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# Hintonia concentrate - for the dietary treatment of increased blood sugar values: Results of a multicentric, prospective, non-interventional study with a defined dry concentrate of hintonia latiflora

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## Abstract

**Background:** Preparations from the bark of *hintonia latiflora* are used to regulate the blood sugar levels. The objective of this study was to prove the nutritional benefit within the framework of a dietary treatment of increased blood sugar values with pre-diabetes and slight diabetes type 2 as well as the assessment of the tolerance and application safety.

**Method:** In an open, prospective, multicentric and non-interventional application study, the effects of a dry concentrate from the bark of *hintonia latiflora* in the form of capsules were examined for the laboratory parameters of the blood sugar levels ($HbA_{1c}$, fasting and postprandial glucose) as well as for the development of diabetic accompanying symptoms (sweating, gastrointestinal symptoms, paraesthesiae, itching and neuropathies). Particular attention was also given to the tolerance and (if available) further clinical (laboratory) parameters (blood pressure, liver values and blood lipids). An eight-month treatment was documented in 178 test persons with type 2 diabetes / pre-diabetes, who were treated with oral antidiabetics and / or insulin or only with a diet.

**Results:** At the end of the study, 177 data records were available. The $HbA_{1c}$ values improved over the course of the study with a high level of clinical relevance and significance from 7.2 ± 0.4% to 6.4 ± 0.5%, in accordance with a relative improvement by 10.4% ($p < 0.0001$). In parallel, the values of fasting and postprandial glucose also improved by an average of 23.3 ± 12.5% (from 152.1 ± 27.4 mmol/l to 114.4 ± 18.2 mmol/l) and 24.9 ± 11.4% (from 189.5 ± 34.1 mmol/l to 140.1 ± 22.3 mmol/l). The sum score of the diabetic accompanying symptoms improved from initially 4.8 points to 1.3 points at the end of the study. Improvements were also determined in blood pressure, blood fats and liver values. The tolerance was excellent, no unwanted effects occurred, in particular no hypoglycaemic episodes. In 55 of 114 patients with antidiabetic medication (39.5%), the substance could be reduced (n = 45) or stopped entirely (n = 10).

**Conclusions:** The study confirms the positive effects of the dry concentrate from the bark of *hintonia latiflora* on the main parameters of the blood sugar levels and the diabetic accompanying symptoms. In the event of pre-diabetes or minor cases of type 2 diabetes mellitus, this can contribute towards stabilising the blood sugar homoeostasis in particular, achieving a lower load from accompanying medication and deferring the necessity of using oral antidiabetic drugs and / or insulin.

**Keywords**: *Hintonia latiflora*, type 2 diabetes, $HbA_{1c}$, blood sugar, diabetic accompanying symptoms, antidiabetic accompanying medication

| Medication | Study start (n = 114, 64,4%) | Study end (n = 104, 58,8%) | Medication terminated/reduced (n) |
|---|---|---|---|
| One oral antidiabetic drug:<br>Metformin<br>Glibenclamid<br>Glimepirid<br>Pioglitazon<br>Acarbose | n = 90<br>78<br>1<br>8<br>2<br>1 | n = 83<br>71<br>1<br>8<br>2<br>1 | n = 10 / 28<br>7 / 21<br>0 / 1<br>0 / 5<br>0 / 1<br>0 / 0 |
| Two oral antidiabetic drugs:<br>Metformin+ Rosiglitazon<br>Metformin+ Glimepirid | n = 13<br>12<br>1 | n = 11<br>10<br>1 | 2 / 2<br>2 / 2 (Rosigl.)<br>0 / 0 |
| Oral antidiabetic drug + Insulin:<br>Metformin+ Insulin<br>Pioglitazon+ Insulin | n = 3<br><br>2<br>1 | n = 2<br><br>1<br>1 | n = 1 / 1<br><br>1 / 0<br>0 / 1 (Insulin) |
| Two antidiabetic drugs + Insulin:<br>Metformin+ Rosiglitazon + Insulin | n = 1 | n = 1 | n = 0 / 0 |
| Only Insulin | n = 7 | n = 7 | n = 0 / 4 |

