REVIEW

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# *Syzygium cumini* (L.) SKEELS (Myrtaceae) against diabetes – 125 years of research

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*Syzygium cumini* (L.) SKEELS (syn. *S. jambolanum* DC, *Eugenia jambolana* LAM.) belongs to the medicinal plants most often recommended as an adjuvant therapy in type 2 diabetes. The plant was extensively studied during the last 125 years, approximately 100 case reports were reported already before the discovery of insulin. After the Second World War, research was concentrated on animal studies. Not all, but many of them reported some success in reducing type 2 diabetes symptoms. However, a state-of-the-art clinical study is still missing. In this review, historical literature dating back to the pre-insulin era was evaluated as were more recent *in vitro*-, animal-, and *in vivo* studies. Results were screened for information still useful today and compared to study results achieved in more recent decades. In view of the knowledge summarized here, a successful clinical study should use *S. cumini* seeds, seed kernels or fruit from India in fairly high doses. Reductions on blood sugar levels by about 30% seem reasonably to be expected. Adverse effects to be expected comprise gastrointestinal disturbances.

## 1. Introduction

A wide variety of medicinal plants is known to decrease blood glucose levels and several hundred species from all over the world have been identified to do so (Atta-Ur-Rahman and Zaman 1989; Baily and Day 1989; Bnouham et al. 2006; Ivorra et al. 1989; Neuwinger 2004; Zareba et al. 2005; Mukherjee et al. 2006; Grover et al. 2002a). It could recently be shown that *Syzygium cumini* (L.) Skeels (syn. *Syzygium jambolanum DC*, *Eugenia jambolana* Lam., Jambul, Java plum) played an outstanding role among these, particularly in Western Europe in the three decades prior to the discovery of insulin (Helmstädter 2007). While in most other cases there is only anecdotal evidence for antidiabetic properties of traditionally used medicinal plants, *S. cumini* was extensively studied already at the end of the 19th century after it had been imported from the West Indies to Europe. The plant traditionally used in India as an astringent and antidiarrhoeal, but also as an antidiabetic agent was introduced into Western medicine after the British company Thomas Christie's had imported the drug in the 1880s (Christy 1885). It became well known under the name "Jambul". A preliminary British report in 1883, which is exactly 125 years ago, had actually shown reduced urine quantity and sugar content in diabetic patients and was followed by a large amount of investigations done in the 1880's and 1890's including four PhD theses (Henrichs 1891; Villy 1891; Benner 1892; Posthumus 1896). These studies include morphological and phytochemical investigations, animal experiments, human case reports and preliminary clinical studies. A historical analysis shows that the results, despite being somewhat contradictory even led to some careful recommendations made by distinguished experts, including Carl von Noorden (1858–1944) who admitted from 1895 onwards that *Syzygium* might have some beneficial effects on diabetes (Noorden 1895; Merck 1900). Around 1900 Jambul seeds had entered therapeutic and phytotherapeutic standard literature (Martindale and Westcott 1901; Hartwich 1897; Zörnig 1911).

In his PhD thesis Posthumus (1896) extensively reviewed the currently available literature and reported four *in vitro* experiments, four animal studies and about 50 case reports and clinical observations with far more than 100 patients after only ten years of the plant's availability in Europe. This might show the high impact the introduction of this foreign medicinal plant had on diabetes research.

As there is an increasing scientific interest in antidiabetic medicinal plants, it might be useful to summarize those early research results, to compare them with recent studies and to see, which conclusions might be drawn. Therefore, historical literature was screened for somewhat significant case reports and studies in a first step. Thereafter, a literature survey was done to see what has been found about the plant's antidiabetes activity after 1945 up to the present day. It should then be clarified, if recent research might be able to support early suggestions or even explain historical findings. Furthermore, the results should give a clue about the question if further research with this antidiabetic agent seems to be appropriate. Historical and re-

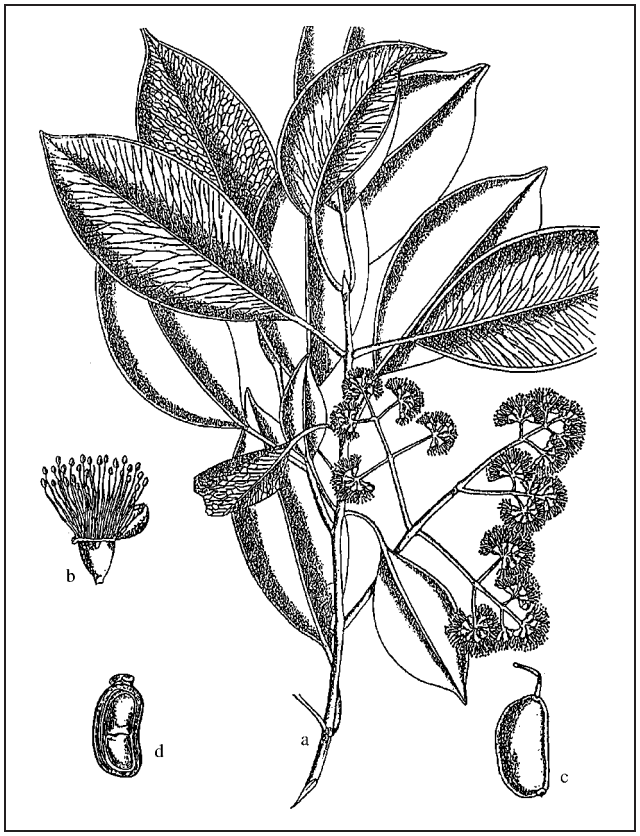


Fig.: *Syzygium cumini* leaves (a), flowers (a, b), and fruits (c, d: longitudinal section) (Basu 1918)

cent studies can be classified in *in vitro*-, animal and human studies, and phytochemical investigations.

