Effect of Supplementation of *Coccinia cordifolia* Extract on Newly Detected Diabetic Patients

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OBJECTIVE — *Coccinia indica* (synonym *Coccinia cordifolia*), an herb growing abundantly in India, has been used in traditional treatment of diabetes. However, carefully controlled studies of its efficacy are lacking. This study aimed to evaluate the effectiveness of *Coccinia cordifolia* on blood glucose levels of incident type 2 diabetic patients requiring only dietary or lifestyle modifications.

RESEARCH DESIGN AND METHODS — The study was a double-blind, placebo-controlled, randomized trial. Sixty incident type 2 diabetic subjects (aged 35–60 years) were recruited from St. Johns Medical College Hospital, Bangalore, India. The subjects were randomly assigned into the placebo or experimental group and were provided with 1 g alcoholic extract of the herb for 90 days. Anthropometric, biochemical, dietary, and physical activity assessment were carried out at baseline and were repeated at days 45 and 90 of the study. All subjects were provided with standard dietary and physical activity advice for blood sugar control.

RESULTS — There was a significant decrease in the fasting, postprandial blood glucose and A1C of the experimental group compared with that of the placebo group. The fasting and postprandial blood glucose levels of the experimental group at day 90 significantly decreased, by 16 and 18%, respectively. There were no significant changes observed in the serum lipid levels.

CONCLUSIONS — This study suggests that *Coccinia cordifolia* extract has a potential hypoglycemic action in patients with mild diabetes. However, further studies are needed to elucidate mechanisms of action.

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Prevalence of diabetes is increasing in all countries, especially in India, at an alarming rate. Various factors that contribute to the rise in prevalence of diabetes include genetic factors that determine body fat distribution, rapid changes in eating habits, and lifestyles that are increasingly sedentary (1). Therefore, appropriate interventions in the form of weight reduction, changes in dietary habits, and increased physical activity could help in preventing or delaying onset of diabetes and reducing the burden due to noncommunicable diseases in India.

Plants or their extracts may also have a potential therapeutic role in treatment for diabetes. Traditional health care systems, including herbal medicine, are widespread in developing countries (2), and the care of diabetic patients has been influenced by a growing interest in complementary and alternative medicine. Indian herbs such as *Momordica charantia*, *Pterocarpus marsupium*, and *Trigonella foenum greacum* have been reported to have a hypoglycemic effect in type 2 diabetes through stimulating or regenerating effects on β-cells or through extrapancreatic effects (3). *Coccinia indica* (synonym *Coccinia cordifolia*), an herb that belongs to the *Cucurbitaceae* family and that grows abundantly in India, has been widely used in traditional treatment of diabetes (4). The plant is a perennial herb that contains tuberous roots often forming a dense covering over the flora. Studies have shown that the plant has an antidiabetic effect on alloxan-induced diabetic rabbits, in which a 95% alcohol extract of the leaves at doses of 2.5 and 5.0 g/kg decreased blood glucose levels by ~50% after 6 hours (5). Oral administration of 200 mg/kg of an aqueous ethanolic extract of *Coccinia indica* leaves and fruits for 45 days to diabetic animals demonstrated a significant reduction in blood glucose and A1C and an increase in total Hb and plasma insulin (6), suggesting that the administration of *Coccinia indica* leaves to diabetic animals normalizes blood glucose. While literature on the potential efficacy of *Coccinia indica* in the treatment of human diabetes does exist, it is relatively sparse and heterogenous. Freeze-dried *Coccinia indica* leaves, when administered orally twice a day for 6 weeks to patients with untreated but uncomplicated maturity-onset diabetes, demonstrated hypoglycemic activity with significant improvement in glucose tolerance (7). However, many details about the exact dose administered or patient characteristics—e.g., whether the body weight or food intake of the patients changed during the course of the treatment—were not clear. These preliminary data suggest that further studies are needed. Therefore, the aim of the present study was to carefully evaluate the effectiveness of an aqueous alcoholic extract of *Coccinia cordifolia* (synonym *Coccinia indica*), in a dose of 1 g/day (equivalent to 15 g of the dried herb), on the blood glucose levels of newly detected type 2 diabetic patients requiring only dietary or lifestyle treatment.

