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A Randomized, Multi-Centre, Double Blind, Placebo-Controlled, Three Arm Study To Evaluate The Safety And Efficacy Of iCoffee In Managing Post-Prandial Blood Glucose Levels In Healthy Volunteers

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ABSTRACT

Prediabetes, also known as intermediate hyperglycaemia, is a high-risk state for diabetes. It is defined as glycaemic variables that are higher than normal, but lower than the diabetes threshold. About 5–10% of people per year with prediabetes will progress to diabetes, with the same proportion converting back to normoglycemia. iCoffee is a proprietary ayurvedic health promoter for blood sugar support. The active component used in iCoffee is *Salacia reticulata.* The root is extracted and is called by the brand name Salcital. The study goal was to assess the safety and efficacy of iCoffee for managing post-prandial blood glucose levels in healthy volunteers. The study included 80 healthy adult male and female subjects who were instructed to take iCoffee twice daily. The investigational product, either active or placebo, was given for a period of 3 months (90 days). All volunteers were randomized into active and placebo groups (3:3:2 ratio). The vital sign parameters were found to be normal for all the study subjects and did not have any clinically or statistically significant abnormal values when compared between and within groups, implying that the test product has no safety issues observed after 90 days of oral administration. iCoffee has demonstrated an excellent safety profile when administered orally. Prediabetic subjects in iCoffee group showed significant improvement in fasting and post prandial blood glucose levels. HbA1c values, Serum insulin, 2 h oral glucose tolerance and insulin sensitivity were same as that of control group arm at the end of the study (Day 90). These results corroborate even with various cholesterol parameters (LDL, HDL, VLDL, TC and TG) and also the mental alertness questionnaire which shows that the mean/average values of mental alertness improved in the iCoffee receiving group. This study clearly indicates that iCoffee has significant anti-inflammatory (hsCRP & IL-6) effect in the pre-diabetic subjects as well. Therefore, it is concluded that iCoffee has a definite role in improving the pre-diabetic condition along with improving the mental alertness when the subjects administered the product orally for 90 consecutive days.

Keywords: iCoffee, Prediabetes, safety, *Salacia reticulata*

INTRODUCTION

Prediabetes, also known as intermediate hyperglycaemia, is a high-risk state for diabetes. It is defined as glycaemic variables that are higher than normal, but lower than the diabetes threshold. About 5–10% of people per year with prediabetes will progress to diabetes, with the same proportion converting back to normoglycemia. The worldwide prevalence of prediabetes is increasing and experts have projected that more than 470 million people will have prediabetes by the year 2030. Prediabetes is associated with the simultaneous presence of insulin resistance and β-cell dysfunction and abnormalities that start before glucose changes are detectable. Those individuals suffering from prediabetes may often suffer from hyperlipidaemia, hypertension, and insulin resistance-linked obesity—all factors that sharply increase the risk of heart disease. Management includes reducing cardiovascular disease risk factors, specifically lipid and blood pressure abnormalities. Intensive lifestyle intervention is required to prevent progression of prediabetes to diabetes.

Ayurveda which means ‘Science of life’ is derived from the Sanskrit words ‘Ayur’ meaning life and ‘Veda’ meaning knowledge. It takes an integrated view of the interactions of the physical, mental, spiritual and social aspects of the life of

human beings. Ayurveda was first referred to in the Vedas (Rigveda and Atharva Veda 1500 BC). Ayurveda aims to keep the structural and physiological entities in a state of equilibrium, which signifies good health. Any imbalance due to internal or external factors may cause disease. Ayurveda largely uses plants as a raw material for the manufacture of drugs, though materials of animal and marine origin, metals and minerals are also used.

Diabetes mellitus (Madhumeha) was known to ancient Indian physicians and an elaborate description of its clinical features and management appears in Ayurvedic texts. The causes of Diabetes mellitus are comparable to the disease entity Prameha/Madhumeha of Ayurveda. The major categories of the etiological factors are genetic and hereditary factors and lifestyle related errors such as sedentary habit and high calorie diet. The texts also describe the pathogenesis of this disorder in an extremely evolved manner, involving the three Doshas (Kapha predominant doshas) and ten Dushyas (ranging from Rasa to Ojas, especially Meda). The idea of significance of Meda (Adipose tissue) as the principal Dushya has been recently confirmed also in modern medicine where the central obesity and dyslipidaemia are being considered as the main components of the basic matrix of this disease. Prediabetes and Type 2 DM is largely a preventable disease, while Type 1 DM is generally manageable. However, it is not curable once it is established in the organism. Ayurvedic practitioners treat diabetes with a multi-pronged approach, using diet modification, Panchkarma to cleanse the system, herbal preparations, yoga and breathing exercises. The Ayurvedic herbal preparations believed to lower sugar levels and also proprietary Ayurvedic medications are also used to treat diabetes. This study uses a polyherbal combination to decrease conversion from prediabetes to diabetes with proposed no reported adverse events. Charaka Samhita written by Acharya Charaka Maharshi is the foundation text of Ayurveda, dating back to the period of 900 BC – 700 BC. Ekanayakam/Saptaranga known as *Salacia reticulata* is documented in Sahasrayogam for the management of madhumeha (Diabetes mellitus) and used extensively for centuries. iCoffee is a proprietary ayurvedic health promoter for blood sugar support. The active component used in iCoffee is *Salacia reticulata* roots extract branded as Salcital. After successfully neutralizing the taste of salcital and other herbal extracts, the poly-herbal synergistic combination is blended with superior quality coffee beans sourced from Coorg region of Karnataka. This product is best to manage Diabetes without compromising the authentic taste of coffee.

iCoffee is basically made from those Ayurvedic ingredients which are more powerful for managing diabetes. This iCoffee helps in reducing sugar level and support in regulating insulin levels in the body. *Salacia reticulata* is a wonder herb for optimum glycemic control in the pre diabetic and diabetes conditions. Polyphenols and mangiferin, supports healthy blood sugar levels. iCoffee known for preventing complications of diabetes and it also helps in supporting metabolic health and obesity related conditions. iCoffee has a potent antioxidant property with significant triglyceride and cholesterol lowering effects that aid in weight loss. It can be predicted that daily intake of this formulation may be beneficial in managing hyperlipidaemia, reduce the risk of an individual in developing micro- and macrovascular complications including coronary heart disease, cardiovascular and cerebrovascular diseases. Salcital has antidiabetic and anti-obesity activity by inhibiting α-glucosidase and pancreatic lipase enzymes for maintaining normal blood glucose level and healthy lipid profile.