## 2. Pre 1945 studies

### *2.1. In vitro studies*

Early *in vitro* studies concentrate on the ability of *Syzygium* preparations to inhibit carbohydrate cleaving enzymes. W. Lascelles-Scott, British colonial analyst, discovered in 1887 that *Syzygium jambolanum* seed powder was able to inhibit the transformation of rice starch into glucose mediated by malt extract in a roughly dose dependent manner. The amount of starch converted into sugar was reduced to approximately 30% by adding 50% of starch weight *Syzygium* seed powder (Jambul) (Christy 1887). Balfour (1889) reported similar results but could not find a strict dose dependency.

A similar study was done by Hildebrandt (1892) using an aqueous extract (1 : 20) of *Syzygium* pericarp. The extract when added to the carbohydrate/enzyme mixture significantly reduced the activity of carbohydrate cleaving enzymes from plants, human saliva and pancreas. The observed phenomenon was even more pronounced after preincubation of the enzyme with *Syzygium* extract. The author already suggested that *Syzygium* pericarp extract could be useful to reduce glucose production from starch and other carbohydrates in diabetic patients. In 1895, experiments carefully performed by Colasanti confirmed the enzyme inhibiting effects of Jambul fruit and bark extract on starch cleaving extracts derived from plants and human saliva (Colosanti 1895). Villy (1891) could not reproduce the results in his investigations but argued that the negative results were due to the bad quality of the seeds he had to use. Colosanti also stated that firstly, seeds harvested in Java seemed to work better than those derived from India and secondly that treatment results in the countries of origin were better than European ones, a fact which also supports Villys hypothesis.

### *2.2. Animal experiments*

Most reports rely on animal experiments done by Graeser at the university of Bonn, Germany, already published in 1889 (Graeser 1889). He induced experimental diabetes in three dogs by administration of 1 g phloridzin/kg body weight. The dogs weighing 2.75–4.57 kg then received up to 18 g *Syzygium* fruit extract a day, which led to a decrease in urine glucose excretion by almost 90% in each case. The dogs received a carbohydrate reduced diet comprised of meat and some milk.

Minkowski (1893) firstly tried *Syzygium* in two pancreatectomized animals and reported the results as an appendix to a large study on diabetes following pancreatectomy. He used two different fluid extracts from *Syzygium* fruits and could not find any benefit. Colasanti (1895) criticized Minkowksis studies as occasional observations and repeated the experiments systematically. He observed a significant decrease in urine sugar content of pancreatectomized dogs having received 3–4 ml *Syzygium* fluid extract per kg body weight. The plant part the extract was derived from was not further specified. When drug treatment was stopped, sugar excretion increased and decreased again after restarting *Syzygium* administration. As an additional result, it was noted that dogs survived longer than without treatment (three vs. two months).

In a research program to explore the value of antidiabetic medicinal plants, Kaufmann (1928) administered *Syzygium* cortex extracts intraveniously to rabbits and guinea pigs. The animals immediately died under convulsions. Surprisingly, the animals suffered from hyperglycemia, most probably due to a release of glycogen from the liver. In cases the injection did not lead to death, initial hyperglycemia was followed by a decrease in blood sugar levels.

### *2.3. Clinical case reports*

Posthumus (1896) summarized approximately 50 case reports and studies done before 1896. They are of different significance but some of them were done with great care, although diagnosis methods were still not very precise. As suitable methods to monitor blood glucose levels had not been developed before 1910 (Schadewaldt 1972), diabetes diagnosis and monitoring relied on urine analysis only. On one hand, the quantity of urine excreted and on the other hand, its sugar content were actually the only monitoring criteria. A rough judgement of the results in retrospective has to take into account type and dose of the *Syzygium* preparation given, age of the patient, concomitant diet (if information is available), and results (amount and sugar content of urine). At the end of the 19$^{th}$ century usually no statistical analysis was made and even studies with several patients were reported as a sequence of case reports, which are not always well documented. Table 1 summarizes such case reports from which relevant results can be deduced. It can clearly seen that results were contradictory but some patients improved significantly under *Syzygium* treatment. While volume or sugar content of urine might not be highly useful criteria for treatment success, it has to be noted that many patients reported improvement subjectively and gained body weight under treatment.

