarrhoea was observed as side effect
Dietering (1938)	More than 50 cats and rabbits	Daily oral doses of 0.15–18 g/kg b.w. aE ("Dispert" preparation)	No reduction in blood (!) glucose levels	Therapeutically not useful No success in animal studies	In high doses toxic due to hydroquinone content
Cignarella (1996)	Streptozotocin-diabetic rats	A dried hydroalcoholic extract of the leaf	Plasma glucose levels dropped by about 26% at two different stages of diabetes		Mt may prove potentially useful for treatment of dyslipidaemia associated with impaired TG-rich lipoprotein clearance

aE: aqueous extract; eE: ethanolic extract; Mt: myrt(h)illin; Mm: myrtomel; PMJ: Pilulae Myrtilli Jasper

the berries (!). Today's research concentrates on the effects of anthocyanidins present in the plant (Morazzoni and Bombardelli 1996).

7. Conclusion

From the perspective of the early 20th century, *Vaccinium myrtillus* was among the most promising antidiabetic medicinal plants, as it was one of the most often used hypoglycemic agents of that era. It was intensively studied in the 1920's when Collip's glykokinin hypothesis strongly stimulated the search for plant ingredients with antidiabetic activity. However, results were inconsistent and serious toxicity was discussed. High quality studies from recent times are rare and do not support the use of *Vaccinium* as an antidiabetic agent. However, some activity may be explained by the ability of extracts to inhibit alpha-amylase and to (weakly) activate the human peroxisome proliferator-activated receptor (PPAR) gamma. Nevertheless, in view of toxicological risks, the use of bilberry leaf preparations is not recommended by the German Commission E monographs and in standard textbooks (Frohne 2002). There seems still to be some confusion about the active ingredients of the plant.
It is well known that screening historical knowledge can lead to important information for today's research (Riddle 2002; Buenz et al. 2004). In the case of *Vaccinium myrtillus*, however, historical analyses of the research which went on during the past century most probably do not provide leads for the development of new oral antidiabetic agents.

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