

Sambiloto (Andrographis Paniculata) Increases Glucagon–Like Peptide 1 Concentration in Prediabetes: A Double–Blind, Randomized, Placebo–Controlled Trial

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Abstract

Background : The extract of *Andrographis paniculata* (Burm. F.) Wall. Ex. Nees. (*sambiloto*) (茵陈 chuān xīn lián) has been reported to have antidiabetic effect on mice models and has been used traditionally in the community. The exact mechanism of *sambiloto* extract in decreasing plasma glucose is unclear, so we investigated the role of *sambiloto* extract in incretin pathway in healthy and prediabetes subjects.

Methods: This study was a double-blind, cross-over, randomized placebo-controlled trial. It was conducted to 38 healthy and 35 prediabetes subjects. All subjects were exposed to both intervention *sambiloto* extract and placebo alternately. All subjects were randomly assigned to receive first intervention for 14 days. There was wash out period between subsequent intervention. Primary outcome was glucagon-like peptide 1 (GLP-1) concentration and secondary outcomes were fasting insulin, 2-hour postprandial insulin, homeostasis model assessment of insulin resistance (HOMA-IR), fasting blood glucose, 2-hour postprandial blood glucose, dipeptidyl peptidase-4 (DPP-4), and glycated albumin before and after intervention.

Result: After the intervention, GLP-1 concentration significantly increased in prediabetes by 19.6% compared to the placebo ($p = 0.043$). There were no significant differences in the changes of fasting insulin, 2-hour postprandial insulin, HOMA-IR, fasting blood glucose, 2-hour postprandial blood glucose, DPP-4, and glycated albumin levels after intervention. *Sambiloto* extract did not inhibit DPP-4 enzyme in healthy and prediabetes subjects.

Conclusion: *Sambiloto* extract increased GLP-1 concentration without inhibiting DPP-4 enzyme in prediabetes subjects.

Trial Registration : Clinical Trials.gov ID : NCT03455049. Registered 6 March 2018 – Retrospectively Registered, <https://clinicaltrials.gov/ct2/show/NCT03455049>.

Background

Type 2 diabetes mellitus (T2DM) affects approximately 8.5 percent of global population or 415 million population. It is expected to increase to 642 million by 2040.¹ There are many groups of antidiabetic drug available but many of them have unfavorable side effects such as hypoglycemia, therefore the quest for a more ideal treatment for T2DM continues. The most current and extensively studied treatment of T2DM is incretin-based therapy.

Incretin are hormones released from the small intestine into the bloodstream as a response of food intake, especially carbohydrates. The main incretin hormones that are produced in the intestine are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which are produced mainly in ileal L cells and yeyunum K cells, respectively. Insulinotropic response of intestinal nutrient is mediated by incretin hormones.²

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From the perspective of incretin activity, there are robust evidences regarding the decrease of incretin effect in T2DM, but the exact mechanism remains unknown. There are several strategies to increase the incretin effect, such as the administration of exogenous subcutaneous GLP-1, oral administration of dipeptidyl peptidase-4 (DPP-4) enzyme inhibitors and oral administration of small molecule of GLP-1 receptor ligand. GLP-1 receptor ligand is a small molecule that can bind to a part of the GLP-1 receptor (GLP-1R), therefore the biological effect due to the binding of GLP-1 and GLP-1 receptor becomes more optimal, thus increasing the insulin secretion. Several phytochemicals were found to act as GLP-1 receptor ligand, however the number of evidences are limited.³

Phytotherapy has been developed for T2DM treatment with a variety of pharmacodynamic and pharmacokinetic properties. In addition, it has a minimal hypoglycemic effect, however only a few are accepted scientifically and have been evaluated for clinical effectivity.⁴ The mixture of phytochemical andrographolide and flavonoid (polyherbs) are more popular for the hypoglycemic effect.^{5,6} Flavonoids are small molecules that can act as ligands at the GLP-1 receptor and subsequently stimulate the insulin production and secretion.³ Natural and synthetic flavonoids can modulate GLP-1R in pancreatic beta cells, therefore more calcium ions can be transported intracellularly and further releasing insulin.⁷ In addition to flavonoid, andrographolide is the active ingredient of diterpene lactone component which has a hypoglycemic and antioxidant effect.⁸ Andrographolide works through the GLP-1 pathway as a voltage amplifier that is dependent on the potassium channel ($K^+ v$), both on the triggering and amplifying pathway.⁹ Andrographolide also has a hydroxyl group, then suspected as a ligand of GLP-1 receptor and modulates insulin production through increasing intracellular calcium.¹⁰