Table 4: Accompanying medication at the start of the study and after 8 months of additional treatment with hintonia dry concentrate

## Accompanying medication

In the design of the study, it was intended that patients in treatment with oral antidiabetic drugs and / or insulin could also be included - the sole requirement was that the target range for the $HbA_{1c}$ was not achieved with the measures already being taken. Accordingly, for a total of 114/177 participants (64.4%; the participant who dropped out of the study had no accompanying medication), a use of medication antidiabetic measures was documented **(table 4)**. At the end of the study, 104 participants were still using accompanying medication (58.8% of the study population). In 45 participants (39.5% of the patients with antidiabetic medication), the daily dosage of the medication could be reduced. This was particularly striking for Metformin as an accompanying drug.

## Global assessment

The in-take recommendation of 3 x 1 capsules was observed well (median and average value 3.0 ± 1.1 for all visits). The effect of the study preparation was assessed by both the doctor and the study participant with a high level of congruence: the doctor assessed the effect to be good to very good in 98.9% of cases, for the patients this was true for 99.4% of cases. The tolerance of the study preparation received similarly high approval of good to very good at 97.2% (doctor) and 97.7% (participant).

## Discussion

The results of this examination match the results received previously from a study involving 41 participants with the same preparation form (Korecova M. and Hladikova M. 2012) as well as the observations from a clinical long-term study with a preparation form as a liquid extract (Korecova M. et al. 2006). It was possible to show consistently that in cases of pre-diabetes and type 2 diabetes with a minor form the blood sugar control can be improved to such an extent that the values for $HbA_{1c}$ can be brought into the target range for antidiabetic measures (6.5% - 7.5%).

In the broadly designed "ADVANCE" study, a positive effect of an improved $HbA_{1c}$ control on risk factors of the diabetes by using oral antidiabetic drugs had been shown (Group A.C. et al. 2008). A further examination published in parallel ("ACCORD" study), however, cast doubt on the effect of an aggressive strategy to reduce the $HbA_{1c}$ values due to the observation of an increased cardiovascular mortality (Action to Control Cardiovascular Risk in Diabetes Study G. et al. 2008). This seemly paradox observation was linked in this discussion of the interpretation of the ACCORD study with side effects of oral andidiabetic drug treatment with hypoglycaemic episodes and with a form of cardiovascular risks for diabetes mellitus existing long in advance (Cefalu W. T. 2008, Hoogwerf B. J. et al. 2008).

This debate shows clearly that measures for the early improvement of the glycaemic control are indeed justified, in particular when no risk of hypoglycaemic episodes emanates from them. Hintonia extract is located in the area of diet basic measures and can, on the basis of the observations to far, contribute to pushing back the time when it becomes necessary to administer oral antidiabetic drugs. This alone already promises a gain in quality of life and a reduction in therapy risks in the treatment of type 2 diabetes - documented by the reduction in the dosage of antidiabetic accompanying medication with simultaneously improved treatment results. In particular in patients with considerable fluctuations of the blood sugar level and difficulties in setting under diet and / or drug treatment, the supportive use of hintonia dry concentrate can help to achieve an even blood sugar level. This supplementing measure can be applied in addition to the diet measures already taken and the treatment with oral antidiabetic drugs and / or insulin.

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## Introduction

Preparations from the bark of the Central American plant *hintonia latiflora* (rubiaceae) have been used successfully as a means of improving the blood sugar levels for more than 100 years in the countries of origin and for several decades in Europe. First publications, which describe the popular use in the event of diabetes and the possibility of a stabilisation of the blood glucose level when using preparations made from the plant, originate from the 19th century (Arevalo R. 1887). A series of additional, partly systematic tests on the substances and effects followed (e.g. Obregon-Jarava X. 1920, Bastien M. 1961, Kaiser H. and Geyer H. 1955, Martinez del Campo J. 1904, Machens R. 1991, Kur R. 1953, Machens R. 1992, 1996, Pinto A. et al. 1997, Schmid P. 1951, Vida F. 1951, Winter B. 1951). The effects on the blood sugar regulation are usually attributed to the fraction of the polyphenoles, such as coutareagenin (Korec R. et al. 2000), which also have antioxidant properties.