STUDY OBJECTIVES

1. The primary objective was to evaluate the safety of iCoffee in male or female subjects.

2. The secondary objective was to evaluate the efficacy of iCoffee in the management of post- prandial blood glucose levels in male or female healthy subjects.

STUDY DESIGN

Design: A Randomized, multi-center, double blind, parallel assignment, placebo-controlled, three arm study.

Study Treatment Allocation: All 80 subjects were randomized into active and placebo groups (3:3:2 ratio) and given the following;

Group I - iC

Group II - Sl®

Group III - Pb

Number of Subjects: 80 subjects (30+30+20) healthy adult male and female subjects.

Randomization (assignment to treatment sequence): Investigational products duly labelled with randomization codes were provided to the investigators by the sponsor. As per the randomization schedule the investigator / designee dispensed IP sachets, two for each subject/day. The IPs sachets were kept by the investigator in a safe but accessible place.

Overall Study Plan

After obtaining the Ethics committee approval subjects were asked to visit the site. Informed consent was administered to study volunteers, and after obtaining their consent in writing, the subjects were asked about their medical history and the Investigator or his/her designee will conduct a physical examination. Demographics and vital signs were recorded. Blood sample were drawn from each subject for analysis of hematology, biochemistry and virology. Subjects were enrolled into the study after all the IC/EC criteria are met. Once the subject was found to be eligible, he or she was asked to visit the site as baseline visit (Day 0) where the IPs was dispensed sufficiently until next scheduled visit.

Clinical Phase

Procedure

I: Procedure

a) Screening Visit:

i. Informed consent
ii. Demographics
iii. Medical History
iv. Physical examination (Height, Weight, BMI)
v. FBG
vi. HbA1c
vii. 2h-OGTT
viii. Concomitant Medication Review
ix. Vital Sign (temp, pulse, BP and respiratory rate)
x. Serum Insulin
xi. Insulin Sensitivity Index
xii. CBC/ Hematology
xiii. RFTs
xiv. LFTs
xv. Lipid profile
xvi. Inflammatory Markers [hsCRP, IL-6]
xvii. Urine Pregnancy Test
xviii. Mental Alertness

b) Visit-1 (Day 0)

i. Randomiztion
ii. IP dispensing and Accountability
iii. Concomitant Medication Review
iv. Vital Sign (temp, pulse, BP and respiratory rate)
v. Nutrition diet chart and subject diary
vi. Adverse Event Review and Evaluation

c) Visit-2 (Day 30±5 days)

i. Physical examination (Height, Weight, BMI)
ii. FBG
iii. IP dispensing and Accountability
iv. Concomitant Medication Review
v. Vital Sign (temp, pulse, BP and respiratory rate)
vi. CBC/ Hematology
vii. RFTs
viii. LFTs
ix. Mental Alertness
x. Adverse Event Review and Evaluation

d) Visit-3 (Day 90±5 days)

i. Physical examination (Height, Weight, BMI)
ii. FBG
iii. HbA1c
iv. 2h-OGTT
v. Concomitant Medication Review
vi. Vital Sign (temp, pulse, BP and respiratory rate)
vii. Serum Insulin
viii. CBC/ Hematology
ix. RFTs
x. LFTs
xi. Lipid profile
xii. Insulin Sensitivity Index
xiii. Inflammatory Markers [hsCRP, IL-6]
xiv. Mental Alertness
xv. Adverse Event Review and Evaluation
xvi. Organoleptic /Feedback Questionnaire

II) Diagnostic Laboratory Tests

The following tests will be performed during screening of volunteers;

i) Hematology

- RBC
- Total and differential leukocyte count
- Platelet count

ii) Serum Chemistry

- FBG
- HbA1c
- 2h-OGTT
- Serum Insulin
- RFT – Creatinine, Urea.
- LFT - Total bilirubin, ALT (SGPT), AST (SGOT)
- Lipid profile.
- Inflammatory Markers [hsCRP, IL-6]

iii) Urine analysis

- Physical Examination – Colour, Appearance and Specific gravity
- Chemical Examination – pH, Protein, Glucose, Bile salt and Bile pigments
- Microscopic examination –Pus cells, Epithelial Cells, Bacteria, RBCs, Casts, Crystals and Bacteria.
- Urine pregnancy test.

Inclusion Criteria

Subjects fulfilling following criteria were included in the study:

1. Adult males and non-pregnant females aged 18 to 55 years
2. Subjects who agree to stop from using supplements during the study period.
3. Willing to give inform consent form
4. Subjects willing to follow the suggested diet plan.
5. Having a diagnosis of pre-diabetes (impaired fasting glucose or impaired glucose tolerance) and meeting one of the following criteria.

i. Fasting Plasma Glucose 100 to 125 mg/dL, fasting is defined as no caloric intake for atleast 8h, **OR**

ii. 2-h Post load Glucose 140 to 199 mg/dL during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75g an hydrous glucose dissolved in water. **OR**

iii. Glycosylated hemoglobin (Hb1A1C) 5.7 to 6.4%. The test should be performed in a laboratory using a method that is NABL certified.

6. Subjects with BMI $\geq$ 25 kg/m^2

Exclusion criteria:

Subjects fulfilling any one of the following criteria were excluded from the study:

1. History of Type I or Type II Diabetes Mellitus
2. A know history or present condition of allergic response to any pharmaceutical products and supplements
3. Any history suggestive of micro vascular or macro vascular disease
4. Administration of any form of pharmacotherapy for the management of pre- diabetes in last 3 months.
5. Impaired renal function; eGFR<60 mls/min/1.73m^2.
6. Known history of any chronic illness taking regular pharmacological agents.
7. Women in child bearing age unable to practice any form of contraception
8. Subjects who are pregnant or lactating
9. Subjects on herbal supplements/any other wellness product
10. History of alcohol, tobacco, substance or drug abuse
11. Subject who has participated in a clinical study within the last 30 days prior to entering this study.
12. Subject with hypersensitivity to any of the ingredients of the study products.
13. Refusing consent or physician uncomfortable with patient compliance to treatments or follow up.