Plants containing andrographolide and flavonoids that is traditionally used as anti-diabetes drug is *Andrographis paniculata* (Burm. F.) Wall. Ex. Nees. (*sambiloto*) (茵陈 chuān xīn lián). Numerous studies had proved the hypoglycemic effects in andrographolide and flavonoids in animals and humans, however there is no available human study with the RCT and cross over method to find mechanism of action *sambiloto* in lowering blood glucose. In addition, studies regarding the role of GLP-1 receptor ligand (incretin enhancers) properties in andrographolide and flavonoid are very limited. Therefore, it's necessary to find small-molecular GLP-1 receptors ligand orally that have minimal side effect as a new antidiabetic drug.

Methods

Study design

This study was a randomized, double-blind, cross over design, placebo-controlled trial conducted at Dr. Cipto Mangunkusumo National Referral Hospital, Makara Health Centre Universitas Indonesia, and at taxi company in Jakarta, Indonesia. Intervention were randomized by using permuted block randomization by two-block size combination, namely *sambiloto* and placebo. The study was conducted according to the Helsinki Declaration and the Guideline for Good Clinical Practice by the International Conference on Harmonization. The protocol of the study was approved by Medical Research Ethic Committee at Faculty of Medicine, Universitas Indonesia. This trial also was registered in

ClinicalTrials.gov (NCT03455049).

Subjects

All subjects received written informed consent and signed it, before any study procedures occur. We performed screening to 184 subjects. There were 73 subjects who met the inclusion criteria. All subjects were enrolled and classified into 2 groups, healthy and prediabetes. All subjects were further randomized for *sambiloto* or placebo intervention.

Inclusion criteria were: (1) 18–60 years old male and female, (2) classified as healthy or prediabetes subjects by oral glucose tolerance test (OGTT), (3) normal liver and kidney function. A minimum sample size of 35 prediabetes and healthy subjects in each group provided a power of 80% with the assumption of a significance level of 0.05. Exclusion criteria were: (1) pregnant (2) breastfeeding (3) severe concomitant diseases and uncontrolled chronic diseases (4) diagnosed as malignancy disease (5) a current consumption of drugs that might affect blood glucose level, such as steroid and herbal supplements (bitter melon, red ginseng, cinnamon, *brotowali*, bay leaves).

Measurement

The subjects were examined three times during 35 days of intervention period: screening, visit 1, visit 2 (14 days after the first intervention), and visit 3 (14 days after the second intervention, end of the study). This study assessed GLP-1, fasting insulin, 2 hours postprandial insulin, homeostasis model assessment of insulin resistance (HOMA-IR), fasting blood glucose, 2 hours postprandial blood glucose, glycated albumin, and DPP-4 before and after intervention.

Treatments

This study used 550 mg of *sambiloto* extract capsule produced by Borobudur Herbs Company containing andrographolide 1.2% and flavonoid 0.8%. The placebo contains lactose 98% and magnesium 2%.

Statistical analyses

Descriptive data were expressed as mean (standard deviation) when the data is normally distributed, and median (minimal-maximal) when the data is not normally distributed. The difference in outcome parameter between intervention was assessed using T pair or Wilcoxon. Significance was considered at $p < 0.05$. All statistical analyses were performed using SPSS version 20.0 (IBM SPSS Inc. Chicago, USA).

To analyze the possible mechanism of *sambiloto* extract in glucose metabolism, we used path analysis with Stata.