Positive here is the determination that preparations from hintonia bark not only have a blood sugar reducing effect, but in fact also contribute to restoring the physiological balance in the blood glucose levels: hypoglycaemiae in the meaning of an excessive correction of increased blood sugar levels do not occur on the basis of past experience. By contrast, in clinical examinations of people, there were regular reports of savings of oral antidiabetic drugs and insulin, as well as of an improvement in the diabetic accompanying symptoms (Kuhr R. 1953, Winter B. 1951, Machens R. 1991, 1992, Ploss O. 2002, Vida F. 1951).

Lately, the blood sugar regulating effect of an extract preparation made from the bark of *hintonia latiflora* has been proven repeatedly in application studies. In these studies, a clear improvement of the $HbA_{1c}$ levels noticeable to the user, togethor with a simultaneous non-occurrence of hypoglycaemic episodes and very good tolerance (Korecova M. et al. 2006) could be observed. This was proven for a liquid extract form over the duration of 33 months. In this study, patients were included who had an average $HbA_{1c}$ level of 7.7% despite dietetic settings, significantly above the target value for diabetic patients, but below the threshold from which the use of antidiabetic drugs is recommended. After 12 months of treatment duration, the clinical blood sugar had on average fallen by 20.6%, the postprandial blood sugar by 19% and the mean $HbA_{1c}$ by 10.3%. The values remained stable for up to 33 months over the entire duration of the study, the improvement was statistically significant ($p < 0.001$). In absolute figures, this resulted in an average reduction of the $HbA_{1c}$ value by 1.04% at the time of 18 months.

Currently, the transferability of the effect on a dry extract was also described (Korecova M. and Hladikova M. 2012). In this six-month, open, prospective study in 41 patients with diabetes mellitus type 2, a 25% reduction of clinical glucose (from 8.0 ± 1.0 mmol/l to 6.0 ± 0.6 mmol/l), a 22% improvement of the postprandial glucose (from 10.2 ± 1.4 mmol/l to 8.0 ± 6.7 mmol/l) and an improvement of the $HbA_{1c}$ value from 7.49 ± 0.72% to 6.82 ± 0.67% were measured.

The objective of this work was to underline the observations from this preceding study in a larger number of patients with typical participants, i.e. also with the integration of patients who were already taking oral andidiabetic drugs and / or insulin. A placebo control was again not used: the previous studies on epidemiology of type 2 diabetes show that no effects on the verifiable parameters of the blood glucose levels can be expected. Untreated type 2 diabetes mellitus is a progressive disease without a tendency to spontaneous improvement. In long-term studies with oral antidiabetic drugs, the $HbA_{1c}$ value in the placebo group remained unchanged or showed worsening values (Del Prato S. et al. 2003, Drent M. L. et al. 2002, Herz M. et al. 2003). In the United Kingdom Prospective Diabetes Study, the $HbA_{1c}$ value during diet remained stable only during the first year and subsequently worsened continuously. For strongly overweight patients, the values improved despite a diet from the very start (Anon. 1995). Currently, with the so-called look-out study, a long-term study on the influence of calorie reducing diet on the cardiovascular risk of strongly overweight type 2 diabetic patients was presented. These study results also confirm that weight control alone does not result in a clinically significant risk reduction as regards death from cardiovascular diseases, which underlines the necessity of further interventions. The laboratory results for glycosidated haemoglobin rose again in the control group, and this despite a small reduction of the body weight. In the diet group, an improvement of the $HbA_{1c}$ was observed at the start with the fall of the body weight. However, the effect did not persist, both body weight and $HbA_{1c}$ rose again (Look A.R.G et al. 2013). On the basis of these observations, placebo effects in the treatment of type 2 diabetes cannot be expected, and in patients where the possibilities of the diet have already been exhausted, a further improvement of the values is unlikely. This justifies - not least for ethical considerations - for explorative studies to assess the potential of a measure with the aim of improving the diabetic setting an open study design without placebo control.