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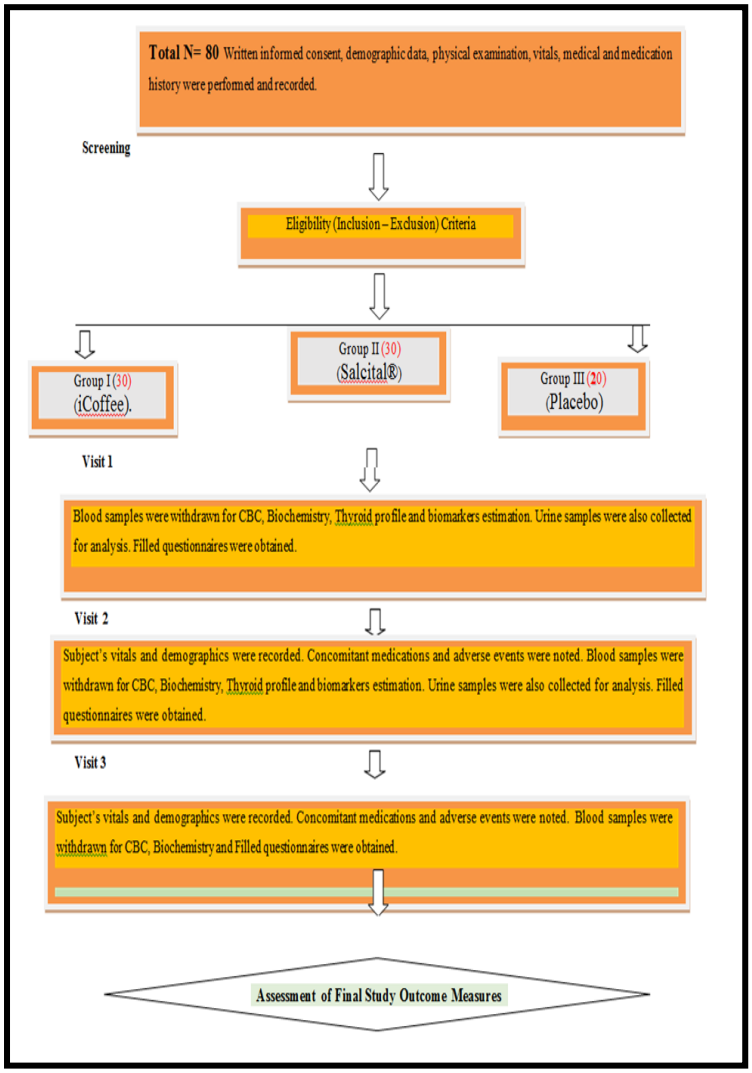
Flow Chart of Study Activities



ASSESSMENT OF SAFETY

Specification of Safety Parameters

The study's safety parameters included vital signs and adverse events, which were compared from the subjects' baseline to the final visit.

Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Adverse Events

AE, if any, were reported as per the guidelines of ICH E6. Any medical condition that was present at the time that the subject was screened were considered as baseline and not reported as an AE. However, if it deteriorated at any time during the study, it was recorded as an AE. All AEs were graded for severity (mild, moderate, severe and life threatening) and relationship to the study product (associated or not associated).

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience (SAE) when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. All SAEs were recorded on the appropriate CRF and SAE form, followed through with resolution by a study clinician reviewed and evaluated by a study clinician.

Reporting Procedures

For Adverse Events (AEs)

- Through telephone contacts and subject visits to the study site, the Investigator and/or designee inquired about adverse experiences and document the inquiry in the subject's medical chart.
- During visits to the site, the Monitor ensured that if an adverse experience was found, the Study Coordinator documented the following in the subject's chart and Case Report Form:
    - Date and time (if applicable) the event started and ended.
    - Description to the event.
    - Severity of the event.
    - Outcome of the event.
    - Action taken and
    - Relationship to study supplement

Treatment of Subjects

All 80 subjects were provided with 1 sachet of the investigational product, either active or placebo, which was administered b.i.d (twice a day) 30 min before breakfast and dinner with 100-120 ml hot water.

Randomization

Investigational products duly labelled were provided to the investigators by the sponsor through Radiant Research. Randomization codes were generated. The IPs were kept by the investigator in a safe but accessible place.

Statistical Analysis

The data generated from individual CRFs were compared between groups from Day 0 till Day 90. Student t test was employed for analyzing efficacy values between different visits, while 'p' value <0.05 was considered as statistical significance for the study.

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RESULTS

The IP codes for the 3 groups were un-blinded towards end of the study during statistical analysis and it was revealed that Group I /Treatment A – received iCoffee, Group II/Treatment B– received Salcital® and Group III/Treatment C -received Placebo products respectively.

Demographics and baseline characteristics

Table1 A: Descriptive statistics–Demographics: Age, Sexand Waist Circumference

Parameter/Statistics	Treatment A	Treatment B	Treatment C
Age (Years)			
N	30	30	20
Mean (SD)	45.5 (5.91)	44.6 (4.83)	46.0 (6.48)
Median	47.0	45.0	47.0
Min, Max	34, 55	35, 55	35, 55
Sex n (%)			
Female	10 (33.3)	14 (46.7)	7 (35.0)
Male	20 (66.7)	16 (53.3)	13 (65.0)
Waist Circumference			
N	30	30	20
Mean (SD)	97.0 (9.93)	93.7 (9.11)	94.3 (11.00)
Median	96.5	91.0	96.0
Min, Max	80, 120	80, 120	80, 112

Table1B: Descriptive statistics–Demographics (Height, Weight, BMI)

Parameter/ Statistics	Visit	Height (in Centimeters)			Weight (in Kilograms)			BMI (in kg/m^2)		
		Treat-ment A	Treat-ment B	Treat-ment C	Treat-ment A	Treat-ment B	Treat-ment C	Treat-ment A	Treat-ment B	Treat-ment C
N	Screening	30	30	20	30	30	20	30	30	20
Mean (SD)	Screening	165.3 (6.76)	164.5 (7.24)	166.9 (7.00)	82.3 (7.81)	82.2 (6.64)	80.1 (8.30)	30.24 (3.831)	30.54 (3.722)	28.80 (3.215)
Median	Screening	166.0	164.0	167.0	81.0	82.0	82.0	30.10	29.75	27.56
Min, Max	Screening	148,175	150,175	152,178	69,96	69,96	63,96	26.1,40.3	25.9,39.1	25.2,37.4
N	Visit 1	30	30	20	30	30	20	30	30	20
Mean (SD)	Visit 1	165.3 (6.76)	164.5 (7.24)	166.9 (7.00)	82.3 (7.81)	82.2 (6.65)	80.1 (8.30)	30.24 (3.831)	30.54 (3.732)	28.80 (3.215)
Median	Visit 1	166.0	164.0	167.0	81.0	82.0	82.0	30.10	29.75	27.56
Min, Max	Visit 1	148,175	150,175	152,178	69,96	69,96	63,96	26.1,40.3	25.9,39.1	25.2,37.4
N	Visit 3	30	30	20	30	30	20	30	30	20
Mean (SD)	Visit 3	165.3 (6.76)	164.5 (7.24)	166.9 (7.00)	77.8 (7.72)	77.7 (6.37)	76.2 (8.15)	28.59 (3.626)	28.88 (3.445)	27.38 (3.033)
Median	Visit 3	166.0	164.0	167.0	78.0	77.5	77.5	27.96	28.58	26.04
Min, Max	Visit 3	148,175	150,175	152,178	62,91	64,92	60,91	24.8,38.5	24.4,36.4	24.4,35.1