Results

Subject characteristics

Among a total of 73 participants who completed the protocol of study, thirty eight subjects were healthy group and 35 subjects were prediabetes group (Fig. 1). The characteristic of the subjects was summarized in Table 1. Table 1 showed the mean of age of the prediabetes group was 47.03 (\pm 8.52) years old, ten years older than healthy subject group 37.55 (\pm 9.29) years old, and 52 (71.23%) of the subjects were male. Obesity rate was higher in prediabetes group (85.70%) than healthy group (60.50%). Prediabetes subjects have higher waist circumference when compared to healthy group. Smoking habits were found more in prediabetes subjects (65.80%) when compared to the healthy subjects (13.20%).

Table 1
Subject characteristics

| | Normal (n = 38) | Prediabetes (n = 35) |
|---------------------------------------|-----------------|----------------------|
| Age, years, mean (SD) | 37.6 (9.3) | 47.0 (8.5) |
| Gender, n (%) | 22 (57.9) | 30 (85.7) |
| Male | 16 (42.1) | 5 (14.3) |
| Female | | |
| Smoking Status, n (%) | 5 (13.2) | 23 (65.8) |
| Yes | 33 (86.8) | 12 (34.2) |
| No | | |
| Family History of T2DM, n (%) | 13 (34.2) | 7 (20) |
| Yes | 25 (65.8) | 28 (80) |
| No | | |
| Family History of Hypertension, n (%) | 8 (21.1) | 15 (42.9) |
| Yes | 30 (78.9) | 20 (57.2) |
| No | | |
| Family History of Dyslipidemia, n (%) | 5 (13.2) | 3 (8.6) |
| Yes | 33 (86.8) | 32 (91.4) |
| No | | |
| BMI, kg/m ² , n (%) | 3 (7.9) | (-) |
| Underweight (< 18.5) | 7 (18.4) | 1 (2.9) |
| Normal (18.5–22.9) | 5 (13.2) | 4 (11.4) |
| Overweight (23-24.9) | 23 (60.5) | 30 (85.7) |
| Obesity grade I and II (≥ 25) | | |
| Waist circumference, cm, mean (SD) | 86.334 (17.9) | 92.07 (12.9) |
| Male | 80.955 (15.6) | 91.50 (10.6) |
| Female | | |

SD: Standard deviation, min-max: minimum-maximum, T2DM: Type 2 diabetes mellitus, BMI: Body mass index, ALT: Alanin Aminotransferase, eGFR: estimated glomerular filtration rate

| | Normal (n = 38) | Prediabetes (n = 35) |
|--|-----------------|----------------------|
| Laboratory test | 19.50 (7–73) | 25 (9-131) |
| ALT, U/L median (min.-max.) | 1.00 (0–1.0) | 1.00 (0.50–1.8) |
| Creatinin, mg/dL, median (min.-max.) | 112.32 (20.0) | 84.71 (12.9) |
| eGFR, mL/1.73 m ² /minute, mean (SD) | | |
| SD: Standard deviation, min-max: minimum-maximum, T2DM: Type 2 diabetes mellitus, BMI: Body mass index, ALT: Alanin Aminotransferase, eGFR: estimated glomerular filtration rate | | |

Changes of parameter values in healthy subjects

After the intervention of *sambiloto* extract or placebo, the level of GLP-1, fasting insulin, fasting blood glucose, DPP-4 enzyme, and HOMA-IR were increased although these changes were not statistically significant. However, the level of two hours postprandial insulin, two hours postprandial blood glucose, and glycated albumin were decreased, although these changes were not statistically significant. The summary was expressed in Table 2.

Table 2

Comparison of parameters before and after *Sambiloto* extract or placebo interventions in normal subjects (n = 38)