The study presented here was designed as an eight-month application observation. This study duration should suffice to prove any changes to the parameters of the blood sugar levels and, retrospectively on the basis of the findings of the look-out study, be short enough so that any easing in the diet setting does not distort the measurement results.

## Study design

The study was designed as a non-interventional, prospective examination of test persons with pre-diabetes and mild type 2 diabetes. The carrying out of the study was based on the ethical principles of the declaration of Helsinki / Somerset West. As study centres, practical doctors and diabetological specialist practices were used. All patients declared their consent after being informed by the doctor.

The preparation examined is capsules with a dry concentrate made from the bark of *hintonia latiflora*. The capsules additionally contained zinc and chrome as well as vitamin C, B vitamins, folic acid[1], amongst other things. The plant material for the extraction of the dry concentrate originates from controlled collection.

The requirement for the inclusion in the study was a $HbA_{1c}$ value of ≤ 8.0%, while type 2 diabetes patients could also be included in whom a further improvement of the values was not achievable when being treated with oral antidiabetic drugs. Patients with allergies against components of the capsules, patients with liver diseases, malign tumours or an anamnesis of al-

[1] Test preparation: Sucontral capsules

| | |
|---|---|
| **Included**<br>**Female**<br>**Male** | 178<br>101 (56,7%)<br>77 (43,3%) |
| **Age (years)**<br>**Range (median)** | 61,0 ± 10,8<br>37 to 93 (61) |
| **Height (cm)**<br>**Range (median)** | 170,8 ± 6,0<br>157 to 187 (170) |
| **Body weight (kg)**<br>**Range (median)** | 84,3 ± 10,4<br>59 to 118 (82,5) |
| **BMI (kg / m3)**<br>**Range (median)** | 28,9 ± 3,2<br>22,2 to 38,6 (28,4) |
| **Diagnosis of a diabetes type 2**<br>**Diabetic accompanying symptoms**<br>**Antidiabetic treatment** | n = 171 (96,1%)<br>n = 110 (61,8%)<br>n = 114 (64,0%) |
| **Dropouts**<br>**→ Effect population** | n = 1 (at the doctor's request)<br>n = 177 |

Table 1: Study participants

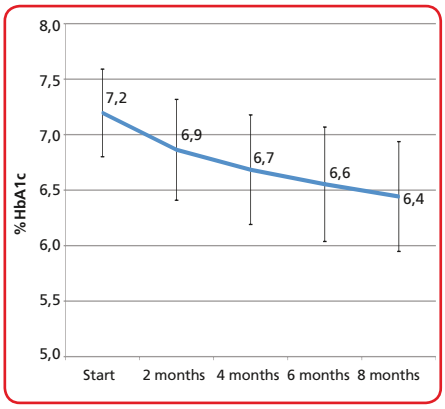


Fig. 1: Development of the HbA1c value over the course of the study (n = 177)

cohol and drug dependency as well as (as a precaution) pregnant and breast feeding women were excluded. The recommended dosage was one capsule three times a day. The patients included were observed over a period of eight months with interim examinations at two-month intervals. The following were measured or documented

- glycaemic parameters (clinical and postprandial blood sugar as well as $HbA_{1c}$ value) as well as body weight and blood pressure on every visit;
- typical diabetic accompanying measures (sweating, obstipation, praesthesiae, itching, neuropathies) on every visit on a four-level scale (not available, minor, moderate or strong);
- liver values and blood lipids at the start and end of the study, if available; and
- the global tolerance and the effect in the doctor's and patient's assessment at the end of the study.

Furthermore, unwanted effects in the exposition period were also queried in a targeted manner.

The analysis was carried out in a descriptive way through intra-individual comparison of the values documented. Missing values were treated by transferring the last known value.

The statistical analysis was carried out using SPSS v20. For the repeated measurements, a Bonferroni correction was applied.

## Results

Included were 178 participants. The demographic data can be found in **table 1**.

## Protocol breaches

In one case, the $HbA_{1c}$ value of the patient included at a value of 8.1% was just above the limit of 8.0% for the inclusion criteria. This was only determined in retrospect. The participant ended the study regularly and was also included in the study.