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Safety Results:

Table 2 A: Descriptive statistics for vital signs: Temperature, Heart rate

Parameter/ Statistics	Visit	Temperature (Fahrenheit)			Heart rate (beats/min)		
		Treatment A	Treatment B	Treatment C	Treatment A	Treatment B	Treatment C
N	Screening	30	30	20	30	30	20
Mean (SD)	Screening	98.04 (0.315)	98.16 (0.353)	98.15 (0.352)	75.9 (5.76)	76.4 (5.30)	78.2 (5.06)
Median	Screening	98.10	98.20	98.15	77.5	76.5	79.0
Min, Max	Screening	97.6,98.6	97.4,98.7	97.6,98.6	64,85	66,84	66,84
N	Visit 1	30	30	20	30	30	20
Mean (SD)	Visit 1	98.06 (0.352)	98.30 (0.425)	98.13 (0.457)	78.0 (6.09)	77.2 (5.71)	78.3 (6.69)
Median	Visit 1	98.10	98.35	98.20	78.5	77.0	79.0
Min, Max	Visit 1	97.4,98.7	97.5,98.9	97.1,98.9	64,91	64,89	66,90
N	Visit 2	30	30	20	30	30	20
Mean (SD)	Visit 2	97.64 (1.030)	97.84 (0.830)	97.60 (1.125)	79.5 (6.52)	78.6 (4.05)	78.7 (6.09)
Median	Visit 2	98.15	98.00	97.80	80.0	78.0	80.5
Min, Max	Visit 2	95.0,98.9	95.3,99.1	95.5,99.2	63,90	68,86	65,88
N	Visit 3	30	30	20	30	30	20
Mean(SD)	Visit 3	97.35 (1.184)	97.29 (1.265)	97.37 (0.914)	75.5 (5.31)	78.1 (5.44)	75.7 (5.56)
Median	Visit 3	97.60	97.70	97.45	76.0	78.5	75.0
Min, Max	Visit 3	94.3,98.6	94.5,98.8	95.4,98.7	62,83	63,88	64,85

Table 2 B: Descriptive statistics for vital signs: Pulse rate, Respiratory rate

Parameter/ Statistics	Visit	Pulse rate (beats/min)			Respiratory rate (breaths/min)		
		Treatment A	Treatment B	Treatment C	Treatment A	Treatment B	Treatment C
N	Screening	30	30	20	30	30	20
Mean (SD)	Screening	75.9(5.76)	76.4(5.30)	78.2(5.06)	18.0(1.38)	17.9(1.43)	18.6(1.31)
Median	Screening	77.5	76.5	79.0	18.0	18.0	19.0
Min, Max	Screening	64,85	66,84	66,84	16,20	16,20	16,20
N	Visit 1	30	30	20	30	30	20
Mean (SD)	Visit 1	78.0(6.09)	77.2(5.71)	78.3(6.69)	18.3(1.53)	18.0(1.79)	18.6(1.14)
Median	Visit 1	78.5	77.0	79.0	18.0	18.0	19.0
Min, Max	Visit 1	64,91	64,89	66,90	16,22	15,22	16,20
N	Visit 2	30	30	20	30	30	20
Mean (SD)	Visit 2	79.6(6.31)	78.9(4.51)	78.8(6.08)	18.4(1.67)	18.3(1.58)	18.4(2.11)
Median	Visit 2	79.5	78.0	80.5	18.5	18.0	18.0
Min, Max	Visit 2	64,90	67,89	66,88	16,22	15,22	15,24
N	Visit 3	30	30	20	30	30	20
Mean(SD)	Visit 3	75.8(5.12)	78.1(5.35)	75.6(5.90)	18.2(1.60)	17.8(2.28)	17.7(1.95)
Median	Visit 3	76.0	79.0	75.0	18.0	17.0	18.0
Min, Max	Visit 3	62,84	64,88	63,85	15,22	14,22	15,22

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Table 2 C: Descriptive statistics for vital signs- Systolic and Diastolic Blood Pressure (mmHg)

Parameter/ Statistics	Visit	Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure (mmHg)		
		Treatment A	Treatment B	Treatment C	Treatment A	Treatment B	Treatment C
N	Screening	30	30	20	30	30	20
Mean(SD)	Screening	124.3(3.03)	123.2(2.96)	122.8(1.86)	79.5(3.89)	80.0(3.94)	81.7(4.15)
Median	Screening	124.0	123.0	123.0	79.5	79.5	82.0
Min,Max	Screening	120,132	120,132	120,126	73,87	72,88	72,87
N	Visit 1	30	30	20	30	30	20
Mean(SD)	Visit 1	125.2(4.21)	124.9(3.96)	124.7(3.66)	82.7(4.70)	81.2(4.26)	82.0(3.58)
Median	Visit 1	125.0	124.0	124.0	82.5	81.0	82.0
Min,Max	Visit 1	118,134	118,133	120,131	74,91	72,88	77,91
N	Visit 2	30	30	20	30	30	20
Mean(SD)	Visit 2	125.3(4.81)	123.6(4.13)	121.9(3.92)	81.1(5.09)	79.7(4.60)	81.1(4.23)
Median	Visit 2	126.0	124.0	121.0	82.5	79.5	82.0
Min,Max	Visit 2	110,133	114,133	114,132	69,88	71,92	72,88
N	Visit 3	30	30	20	30	30	20
Mean(SD)	Visit 3	124.7(3.70)	124.1(4.41)	123.0(4.57)	81.4(4.54)	80.2(3.13)	82.1(2.98)
Median	Visit 3	126.0	124.0	122.0	81.0	80.0	82.0
Min,Max	Visit 3	118,131	116,132	116,132	74,92	72,86	76,86