| Parameter | Pre <i>Sambiloto</i> | Post <i>Sambiloto</i> | Δ <i>Sambiloto</i> | Pre Placebo | Post Placebo | Δ Placebo | P-Value Δ |
|---|-----------------------|-----------------------|---------------------------|-----------------------|----------------------|------------------------|--------------------|
| GLP-1, pmol/L, Median (min.-max.) | 1.9 (0.8– 15.4) | 2.9 (0.7– 12.4) | 0.4 (-11.9- 10.5) | 1.9 (0.8– 15.4) | 2.8 (0.7– 9.9) | 0.5 (-12.7- 8.2) | 0.911 ^a |
| Fasting Insulin, mU/L, Mean (SD) | 16.5 (12.1) | 18.1 (9.2) | 1.6 (6.7) | 16.5 (12.1) | 17.6 (11.0) | 1.1 (7.5) | 0.605 ^a |
| 2 Hour Postprandial Insulin, mU/L, Mean (SD) | 65.2 (44.1) | 65.1 (43.6) | -0.1 (52.0) | 65.2 (44.1) | 62.1 (35.8) | -3.1 (39.6) | 0.613 ^a |
| HOMA-IR, Mean (SD) | 3.3 (2.7) | 3.7 (2.2) | 0.4 (1.6) | 3.3 (2.7) | 3.5 (2.4) | 0.2 (1.7) | 0.204 ^a |
| FBG, mg/dL, Mean (SD) | 78.79 (8.91) | 80.55 (9.17) | 1.76 (8.18) | 78.79 (8.91) | 80.08 (8.97) | 1.29 (8.52) | 0.691 ^a |
| 2 Hour Postprandial Blood Glucose, mg/dL, Mean (SD) | 93.84 (20.94) | 93.71 (26.38) | -0.13 (29.51) | 93.84 (20.94) | 88.39 (23.95) | -5.45 (25.44) | 0.253 ^a |
| DPP-4, ng/mL, Mean (SD) | 421.51 (115.35) | 431.04 (110.31) | 9.53 (65.80) | 421.51 (115.35) | 433.11 (123.29) | 11.59 (61.78) | 0.838 ^a |
| GA, %, Mean (SD) | 12.54 (1.12) | 11.63 (1.29) | -0.91 (1.17) | 12.54 (1.12) | 11.63 (1.44) | -0.91 (1.00) | 0.973 ^a |
| GA: Glycated albumin. Comparative analysis using ^a : paired t-test | | | | | | | |

Changes of parameter values in prediabetes subjects

There was a statistically significant increasing in GLP-1 levels in prediabetes subjects after intervention ($p = 0.043$) compared with placebo. Changes also occurred in other parameters but not found to be statistically significant. Changes in parameters after intervention can be seen in Table 3.

Table 3

Comparison of parameters before and after *Sambiloto* extract or placebo interventions in prediabetes subjects (n = 35)

| Parameter | Pre <i>Sambiloto</i> | Post <i>Sambiloto</i> | Δ <i>Sambiloto</i> | Pre Placebo | Post Placebo | Δ Placebo | P-Value Δ |
|--|----------------------|-----------------------|---------------------------|--------------------|--------------------|----------------------|---------------------|
| GLP-1, pmol/L, Median (min.-max.) | 2.7 (0.2–40.1) | 3.2 (1.0-35.5) | 0.3 (-4.6-5.9) | 2.7 (0.2–40.1) | 2.96 (0.6–34.6) | -0.2 (-5.5-4.4) | 0.043 ^{a*} |
| Fasting Insulin, mU/L, mean (SD) | 18.7 (6.4–60.2) | 18.9 (8.6–74.8) | 0.0 (-30.0-14.8) | 18.7 (6.4–60.2) | 20.0 (9.3–79.6) | 0.2 (-32.5-54.3) | 0.363 ^b |
| 2 Hour Postprandial Insulin, mU/L, Mean (SD) | 96.4 (26.7) | 89.20 (31.84) | -7.27 (25.87) | 96.47 (26.70) | 90.11 (32.37) | -6.36 (28.14) | 0.869 ^a |
| HOMA-IR, Mean (SD) | 4.8 (1.9–14.2) | 5.1 (2.0-19.4) | -0.1 (-10.2-6.2) | 4.8 (1.9–14.2) | 4.6 (2.2–20.4) | -0.2 (-10.6-14.2) | 0.523 ^b |
| FBG, mg/dL, Mean (SD) | 106.2 (11.3) | 102.2 (12.2) | -4.0 (15.4) | 106.2 (11.3) | 101.1 (12.2) | -5.1 (14.7) | 0.578 ^a |
| 2 Hour Postprandial Blood Glucose, mg/dL, Mean (SD) | 140.5 (33.6) | 146.9 (40.0) | 6.5 (35.5) | 140.5 (33.6) | 140.5 (38.9) | 0.1 (42.3) | 0.336 ^a |
| DPP-4, ng/mL, Mean (SD) | 561.8 (175.8) | 598.6 (207.4) | 36.8 (113.1) | 561.8 (175.8) | 610.6 (208.5) | 48.8 (98.7) | 0.515 ^a |
| GA, %, Mean (SD) | 12.7 (1.7) | 12.6 (1.8) | -0.1 (0.8) | 12.7 (1.7) | 12.6 (1.7) | -0.1 (1.0) | 0.937 ^a |
| Comparative analysis using ^a : pair t-test and ^b :Wilcoxon. *: statistically significant if p < 0.05 | | | | | | | |