**Table 1: Examples for significant pre-1900 case reports on *Syzygium cumini* against diabetes**

| Author (year) | Patient's, age (years since diagnosis) | *Syzygium* preparation and dose | Effect on urine volume | Effect on glucose excretion | Other important facts/remarks |
|---|---|---|---|---|---|
| Clacius (1885) | 71 (5) | 325 mg seed powder 4×/day | −35–50% | −25% after one week<br>−65% after 3 weeks | |
| | 47 (4) | 325 mg seed powder 4×/day (?) | −approx. 30% | −50% | Improvement in general feeling; reduced frequency of urination |
| | ? | 325 mg seed powder 4×/day | Significantly reduced | | |
| Cauldwell (1886) | 6 patients (not further specified) | 325 mg seed powder 3×/day | −50−−75% after 1 month in 4 cases | | In two out of six cases no effect |
| Saundby (1887) | 8 trials with 5 patients | 325 mg seed powder 3–4×/day | −25% in 1 case | −23% in 1 case after 24 days | In 5 out of 8 trials increase in sugar excretion |
| Quirini (1888) | 5 | Seed powder 250–300 mg; Fluid extract 3 × 10 drops/d | Reduced to normal values within 2 weeks | | |
| Balfour (1889) | 65 | 325 mg seed powder 4×/day | Great variation; no clear trend within 3 weeks | Great variation; no clear trend within 3 weeks | |
| | Same patient | 650 mg seed powder 4×/day | −8% within 10 days | Significant reduction | Other drug charge as above; patient gained some weight. Author overall disappointed |
| | ? (1,5) | 162,5 "in perles" 3×/day | −50% within one week | | Ulcers healed rapidly |
| | 64 | | "decided diminuition" | | Effects most satisfactory |
| | | | | | P. became much better under treatment (despite poor compliance) |
| | 60 | | | | No appreciable effect |
| | 25 | 325 mg "powder" | | | No appreciable effect |
| Mahomed (1888) | 60 | 130 mg "in perles" 3×/day | | "Diminution"; urine completely sugar free after 1 week | Effect reproducible in withdrawal experiment |
| Coates Cole (1888) | 65 (12) | 1 tablet (content unknown) 3–4×/day | | | No improvement whatever |
| Birch (1888) | | up to 325 mg 3×/day | +50% | Always present | |
| Fichtner (1889) | 10 (3 weeks) | 3–4.5 g seeds | No clear trend observable within 5 months | unchanged | Obviously type 1 diabetes |
| | 48 (8 months) | 4.5–6 g | No effect | No effect | Urine gets red colour in the air, red dye isolated |
| Henrichs (1891) | 39 (appr. 1) | 10–35 g seed powder | | | No benefit at all |
| Posner/Epenstein (1891) | 3 patients (not further specified) | 3 × 4–3 × 10 g | −30−−50% | −25−−50% | Significantly reduced peaks in urine sugar content after meals<br>Considerable subjective improvement, weight gain |
| Lewaschew (1891) | 62 (> 5) | 20–30 g seed powder/day | −60% after 3 weeks | −60% after 3 weeks | Considerable weight gain<br>Further 7 patients with same benefit<br>Initially no effect with old and mouldy drug material<br>Successful withdrawal experiment |
| Benner (1892) | 30 (1 month) | 3–5 × 15 ml extract (prep. from powder with 55–70% ethanol); 4 × 1 g powder | | Max −10% | Patient reported subjective improvement |
| | 54 (1) | 2–5 × 15 ml extract | | −20% | Weight gain, initially increased appetite, later uncomfortable feeling with *Syzygium* |
| | 48 (?) | 3 × 15 ml extract 1g powder/hour (!) | | −50% | Weight gain |
| | 53 (4) | 3 × 25 ml 1 g powder/hour (!) | | | No effect |

**Table 1:** (Continued)

| Author (year) | Patient's, age (years since diagnosis) | Syzygium preparation and dose | Effect on urine volume | Effect on glucose excretion | Other important facts/remarks |
|---|---|---|---|---|---|
| Gerlach (1892) | 2 patients | 20–60 g fruit powder | | | Not a considerable improvement |
| Lenné (1892a) | 41 (1) | 30 g fruit powder | | Sugar content even increased | Reduced peaks in urine sugar content |
| Lenné (1892b) | 5 patients | 3 × 10 g fruit powder | | | No improvement (even worse) |
| Graeser (1983) | Several | 30 g seed | −60% | | Rapid reduction of glucosuria induced by oxalic acid |
| Vix (1893) | 56 | 40 g fruit extract | | −100% after 4 days | |
| | Ca. 56 (3) | 45 g bark extract | | −100% after 10 days | |
| Lenné (1894) | 22 (1) | 8 × 15 g fluid bark extract | | | No effect |
| Colasanti (1895) | 27 (1) | 10–100 g/day | −10% | −25–50% | Small weight gain |
| | 61 (1) | | −20% | Max. −20% | Weight gain, subjective improvement<br>Successful withdrawal exp. |
| | 40 (6 months) | | | +10% and more | Weight gain, subjective improvement |
| | 25 (5) | | | −20% | Weight gain, subjective improvement |
| Posthumus (1896) | | 15 g Succus inspissatus Fruct. S.j. | | | No positive results |
| | | 45 g bark fluid extract/day | | −10% | |
| | | 765 g bark extract in 8 days | Reduced | Reduced | |
| | | 615 g bark extract in 8 days | | Significantly reduced | |

Some authors note that sugar excretion could be lowered but never vanished completely (Martindale and Westcott 1901; Lewaschew 1891).

As can be seen from Table 1, doses were usually very high, either in the form of seed powder or in the form of fluid extracts (fruit or bark). Some patients received up to 100 g seed powder a day.

### *2.4. Side effects*

While in general the drug was well tolerated, side effects were reported occasionally with high doses. Gastrointestinal disturbances were reported by several authors and focus on diarrhoea (Benner 1892; Colasanti 1895; Posner and Epenstein 1891; Vix 1893) while obstipation (Colasanti 1895), nausea (Benner 1892; Posthumus 1896; Gerlach 1892) and sickness (Benner 1892; Zörnig 1911; Gerlach 1892) are also mentioned occasionally. A patient expressed the feeling that the drug does not "agree with his stomach" (Balfour 1889). In addition to this, Vix (1893) reported a red discoloration of the urine on the air, which did Fichtner (1889) as well, who was able to isolate a red dye out of the patient's urine. Lenné (1892b, 1894) reported a peculiar weakness in the lower legs, and the drug was found to be incompatible with large amounts of mineral water when taken concomitantly (Merck 1891/92). Balfour (1889) reported a patient with "considerable temporary depression" while taking the drug.