RESEARCH DESIGN AND METHODS

— The study was a double-blind, placebo-controlled, randomized trial. Sixty newly detected type 2 diabetic patients needing only dietary or lifestyle modifications (with fasting blood

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glucose in the range of 110–180 mg/dl) were recruited into the study. One subject dropped out of the study, and 59 subjects completed the study, such that there were 30 subjects in the placebo group and 29 subjects in the experimental group. The subjects (33 male and 26 female) were aged between 35 and 60 years. Exclusion criteria were the presence of any chronic disease and the concurrent use of any medication for the control of blood glucose levels. Subjects were recruited from patients who were referred for dietary advice to the Nutrition and Lifestyle Management Clinic of St. John's Medical College Hospital, Bangalore, India. After recruitment, subjects were randomly assigned into the placebo or experimental group. The study was approved by the institutional ethical review committee of St. John's Medical College, and informed consent was obtained from the subjects.

The aerial parts of *Coccinia cordifolia* (leaves and fruits) were extracted with aqueous alcohol. The extraction was with 50% alcohol (1:1 alcohol and water). The extracts were combined, concentrated, and purified to get a specific fraction of the extract, and then dissolved in water and filtered. The clear filtrate was spray dried. Fifteen kilograms of the herb provided 1 kg of the final extract. Maltodextrin capsules (500 mg) were used as placebo, and both capsules were prepared by Green Chem, Bangalore, India. Before the intervention, the subjects underwent baseline investigations, which included anthropometric, biochemical, dietary, and physical activity assessment. The extract was administered as two 500-mg capsules daily (1 g/day) for 90 days, during which the subjects reported weekly to the Nutrition Clinic to record their body weight, collect their weekly capsule supply, and report adverse events, if any. Compliance of the subjects to the ingestion of capsules was documented at every visit. The subjects were provided a capsule calendar in which they were required to tick mark boxes relating to the daily intake of capsules and to note down any missed capsule. The calendar and the missed pill count were monitored every week. All the study subjects were provided with standard dietary and physical activity advice for control of blood sugar. In case of overweight patients, advice was provided to achieve moderate weight loss of about 5%. The standard advice also included regular physical activity, with dietary strategies to increase dietary fiber (legume, fruits, and vegetables) and decrease intake of fat. The compliance of the subjects to the prescribed diet and physical activity was assessed weekly by asking the subjects to rate their compliance on a scale of 0–100%.

Anthropometric measurements.
Anthropometric measurements were standardized (8) and included body weight, height, skinfold thickness, and midarm, waist, and hip circumferences. Skinfold measurements in triplicates were carried out using Holtain skinfold calipers at four sites, i.e., biceps, triceps, subscapular, and suprailiac. The average sum of four skinfold measurements was used to compute body density using an age- and sex-specific equation (9), and percentage of body fat was derived from body density (10). These equations were previously validated in a group of Indian men and women (11). The measurements were taken at baseline and repeated at days 45 90 of the intervention period.

Biochemical measurements.
Fasting and postprandial blood glucose (collected 2 h after breakfast), A1C, and lipid profile were measured at baseline and days 45 and 90 of the study period. Blood glucose, triglycerides, and total and HDL cholesterol were estimated by spectrophotometric assays on automated clinical chemistry analyzer Dimension RxL (Dade Behring, Newark, NJ), while LDL cholesterol was calculated from primary measurements using the empirical formula of the Friedewald equation (12). Glycosylated Hb (A1C) was based on the turbidimetric inhibition immunoassay principle using the Dimension RxL. All assays were calibrated by use of the Dade Dimension human calibrator (Dade Behring). The analytical coefficients of variation (interassay) for total cholesterol, triglycerides, and HDL cholesterol were 4.1, 4.7, and 4.1%, respectively; 2.6% for glucose; and 3.2% for A1C.

Dietary and physical activity assessment.
Dietary assessment was carried out using a 24-h recall at baseline and days 45 and 90 of the intervention period. The data from the dietary recall were used to arrive at estimates of daily nutrient intake from standard recipes, using published food composition databases (13,14). The routine physical activity pattern of the subjects was assessed using a questionnaire carried out at baseline and days 45 and 90 of the study period. The questionnaire requested details regarding the time spent by patients in different activities such as occupation, travel, household, and leisure activities. This allowed for an assessment of time spent in sedentary, moderately active, or vigorously active domains of activity during the day, and any changes thereof, during the experiment.

Statistical analyses.
The data are presented as means ± SD. An independent *t* test was performed to ascertain whether significant differences existed between the anthropometric and biochemical parameters of the subjects in the experimental and placebo groups at baseline. Repeated-measures ANOVA, with group as a factor, was performed to assess the change over time in the anthropometric, biochemical, and food intake parameters between the two groups. Repeated-measures ANOVA was then used to assess for significant differences between the various time points in the subjects of both groups independently. The significance level was set at $P < 0.05$.

