Effect of supplementation of Coccinia Cordifolia extract on newly detected diabetic patients

Rebecca Kuriyan PhD, Rajendran R MSc, Ganapathi Bantwal MD DM, Anura V Kurpad MD PhD

1 Division of Nutrition
Institute of Population Health and Clinical Research, Bangalore 560034, India
2 Green Chem Limited
Domlur, Bangalore, India
3 Associate Professor
Division of Endocrinology, Department of Medicine
St. John’s Medical College Hospital, St John’s National Academy of Health Sciences, Bangalore 560034, India

Running Title: Coccinia Cordifolia and diabetic patients

Corresponding author:
Rebecca Kuriyan
Division of Nutrition, Institute of Population Health and Clinical Research, St John’s National Academy of Health Sciences, Bangalore 560034, India
rebecca@iphcr.res.in

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ABSTRACT

Objective: Coccinia indica (synonym Coccinia cordifolia), a herb growing abundantly in India, has been used in the traditional treatment of diabetes mellitus. However, carefully controlled studies of its efficacy are lacking. This study aimed to evaluate the effectiveness of Coccinia 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 control, randomized study trial. Sixty incident type 2 diabetics (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 of an alcoholic extract of the herb for 90 days. Anthropometric, biochemical, dietary and physical activity assessment were carried out at baseline and were repeated at day 45 and day 90 of the study. All the subjects were provided with standard dietary and physical activity advice for the control of their blood sugars.

Results: There was a significant decrease in the fasting, post prandial blood glucose and glycosylated hemoglobin of the experimental group when compared to the placebo group. The fasting and post prandial 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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The prevalence of diabetes is increasing in all countries, especially in India, at an alarming rate. The various factors that contribute to the rise in the 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 the onset of diabetes and reducing the burden due to non-communicable diseases in India.

Plants or their extracts may also have a potential therapeutic role in the treatment for diabetes. Traditional health care systems, including herbal medicine are widespread in developing countries (2), and the care of diabetics 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 beta cells, or through extrapancreatic effects (3). Coccinia indica (synonym Coccinia cordifolia), a herb that belongs to the Cucurbitaceae family and that grows abundantly in India, has been widely used in the traditional treatment of diabetes mellitus (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 g/kg and 5.0 g/kg decreased blood glucose levels by approximately 50% after six hours (5). Oral administration of 200 mg/kg of an aqueous ethanolic extract of the Coccinia leaf and fruits for 45 days to diabetic animals demonstrated a significant reduction in blood glucose, glycosylated hemoglobin and increase in total hemoglobin and plasma insulin (6), suggesting that the administration of coccinia 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 six 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, for example, if 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/d (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

Subjects. 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 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 subjects) 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 sugar levels. The 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. After recruitment, the 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.

**Experimental Protocol.** 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 and concentrated. It was then purified to get a specific fraction of the extract, then dissolved in water and filtered. The clear filtrate was spray dried. Fifteen kg 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. Prior to 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 gm/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. The 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 the control of their blood sugars. 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 mid-arm, waist and hip circumferences. Skinfold measurements in triplicates were carried out using Holtain skinfold calipers, at four sites (i.e.) biceps, triceps, subscapular and suprailliac. The average sum of four skinfold measurements were used to compute body density using the age and gender specific equation (9) and percent 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 day 45 and day 90 of the intervention period.

**Biochemical measurements.** Fasting and post prandial blood glucose (collected 2 hours after breakfast), glycosylated hemoglobin and lipid profile were measured at baseline, day 45 and day 90 of the study period. The blood glucose, triglyceride, total and HDL cholesterol were estimated by spectrophotometric assays on automated clinical chemistry analyzer -Dimension RxL (Dade Behring, Newark, USA), while LDL cholesterol was calculated from primary measurements using the empirical formula of Friedewald equation (12). The glycosylated hemoglobin (HbA1c) was based on the turbidimetric inhibition immunoassay (TINIA) principle using the Dimension RxL (Dade Behring, Newark, USA). All assays were calibrated by use of Dade Dimension human calibrator (Dade Behring Inc, Newark, USA). The analytical coefficient of variation (inter-assay) for total cholesterol, triglycerides and HDL cholesterol were 4.1%, 4.7% and 4.1% respectively, while it was 2.6 % for glucose and 3.2 % for HbA1c.