Safety

In this research there were 5 adverse events (2 participants in healthy subjects and 3 participants in prediabetes subject). Complaints were hand tremor, red spots in faces, itchiness, lethargy, weakness, diarrhea, and palpitation after the consumption of the capsules. All the subjects were withdrawn from the study and considered as drop out. All events were recorded and submitted as written report to the ethical committee. There were no serious adverse event occurred during clinical trials.

Discussion

Most of the subjects in this study were male, similar to a previous study completed by Soewondo et al.¹⁷ which identified male gender as a prediction factor for prediabetes in Indonesia (OR 0.8). This finding was due to that most of the subjects screened were taxi drivers (57.60%). Most of the prediabetes subjects was in obesity and overweight condition. The study by Sirait et al.¹⁸ found that risk of T2DM in mild obesity was two times greater, in moderate obesity was five times greater, while severe obesity was ten times greater than in non-obese individuals. Waist circumference was also showed to be greater in prediabetes subject compared to healthy subjects. From the description of the characteristics, it can be concluded that cardiovascular risk factors were more common found in the prediabetes subjects. According to the study of Michaliszyn et al.¹⁹ beta cell glucose sensitivity decreased 30% in prediabetes and 65% in T2DM. Similar condition with the incretin effect that decrease 32% in prediabetes and 38% in T2DM.

Effects of sambiloto (*Andrographis paniculata*) extract on GLP-1 and DPP-4 enzyme levels

This study showed that administration of *sambiloto* extract in healthy subjects increased GLP-1 level, but the increasing GLP-1 level also occurred in the placebo group. These findings indicate that an increased GLP-1 level is not caused by *sambiloto* effect, but other confounding factors such as the physiological response of postprandial glucose test with 75 gram of oral glucose solution.

The administration of *sambiloto* extract in the prediabetes subjects increased GLP-1 levels by 19.6% and was statistically significant when compared with placebo ($p = 0.043$). These results were similar to the study of Purnomo et al. in diabetic rats given *Urena lobata*, herbs contains flavonoids that can increase GLP-1 level.¹¹

This study found an increasing of DPP-4 enzyme levels in both healthy and prediabetes subjects. The purpose of testing DPP-4 enzyme levels in this study was to show that the mechanism of action of *sambiloto* extract was through the GLP-1 pathway and not through the inhibition of DPP-4 enzyme. If the *sambiloto* extract worked through the DPP-4 enzyme inhibition, it was expected that there will be a decrease of the enzyme.¹² In this study we found an increasing of GLP-1 and DPP-4 enzymes, therefore it could be concluded that the *sambiloto* extract works through the GLP-1 pathway and not through the inhibition of DPP-4 enzyme. This result was in accordance with the study conducted by Riyanti that the *Andrographis paniculata* extract only inhibits the DPP-4 enzyme by 37%, while other plants such as *Trigonella foenum-graecum L* can inhibit the DPP-4 enzyme by 71%.¹³

Effects of sambiloto (*Andrographis paniculata*) extract on fasting insulin levels and HOMA-IR

The fasting insulin levels increased after administration of *sambiloto* extract and placebo in the healthy subjects. This result was in line with the increasing HOMA-IR in the healthy subjects which reflects an insulin resistance status. In healthy subjects insulin resistance status can change rapidly because of

many factors such as physical activity, food intake consumed, psychological condition, the presence of other metabolic stresses, and hormonal changes associated with glucose and insulin homeostasis.

