6/2006
Volume 27

Journal of
Phytotherapy

Research

Hintonia latiflora with Type 2 Diabetes

Long-term clinical study

Marta Korecova
Marie Hladícova
Rudolf Korec*

Reprint **Hippokrates**

Hintonia latiflora with Type 2 Diabetes

Long-term clinical study

Marta Korecova, Marie Hladícova, Rudolf Korec*

SUMMARY

***Hintonia latiflora* in patients with type 2 diabetes: A long-term study**

The antidiabetic efficacy and safety of an extract from *Hintonia latiflora* (drug-extract ratio 1:4.5, extraction solvent 32% ethanol) was tested in a monocenter open, uncontrolled study on 30 patients with type 2 diabetes. Patients were adjusted to a stable diet at least two months prior to therapy and during the entire duration of the study in order to rule out a dietary impact on the study outcome. After 12 months of treatment, fasting blood glucose was reduced by 20.6%, postprandial glucose by 19% and the mean HbA_{1c} by 10.3% ($p < 0.001$). In the patients remaining in the study, these parameters were stable thereafter (up to 33 months of treatment). There were no hypoglycemic episodes or adverse events throughout the entire treatment period.

Keywords

Hintonia latiflora, Rubiaceae, herbal antidiabetic drug, type 2 diabetes, long-term efficacy, safety, HbA_{1c}

Manifest type 2 diabetes mellitus requires a long-term treatment via dietary measures and in the course of development also oral antidiabetic drugs or insulin. Accordingly with the risk–benefit assessment of antidiabetic preparations, not only long-term effects but also the safety of use and tolerance must be taken into account (11). One known undesirable effect of oral antidiabetics is the over-regulation of the blood sugar in the direction of an intermittent hypoglycemia. Correspondingly, the treatment with antidiabetics should also aim at reducing hypoglycemic episodes (8).

Compared with pure substance preparations, preparations from medicinal plants with an antidiabetic effect seem to have an advantage here that can possibly be attributed to the active substance complex and therefore to the interaction of several components. Thus it was observed decades ago with extracts of the bark of the Central American plant *Hintonia latiflora* (Rubiaceae) that they effectively lower parameters of the blood glucose balance without causing hypoglycemic episodes (12, 20, 21). Using *Hintonia latiflora* extract, the dose of antidiabetic drugs could be reduced or completely discontinued (13, 14). Antidiabetic effects and the absence of hypoglycemic reactions were verified in vivo in pharmacological experiments in various animal species (2, 9, 15, 16, 18). Recently the neoflavonoid coutareagenin isolated from the bark of *Hintonia latiflora* was identified in the model of streptozotocin-induced diabetes in rats as one of the antidiabetic active substances of the

* Dedicated in memory of Prof. Rudolf Korec MD (diseased on 23 February 2003) whose advice and experience in the planning made it possible to carry out this study.

herbal drug (10). A recently published study on the closely related species *Hintonia standleyana* confirmed the antidiabetic effects of the neoflavonoids in the same pharmacological model (6).

Until now knowledge of the clinical applicability of extracts from *Hintonia latiflora* came from clinical observation studies and case histories (12, 13, 14, 20, 21). Below we report on a clinical long-term study on the efficacy and safety of an aqueous-alcoholic preparation from the bark of *Hintonia latiflora* in patients with type 2 diabetes.

Methods

Study design

The study takes account of the principles of the Declaration of Helsinki/Somerset West and the ICH-GCP guidelines (CMPH/ICH/135/95) as well as the relevant formal and legal requirements on the conduct of clinical studies. A signed informed consent form from the study participants is available, An approving vote of the responsible ethics committee and an approval of the Slovakian State Institute for Drug Control (SUKI) were obtained.
The study was designed as an open, monocentric long-term study in patients with type 2 diabetes mellitus. It began on 17 June 2002 with the inclusion of the first patient and ended on 21 June 2005 with the last visit of the last patient.