## 3. Post 1945 studies

*Syzygium cumini* has been studied to the present day *in vitro* and *in vivo* and in recent years an increase in research efforts can be observed.

### *3.1. In vitro studies*

*In vitro* experiments were done in view of a potential alpha-amylase inhibiting effect of *Syzygium* extracts. Karthic et al. found porcine pancreatic amylase inhibiting properties of a certain fraction of an aqueous extract made from *S. cumini* seeds, while Kotowaroo et al. (2006) found no activity with a leaf extract. Activity was confirmed by Anadharajan et al. (2006) who found a certain methanolic extract fraction to activate glucose transport in a phosphatidylinositol 3'kinase-dependent fashion in a cell culture model. They also found up-regulation of the glucose transporter Glut-4 and a peroxisome proliferator-activated receptor gamma activation, which did also Rau et al. (2006) with an ethanolic extract. Achrekar et al. (1991) investigated the insulin releasing effect of pulp and seed extracts on isolated Langerhans cells from normal and diabetic rats. They found that the extracts stimulated insulin release but the effect was more pronounced with cells from normoglycemic animals. Pulp and seed extracts significantly inhibited hepatic and renal insulinase activity in a dose-dependent fashion (Achrekar 1991). Aqueous extracts from *Eugenia jambolana* were also shown to inhibit glucose utilization (Khan et al. 2005) as did methanolic extracts. The effect seems to be more prominent in neutral and basic media than in an acidic one (Arayne et al. 2007).

### *3.2. Animal studies*

Although in 1947, Wastl et al. almost ultimately concluded from their studies that "Syzygium Jambolanum cannot be considered of any value in the oral treatment of alloxan diabetes in rats", a literature survey revealed a great number of successful animal studies up to the present day. In-

vestigations were performed in rats, mice and rabbits, being normoglycemic or made diabetic by injection of alloxan or streptozotocin. Characteristics of these studies are summarized in Table 2.

In 1967, French researchers determined toxicity levels of *S. jambolanum* extracts, which were prepared with boiling water and ethanol (95%) and described as having "powerful hypoglycemic activity". The LD50 values for mice were found to be 4 g/kg orally and 0.4 g/kg parenterally (Laboratoires Laroche 1967). Just recently, a commercial product containing powdered aqueous extracts of seven anti-diabetic plant species including *S. jambolanum* was shown to be safe in long-term treatment at a dose of 1600 mg/kg p.o. (Joshi et al. 2007).

### *3.3. Clinical studies*

In contrast to the large amount of animal data, there is a rather limited number of clinical studies done after the second World War. Sepaha and Bose (1956) reported about treatment of 7 NIDDM patients with dried pericarp-free seeds of *Eugenia jambolana*. Three of those patients showed a definite fall in urinary and blood sugar values. This study does not at all meet modern criteria for clinical studies as do not more recent studies done in India and Brazil.

Nande et al. (1981) administered approx. 110 g *E. jambolana* fruit pulp without seeds in seven healthy volunteers and five diabetics. They found a small but significant drop in blood sugar levels after three hours in healthy people but even an – not significant – increase in diabetes patients. Thus, it was concluded that *E. jambolana* fruit pulp is not a suitable anti-diabetes agent.

Srivastava et al. (1983) treated 28, not further specified "severe diabetic patients" with 4 to 24 g *S. cumini* seed powder TDS in gelatine capsules and reported a significant reduction in mean fasting (−18%) and post-prandial (−32%) blood sugar levels. Five patients developed adverse drug reactions, including nausea, diarrhoea, and epigastric pain.

Kohli and Singh (1993) reported a study on 30 patients with "uncomplicated" NIDDM. Patients received 12 g *S. cumini* seed powder in three divided doses for three months. An oral glucose tolerance test was performed every month and subjective parameters were monitored. There was a considerable and progressively increasing relief of symptoms like polyurea, polyphagia, weakness, weight loss and others. Results of the GTT were significantly improved after three months of treatment. One and two hour values were reduced by up to 30% after two months of treatment compared to control. It was concluded that the drug "has definite, moderate hypoglycaemic effect comparable to effect of chlorpropamide". The seed powder did not show any side effects in this study.

Teixeira et al. (2000) submitted 30 non-diabetic young volunteers to a glucose tolerance test with and without concomitant treatment with *S. cumini* leaf (!) extract. The extract did not lead to glucose levels lower than those of the untreated control group. The same researchers investigated the effect of *S. cumini* leaf preparation on type 2 diabetes patients. In a randomized, double-blind clinical study, again, no benefit could be seen (Teixeira 2004). This negative result was confirmed in another double-blind, placebo controlled study on 27 diabetes patients treated with a tea made from *S. cumini* leaves – the preparation was ineffective (Teixeira 2006a).