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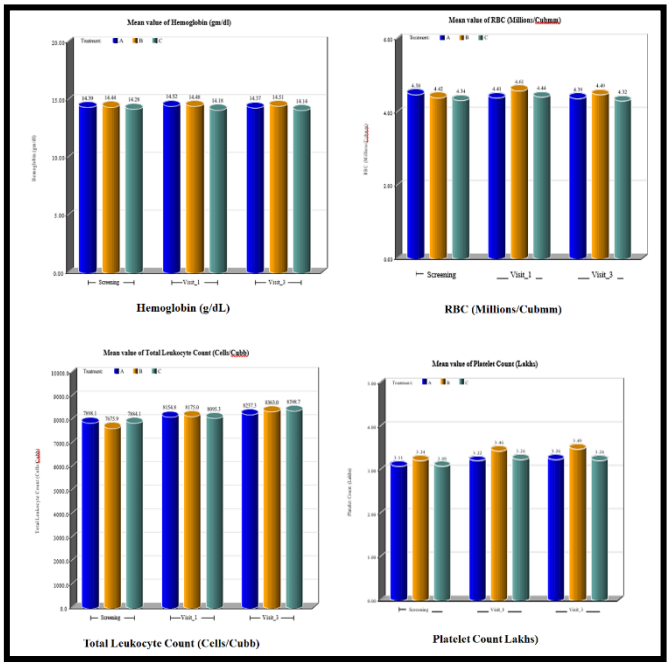

Fig 1: Descriptive statistics for Lab Data: Haemoglobin, RBC, Total Leucocyte Count and Platelet Count

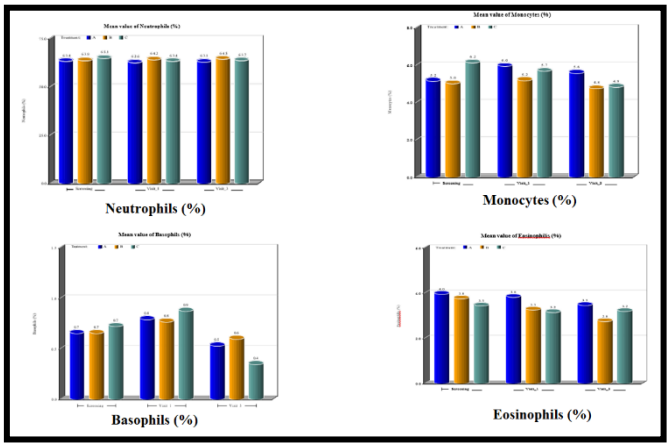

Fig 2: Descriptive statistics for Lab Data: Neutrophils, Monocytes, Basophils and eosinophils

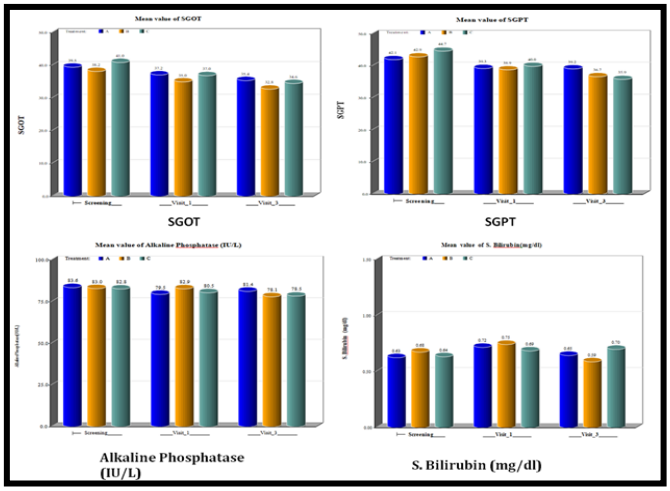

Fig 3: Descriptive statistics for Lab Data: SGOT, SGPT, Alkaline Phosphatase and S. Bilirubin

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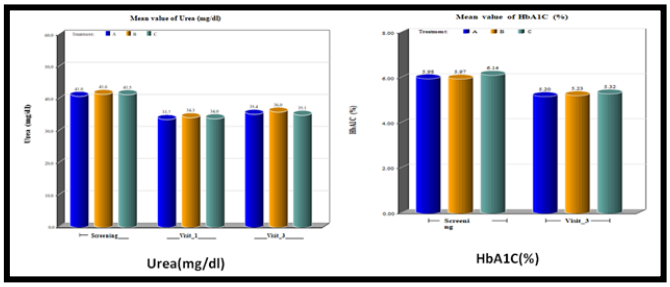

Fig 4: Descriptive statistics for Lab Data: Urea and HbA1C

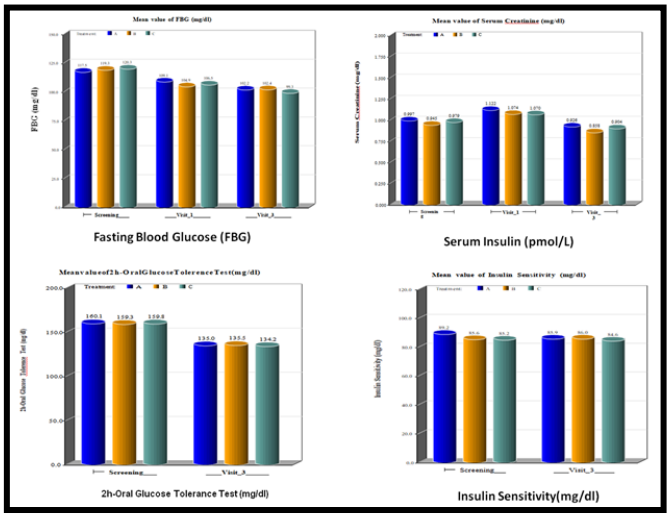

Fig 5: Descriptive statistics for Lab Data: Fasting blood Glucose, Serum Insulin, 2h-Oral Glucose Tolerance Test and Insulin Sensitivity