In the prediabetes subjects, fasting insulin levels had no change after the administration of *sambiloto* extract, however there was a decrease of HOMA-IR. In contrast, the administration of placebo increased the fasting insulin level but also followed by a decrease of HOMA-IR. These findings suggesting the improvement of insulin resistance could be followed by the decreasing level of fasting insulin. This finding similar with study in diabetes rats that andrographolid can ameliorate HOMA-IR .14

Effect of *sambiloto* (*Andrographis paniculata*) extract on 2-hour postprandial insulin level

Two-hour postprandial insulin level was decreasing followed by a decrease of blood glucose level after intervention *sambiloto* and placebo in healthy subjects. A decrease in insulin levels in this study was not necessarily followed by an increase of blood glucose levels due to many confounding factors such as counterregulatory hormones, peripheral glucose uptake, and insulin levels in the blood.15

There was a decrease of 2-hours postprandial insulin levels followed by an increase of 2-hours postprandial blood glucose levels after intervention *sambiloto* and placebo in prediabetes subjects, therefore suggesting a decrease in insulin would further increase the level of blood glucose. A decrease in postprandial insulin levels was not appropriate as there was an increase of GLP-1 level in prediabetes subjects. It was difficult to answer this discrepancy due to the unavailable serial examinations of the blood glucose, GLP-1, and insulin levels. A serial examination would demonstrate the dynamics of each parameter, therefore we can observe the exact interactions between the three parameters. There were some factors that can influence the postprandial insulin level, such as a standardized daily calorie intake, physical activity before the examination, and psychological factors of the subject. Those factors were not standardized in this study.16–18

Effects of *sambiloto* (*Andrographis paniculata*) extract on glycemic control

In both groups, healthy and prediabetes, there was a decrease in the glycated albumin for 14 day of treatment. However, the changes were not statistically significant when compared to placebo. This finding suggested that during treatment the average blood glucose level was decreasing.

In healthy subjects, there was an increase in fasting blood glucose in both interventions. This finding suggested that in healthy subjects, the homeostasis of blood glucose is still adequate to compensate any changes of hormonal condition. In prediabetes subjects, the fasting blood glucose also decreased in both interventions and consistent with a decrease in glycated albumin. This finding was similar with a study in prediabetes rats which was given *Psidium guajava*, the herbs that contains flavonoid.19 Another study explained that andrographolide can inhibit gluconeogenesis, subsequently followed by a decreased of fasting blood glucose.20

In healthy subject found the decrement of 2-hour postprandial blood glucose after intervention either *sambiloto* extract or placebo. Contrary in prediabetes subject there was a decrease of 2-hour postprandial

insulin followed by increasing of 2-hour postprandial blood glucose. This finding was unexpected because there was the increment of GLP-1 after receiving *sambiloto* intervention. The explanation of this phenomenon was possibly due to the GLP-1 resistance in prediabetes, in which GLP-1 failed to stimulate the production of insulin, therefore followed by the increased in 2-hour postprandial level of blood glucose. Many studies reported GLP-1 resistance in prediabetes and T2DM, therefore one method of diabetes treatment today is to increase incretin effect.^{21,22}

Conclusion

The extract of *sambiloto* increased GLP-1 concentration without inhibiting the DPP-4 enzyme in prediabetes subjects.

List Of Abbreviations

DPP-4: Dipeptidyl peptidase-4;

GIP: Glucose-dependent insulinotropic peptide;

GLP-1: Glucagon-like peptide 1;

GLP-1R: Glucagon-like peptide 1 receptor;

HOMA-IR: Homeostasis model assessment of insulin resistance;

OGTT : Oral glucose tolerance test

RCT: Randomized controlled trial;

T2DM: Type 2 diabetes mellitus.

Declarations

Ethic approval and consent to participate

This study was approved by Health Research Ethics Committee, Faculty of Medicine, University of Indonesia (No: 798/UN2.F1/ETIK/2017), and registered in Clinical Trials.gov (ID : NCT03455049).

Consent for Publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they no have a conflict of interest.