## 4. Phytochemical research

The dispute about potential efficacy of the plant's preparations was always accompanied by a search for the active ingredient(s). As early as in 1888, Balfour published a first analysis done by Ellborne in Manchester (Balfour 1889; Ellborne 1888). He investigated petroleum ether, ether and alcohol extracts and gave a rough estimation of Jambul seed composition. He found traces of essential oil, a resin soluble in alcohol and ether, gallic acid (1.65%), a coloured extractive soluble in water (2.7%) and a quantity of 83.73% of an "insoluble residue". The author then refers to the proposal of "jambulin", a "very unstable glucoside" having "the power of stopping the diastatic conversion of starch into sugar" (Balfour 1889). Steinmetz (1960) referred to the glucoside as "jamb*o*lin". In 1899, Boersch proposed to have identified this glycoside, which he made responsible for the glucose lowering effects and therefore called it "antimellin". It was said to appear as a yellow crystalline substance (Boersch 1899; N.N. 1899, 1901) and was received from an water/alcohol extract. This compound was said to have the formula $C_{13}H_{18}O_6$, a melting point of 182 °C and reactivity toward alkaloid identifying reagents. Without further proof, it is stated that this compound is also present in the plant's bark (Boersch 1899). It is interesting to note that Merck already stated in 1900 that "antimellin" was six times weaker in reducing the activity of carbohydrate cleaving enzymes than the whole alcoholic extract (Merck 1900) and was unable to reduce sugar excretion in diabetes patients (N.N. 1901). Srivastava et al. still refer to "antimellin" in 1983, despite as early as in 1947, Wastl et al. stated that "no substance of glycosidic nature" could be found in *Syzygium*. French researchers proposed a compound named "jambosin" (Power and Callan 1912) or "jambo*i*sin" (Colasanti 1895). Power and Callan extracted almost 54 kg seed powder with hot alcohol and received approximately 18 kg extract which was further fractionated. At least, the investigators found starch, tannin, a small amount of essential oil, tannic and gallic acid, fatty acids, a phytosterol and a phenolic substance called "jambulol". This compound was said to be a light powder, which could be crystallized and formed derivatives with acetic and benzoic acid. No glycoside could be found (Power and Callan 1912). These results were confirmed by Hart and Heyl (1916) who again independently investigated the composition of jambul seeds. They found among others in different fractions the compounds ellagic acid, gallic acid, phytosterols, mainly phytosterol-d-glucoside, d-phenylglucosazone, and fatty acids. Tannins had already been suggested as constituents of *S. jambolanum* bark in 1891 (Johannson 1891). In recent years, the presence of gallic acid, ellagic acid, derivatives thereof, other tannins and polyphenols was confirmed (Bhatia and Bajaj 1972, 1975). Bhatia et al. (1971) further investigated the tannin content of *Syzygium* seeds and found 35 phenolic compounds in total, including gallic acid and ellagic acid, and corilagin. Currently, the term "jambulol" is used for ellagic acid (Burger and Wachter 1998). Kopanski and Schnelle (1988) isolated bergenin out of *Syzygium* bark in addition the known tannins. Bajpai et al. (2005) point out that *S. cumini* seeds are rich in phenolic compounds and show high antioxidant activity. An alkaloid named "jambosin" was still proposed in 2006 along with a wide variety of carbohydrates, tannins, phytosterols, water soluble and water insoluble fibers, polyphenols, flavonol glycosides and a small amount of essential oil (Sagrawat et al. 2006). In their patent application,

**Table 2: Post 1945 animal studies with *Syzygium cumini* preparations**

| Author | Species | Model | Agent | Blood glucose level | Other observations, remarks |
|---|---|---|---|---|---|
| Wastl et al. (1947) | R | A | Seed powder added to food (2–4% = 2–4 g/kg) Alcoholic extract | Not determined | No significant effect on glucosuria |
| Brahmachari and Augusti (1961) | Rb | N | Ethanolic (95%) and aqueous seed extracts | Reduced | Effect of ethanolic extracts comparable to that of tolbutamide; aq. extract "slight" hypoglycemic acticity |
| Shrotri et al. (1963) | Rb D | A | Aqueous extract of fruits and seeds | −20% with seed extract (Rb and D) | No significant effect with fruit extract |
| Laboratoires Laroche (1967) | M | | Hot water extract Ethanol (95%) extract | "Powerful hypoglycemic acticity" | LD50 (mice) 4 g/kg orally 0.4 g/kg parenterally |
| Sigogneau-Jagodzinski et al. (1967a) | R | A | Seed powder extract (alc/water) fraction 50–250 mg/kg/d up to 32 days p.o. | Highly significant reduction in severe diabetes and high doses | No rise in glucose levels after glucose ingestion in treated animals Significant reduced quantity of animals water ingestion Initial transient hyperglycemia |
| Sigogneau-Jagodzinski et al. (1967b) | R | N | Seed powder extract (alc/water) buc., i.p. (1–500 mg/kg) | Dose dependent reduction up to −50% compared to control | No effect after a single buc. dose Effects not as pronounced as with diabetic animals |
| Sigogneau-Jagodzinski et al. (1968) | R | N | Seed powder extract dissolved/suspended in drinking water | Reduced compared to control after glucose load (−10−−30%) | Reduction of water uptake Limited action in normoglycemic animals Analogous action to sulfonylurea agents suggested |
| Chirvan-Nia et al. (1972) | Po | V | Eugenia jambolana (Syzygium cumini) extract (not further specified) | Reduction (−60−−70%) | Reduced cataract symptoms of diabetic rats No glucosuria in treated animals |
| Ratsimamanga et al. (1972) | R | N | Eugenia jambolana bark extract adm. via gastric tube 10 mg/100 g rat | Reduced hyperglycemia after glucose load | Effect comparable to that of sulfonylureas and biguanides |
| Ratsimamanga et al. (1973) | Rb | N | Ethanolic bark extract 10 g/kg | Reduced hyperglycemia after glucose load Delayed blood glucose peak | Results comparable to those received with the sulfonylurea derivative glybutamide 16.5 mg/kg |
| Bansal et al. (1981) | R | N | Aqueous suspension of seed powder 170–510 mg/rat | −50% | Effect comparable to that of chlorpropamide Up to 6-fold increase in pancreatic cathepsin B activity |
| Kedar and Chakrabarti (1983) | Rb | S | Seed powder 1 g/kg | Reduction to near normal values | Slight increase in body weight Slight rise in liver glycogen No rise in muscle glycogen Significant reduction in serum cholesterol and triglycerides Effect comparable to that of phenformin (except for creatinine levels) |
| Bhaskaran Nair and Santhakumari (1986) | Rb | N | Dried seed kernels, powder suspended in water 1, 2, 4, 6 g/kg | Reduction by 42.4% (dose optimum 4 g/kg) Improved glucose tolerance | Effect comparable to tolbutamide and phenformin, but later onset and shorter duration of action Effects quicker than with whole seeds |
| | R | A | Dried seed kernels, powder suspended in water 1, 2, 4, 6 g/kg | Significant decrease (3 h:−ca. 20%) | |
| Achrekar et al. (1991) | R | N | Aqueous pulp extract Aqueous seed extract Orally administered | Pulp: −23% (30 min) −40% (5 days) Seed: −5% (30 min) −37% (5 days) | Pulp extract obviously acts faster No influence on hepatic glycogen Insulin levels increased by 10–40% Dramatic rise in cathepsin B activity |
| | R | S | Aqueous pulp extract Aqueous seed extract Orally administered | Pulp: −68% Seed: −76% | Effect exceeds that of chlorpropamide Good recovery from decreased liver glycogen levels Reduced degree of hepatic hyperlipidemia under treatment (+10 vs. +40%) |