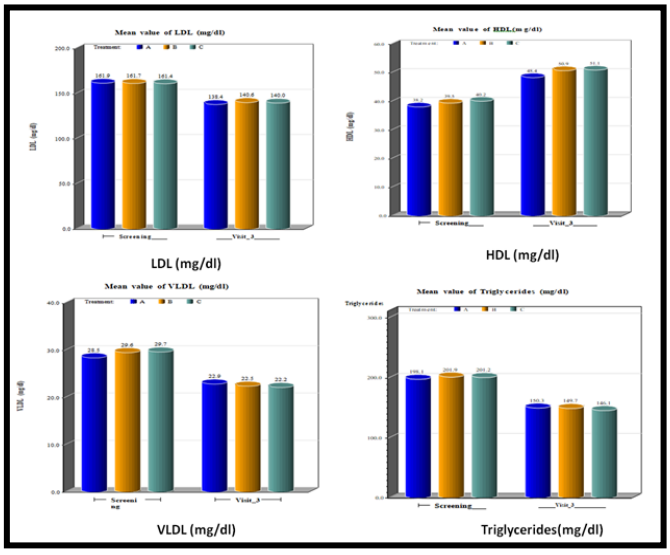

Fig 6: Descriptive statistics for Lab Data: LDL, HDL, VLDL and Triglycerides

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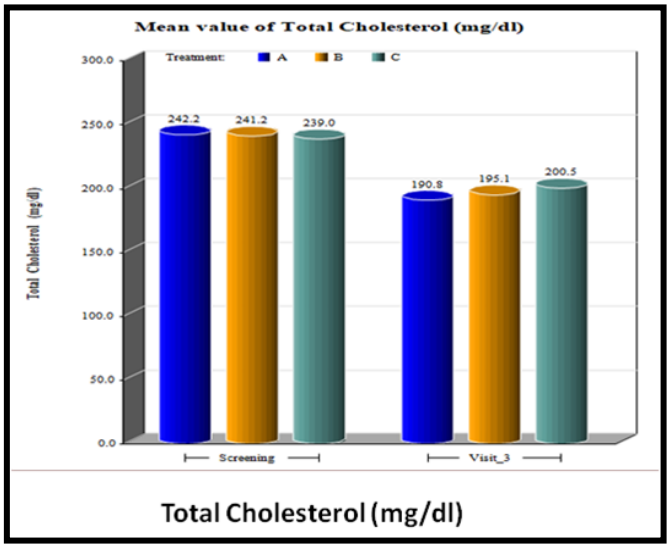

Fig 7: Descriptive statistics for Lab Data: Total Cholesterol

Table 3: Descriptive statistics for Lab Data Urine Color (mg/dl) and Urine Appearance

Parameter/Statistics	Visit	Treatment A	Treatment B	Treatment C
Urine Color, n [%]				
Pale yellow	Screening	30 (100.0)	30 (100.0)	20 (100.0)
Pale yellow	Visit 3	30 (100.0)	30 (100.0)	20 (100.0)
Urine Appearance				
Clear	Screening	24 (100.0)	38 (100.0)	18 (100.0)
Clear	Visit 3	24 (100.0)	38 (100.0)	18 (100.0)

Table 4: Descriptive statistics for Lab Data Pus cells (/HPF) and Red Cells (/HPF)

Parameter/ Statistics	Visit	Pus cells (/HPF), n[%]			Red Cells (/HPF), n[%]		
		Treatment A	Treatment B	Treatment C	Treatment A	Treatment B	Treatment C
0-1	Screening	2(6.7)	3(10.0)	2(10.0)	0(0.0)	1(3.3)	0(0.0)
0-2	Screening	4(13.3)	5(16.7)	2(10.0)	16(53.3)	19(63.3)	10(50.0)
0-3	Screening	14(46.7)	10(33.3)	12(60.0)	14(46.7)	10(33.3)	10(50.0)
0-4	Screening	9(30.0)	10(33.3)	3(15.0)	0(0.0)	0(0.0)	0(0.0)
0-5	Screening	1(3.3)	2(6.7)	1(5.0)	1(3.3)	1(3.3)	0(0.0)
0-1	Visit 3	3(10.0)	6(20.0)	2(10.0)	12(40.0)	14(46.7)	6(30.0)
0-2	Visit 3	4(13.3)	7(23.3)	6(30.0)	17(56.7)	14(46.7)	12(60.0)
0-3	Visit 3	8(26.7)	6(20.0)	6(30.0)	0(0.0)	1(3.3)	2(10.0)
0-4	Visit 3	9(30.0)	8(26.7)	6(30.0)	--	--	--
0-5	Visit 3	6(20.0)	3(10.0)	0(0.0)	--	--	--

Table 5: Descriptive statistics for Lab Data: Urine Pregnancy Test

Parameter/Statistics	Visit	Treatment A	Treatment B	Treatment C
NA	Screening	23 (76.7)	19 (63.3)	14 (70.0)
Negative	Screening	7 (23.3)	11 (36.7)	6 (30.0)

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ASSESSMENT OF EFFICACY

Efficacy variable(s)

Table 6: Comparative Descriptive Statistics for Efficacy parameters- High Sensitivity C-Reactive Protein (ng/ml) and Interleukin-6

Parameter/ Statistics	Visit	High Sensitivity C-Reactive Protein (ng/ml)			Red Cells (/HPF), n[%]		
		Treatment A	Treatment B	Treatment C	Treatment A	Treatment B	Treatment C
N	Screening	30	30	20	30	30	20
Mean (SD)	Screening	7.026(1.0419)	6.932(0.9259)	7.093(1.1462)	17.790(2.2566)	17.424(2.1860)	17.888(2.4226)
Median	Screening	7.114	7.165	7.045	18	17.85	18.017
Min, Max	Screening	4.77,8.54	4.96,8.24	5.21,8.64	13.20,21.70	13.40,20.90	13.90,21.60
N	Visit 3	30	30	20	30	30	20
Mean (SD)	Visit 3	6.325(0.6800)	6.191(0.6480)	6.340(0.8732)	15.679(1.3427)	15.521(1.2728)	15.819(1.5309)
Median	Visit 3	6.32	6.27	6.455	15.835	15.65	16.11
Min, Max	Visit 3	4.84,7.32	5.01,7.65	5.01,7.66	13.34,18.32	13.34,17.68	13.21,18.01

Table 7: Descriptive Statistics for Efficacy parameters: Losing about 30 min of nightmare sleep and doing about 30 min of exercise

Parameter/ Statistics	Visit	Losing about 30 min of nightmare sleep N [%]			Doing about 30 min of exercise N [%]		
		Treatment A	Treatment B	Treatment C	Treatment A	Treatment B	Treatment C
Extremely	Screening	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Largely	Screening	1(3.3)	1(3.3)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Moderately	Screening	12(40.0)	10(33.3)	6(30.0)	0(0.0)	0(0.0)	0(0.0)
Slightly	Screening	9(30.0)	8(26.7)	8(40.0)	9(30.0)	9(30.0)	5(25.0)
Not at all	Screening	8(26.7)	11(36.7)	5(25.0)	21(70.0)	21(70.0)	15(75.0)
Extremely	Visit 3	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Largely	Visit 3	1(3.3)	0(0.0)	1(5.0)	7(23.3)	8(26.7)	2(10.0)
Moderately	Visit 3	7(23.3)	7(23.3)	4(20.0)	13(43.3)	11(36.7)	11(55.0)
Slightly	Visit 3	7(23.3)	5(16.7)	5(25.0)	3(10.0)	2(6.7)	0(0.0)
Not at all	Visit 3	15(50.0)	18(60.0)	10(50.0)	7(23.3)	9(30.0)	7(35.0)

Table 8: Descriptive Statistics for Efficacy parameters: Not drinking coffee or other foods that contain Caffeine and Taking a 1 Week Vacation