The study was carried out open (i.e. unblinded) because as a consequence of the United Kingdom Prospective Diabetes Study (UKPDS), the ethics committee regarded a placebo-controlled study as not ethically justifiable. Since only patients were to be admitted for whom the previous diet as the sole measure was not quite sufficient but until now were not additionally stabilized on oral antidiabetics or insulin, a control group under such a medication was not accepted. A stabilization of previously untreated diabetics on a medical treatment without the previous exhaustion of dietary measures was regarded as unacceptable. Accordingly an open design was selected, particularly since objective parameters of blood sugar control were measured and continuously recorded. Since with the long-term treatment of diabetes mellitus the exceptional situation exists that laboratory values objectivize the blood sugar lowering effect, a placebo effect with long-term treatment can be ruled out.

Test preparation investigated

An aqueous-ethanolic preparation from the bark of the Central American plant *Hintonia latiflora* (SESSÉ & MOC. ex DC.) BULLOCK (Rubiaceae) with a drug-extract ratio of 1:4.5 (extractive substance 32% ethanol) was used. The bark has been collected for more than 15 years in a defined area in Guatemala by trained collectors. On-site audits and training sessions for collection and harvesting were carried out by the extract producer. The preparation used corresponds to the German commercial preparation Sucontral® (Harras Pharma Curarina, Munich). In accordance with the intake recommendation, the patients took 2 ml 3 times daily before meals.

Inclusion and exclusion criteria

Since the study took place at a diabetes center, the dietary control and monitoring as well as the treatment were carried out by the same clinician. For recruiting, only patients for whom a stabilization on insulin or oral antidiabetics was not yet indicated came into question. Patients with a history of an existing diabetes mellitus for a least one year had to show, under the

supervision of a diabetologist, stable values under a stringent diabetes diet for at least two months. Inclusion in the study was only permitted then if the patients were stabilized with this diet (and accordingly a change in the HbA_{1c} value had not occurred between two follow-up examinations) and on the other hand, the stabilization achieved by the diet was not sufficient to induce a largely normoglycemic situation. At the time of inclusion in the study, the values for fasting blood glucose had to be within the range from 7-14 mmol/l (standard value: 3.9-5.4 mmol/l). The HbA_{1c} value could not be higher than 12% (standard value: 4.4-6.4%).

To exclude dietetic influence factors on the blood sugar values considering the planned up to three-year treatment with the *Hintonia* extract, it was necessary to select patients with a sufficient degree of reliability with regard to maintaining the dietary measures because the dietary pretreatment had to be continued during the treatment phase. Patients who were not willing to follow the dietary guidelines for the duration of the study were not admitted to the study or were excluded for not following them. Among the guidelines was also the prohibition of consuming alcohol during the entire course of the study. Alcohol consumptions led to exclusion.

Other exclusion criteria were progressive life-threatening diseases, elevations of GOT, ɣ -GT and AP to more than twice the normal value, serum creatinine > 130 µmol/l, hypoglycemic crises not noticed in time, pregnancy, malignant tumors and hematological diseases and/or drug or alcohol dependence in the history.

Oral antidiabetics and insulin were only permitted in emergencies; their use led to termination of the study.

Study duration and course

The total duration of the study was 36 months. Patients were recruited from June 2002 to January 2005. All of the patients admitted to the study were monitored and regularly examined until they left the study or until the end of the official study duration (depending on which event came first). At the time of the official end of the study (June 2005), 10 patients were still being treated and the maximum individual treatment duration was 33 months. During the first 6 months of treatment, monthly examinations took place, and afterwards control examinations every 3 months.

Blood glucose (fasting, 2 h postprandial), blood pressure and body mass index (BMI) were determined at each control examination. The primary efficacy criterion HbA_{1c}, the liver values (GOT, AP and GGT), total cholesterol, HDL cholesterol and triglycerides were determined every three months. Additionally, at each control examination patients were questioned about the occurrence of diabetic symptoms like neuropathies, paresthesias, constipation and sweating as well as compliance with the dietary instructions.

Biometric analysis

The number of patients to be included was oriented to the capacity of the study center: the aim was the documentation of the course of treatment for at least 10 patients over a period of at least 12 months. Of the 30 patients recruited, 11 achieved a treatment duration of at least 12 months.