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Authors' contribution

Idea, study design: TJET, EHP, Y, N, IS; Data collection and analysis: TJET, JP, MRS; Writing draft for publication: TJET, IS

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Figures

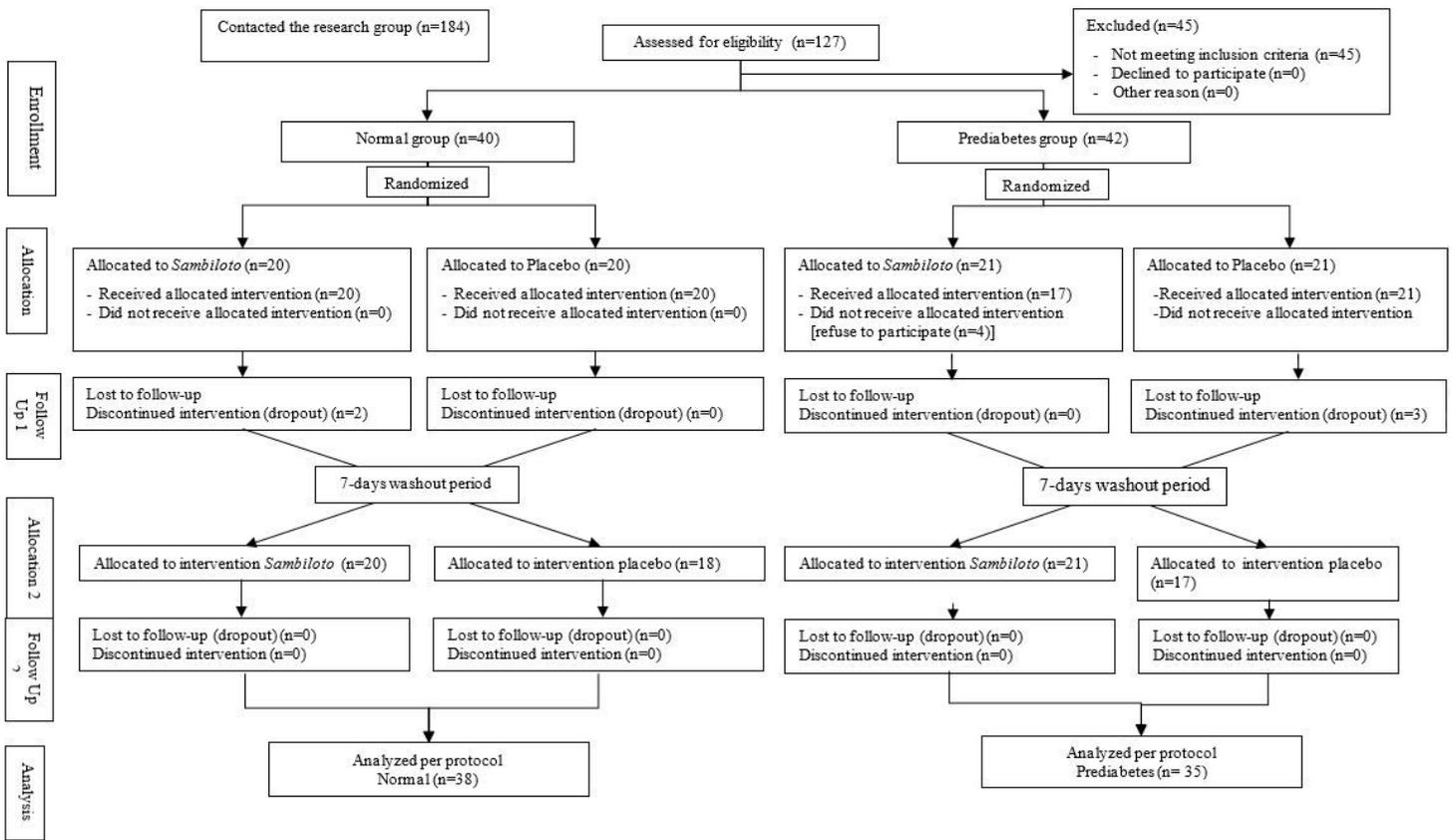


Figure 1

Consort flow diagram