Parameter/ Statistics	Visit	Not Drinking coffee or other foods that contain Caffeine N [%]			Taking a 1 Week Vacation		
		Treatment A	Treatment B	Treatment C	Treatment A	Treatment B	Treatment C
Extremely	Screening	6(20.0)	4(13.3)	4(20.0)	0(0.0)	0(0.0)	0(0.0)
Largely	Screening	13(43.3)	12(40.0)	9(45.0)	0(0.0)	0(0.0)	0(0.0)
Moderately	Screening	9(30.0)	14(46.7)	7(35.0)	5(20.8)	13(34.2)	2(11.1)
Slightly	Screening	0(0.0)	0(0.0)	0(0.0)	8(33.3)	14(36.8)	9(50.0)
Not at all	Screening	2(6.7)	0(0.0)	0(0.0)	11(45.8)	11(28.9)	7(38.9)
Extremely	Visit 3	7(23.3)	9(30.0)	5(25.0)	3(12.5)	8(21.1)	2(11.1)
Largely	Visit 3	8(26.7)	7(23.3)	5(25.0)	8(33.3)	9(23.7)	3(16.7)
Moderately	Visit 3	1(3.3)	0(0.0)	0(0.0)	2(8.3)	10(26.3)	5(27.8)
Slightly	Visit 3	10(33.3)	11(36.7)	7(35.0)	2(8.3)	4(10.5)	1(5.6)
Not at all	Visit 3	2(6.7)	0(0.0)	1(5.0)	9(37.5)	7(18.4)	7(38.9)

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Table 9: Descriptive Statistics for Efficacy Parameter– Forgetting about your worries and would you able to Organize your day-to-day activities more effectively

Parameter/ Statistics	Visit	Forgetting about your worries N [%]			Would you able to Organize your day-to-day activities more effectively N[%]		
		Treatment A	Treatment B	Treatment C	Treatment A	Treatment B	Treatment C
Extremely	Screening	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Largely	Screening	4(13.3)	3(10.0)	2(10.0)	0(0.0)	0(0.0)	0(0.0)
Moderately	Screening	12(40.0)	13(43.3)	11(55.0)	11(36.7)	10(33.3)	8(40.0)
Slightly	Screening	7(23.3)	8(26.7)	3(15.0)	13(43.3)	15(50.0)	10(50.0)
Not at all	Screening	7(23.3)	6(20.0)	4(20.0)	6(20.0)	5(16.7)	2(10.0)
Extremely	Visit 3	6(20.0)	5(16.7)	5(25.0)	8(26.7)	6(20.0)	5(25.0)
Largely	Visit 3	6(20.0)	8(26.7)	4(20.0)	6(20.0)	10(33.3)	7(35.0)
Moderately	Visit 3	7(23.3)	6(20.0)	4(20.0)	6(20.0)	4(13.3)	1(5.0)
Slightly	Visit 3	11(36.7)	10(33.3)	6(30.0)	5(16.7)	4(13.3)	1(5.0)
Not at all	Visit 3	0(0.0)	1(3.3)	1(5.0)	5(16.7)	6(20.0)	6(30.0)

Table 10: Descriptive Statistics for Efficacy Parameter–Would be able complete the tasks More Methodically and Would your ideas occur to you more readily

Parameter/ Statistics	Visit	Would be able complete the tasks More Methodically N [%]			Would your ideas occur to you more readily N [%]		
		Treatment A	Treatment B	Treatment C	Treatment A	Treatment B	Treatment C
Extremely	Screening	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Largely	Screening	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Moderately	Screening	11(36.7)	10(33.3)	8(40.0)	1(3.3)	3(10.0)	2(10.0)
Slightly	Screening	13(43.3)	15(50.0)	10(50.0)	15(50.0)	16(53.3)	10(50.0)
Not at all	Screening	6(20.0)	5(16.7)	2(10.0)	14(46.7)	11(36.7)	8(40.0)
Extremely	Visit 3	8(26.7)	6(20.0)	5(25.0)	1(3.3)	3(10.0)	2(10.0)
Largely	Visit 3	6(20.0)	10(33.3)	7(35.0)	9(30.0)	11(36.7)	5(25.0)
Moderately	Visit 3	6(20.0)	4(13.3)	1(5.0)	9(30.0)	5(16.7)	5(25.0)
Slightly	Visit 3	5(16.7)	4(13.3)	1(5.0)	4(13.3)	3(10.0)	1(5.0)
Not at all	Visit 3	5(16.7)	6(20.0)	6(30.0)	7(23.3)	8(26.7)	7(35.0)

Table 11: Descriptive Statistics for Efficacy Parameter–Would you make Fewer Carless Mistakes and What Proportion of the day do you have high level of alertness

Parameter/ Statistics	Visit	Would you make Fewer Carless Mistakes N [%]			What Proportion of the day do you have high level of alertness		
		Treatment A	Treatment B	Treatment C	Treatment A	Treatment B	Treatment C
Extremely	Screening	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Largely	Screening	1(3.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Moderately	Screening	17(56.7)	17(56.7)	10(50.0)	10(33.3)	11(36.7)	5(25.0)
Slightly	Screening	11(36.7)	13(43.3)	10(50.0)	13(43.3)	11(36.7)	10(50.0)
Not at all	Screening	1(3.3)	0(0.0)	0(0.0)	7(23.3)	8(26.7)	5(25.0)
Extremely	Visit 3	9(30.0)	12(40.0)	6(30.0)	6(20.0)	8(26.7)	4(20.0)
Largely	Visit 3	9(30.0)	7(23.3)	6(30.0)	8(26.7)	7(23.3)	5(25.0)
Moderately	Visit 3	0(0.0)	0(0.0)	0(0.0)	6(20.0)	4(13.3)	3(15.0)
Slightly	Visit 3	5(16.7)	1(3.3)	2(10.0)	2(6.7)	1(3.3)	2(10.0)
Not at all	Visit 3	6(20.0)	10(33.3)	6(30.0)	8(26.7)	10(33.3)	6(30.0)

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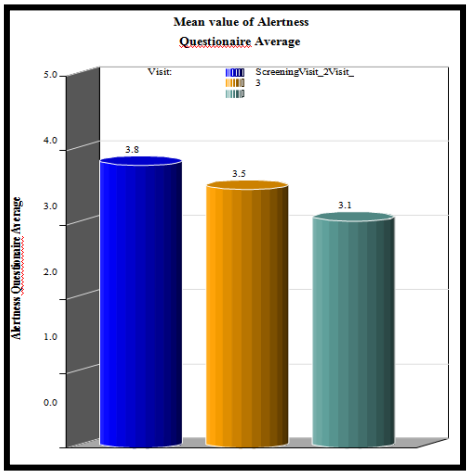