RESULTS — The profile of the subjects in the experimental and placebo groups at baseline is summarized in Table 1. The age range of the subjects in the experimental group was 35–58 years and in the placebo group 38–60 years. There were no significant differences in mean age, weight, percentage of body fat, Hb, A1C, fasting blood glucose, postprandial blood glucose, or lipid profile between the experimental and placebo groups (Table 1).

The anthropometric parameters of the subjects in the experimental and placebo groups at various time points of the study are summarized in Table 2. There were no significant differences observed in change of body weight, BMI, waist circumference, hip circumference, or percentage of body fat over time between the two groups (repeated-measures ANOVA). At the end of the study period, no significant changes in body weight, BMI, percentage of body fat, or waist and hip circumferences were observed in any of the group when compared with baseline parameters.

A significant interaction effect was observed between time and group (repeated-measures ANOVA) in fasting and postprandial blood glucose. The significant decrease (at day 90) in fasting blood glucose of the experimental group accounted for a mean change of 15.6%

Table 1—*Profile of subjects at baseline*

Parameter	Placebo	Experimental	*P*
Age (years)	47.9 ± 5.9	46.2 ± 6.1	0.29
Body weight (kg)	69.6 ± 13.2	65.0 ± 9.6	0.14
Percentage of fat*	30.1 ± 7.9	28.6 ± 5.2	0.38
Hb (%)†	14.3 ± 2.1	14.6 ± 1.6	0.54
A1C (%)	6.4 ± 0.9	6.7 ± 1.2	0.21
Fasting blood glucose (mg/dl)	125.3 ± 13.8	132.0 ± 20.6	0.15
Postprandial blood glucose (mg/dl)	154.7 ± 44.0	183.2 ± 75.6	0.08
Total cholesterol (mg/dl)	203.6 ± 46.2	207.1 ± 64.6	0.81
HDL cholesterol (mg/dl)	39.4 ± 10.1	44.7 ± 13.4	0.09
LDL cholesterol (mg/dl)	138.3 ± 48.8	141.8 ± 50.3	0.79
Triglycerides (mg/dl)	185.0 ± 74.6	184.0 ± 131.3	0.97

Data are means ± SD. No significant differences were observed in any of the parameters of the subjects of the two groups (independent *t* test). *Calculated from the sum of four skinfold measurements and applying the formulae of Durnin and Womersley (ref. 9). †Measured in grams.

(20.6 mg/dl) of the initial value. In contrast, the placebo group had a nonsignificant mean increase in fasting blood glucose of 6% (8 mg/dl) during the study period. Similarly, there was an 18.5% (34 mg/dl) significant decrease in the postprandial blood glucose of the experimental group (day 90) compared with baseline values, while in the placebo group there was a nonsignificant 7% (12 mg/dl) increase during the study period (Fig. 1). There was a significant decrease in the A1C of the experimental group at day 90 (6.1 ± 1.1%) compared with baseline (6.7 ± 1.2%), while there was no change in the placebo group. There were no significant differences observed in change of Hb, total cholesterol, HDL cholesterol, LDL cholesterol, or serum triglycerides over time between the two groups (repeated-measures ANOVA). The LDL cholesterol of the experimental group was significantly lower (14.6%) at day 90 compared with the initial values (repeated-measures ANOVA). The total cholesterol of the placebo group had a nonsignificant 8% reduction at day 90 (187.3 ± 37.9 mg/dl) compared with baseline (203.6 ± 46.2 mg/dl), while the experimental group showed a nonsignificant decrease of 7.6% from baseline to day 90 (207.1 ± 64.6 vs. 191.3 ± 41.8 mg/dl). Similar nonsignificant results were observed in the HDL and triglyceride levels of the placebo and experimental groups between baseline and day 90 values.

There was no significant change in daily energy intake of the subjects (n = 59), from 1740.5 ± 500.4 kcals at baseline and 1679.7 ± 516.8 kcals at day 90. The protein, fat, and carbohydrate intake of the subjects also did not show any significant change. When these data were analyzed between groups, there was also no significant difference. Additionally, the body weight (67.3 ± 11.7 kg at baseline and 67.2 ± 11.4 kg at day 90) and BMI (26.2 ± 4.2 kg/m^2 at baseline and 26.2 ± 4.1 kg/m^2 at day 90) of the subjects did not change significantly at the end of the study.

The mean reported compliance of the subjects in the experimental group to their prescribed diet was 93% (range 65–100) and to the prescribed physical activity 88% (38–100), while in the placebo group compliance to the prescribed diet was 94% (50–100) and to the prescribed physical activity 84% (16.7–100). The physical activity patterns of both the experimental and placebo groups did not change during the study.