The test hypothesis for the confirmatory analysis was the hypothesis of a significant reduction of the HbA_{1c} value between the 6^{th} and 18^{th} month of test medication administration compared with the starting value. The null hypothesis was tested.

For the evaluation of statistical differences, the ANOVA test for repeated measurements (pairwise comparisons from baseline versus T6, T12 and T18) was used. According to the study protocol, a significance level of $\alpha = 0.05$ was specified for the rejection of the null hypothesis for the measurements after 6-18 months of treatment. The confirmatory testing at times T6, T12 and T18 required an adjustment of the significance level with the use of repeated ANOVA tests. Based on the Bonferroni correction, a level of significance of $p = 0.05/3 = 0.0166$ is calculated. The average reductions of HbA_{1c}, fasting blood sugar and postprandial blood sugar were calculated for each visit from the paired data T_0-T_x of the individual patients. SPSS v.10.0 was used as the statistical program.

Results

The demographic data of the patients are presented in **Table 1**. The great prominence of female study participants is a manifestation of the well-known problem of a clearly lower dietary compliance in men and particularly the clearly more frequent alcohol consumption in men.

Table 1: Demographic and anamnestic patient data

No. of patients	**n = 30 (100%)**
Female	**n = 28**
Male	**n = 2**
Age	**59.6 ± 8.7 years**
Age range	**41 – 79 years**
History:	
Arterial hypertension	**n = 16 (53.4%)**
Hyperlipidemia	**n = 7 (23.3%)**
Heart disease	**n = 4 (13.3%)**
Neurological disease	**n = 2 (6.7%)**
Thyroid disease	**n = 1 (3.3%)**

The run-in phase under diet for attaining stable starting values was variably long for the individual patients and was up to 19 months (on average 7.4 ± 5.1 months). Since the intake duration of the study medication varied for the individual patients (continuation of the treatment until dropping out of the study or the official study end), the number of treated patients for the different examination points also varied (**Table 2** and **Table 3**). For five patients, the values for 21 and 24 months are available, and for two patients data for 27, 30 and 33 months.

Table 2: Individual therapeutic results (HbA_{1c}) and reasons for withdrawal from the study

Patient No.	Starting value	Treatment duration (months)	Value at T12	Last value	Change compared with initial value at T12 in %	Reason for ending the participation
1	7.9	33		7.0	-11.4	Reaching the time of the official study end
2	-					Dropout due to impermissible use of metformin
3	7.4	18	7.0	6.5	-5.4	Unknown
4	6.8	33	6.1	6.0	-10.3	Reaching the time of the official study end
5	8.3	15	7.3	7.2	-12.1	Patient wish (stay abroad)
6	7.9	6		7.2	-8.9	Excluded by physician for non-compliance with the dietary guidelines
7	7.9	24	6.9	6.6	-12.7	Reaching the time of the official study end
8	8.5	24	7.6	7.8	-10.6	Reaching the time of the official study end
9	7.3	24	6.4	6.1	-12.3	Reaching the time of the official study end
10	7.5	9		6.1	-18.7	Poor compliance, changed over to oral antidiabetic agent
11	7.9	1				Consent withdrawn due to dietary restrictions
12	7.6	3		7.3	-4.0	Consent withdrawn due to dietary restrictions
13	7.8	12	6.9	6.9	-11.5	Consent withdrawn due to dietary restrictions
14	7.7	18	7.2	7.0	-6.5	Reaching the time of the official study end
15	7.5	9		6.8	-9.3	Consent withdrawn due to dietary restrictions
16	7.4	3		7.3	-1.4	Infection, changeover to insulin
17	10.7	9		8.0	-25.2	Excluded by physician for non-compliance with the dietary guidelines
18	7.8	9		6.9	-11.5	Reaching the time of the official study end
19	7.8	12	6.7	6.7	-14.1	Reaching the time of the official study end
20	7.3	6		6.7	-8.2	Consent withdrawn due to dietary restrictions
21	7.1	12	6.5	6.5	-8.5	Reaching the time of the official study end
22	7.1	1				Consent withdrawn due to dietary restrictions
23	7.8	9		7.0	-10.3	Reaching the time of the official study end
24	7.1	3		6.5	-8.5	Consent withdrawn due to dietary restrictions
25	7.2	3		7.1	-1.4	Excluded by physician for non-compliance with the dietary guidelines
26	7.7	1				Consent withdrawn due to dietary restrictions
27	6.9	1				Consent withdrawn due to dietary restrictions
28	7.1	6		6.2	-12.7	Reaching the time of the official study end
29	7.4	6		7.1	-4.1	Reaching the time of the official study end
30	8.8	1				Consent withdrawn due to dietary restrictions