## Study termination

One participant dropped out of the study after four months on the request of the doctor: As a new medication was prescribed due to Parkinson's disease, interactions with the vitamin B included in the study preparation were feared. Until this time, a consistent improvement of the $HbA_{1c}$ value had been observed: the values had improved with clinical relevance from initially 6.7% to 5.8% after four months.

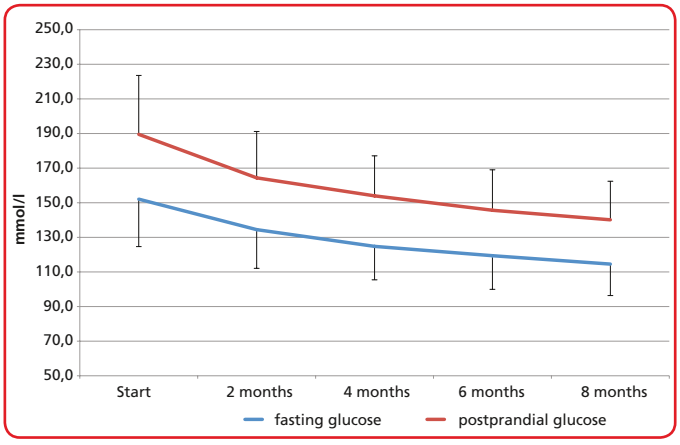


Fig. 2: Development of fasting glucose and postprandial blood sugar over the course of the study (n = 177)

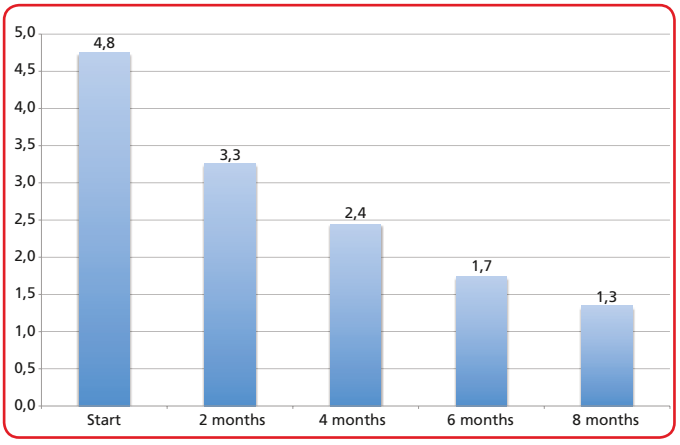


Fig. 3: Development of the sum score of the form of the diabetic accompanying symptoms over the course of the study

## $HbA_{1c}$ and blood glucose values

A total of 177 study participants were included in the analysis. Statistically analysed were both the comparison of the test result after eight months with the initial value (Friedman test) as well as the comparison of every single interim result after 2, 4 and 8 months with the previous value (Wilcoxon row series test, followed by the Friedman test with Bonferroni correction for repeated measurements). In all cases, the differences between the measurement values turned out to be statistically highly significant ($p < 0.0001$ for $HbA_{1c}$, clinical glucose and postprandial blood sugar, including all interim values).

In the overall group, the $HbA_{1c}$ values of initially 7.2 ± 0.4% (in absolute figures) improved by 0.8% ± 0.5% to 6.4 ± 0.5% after 8 months **(Fig. 1)**. In relative values, this corresponded to an average improvement by 10.4% ± 6.1% with reference to the initial value.

Only in three participants there was no change to the initial $HbA_{1c}$ value, and in one further participant the values worsened gradually from initially 6.8 to 7.4% at the end of the study. This corresponds to a rate of 2.3% of "non-respondents", if a positive development of the $HbA_{1c}$ is rated as a response. The values for the clinical blood sugar improved with great significance for the statistics over the course of the study compared to the initial value by an average of 23.3 ± 12.5% (from 152.1 ± 27.4 mmol/l to 114.5 ± 18.2 mmol/l, n = 177), the values for postprandial glucose by 24.9 ± 11.4% (from 189.5 ± 34.1 mmol/l to 140.1 ± 22.3 mmol/l; n = 177; **Fig. 2)**.