There were no serious adverse events reported by subjects. In the experimental group, 17 (59%) experienced mild hypoglycemic symptoms such as perspiration, excessive hunger, and slight dizziness once or twice during the study period. The symptoms were mainly observed postprandially (midmorning). These subjects were advised to consume a snack at such times, following which the symptoms subsided. The other observed adverse events were minor and limited to mild symptoms of the gastrointestinal tract such as abdominal distention, flatulence, constipation, and gastritis. Seven (24%) of the subjects from the experimental group and eight (27%) of the subjects from the placebo group experienced these minor adverse effects. These symptoms were present in both groups of subjects and subsided within a week.

CONCLUSIONS — Approaches to the control of and prevention of hyperglycemia are central to the management of diabetes. While drugs, diet, and physical activity are the cornerstone for the treatment of diabetes, there is growing interest in complementary and alternative medicine for diabetes, not only among the general public, but also among health care providers, researchers, and educators (15). Plant remedies may be appealing as an alternative and adjunctive treatment for diabetes.

There were no significant changes in daily energy intake, body weight, and BMI of the subjects between baseline and day 90. It is possible that the prescribed dietary and physical activity advice was either not followed or not completely ini-

Table 2—*Anthropometric parameters of subjects at baseline and days 45 and 90 of the study*

	Placebo			Experimental			
Parameter	Baseline	Day 45	Day 90	Baseline	Day 45	Day 90	*P*
Body weight (kg)	69.6 ± 13.2	69.4 ± 12.9	69.2 ± 13.1	65.0 ± 9.6	64.7 ± 9.4	65.1 ± 9.2	0.55
BMI (kg/m^2)	27.5 ± 4.6	27.4 ± 4.7	27.3 ± 4.6	25.1 ± 3.3	25.0 ± 3.2	25.1 ± 3.0	0.46
Waist circumference (cm)	90.2 ± 9.0	90.1 ± 8.2	90.0 ± 8.9	87.9 ± 7.3	87.5 ± 6.9	87.6 ± 6.8	0.83
Hip circumference (cm)	97.0 ± 10.3	96.9 ± 10.3	97.6 ± 10.8	94.7 ± 7.0	94.6 ± 7.1	94.8 ± 6.9	0.49
Percentage of fat (%)*	30.1 ± 7.9	30.1 ± 7.3	31.1 ± 7.4	28.6 ± 5.2	28.3 ± 5.5	28.3 ± 5.6	0.20

Data are means ± SD. n = 30 in the placebo group, and n = 29 in the experimental group. There were no significant interaction between time points and group (repeated-measures ANOVA with group as between-subject factor). There were no significant difference observed between time points for each group (repeated-measures ANOVA). *Calculated from the sum of four skinfold measurements and applying the formulae of Durnin and Womersley (ref. 9).

tiated by the subjects, even though the self-rated compliance to the dietary and physical activity advice was >80% in both groups. Therefore, the results of the present study suggest that the decrease in fasting (16%) and postprandial blood (18%) glucose observed in the experimental group could be attributed to the hypoglycemic effect of the *Coccinia cordifolia* extract.

Coccinia indica (ivy gourd) is a creeper that grows widely in India and Bangladesh. The plant has been used since ancient times as an antidiabetic drug by physicians who practice Ayurveda. A double-blind control trial ($n = 32$), conducted in India, demonstrated significant improvement in glycemic control following 6 weeks' use of powder from locally obtained crushed dried leaves of *Coccinia indica* in patients with poorly controlled or otherwise untreated type 2 diabetes; however, there were no data available regarding whether body weight changed (7). In another three-arm, controlled clinical trial ($n = 70$), the use of dried herb pellets made from fresh leaves of *Coccinia indica* was compared with no treatment and treatment with oral hypoglycemic agents (chlopropamide) (16). The improvement in glycemic control observed in the group that was treated with the herb was similar to that associated with use of a conventional drug. However, no details were available on whether body weight or food intake of the patients changed during the study period. Additional studies (17,18) have provided supporting evidence for the hypopglycemic effect of *Coccinia indica*. In 2003, Yeh et al. (19), while assessing the quality of the evidence of the herb for glycemic control, employed the American Diabetes Association Criteria for Clinical Guidelines (20) and rated *Coccinia indica* with an A rating, having supportive evidence with at least one adequate randomized clinical trial. In the present study, the dose of the aqueous alcoholic extract of *Coccinia indica* was higher than that in the previous two human studies (7,16), in which 2–6 g/day of the dried leaves were administered (19). The higher dose in the present study (1 g of the aqueous alcoholic extract was equivalent to 15 g of the dried herb) was chosen, since personal discussions with local ayurvedic practitioners revealed that they empirically used "a handful" of the dried herb (equivalent to 15 g) daily in their treatments. In addition, they also reported absolutely no adverse events, which was also reflected in the published studies (7,16), albeit at lower doses. In the present study, very minor side effects were reported, which could not be attributed specifically to the herb.