Table 3: Individual therapeutic results (fasting glucose/postprandial glucose)

Patient No.	Starting value fasting/ postprandial	Treatment duration (months)	Value at T12	Last value	Change compared with initial value at T12 in %
1	8.4/10.6	33	5.7/8.4	7.1/9.2	-32.1/-20.8
3	7.4/10.3	18	6.2/8.1	4.9/8.2	-16.2/-21.4
4	7.3/9.0	33	6.6/9.9	5.8/8.1	-9.6/+10.0
5	9.7/12.4	15	6.0/6.7	5.8/8.1	-38.1/-46.0
6	8.2/10.4	6		5.7/8.4	-30.5/-19.2
7	6.6/9.8	24	6.2/8.3	5.9/8.1	-6.1/-15.3
8	9.4/11.7	24	6.3/9.9	7.8/9.9	-33.0/-15.4
9	6.8/9.8	24	5.7/8.8	5.7/7.7	-16.2/-10.2
10	7.1/9.4	9		5.9/7.4	-16.9/-21.3
11	7.3/10.6	2		6.0/8.8	-17.8/-17.0
12	8.9/10.3	3		5.7/8.8	-36.0/-14.6
13	7.3/11.2	12	6.7/10.1	6.7/10.1	-8.2/-9.8
14	8.1/10.9	18	6.1/7.9	6.3/7.8	-24.7/-27.5
15	7.2/9.2	9		6.4/7.8	-11.1/-15.2
16	8.2/10.9	3		6.6/8.4	-19.5/-22.9
17	10.2/13.7	9		6.7/9.8	-34.3/-28.5
18	9.6/12.6	9		6.1/8.5	-36.5/-32.5
19	7.1/12.4	12	5.9/9.1	5.9/9.1	-19.9/-26.1
20	7.1/9.8	6		4.9/7.3	-31.0/-25.5
21	7.9/10.1	12		5.9/7.5	-25.3/-25.7
22	7.3/10.0	1		6.0/8.1	-17.8/-19.0
23	8.8/10.7	9		5.1/7.8	-42.1/-27.1
24	7.3/8.8	3		5.2/8.0	-28.8/-9.1
25	6.2/8.9	3		6.3/7.9	+1.6/-11.2
26	7.3/10.1	1		6.9/9.4	-5.5/-6.9
27	6.6/8.4	1		6.1/7.8	-7.6/-7.1
28	7.9/10.4	6		5.9/7.7	-25.3/-26.0
29	10.7/12.9	6		6.7/8.0	-37.4/-38.0
30	8.5/10.1	1		6.8/7.9	-20.0/-21.8

Reasons for study discontinuations

Thirty patients were admitted to the study. In one case (No. 2), the study was terminated before the ingestion of the study medication by the attending physician because the taking of an oral antidiabetic became known shortly after inclusion. Four patients (No. 22, 26, 27 and 30) withdrew from the study already after one month and one patient (No. 11) after two months because they couldn't or didn't want to follow the dietetic guidelines of the study. For these patients, only blood sugar values from the visit after one month are available, but no HbA_{1c} value after the initial value.

Overall therefore, HbA_{1c} data beyond the time of the initial examination are available for 24 patients; of these 11 patients have measurement data beyond the observation period of 12 months.