**Dietary and Physical activity assessment.** Dietary assessment was carried out using a
24 hr recall at baseline, day 45 and day 90 of the intervention period. The data from the dietary recall was used to arrive at estimates of daily nutrient intake from standard recipes, using the published food composition databases (13,14). The routine physical activity pattern of the subjects was assessed using a questionnaire carried out at baseline, day 45 and day 90 of 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 Mean ± SD. An independent ‘t’ test analysis was performed to ascertain whether significant differences existed between the anthropometric and biochemical parameters of the subjects in the experimental and placebo group at baseline. A repeated measure 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. The repeated measure 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 are summarized in Table 1. The age range of the subjects in the experimental group was 35 to 58 years and 38 to 60 years in the placebo group. There were no significant differences in the mean age, weight, percent body fat, hemoglobin (Hb), glycosylated Hb, fasting blood glucose, post prandial blood glucose and 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 the change of body weight, BMI, waist circumference, hip circumference and percent body fat over time between the two groups (repeated measure ANOVA). At the end of the study period, no significant changes in body weight, BMI, percent body fat, waist and hip circumferences were observed in any of the group, when compared to baseline parameters.

A significant interaction effect was observed between time and the group (repeated measure ANOVA) in the fasting and post prandial blood glucose. The significant decrease (at day 90) in fasting blood glucose of the experimental group accounted for a mean change of 15.6% (20.6mg/dl) of the initial value. In contrast, the placebo group had a non significant 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 post prandial blood glucose of the experimental group (day 90) when compared to baseline values, while in the placebo group there was a non significant 7% (12 mg/dl) increase during the study period (Figure 1). There was a significant decrease in the glycosylated Hb of the experimental group at day 90 (6.1 ± 1.1 %) when compared to the baseline (6.7 ± 1.2%), while there was no change in the placebo group. There were no significant differences observed in the change of hemoglobin, total cholesterol, HDL cholesterol, LDL cholesterol and serum triglycerides over time between the two groups (repeated measure ANOVA). The LDL cholesterol of the experimental group was significantly lower (14.6%) at day 90 when compared to the initial values (repeated measures ANOVA). The total cholesterol of the placebo group had a non significant 8% reduction at day 90 (187.3 ± 37.9 mg/dl) when compared to baseline.
(203.6 ± 46.2 mg/dl), while the experimental group showed a non significant decrease of 7.6% from baseline to day 90 (207.1 ± 64.6 mg/dl vs 191.3 ± 41.8 mg/dl). Similar non significant results were observed in the HDL and triglyceride levels of placebo and experimental group 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 body mass index (26.2 ± 4.2 kg/m² at baseline and 26.2 ± 4.1 kg/m² 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% (65-100%) and 88% (38-100%) to prescribed physical activity, while in the placebo group it was 94% (50-100%) to prescribed diet and 84% (16.7-100%) to prescribed physical activity. The physical activity pattern of both the experimental and placebo group did not change during the study.

There were no serious adverse events reported by the subjects of the present study. In the experimental group, 17 (59%) of the subjects experienced mild hypoglycemic symptoms such as perspiration, excessive hunger and slight dizziness once or twice during the study period. The symptoms were mainly observed post prandially (mid-morning). These subjects were advised to consume a snack at that time, 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 the group of subjects and subsided within a week.

CONCLUSIONS

Approaches to the control of and prevention of hyperglycemia are central to the management of diabetes mellitus. 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 general public but also among health care providers, researchers, educators (15). Plant remedies may be appealing as an alternative and adjunctive treatment for diabetes.

There were no significant change in daily energy intake, body weight and body mass index 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 initiated by the subjects, even though self rated compliance to the dietary and physical activity advice was greater than 80% in both groups. Therefore, the results of the present study suggest that the decrease in fasting (16%) and post prandial blood (18%) glucose observed in experimental group could be attributed to the hypoglycemic effect of the coccinia cordifolia extract.

Coccinia indica (ivy gourd) synonym Coccinia cordifolia, 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 poorly controlled or otherwise untreated patients with type 2 diabetes, however there was no data
available if the 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 oral hypoglycemic agents (chlorpropamide) (16). The improvement in glycemic control observed in the group that was treated with the herb was similar to that with a conventional drug. However, no details were available on whether the body weight or food intake of the patients changed during the study period. Additional studies (17, 18) have also provided supporting evidence for the hypoglycemic effect of Coccinia indica. Yeh et al., 2003 (19), while assessing the quality of the evidence of herb for glycemic control, employed the American Diabetes Association Criteria for Clinical Guidelines (20) and rated Coccinia indica with 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 in the previous two human studies (7,16), in which 2-6 g/d 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 Glucose-6-phosphatase, lactase dehydrogenase (LDH) in glycolytic pathway and restore the LPL activity in 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 (PPAR γ) (24). Ethanolic extracts from Gynostemma pentaphyllum, a 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 synthesis by inhibiting iNOS enzymatic activity and attenuating NFKB-mediated iNOS protein expression (26). Similarly, other reports also suggest that the Coccinia extract could act through a variety of mechanisms including mimetic actions to sulfonylureas as well as biguanides (27).