The mechanism of action of *Coccinia indica* is not well understood, but the herb appears to be insulin mimetic (16,18). The oral administration of pectin isolated from *Coccinia indica* fruit showed a significant hypoglycemia effect in normal rats (21). It has been postulated that the ingredients present in the extract of *Coccinia indica* act like insulin, correcting the elevated enzymes gluocose-6-phosphatase and lactase dehydrogenase in the glycolytic pathway and restore the lipoprotein lipase activity in the lipolytic pathway with the control of hyperglycemia in diabetes (18). When *Coccinia indica* and *Momordica charantia* extracts were administered to diabetic rats, the results indicated that there was lowering of blood glucose by depressing its synthesis through depression of the key gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-biphosphatase and also by enhancing glucose oxidation by the shunt pathway through activation of its principal enzyme, G6PDH (22).

Some reports suggest that the toluene extract *Coccinia*, which has triterpenes, has an effect of reducing alloxan-induced B-cell damage and therefore potentially increasing insulin secretion (23). Similar findings have been reported in obese hyperglycemic *db/db* mice, in which the the triterpene compound dehydrotrametenolic acid reduced glucose levels and also appeared to act as an insulin sensitizer, possibly through its role in the activation of peroxisome proliferator–activated receptor-γ (24). Ethanolic extracts from *Gynostemma pentaphyllum*, an herb of the same Cucurbitaceae family, was shown to stimulate insulin secretion from isolated rat pancreatic islets (25). The main active compound was saponins (gypenosides), which is thought to stimulate insulin secretion by suppressing nitric oxide (NO) synthesis by inhibiting inducible NO synthase enzymatic activity and attenuating nuclear factor-κB–mediated inducible NO synthase protein expression (26). Similarly, other reports also suggest that the *Coccinia cordifolia* extract could act through a variety of mechanisms including actions mimetic of those of sulfonylureas and biguanides (27).

The results of the present study suggest that *Coccinia cordifolia* has a potential hypoglycemic action independent of energy/food intake or weight loss and thus

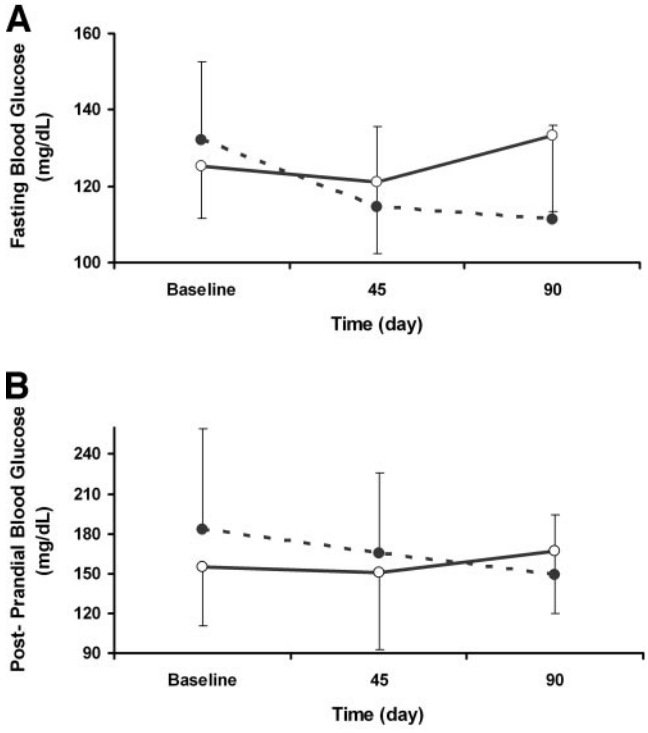

Figure 1—*Fasting and postprandial blood glucose levels of the subjects of the experimental (dashed line) and placebo (solid line) groups at baseline, day 45, and day 90 of the study.* n = *30 in the placebo group and 29 in the experimental group.* A*: Fasting blood glucose levels at the three different time points.* B*: Postprandial blood glucose levels at the three time points.*

could represent a possible dietary adjunct for the treatment of diabetes in patients with mild diabetes. However, the limitation of the present study is that insulin levels were not measured. Future studies are needed to more precisely define targeted populations with regard to disease classification, severity, and optimal adjunctive interventions. It will also be important to elucidate mechanisms of action so that the applicability to type 1 or type 2 diabetes can be clarified.

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