Fig 8: Mean Value of Mental Alertness Questionnaires

DISCUSSION

Prediabetes is associated with the simultaneous presence of insulin resistance and beta-cell dysfunction and abnormalities that start before glucose changes are detectable. The major categories of the etiological factors are genetic and hereditary factors and lifestyle related errors such as sedentary habit and high calorie diet. The Ayurvedic herbal preparations believed to lower sugar levels and also proprietary Ayurvedic medications are also used to treat diabetes. This study uses a polyherbal combination to decrease conversion from prediabetes to diabetes with proposed no reported adverse events. The active component used in iCoffee is *Salacia reticulata* roots extract branded as Salcital. After successfully neutralizing the taste of Salcital and other herbal extracts, the poly-herbal synergistic combination is blended with superior quality coffee beans sourced from Coorg region of Karnataka. This product is best to manage Diabetes without compromising the authentic taste of coffee.

The trial was conducted in Government General Hospital (Old RIMSGGH), Srikakulam –532001, Andhra Pradesh, India and Medstar Hospital 614, 171/3, Kodigehalli Main Rd, opp. Chairman's Club, Shanthivana, Sanjeevini Nagar, Bengaluru, Karnataka 560092 India with Dr. A Gopal Rao and Dr. Chikkalingaiah Sidde Gowda as Principal investigator, post Institutional Ethics Committee approval/favorable opinion on the trial proposal. Eligible subjects were enrolled into the study only after obtaining their consent in writing. The first patient's first visit was on 08 Sep 2021, last patient's first visit was on 09 Oct 2021 and last patient's last visit was on 07 Jan 2022. Subjects of same age group, height, weight, BMI and other demographics (Table 1A and 1B) between the 3 treatment arms with majority being male were enrolled.

Safety Parameters: Vital signs for the 3 treatment group subjects were measured at all the study visits. Table 2A shows average temperature of study subjects across all the visits. Similarly other vital parameters like heart rate, pulse rate, respiratory rate, systolic blood pressure and diastolic blood pressure (Table 2A, 2B, 2C). These vital sign parameters were found to be normal for all the study subjects and did not have any clinical or statistically significant abnormal values when compared between and within groups, implying that the test product has no safety issues post 90 days of oral administration.

Physical examination, Medical history, was completely normal across all the treatment groups across all the study visits. None of these safety lab data has any statistically significant changes from baseline (Day 0) visit values to that of their respective last (Day 90) visit values. This indicates that the product under testing is completely safe for oral consumption.

Laboratory safety Data: Hematology parameters like Hemoglobin, RBC, WBC, Platelet count (Fig 1), Neutrophils, Monocytes, Basophils, Eosinophils (Fig 2), SGOT, SGPT, ALP, Total Bilirubin (Fig 3), Blood urea (Fig 4) are completely normal before and after the treatment periods across all the study groups.

Glycemic control in diabetes mellitus is best assessed through HbA1c and is considered as a gold standard. Multiple clinical studies confirmed that mean HbA1c level is usually elevated with a higher incidence of diabetic and associated cardiovascular complications [21-23].

Efficacy parameters: HbA1c (Fig 4) showed a very good response in the groups receiving the investigational product iCoffee. Similarly, fasting blood glucose (Fig 5), Serum Insulin (Fig 5), also demonstrated a similar response to that of active comparator group. The important finding is that the 2h-Oral Glucose Tolerance Test (Fig 5), and the Insulin sensitivity (Fig 5) had left an extremely remarkable change in the iCoffee group of subjects from screening to last visit (day 90), not only within the group but also when compared to placebo and comparator group values. Other parameters like LDL data (Fig 6), HDL data (Fig 6), VLDL data (Fig 6), TG (Fig 6), Total Cholesterol (Fig 7) also showed a good and positive response by the iCoffee receiving group of subjects.

Urine analysis: Urine color, Specific gravity, Epithelial Cells, pH, Pus cells, Red cells had no major changes (Table 3 and 4).

Urine pregnancy test was performed at the time of screening (Table 5) to ensure no women of child bearing potential were enrolled into the trial.

Additional parameters - This study extensively evaluated iCoffee for its activity as efficacy in pre-diabetic volunteers.

CRP: In this study the CRP, an anti-inflammatory marker values were compared amongst the 3 study groups from baseline through all study visits (Table 06) and the values did not reach any statistical significance amongst the treatment groups towards end of the study (Day 90), however, the iCoffee group showed some minor difference and reduction in the values from its respective screening visit values.

IL6: This immune/anti-inflammatory marker when compared between the 3 treatment groups had shown a decrease within the treatment groups but did not show a statistical change between the groups (Table 6).

Mental alertness questionnaire: A set of 10 wide variety of questions related to mental alertness were administered amongst all study participants. All the study subjects responded voluntarily to this questionnaire as a part of this trial (Table 7-11, Fig 8). An average or mean value of the alertness questionnaire score is reflected in Table 50, with a good sign of improvement in the overall mental alertness of the iCoffee receiving group of subjects.

There were no Serious Adverse Events reported, however a few adverse events of mild to moderate in severity were noted for 3 different occasions.

Overheat - Reported on 28-Sep-2021 from 09:25 to 11:30 self-resolved and not related to IP. Gastric Pain - Reported ADR on 29-Nov-2021 from 14:35 to 18:24 self -resolved may be not related to IP. Headache - Reported ADR on 01-Jan-2022 from 11:35 to 14:25 self-resolved and not related to IP. The protocol was not amended during the course of the study and the initial version of Ethics Committees approved protocol was executed throughout the study duration across all the sites. There were no protocol deviations and the compliance of investigational product is 100% by all the completed study subjects.

CONCLUSION:

In the present study iCoffee has demonstrated an excellent safety profile when administered orally. Prediabetic subjects in iCoffee group showed significant improvement in fasting and post prandial blood glucose levels, HbA1c values. Serum insulin, 2h oral glucose tolerance and insulin sensitivity were same as that of control group arm at the end of the study(Day 90). These results corroborate even with various cholesterol parameters (LDL, HDL, VLDL, TC and TG) and also the mental alertness questionnaire which shows that the mean/average values of mental alertness improved in the iCoffee receiving group. This study clearly indicates that iCoffee has significant anti-inflammatory (hsCRP & IL-6) in the pre-diabetic subjects as well. Therefore, it is concluded that iCoffee has a definite role in improving the pre-diabetic condition along with improving the mental alertness when the subjects were administered the product orally for 90 consecutive days.

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