The results of the present study suggest that Coccinia cordifolia (synonym Coccinia indica) has a potential hypoglycemic action independent of energy/food intake or weight loss and thus 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 can be clarified.

**ACKNOWLEDGEMENTS**

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REFERENCES

5. Faculty of Pharmacy, Mahidol University: *Thai Medicinal Plants*. Bangkok, Thailand, 1992.


### TABLE 1. Profile of subjects at baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (Mean ± SD)</th>
<th>Experimental (Mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>47.9 ± 5.9</td>
<td>46.2 ± 6.1</td>
<td>0.29</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>69.6 ± 13.2</td>
<td>65.0 ± 9.6</td>
<td>0.14</td>
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<tr>
<td>% Fat#</td>
<td>30.1 ± 7.9</td>
<td>28.6 ± 5.2</td>
<td>0.38</td>
</tr>
<tr>
<td>Hemoglobin (g %)</td>
<td>14.3 ± 2.1</td>
<td>14.6 ± 1.6</td>
<td>0.54</td>
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<tr>
<td>Glycosylated Hb (HbA1c) (%)</td>
<td>6.4 ± 0.9</td>
<td>6.7 ± 1.2</td>
<td>0.21</td>
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<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>125.3 ± 13.8</td>
<td>132.0 ± 20.6</td>
<td>0.15</td>
</tr>
<tr>
<td>Post prandial blood glucose (mg/dl)</td>
<td>154.7 ± 44.0</td>
<td>183.2 ± 75.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>203.6 ± 46.2</td>
<td>207.1 ± 64.6</td>
<td>0.81</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>39.4 ± 10.1</td>
<td>44.7 ± 13.4</td>
<td>0.09</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>138.3 ± 48.8</td>
<td>141.8 ± 50.3</td>
<td>0.79</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>185.0 ± 74.6</td>
<td>184.0 ± 131.3</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Mean ± Standard deviation (SD)

# - Calculated from the sum of four skinfold measurements and applying the formulae of Durnin and Womersley (1974)

No significant differences were observed in any of the parameters of the subjects of the two groups (independent 't' test)
**TABLE 2.** Anthropometric parameters of the subjects at baseline, day 45 and day 90 of the study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (Mean ± SD)</th>
<th>Experimental (Mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 45</td>
<td>Day 90</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>69.6 ± 13.2</td>
<td>69.4 ± 12.9</td>
<td>69.2 ± 13.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.5 ± 4.6</td>
<td>27.4 ± 4.7</td>
<td>27.3 ± 4.6</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.2 ± 9.0</td>
<td>90.1 ± 8.2</td>
<td>90.0 ± 8.9</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>97.0 ± 10.3</td>
<td>96.9 ± 10.3</td>
<td>97.6 ± 10.8</td>
</tr>
<tr>
<td>Percent Fat (%) #</td>
<td>30.1 ± 7.9</td>
<td>30.1 ± 7.3</td>
<td>31.1 ± 7.4</td>
</tr>
</tbody>
</table>

Mean ± SD

# - Calculated from the sum of four skinfold measurements and applying the formulae of Durnin and Womersley (1974)

n= 30 in placebo & n = 29 in experimental group

No significant interaction between time points and group (repeated measure ANOVA with group as between subject factor)

No significant difference observed between time points for each group (repeated measure ANOVA)
FIGURE 1

Fasting and Post-Prandial Blood Glucose Levels of the subjects of the Experimental and Placebo Group at Baseline, Day 45 and Day 90 of the study

n = 30 in placebo group and 29 in experimental group

Panel A – Fasting Blood Glucose levels at the different three time points
Panel B- Post-Prandial Blood Glucose levels at the three time points

X axis – Time point (experiment day)
Y- axis – Fasting/Post Prandial Plasma Glucose
Solid line refers Placebo group
Dashed line refers to experimental group