**Table 2:** (Continued)

| Author | Species | Model | Agent | Blood glucose level | Other observations, remarks |
|---|---|---|---|---|---|
| Ratsimamanga et al. (1996) | M<br>N | S<br>N | Alcoholic seed extract<br>fraction<br>Isolated compounds therefrom | S: Up to −50%<br>N (post-prand. hyperglycemia): up to −30% | Remarkably low toxicity<br>Fractions and compounds are said not to increase insulin secretion, but need some insulin to be effective |
| Teixeira et al. (1997) | R | N | Aqueous leaf extract (tea) 2–32 g/l<br>Aqueous seed extract (tea) 64 g/l | No effect | |
| | R | S | Aqueous leaf extract (tea) 8–32 g/l | No effect | |
| Prince et al. (1998) | R | A | Aqueous seed extract (100 g/200 ml water × 3) 2.5/5/7.5 g extract/kg | 2 and 5 g/kg lead to almost normoglycemic state | Effect comparable to that of glibenclamide<br>Reduction of TBARS, GSH, SOD, CAT to near normal values<br>Sign. reduced glucosuria<br>Weight loss reversed in treated animals<br>No effect with higher dose (7.5 g, reason not discussed) |
| Mendes Soares (2000) | R | A | Aqueous extract | "efficient in the control of hyperglycemia" | |
| Grover et al. (2000) | R<br>M | A | Lyophilized aqueous seed extract (LASE)<br>Alcoholic extract | Mild diabetes −73%<br>Moderate d.: −65%<br>Severe d.: −18% | Effective dose 200 mg/kg LASE<br>Proposed effects: increased insulin release from β-cells, insulinomimetic effect<br>Improvement in hepatic and skeletal muscle (but not renal) glycogen content<br>Delayed onset of action<br>Combines mechanism of sulfonylureas and biguanides |
| Pepato et al. (2001) | R | S | Aqueous leaf extract | No activity | |
| Vikrant et al. (2001) | R | F | Lyophilized aqueous seed extract 400 mg/d | Dose prevented hyperglycemia and hyperinsulinemia | Alcoholic extract did not |
| Grover et al. (2001) | M | S | Lyophilized aqueous seed extract 200 mg/d | −20% | No effect on body weight<br>Reduced urine volume<br>Reduced urinary albumin levels<br>Not significant reduction in renal hypertrophy<br>No effect on plasma creatinine |
| Pandey and Khan (2002) | R | N<br>A | Seed powder | Significantly lowered | Effect induced by water soluble gummy fibre |
| Rathi et al. (2002) | R | A | Lyophilized aqueous seed extract<br>Ethanolic extract | −60% after 4 months | |
| Grover et al. (2002b) | M | S | Extract 200 mg/kg | −20% | Positive influence on tail flick latency and gastric transit percentage |
| Stanely Mainzen Prince et al. (2003) | R | A | Aqueous seed extract 5 g/kg<br>Ethanolic seed extract 100 mg/kg | | Decrease in lipids, TBARS, increase in CAT and SOD in rat brain<br>Effects exceed those of glibenclamide<br>Effects of ethanolic extract exceed those of aqueous extracts |
| Sharma et al. (2003) | Rb | A | Ethanolic extract (100 mg/kg) | up to −30% | −25% $HbA_{1c}$ after 15 days<br>Serum insulin +30%<br>Increase in liver and muscle glycogen content<br>Hypolipidemic activity |
| Kar et al. (2003) | R | A | Ethanolic extract (250 mg/kg) | Reduction down to near normal values | |
| Ravi et al. (2004a) | R | S | Ash of seeds | Reduction to near normal values | Reduction of $HbA_1$ to near normal values<br>Effect ascribed to trace elements contained |