In 12 cases, study participation was terminated as a result of reaching the date defined as the study end (No. 1, 4, 7, 8, 9, 14, 18, 19, 21, 23, 28 and 29). Only one of these patients (No. 28) started treatment with an oral antidiabetic at his own request after the end of study even though in this case a very good reduction of the HbA_{1c} was observed. In one case (No. 5), the study was discontinued at the request of the patient due to an upcoming stay abroad and in five cases, the patients wished to end their participation because they found the dietary

measures too burdensome (No. 12, 13, 15, 20 and 24). In all cases, the patients had responded to the treatment. Three further patients were excluded during the course of the study by the attending physician due to noncompliance with the diet (e.g. alcohol consumption) and/or irregular taking of the study medication (No. 6, 17 and 25). One patient (No. 16) had to be changed over to insulin during the treatment of an infection (no causal connection with the study medication) and was therefore excluded.

Primary efficacy parameter: HbA_{1c}

At the start of treatment with the *Hintonia* extract, the HbA_{1c} value was 7.69 ± 0.74%. The maximum was 10.7%. It had already significantly decreased ($p > 0.05$) after three months. After 6, 12 and 18 months of treatment, a reduction of the mean HbA_{1c} of 10.4%, 10.3% and 12.4% respectively compared with the starting value was achieved (absolute values: -0.76, -0.82 and -1.04 (**Fig. 1**). In the patients that continued the treatment further, a further decrease occurred. The difference from the initial value was for the period of the measuring times evaluated for the confirmatory analysis T6, T12 and T18 statistically significant ($p < 0.0005$; all values were clearly below the defined significance level according to the Bonferroni correction taking account of the three measuring points). However at time T18, the number of patients had decreased below the target value of 10.

Fig. 1: Course of the HbA_{1c} values under long-term treatment with *Hintonia* extract. All measured values were statistically significant in the intraindividual comparison to the initial value ($p < 0.05$). The testing of significance for T6-T18 served as the confirmatory hypothesis testing ($p < 0.005$ for all three times)

[Insert Fig. 1 here]
Insert translated figure terms:
Mean HbA_{1c} ± SD (%)
Months
Target value
8.5
8.0 etc.

Fasting blood sugar and postprandial glucose

The starting values for fasting glucose and postprandial blood sugar were 7.94 ± 1.14 and 10.53 ± 1.30 mmol/l respectively and had significantly decreased already after one month ($p < 0.05$). After 6, 12 and 18 months, the fasting blood sugar had decreased by 23.9%, 20.6% and 21.9% respectively (corresponding to -1.8 to -2.0 mmol/l) and postprandial by 24.4%, 19.0 and 16.5% respectively [corresponding to -2.4, -1.9 and -2.0 mmol/l respectively ($p < 0.001$)] (**Fig. 2**). The confirmatory analysis for T6-T18 resulted for all three visits in a significant decrease compared with the starting value ($p < 0.0005$ for fasting blood sugar and $p < 0.001$ for postprandial glucose).

Fig. 2: Course of the fasting glucose and postprandial blood sugar under long-term treatment with *Hintonia* extract. All measured values were statistically significant in the intraindividual comparison to the initial value ($p < 0.05$). For the three times of the confirmatory hypothesis testing T6-T18, the measured values differed from the respective starting value at a level of $p < 0.01$ for both parameters.

[Insert Fig. 2 here]
Insert translated figure terms:
Fasting glucose **Postprandial glucose**
Mean ± SD (mmol/l)
Months

Accompanying diabetes symptoms

At the start of the study, concomitant gastrointestinal symptoms (constipation, flatulence, dyspepsia) and severe transpiration complaints in the upper body region occurred in each of two cases. In a further case, paresthesias were observed. In all cases, the symptoms disappeared within three months while taking the study preparation. The course of the body mass index (**Table 4**) showed for the patients included in the confirmatory testing at time T12 a slight decrease of an average of 3.2 ± 4.3% compared with the starting value (not statistically tested).