## Diabetic symptoms

The diabetic accompanying symptoms observed at the start of the study (sweating, gastrointestinal symptoms, paraesthesiae, itching and neuropathies) reduced strongly in the course of the study **(table 2)**. As expected, the ailments in the group of patients included with mild forms of type 2 diabetes were comparatively small: at the start of the study, 26.4 to 37.6% of study participants noted moderate to high levels (with reference to the individual symptoms). At the end of the study, only 0.6 to 3.4% of participants noted moderate to high levels of diabetic accompanying symptoms.

| Form | No ailments | | Minor | | Moderate | | Strong | |
|---|---|---|---|---|---|---|---|---|
| | Start | End | Start | End | Start | End | Start | End |
| Sweating | 32,6% | 64,4% | 29,8% | 29,4% | 28,7% | 2,3% | 9,0% | 0,0% |
| Gastrointestinal symptoms | 37,6% | 67,2% | 28,1% | 29,4% | 28,1% | 3,4% | 6,2% | 0,0% |
| Paraesthesiae | 48,9% | 78,5% | 19,1% | 18,1% | 28,1% | 3,4% | 3,9% | 0,0% |
| Itching | 51,7% | 85,9% | 21,9% | 13,6% | 20,2% | 0,6% | 6,2% | 0,0% |
| Neuropathies | 56,2% | 78,0% | 15,7% | 19,2% | 11,2% | 2,8% | 16,9% | 0,0% |

Table 2: Percentage range of the pattern of ailments of diabetic accompanying symptoms over the course of the 8 months of the study (start: n = 178; end: n = 177)

From the five patterns of ailments queried, a sum score was then formed that could reach a theoretical maximum value of 15. In accordance with the relatively low-level occurrence of the ailments, the sum score at the start of the study was 4.8. By the end of the study it had improved continuously to a final value of 1.3 - in accordance with a now only very small form **(Fig. 3)**.

## Body weight, blood pressure and laboratory parameters

The values for the laboratory parameters were not available for all patients. the deviation of the theoretical number of participants of n = 177 in the event of the BMI parameter was down to the lack of information on the body size for one participant **(table 3)**. Over the course of the study, a slight reduction of body weight and BMI was observed. In parallel, the values for systolic and diastolic blood pressure and blood lipids also improved (triglycerides and overall cholesterol).

## Liver values

In the overall collective, the liver values improved significantly: the GOT values improved on average by 9.9%, GPT by 6.5% and GGT by 12.2%.

| Parameter | n | Start / end | Range | Change (%) |
|---|---|---|---|---|
| Body weight (kg) | 177 | 84,3 ± 10,4<br>81,6 ± 9,4 | 59–118<br>58–117 | - 3,2 % |
| BMI | 176 | 28,9 ± 3,2<br>28,0 ± 3,0 | 22,2–38,6<br>21,5–37,7 | - 3,2 % |
| Blood pressure systolic | 177 | 142,2 ± 14,1<br>132,8 ± 10,3 | 105–185<br>110–182 | - 6,6 % |
| Blood pressure diastolic | 177 | 86,6 ± 8,7<br>82,0 ± 6,5 | 68–125<br>50–105 | - 5,2 % |
| Triglycerides (mmol/l) | 62 | 181,6 ± 44,8<br>168,8 ± 35,5 | 61–315<br>60–284 | - 7,1 % |
| Overall cholesterol (mmol/l) | 63 | 237,7 ± 56,9<br>220,4 ± 52,1 | 154–398<br>155–371 | - 7,3 % |
| GOT (AST, U/l) | 34 | 38,4 ± 15,4<br>34,6 ± 12,8 | 18–96<br>17–84 | - 9,9 % |
| GPT (ALT, U/l) | 34 | 39,9 ± 15,9<br>37,3 ± 14,8 | 13–75<br>14–79 | - 6,5 % |
| GGT (U/l) | 37 | 40,2 ± 26,6<br>35,3 ± 20,5 | 1–110<br>1–78 | - 12,2 % |

Table 3: Change of body weight, blood pressure and laboratory values over the course of the study