**Table 2:** (Continued)

| Author | Species | Model | Agent | Blood glucose level | Other observations, remarks |
|---|---|---|---|---|---|
| Ravi at al. (2004b) | R | S | Ethanolic extract of defatted seed kernel powder kernel (100 mg/kg) | Extract: Significant decrease<br>Whole seed: moderate effect, seed coat: no effect | Significant decrease in cholesterol, blood urea, cholesterol, increase in glucose tolerance, liver glycogen |
| Prince et al. (2004) | R | A | Alcoholic extract 100 mg/kg | Significant reduction | Significant reduction in serum and tissue lipid levels<br>Effect similar to that of insulin |
| Ravi et al. (2004c) | R | S | Ethanolic extract of defatted seed kernel powder kernel | | Extract reverted antioxidant enzymes to near normal levels<br>Extract protects pancreatic beta cells<br>Enzyme decreases oxidative stress |
| Ravi et al. (2004d) | R | S | Ethanolic extract of defatted seed kernel powder kernel | Reduction comparable to glibenclamide | $HbA_{1c}$ reduced, extent comparable to glibenclamide<br>TBARS and hydroperoxides reduced<br>Stimulation of insulin release from beta-cells proposed<br>Extract improved body weight |
| Babu et al. (2004) | R | S | Hyponidd 100 and 200 mg/kg containing 10 plant extracts) | Significantly lowered | Antioxidant activity<br>200 mg/kg more effective than glibenclamide |
| Oliveira et al. (2005) | M | N<br>S | Aqueus extract, ethanolic extract, butanolic fraction from leaves 200–2000 mg/kg | Reduction in glycemia after 7 days (N)<br>No other pos. results | |
| Sridhar et al. (2005) | R | S | Seed powder 250–1000 g/kg | Up to −50% (fasting and peak after GTT) | Increased body weight<br>Reduced fluid intake<br>Increase in liver glycogen<br>Glucose lowering effect comparable to that of glibenclamide<br>Increased insulin levels proposed<br>No signs of toxicity observed |
| Pepato et al. (2005) | R | S | Lyophilized fruit-pulp extract 50 mg/d | No effect | Lack of any apparent effect |
| Mutalik et al. (2005) | M | N<br>S | Dianex, cont. 8 aqueous extracts incl. *S. cumini* 500 mg/kg | N: −38% (500 mg, 6 h)<br>−30% (6 weeks)<br>S: −35% | Most effects comparable to those of glibenclamide<br>Increase in body weight, liver glycogen, liver protein content<br>Radical scavenging activity observed |
| Sharma et al. (2006) | Rb | A | Fractions from aqueous and ethanolic fruit-pulp extracts (25 mg/kg/d) | −20−−40% | Water extract more effective than ethanolic extract<br>Increase in plasma insulin levels<br>Insulin release from β-cells 2.5 times that of untreated animals |
| Villasenor and Lamadrid (2006) | M | | Dried bark 5 mg/20 g mouse | Significant decrease in glucose levels after GTT | |
| Mallick et al. (2007) | R | S | MTEC, cont. 4 aqueous methanol. extracts incl. *S. cumini* 120 mg/d | Fasting blood gluc. levels reduced to almost normal values after 2 weeks | Positive effects of fertility in diabetic rats |

R: Wistar rats, M: mice, Rb: rabbits, D: dogs Po: spontaneously diabetic desert rats Psammomys obesus A: alloxan induced diabetes, S: streptozotocin induced diabetes, N: normoglycemic animals; V: vegetable diet, F: fructose diet induced hyperinsulinemia and insulin resistance
p.o.: oral administration, i.p.: intraperitoneal administration, buc.: buccal administration
TBARS: Thiobarbituric acid reactive substances; GSH: Glutathione; SOD: superoxide dismutase, CAT: Catalase, GTT: Glucose tolerance test

Ratsimamanga et al. (1996) propose – besides a polyphenol-sterol complex – sodium oxamate, and the compounds 2-(tetrahydroxybutyl)-5-(2′,3′,4′-trihydroxybutyl)-pyrazin and 2-(tetrahydroxybutyl)-6-(2′,3′,4′-trihydroxybutyl)-pyrazin, and 2,5-di(tetrahydroxybutyl) pyrazin. These compounds proved to be highly active in reducing blood glucose in diabetic mice while showing little toxicity (LD50 in mice: >2000 mg/kg).

## 5. Proposed mechanisms of action

Early and recent studies not only investigated reduction in blood glucose levels but recorded other parameters, which give some hints on mechanisms of action. Thus, stimulation of insulin from remaining beta cells (Grover et al. 2000; Ravi et al. 2004d; Sridhar et al. 2005; Sharma et al. 2006) was suggested as well as reduced oxidative stress

(Prince and Menon 1998; Stanely Mainzen Prince et al. 2003; Kar et al. 2003; Ravi et al. 2004c). Some studies report an increased glycogen content in liver and muscle cells (Achrekar et al. 1991; Grover et al. 2000; Sharma et al. 2003; Ravi et al. 2003). In several studies, effects were comparable to those of sulfonylurea and biguanide derivatives (Ratismamanga et al. 1972, 1973; Kedar and Chakrabarti 1983; Prince et al. 1998; Babu and Stanely Mainzen Prince 2004; Sridhar et al. 2005; Mutalik et al. 2005).

*In vitro* investigations suggest some other mechanisms of action, including inhibition of carbohydrate cleaving enzymes (Christy 1887; Hildebrandt 1892; Colasanti 1895; Khartic et al.), which again could not be seen with a preparation made from leaves (Kotowaroo et al. 2006). Other mechanisms proposed include inhibition of the human peroxisome proliferator-activated receptor gamma (Rau et al. 2006), up-regulation of the glucose transporter Glut-4 (Anantharajan et al. 2006), rise in cathepsin-B activity (Bansal et al. 1981; Achrekar et al. 1991) and inhibition of insulinase in liver and kidney, or even the development of insulin positive cells from the pancreatic duct epithelial cells (Schossler et al. 2004).