Table 4: Course of the BMI of the patients included in the confirmatory testing at time T12

Patient No.	BMI (T0)	BMI (T12)	Change BMI
1	37.95	37.11	-2.22%
3	26.49	27.34	+3.23%
4	39.26	39.66	+1.02%
5	38.09	35.49	-6.82%
7	27.92	27.18	-2.63%
8	35.82	36.58	+2.13%
9	28.34	27.64	-2.50%
13	37.32	35.70	-4.35%
14	30.73	29.22	-4.93%
19	34.77	32.42	-7.74%
21	47.65	42.17	-11.50%
Average change			-3.2 ± 4.3%

Safety parameters and blood lipids

During the entire duration of the study, no adverse events that might possibly have a causal connection with the study preparation were recorded. No hypoglycemic episodes occurred and the liver function parameters of GOT, ɣ -GT and AP didn't change over the entire study duration compared with the starting values. At the start of the study, the total cholesterol and triglyceride values were, with an average of 5.79 ± 0.87 mmol/l and 2.32 ± 1.09 mmol/l respectively, above the norm (cholesterol: up to 5.2 mmol/l; triglycerides up to 1.91 mmol/l). The cholesterol decreased slightly by 0.34 mmol/l between T0 and T12 and the triglycerides had decreased significantly at time T3 and T6 by 0.4 mmol/l (9%) ($p < 0.03$). The values for systolic and diastolic blood pressure were not affected to a relevant extent under the influence of the study medication. The changes from measuring point to measuring point were within the normal range of fluctuations.

Discussion

HbA_{1c}, fasting glucose and postprandial blood sugar were significantly lowered under treatment with the extract from *Hintonia latiflora* bark: HbA_{1c} had decreased by an average of 0.82% after 12 months and decreased further afterwards. A percentage reduction of the HbA_{1c} values correlated with an 18-37% reduction of the risk of macro- and microangiopathies (3, 19). Even without the use of a control group, this result is clearly relevant for therapy. Before the start of study, the patients were stable on a stringent diabetes diet for an average of 7.4 months without anywhere near reaching normoglycemic values. Since the diet was continued during the entire duration of the study, and therefore represented no variable, the reduction of the diabetic parameters cannot be simply related to nutritional effects but rather was the result of the intake of the study preparation. Therefore by the measurement of objective parameters, the study design allows valid statements on the efficacy of the test preparation to be made even without the explicit use of a parallel control group.

The use of a parallel control group is required especially for indications with a pronounced placebo effect in order to be able to make statements on the efficacy. With diabetes mellitus, placebo effects play no role with long-term use. Typically the spontaneous course of untreated diabetes mellitus shows a progression. In long-term studies with oral antidiabetics, the HbA_{1c} value remains unchanged or even increases in the placebo group (4, 5, 7). In the United Kingdom Prospective Diabetes Study, the HbA_{1c} value under diet remained stable only in the first year and then continually worsened afterwards. With highly overweight patients, the HbA_{1c} values continued to increase even further in spite of diet (1).

After placebo and diet effects can be excluded in the present study, and reliable laboratory analytic data on the course of the glycemic parameters are available, the study results should be assessed as clear evidence for the antidiabetic efficacy of the preparation from the bark of *Hintonia latiflora*.

To ensure an observation phase of the individual patients that is as long as possible, the study deliberately refrained from defining a temporal endpoint or rather the endpoint of the study was determined by the official completion of the study. The design of the study could give rise to misinterpretations in the sense of a loss of the treatment nonresponders and retention of the responders. By closely examining the individual measurement results, this suspicion can be ruled out: improvements of the blood parameters invariably took place with all patients for whom at least one measured value from the treatment phase existed. The reasons for withdrawal from the study are summarized in **Table 2**. Only one patient was changed over to oral antidiabetics because of an insufficient reduction of the HbA_{1c} value before the end of 12 months.

The fact that hypoglycemic episodes were not observed in the course of the study is relevant from the clinical point of view. For comparison: under long-term treatment with glibenclamide, hypoglycemic episodes were observed in 25% of the cases (1). Also the absence of changes in the liver function parameters underscores the applicability of *Hintonia* extracts in the diabetic long-term adjustment, particularly because diabetes patients tend to changes of the GOT and ɣ -GT values (also under stringent dietetic therapy; see UKPDS study) (17).

An observation outside of the study

After 15-month intake, female patient No. 5 had discontinued the treatment for a 6-month stay abroad while maintaining the dietary measures. After the stay abroad, the patient took the

study preparation again. Although she no longer was an official study participant, results for measurements of the fasting blood sugar and postprandial glucose values for a further 4 weeks were available to the study center from the patient's file. Afterwards the patient was no longer available due to the resumption of her activities abroad. Until time T15, the HbA_{1c} had continually decreased from initially 8.3 to 7.16%. Fasting blood sugar and postprandial glucose at this time showed normal values.

Six months after discontinuance of the study preparation, fasting and postprandial blood sugar increased again to or above the initial values. Within only four weeks of renewed intake of the study preparation, both parameters had already almost reached again the value at the time of discontinuation of the study.

Conclusion

The long-term intake of an extract from the bark of *Hintonia latiflora* lastingly improved the parameters of blood sugar monitoring in patients with type 2 diabetes mellitus. Cardiovascular functions and liver function values were not adversely affected. A tolerance development, that is a loss of efficacy with long-term intake, was not observed over a period of 12 months or in the follow-up phase of up to 21 months. The tolerance was very good: neither hypoglycemic episodes nor adverse reactions to the study preparation were observed. Overall the results of this study confirm case observations with the use of the study preparation for mild to moderately severe type 2 diabetes. Naturally in diabetes therapy, information on the adherence to dietary instructions is based first and foremost on statements from the patients themselves and is therefore associated with uncertainties. Clear indications of discrepancies however can be derived in practice from the course of BMI and HbA_{1c} values. In the present study, the data on dietary compliance ascertained from patient statements is supported by the course of the BMI (**Table 4**) and HbA_{1c} (**Fig. 1**),

According to the present results, the use of the study preparation in these kinds of type 2 diabetics can be regarded as safe, efficacious and reasonable in those for whom even with stringent dietary measures including complete alcohol abstinence, sufficient control of the blood sugar balance cannot be achieved and drug intervention is still not required. Control examinations of the diabetes-relevant parameters at three-month intervals, as is usual in diabetes therapy generally, are also to be recommended with the use of *Hintonia* extract.

Dr. Marta Korecova MD
Head of Diabetes Department, IDF President
Rc: 425201/734,
Vel'komoravská 2
SK-91101 Trencin
(correspondence author)

Marie Hladícova
Department for Medical Informatics
2nd Medical Faculty of Charles University Prague
V Úvalu 84
CZ-15006 Praha 5