## 6. Conclusions

In summary, it can be stated that *S. cumini* has been investigated to a considerable amount during the past 125 years – the drug has always been a subject of research at least since it has been introduced in Europe in the 1880s. In recent years, even increasing interest is obvious. While in the beginning, particularly before the discovery of insulin, clinical case reports were the predominant subject of publications (Table 1), after the second World War animal studies were in the focus of research. Overall, there is convincing evidence that parts of *S. cumini* have antihyperglycemic properties which has mainly been confirmed in a large amount of animal studies. Comparative studies show that in some models, drug preparations were equivalent to widely used oral antidiabetic agents. In contrast to that, clinical studies done so far are insufficient to judge the actual value of *S. cumini* in adjuvant diabetes therapy. Most clinical data seem not to be much more reliable than pre-1900 case reports.

Thus, no animal experiments are needed anymore and it is now time for a large scale clinical study meeting the criteria of evidence based medicine. *In vitro* studies may contribute to a better understanding of the drug's mechanisms of action. In design and subsequent interpretation of such a study, as much as possible information should be taken into account and even information from historical case reports summarized here might be useful to some extent.

Firstly, it can be concluded from patient characteristics, that patients treated successfully most probably suffered from type 2 diabetes and that *S. cumini* application more often than occasionally led to improvement of diabetes symptoms, although urine volume and sugar content, main endpoints of pre-1945 studies can only give a rough estimate of the drug's clinical effect. Those criteria are influenced by several other effects and in general, disappearance of glucose in urine – which was rarely achieved (Martindale and Westcott 1901) – only shows that blood sugar levels are no longer above approximately 180 mg/dl, which is still insufficient. Nevertheless, patients usually showed an improvement in subjective parameters – most patients under treatment tended to gain weight and felt better in general – or give other hints on effectiveness like improved healing of leg ulcers (Balfour 1889).

Concerning the negative results reported in early case reports, it should be kept in mind that some of them were published by A. Lenné, who was leading physician in the German spa town of Bad Neuenahr. Neuenahr water was among the most recommended treatment methods that time (Helmstädter 2007) and he might be biased by the fact that promoting a phytomedical treatment would have been prevented patients from visiting the spa and drinking the water. Objective reasons for negative or contradictory results may have been insufficient quality of the drug (Colasanti 1895; Lewaschew 1891; Graeser 1893) or even uncertainty about its true botanical nature. Already in the 1880s it was stated that what was commonly called "Jambul" was derived from different plant species (Quirini 1888; N.N. 1890). Species potentially to be confused with *S. cumini* include *S. jambos* (L.) Alst. (syn. *Eugenia jambosa*, *Jambosa vulgaris* DC).

Concerning the choice of the active agents and their dose it has to be stated that most successful studies used fruits or seed powder or seed kernels in rather high doses for some weeks. Some positive results were achieved with a total of about 1.2 g/day (Christy 1887; Balfour 1889), others used 20–30 g (Posner and Epenstein 1891; Lewaschew 1891) or even up to 100 g seed powder a day (Colasanti 1895). Extracts of *S. cumini* fruit or bark were also used successfully in some cases, extract doses of more than 40 g/day were given (Posthumus 1896; Vix 1893). There are no historical reports on *Syzygium* leaves at all, and in view of this it might be somewhat surprising that the only high standard clinical trials so far have been done with leaf extract. Not unexpectedly from the historian's point of view, no effect was seen with leaf extracts obviously used in traditional South American medicine (Teixeira et al. 2000, 2004, 2006a). Authors of these studies argue in view of their negative results, ethnopharmacological habits should form the basis for clinical studies (Teixeira et al. 2006b), in this case the use of *S. cumini* leaves in their own country, but did not recognize the worldwide historical knowledge pointing into another direction.

The more than 100 early case reports can also give some hints about potential adverse effects to be looked upon in a future large scale study. Adverse effects of the treatment were obviously rare and concentrated on the digestive tract. Diarrhoea – despite the drug has been recommended as antidiarrhoeal as well (Mukherjee 1998) –, nausea and sickness might be a result of the large amount of extract or powder ingested. An initial hyperglycemia observed shortly after ingestion of the drug (Sigogneau-Jagodzinski et al. 1967a), is certainly due to the carbohydrate content of the seeds and their aqueous extracts and may have been the reason for some negative results in short term studies. Reports on urine discoloration, depression, and a peculiar feeling of weakness should also be kept in mind observing patients in a clinical study. The reported incompatibility with mineral waters might have been part of Lenné's spa promoting strategy.

Animal experiments reported in almost 40 publications after the second World War (Table 2) clearly confirm antihyperglycemic effects of the drug, fasting and postprandial blood glucose levels were typically reduced by about 30%. Most successful studies used *S. cumini* seed powder or more often an aqueous or alcoholic extract thereof. Typical extract doses were 100–200 mg/kg animal (rat, mouse, rabbit) corresponding well with the dose levels given in early case reports.

In view of these findings from 125 years of research, a state-of-the-art clinical trial in type 2 diabetics seems ap-

propriate as has recently been recommended (Elfahmi 2006). The study results summarized here might help in actually designing such a study, which should certainly be done in type-2-diabetes patients with fairly high doses of a carbohydrate free aqueous/ethanolic extract of fresh fruits, seeds or seed kernels (for example prepared as described by Ravi et al. 2004b-d) from Indian origin in comparison to placebo or standard oral antidiabetic therapy.

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