REFERENCES

1. United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 1995; 310(6972): 83-88.
2. Bastien M: Recherches sur les Copalchi, drogues hypoglycemiantes et en particulier sur le *Coutarea latiflora* D.C. (Rubiacee) [Diss.]. Université de Paris, 1961.
3. Bretzel RG, Voigt K, Schatz H: The United Kingdom Prospective Diabetes Study (UKPDS) implications for the pharmacotherapy of type 2 diabetes mellitus. Exp.Clin Endocrinol.Diabetes 1998; 106(5): 369-372.
4. Del Prato S, Erkelens DW, Leutenegger M: Six-month efficacy of benfluorex vs. placebo or metformin in diet-failed type 2 diabetic patients. Acta Diabetol. 2003: 40(1): 20-27.
5. Drent ML, Tollefsen AT, van Heusden FH, Hoenderdos EB, et al.: Dose-dependent efficacy of miglitol, an alpha-glucosidase inhibitor, in type 2 diabetic patients on diet alone: results of a 24-week double-blind placebo-controlled study. Diabetes Nutr Metab 2002; 15(3):152-159.
6. Guerrera-Analco JA, Hersch-Martinez P, Pedraza-Chaverri J, Navarete A, Mata R: Antihyperglycemic effect of constituents from *Hintonia standleyana* in streptozotocin-induced diabetic rats. Planta Med 2005; 71(12): 1099-1105.
7. Herz M, Johns D, Reviriego J, Grossman LD, et al.: A randomized, double-blind, placebo-controlled, clinical trial of the effects of pioglitazone on glycemic control and dyslipidemia in oral antihyperglycemic medication-naive patients with type 2 diabetes mellitus. Clin Ther 2003; 25(4): 1074-1095.
8. Holstein A, Egberts EH: Risk of hypoglycaemia with oral antidiabetic agents in patients with type 2 diabetes. Exp Clin Endocrinol Diabetes 2003; 111(7): 405-414.
9. Kaiser H, Geyer H: Zur Pharmakologie der Rinde von Coutarea latiflora D.C. Arch Pharm 1955; 288/60(11-12): 595-608.
10. Korec R, Sensch KH, Zoukas T: Effects of the neoflavonoid coutareagenin, one of the antidiabetic active substances of *Hintonia latiflora*, on streptozotocin-induced diabetes mellitus in rats. Arzneim.-Forsch./Drug Res. 2000; 50(2): 122-128.
11. Krentz AJ, Bailey CJ: Oral antidiabetic agents: current role in type 2 diabetes mellitus. Drugs 2005; 65(3): 385-411.
12. Kuhr R: Orale Diabetestherapie mit einem Euphorbiazeenextrakt. Landarzt 1953; 29(23): 542-549.
13. Machens R: Zwei Fälle spontaner Regression des Diabetes mellitus Typ II nach Behandlung mit einem Phytotherapeutikum. Erfahrungsheilkunde 1991; 40(6): 433-434.
14. Machens R: Ein Langzeitversuch mit Copalchi-Fluidextrakt, einem pflanzlichen Antidiabeticum. Erfahrungsheilkunde 1992; 41(6): 416-420.
15. Paris R, Bastien M: A propos de l'action hypoglycémicante de deux drogues dénommées "Copalchi": Coutarea latiflora (Rubiacées) et Croton niveus (Euphorbiacées). Ann Pharm Fr 1960; 18: 205-219.
16. Pinto A, Capasso A, Sorrentino L: Experimental animal studies on the hypoglycemic effects of a Copalchi extract. Arzneim-Forschung/Drug Res. 1997; 47(7): 829-833.
17. Salmela PI, Sotaniemi EA, Niemi M, Maentausta O: Liver function tests in diabetic patients. Diabetes Care 1984; 7(3): 248-254.
18. Slijepcevic N, Kraus L: The diabetic mouse as an experimental model for measuring the blood-glucose lowering effects of plant extracts and insulin preparations. Acta Therap 1997; 23: 47-58.

19. Stratton IM, Adler AI, Neil HA, Matthews DR, et al.: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321(7258): 405-412.
20. Vida F: Erfahrungsbericht mit dem peroralen Antidiabetikum Sucontral. Med Welt 1951; 20: 1623-1624.
21. Winter B: Zur Behandlung des Diabetes mellitus. Hippokrates 1951; 22(9): 249-250.

ZUSAMMENFASSUNG

In einer monozentrischen offenen, nicht kontrollierten Studie bei 30 Patienten mit diätetisch nicht einstellbarem Diabetes mellitus vom Typ 2 wurden die antidiabetische Wirkung und die Sicherheit einer Zubereitung aus *Hintonia latiflora* (DEV 1:4,5. Extraktionsmittel 32% Ethanol) geprüft. Zum Ausschluss diätetischer Einflussfaktoren waren die Patienten mindestens zwei Monate vor und während der gesamten Studiendauer stabil auf diätetische Maßnamen eingestellt. Nach 12 Monaten Therapie mit dem Extrakt waren der Nüchternblutzucker im Mittel um 20,6%, der postprandiale Blutzucker um 19%, und der mittlere HbA_{1c} um 10,3% abgefallen ($p < 0,001$); die Werte blieben bei den in der Studie verbliebenen Patienten auch in der Folgezeit (bis zu 33 Monate) stabil. Über die gesamte Beobachtungsdauer traten keine hypoglykämischen Episoden oder unerwünschte Arzneimittellwirkungen auf.

Schlüsselwörter

Hintonia latiflora, Rubiaceae, Phyto-Antidiabetikum, Typ-2-Diabetes, Langzeitwirkung, Arzneimittelsicherheit, HbA_{1c}